A. Gullo (Ed)

A.P.I.C.E.

Anaesthesia Pain Intensive Care and Emergency Medicine

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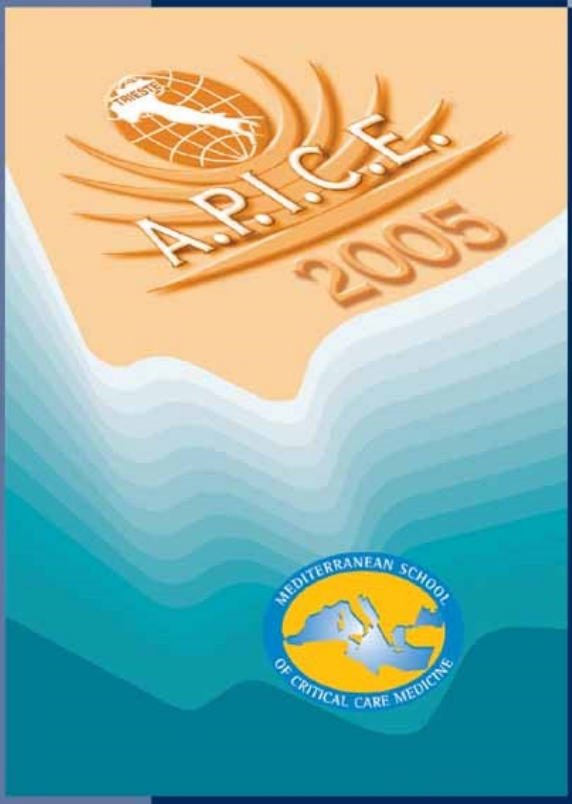

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Antonino Gullo, M.D.
Head, Department of Perioperative Medicine,
Intensive Care and Emergency
Trieste University School of Medicine
Trieste, Italy

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PERIOPERATIVE MEDICINE

List of Contributors

Adducci A.
Anesthesia Research Staff, IRCCS Istituti Ortopedici Rizzoli, Bologna, Italy

Allaria B.
2nd School of Specialisation in Anaesthesia and Intensive Care, University of Milan, Milan, Italy

Almeida de Oliveira S.
Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

Antonucci A.
Department of Anaestesia and Intensive Care, Policlinico Umberto I, 'La Sapienza' University, Rome, Italy

Atlee J.L.
Department of Anesthesiology, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, Milwaukee, Winsconsin, United States

Auler J.O.C. Jr.
Department of Anesthesiology and Surgical Intensive Care, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil

Auricchio A.
Division of Cardiology, University Hospital of Magdeburg, Magdeburg, Germany

Behringer W.
Department of Emergency Medicine, Vienna General Hospital, Vienna, Austria

Berlot G.
Department of Perioperative Medicine, Intensive Care and Emergency, School of Anaesthesia and Intensive Care, Cattinara University Hospital, Trieste, Italy

Bertacchini S.
Department of Surgical, Anaesthetic and Radiological Sciences, Section of Anaesthesiology and Intensive Care, University Hospital of Ferrara, Ferrara, Italy

Biagioli B.
Department of Surgery and Bioengineering, Unit of Cardiothoracic Anaesthesiology, University of Siena, Italy

Bigi E
U.O. Rianimazione – 118 Ospedale Maggiore, Bologna, Italy

Boldt J.
Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany

Boogaerts J
Department of Anesthesia CHU-Charleroi, Charleroi, Belgium

Borghi B.
Anesthesia Research Staff, IRCCS Istituti Ortopedici Rizzoli, Bologna, Italy

Böttiger B.W.
Department of Anaesthesiology, University of Heidelberg, Heidelberg, Germany

Brudniewski M.
Department of Anesthesiology, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil

Busani S.
Surgical Intensive Care Unit, Policlinico di Modena, Modena, Italy

Calderini E.
Terapia Intensiva de Marchi, Fondazione Policlinico Mangiagalli Regina Elena, Milan, Italy

Capuzzo M.
Department of Surgical, Anaesthetic and Radiological Sciences, Section of Anaesthesiology and Intensive Care, University Hospital of Ferrara, Ferrara, Italy

Caristi D.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara University Hospital, Trieste, Italy

Casadei E.
Department of Surgery and Bioengineering, Anaesthesiology and Intensive Care Unit, University of Siena, Italy

Cerchiari E.
U.O. Anestesia e Terapia Intensiva, Ospedale Maggiore, Bologna, Italy

Chiani C.
Department of Surgical, Anaesthetic and Radiological Sciences, Section of Anaesthesiology and Intensive Care, University Hospital of Ferrara, Ferrara, Italy

Chidini G.
Terapia Intensiva de Marchi, Fondazione Policlinico Mangiagalli Regina Elena, Milan, Italy

Cilloni N.
U.O. Anestesia e Terapia Intensiva, Ospedale Maggiore, Bologna, Italy

Cross A.S.
Division of Infectious Diseases, Brown Medical School, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island, United States

De Backer D.
Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Belgium

De Gaudio A.R.
Istituto di Anestesiologia e Rianimazione, Policlinico Careggi, Florence University, Florence, Italy

Della Corte F.
SCDU Anestesia e Rianimazione, Ospedale Maggiore della Carità, Università del Piemonte Orientale 'A. Avogadro', Novara, Italy

Delogu G.
Department of Anaestesia and Intensive Care, Policlinico Umberto I, 'La Sapienza' University, Rome, Italy

Doglioni N.
Paediatric Department, Medical School, Padua University, Padua, Italy

Dos Santos C.
Department of Critical Care Medicine, and Interdepartmental Division of Critical Care, Saint Michael's Hospital, University of Toronto, Toronto, Canada

Drenger B.
Department of Anaesthesia, Hadassah University Hospital at Mount Scopus, Jerusalem, Israel

Emmi V.
Servizio di Anestesia e Rianimazione I, IRCCS, Policlinico San Matteo, Pavia, Italy

Esposito G.
Medicina d'Urgenza Ospedale S. Paolo, Naples, Italy

Fantoni C.
Division of Cardiology, University Hospital of Magdeburg, Magdeburg, Germany

Feminò R.
Institute of Anesthesiology and Intensive Care, A.O.U. Careggi, University of Florence, Florence, Italy

Fodale V.
Department of Neuroscience, Psychiatric and Anesthesiological Sciences, School of Medicine. Policlinico Universitario 'G. Martino', University of Messina, Messina, Italy

Foëx P.
Nuffield Department of Anaesthetics, University of Oxford, The John Radcliffe Hospital, Oxford, United Kingdom

Freye E.
Clinics of Vascular Surgery and Renal Transplantation, Heinrich-Heine-University Clinics, Düsseldorf, Germany

Frugiuele J.
Anesthesia Research Staff, IRCCS Istituti Ortopedici Rizzoli, Bologna, Italy

Furlanut M.
Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, University of Udine, Udine, Italy

Garcia C.S.N.B.
Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Gazmuri R.J.
Department of Medicine, Division of Critical Care, and Department of Physiology and Biophysics, Rosalind Franklin University of Medicine and Science, and Medical Service, Section of Critical Care Medicine, North Chicago VA Medical Center, North Chicago, Illinois, United States

Gerlach H.
Vivantes – Klinikum Neukoelln, Klinik für Anaesthesie, operative Intensivmedizin und Schmerztherapie, Berlin, Germany

Giomarelli P.
Department of Surgery and Bioengineering, Anaesthesiology and Intensive Care Unit, University of Siena, Italy

Girardis M.
Surgical Intensive Care Unit, Policlinico di Modena, Modena, Italy

Gommers D.
Department of Anesthesiology, Erasmus Medical Centre, Rotterdam, The Netherlands

Goosen J.
Trauma Unit Johannesburg Hospital, Division of Trauma and Critical Care, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Gordini G.
U.O. Rianimazione – 118 Ospedale Maggiore, Bologna, Italy

Gowdak L.H.W.
Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

Gratarola A.
SCDU Anestesia e Rianimazione, Ospedale Maggiore della Carità, Università del Piemonte Orientale 'A. Avogadro', Novara, Italy

Grazzina N.
Paediatric Department, Medical School, Padua University, Padua, Italy

Gregoretti C.
Dipartimento di emergenza e accettazione, Azienda Ospedaliera CTO-CRF-ICOR-MA, Turin, Italy

Grüne F.
Department of Anesthesiology, Erasmus University Medical Centre, Rotterdam, The Netherlands

Gunnerson K.J.
The Virginia Commonwealth University Reanimation Engineering and Shock Center (VCURES) Laboratory, Departments of Anesthesiology/Critical Care and Emergency Medicine, Virginia Commonwealth University Medical Center, Richmond, Virginia, United States

Hahn R.
Department of Anesthesiology and General Intensive Care, Medical University of Vienna, Vienna, Austria

Hedenstierna G.
Department of Medical Sciences, Clinical Physiology, University Hospital, Uppsala, Sweden

Hiesmayr M.
Department of Cardiac Thoracic Vascular Anaesthesia and Intensive Care,Medical University Vienna,Austria

Hillman K
Division of Critical Care,The Simpson Centre for Health Service Innovation,Liverpool Hospital,Sydney,Australia

Himmelseher S.
Klinik für Anaesthesiologie,Klinikum rechts der Isar,Technische Universität München,München,Germany

Holzer M.
Department of Emergency Medicine, Vienna General Hospital,Vienna,Austria

Huang C.-H.
Department of Computer Science and Engineering,University of Connecticut, Storrs,Connecticut,United States

Ince C.
Department of Physiology,Academic Medical Center,University of Amsterdam, Amsterdam,The Netherlands

Izzo F.
Department of Anesthesia and Intensive Care Unit,Children Hospital V.Buzzi, Milan,Italy

Jevtovic-Todorovic V.
Department of Anesthesiology,University of Virginia Health System,Charlottesville,Virginia,United States

Kellum J.A.
The CRISMA (Clinical Research,Investigation,and Systems Modeling of Acute Illness)Laboratory,Department of Critical Care Medicine,University of Pittsburgh,Pittsburgh,Pennsylvania,United States

Klimek M.
Department of Anesthesiology,Erasmus University Medical Centre,Rotterdam, The Netherlands

Kochs E.F.
Klinik für Anaesthesiologie,Klinikum rechts der Isar,Technische Universität München,München,Germany

Krieger J.E.
Heart Institute (InCor),University of São Paulo Medical School,São Paulo,Brazil

La Mura F.
SCDU Anestesia e Rianimazione,Ospedale Maggiore della Carità,Università del Piemonte Orientale "A.Avogadro",Novara,Italy

Lachmann B.
Department of Anesthesiology,Erasmus Medical Centre,Rotterdam,The Netherlands

Latronico N.
Institute of Anesthesiology-Intensive Care,University of Brescia,Spedali Civili, Brescia,Italy

Lindeboom J.A.H.
Department of Oral and Maxillofacial Surgery,Academic Medical Center,University of Amsterdam,Amsterdam,The Netherlands

Malbouisson L.
Department of Anesthesiology and Surgical Intensive Care,Heart Institute,Hospital das Clínicas,University of São Paulo Medical School,São Paulo,Brazil

Marietta M.
Surgical Intensive Care Unit,Policlinico di Modena,Modena,Italy

Marraro G.A.
Anaesthesia and Intensive Care Department,and Paediatric Intensive Care Unit, Fatebenefratelli and Ophthalmiatric Hospital,Milan,Italy

Menarini M.
U.O.Rianimazione - Ospedale Maggiore,Bologna,Italy

Milstein D.M.J.
Department of Physiology;Department of Oral and Maxillofacial Surgery,Academic Medical Center,University of Amsterdam,Amsterdam,The Netherlands

Miotto L.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara University Hospital, Trieste, Italy

Mirante E.
Medicina d'Urgenza Ospedale S. Paolo, Naples, Italy

Morales M.M.
Laboratory of Cellular and Molecular Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Muchada R.
Department of Anaesthesia and Intensive Care, 'Eugène Andre' Hospital, Lyon, France

Nordström C.-H.
Department of Clinical Science, Division of Neurosurgery, University Hospital, Lund, Sweden

Opal S.M.
Division of Infectious Diseases, Brown Medical School, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island, United States

Paladino F.
Medicina d'Urgenza Ospedale S. Paolo, Naples, Italy

Palazzo M.
Department of Critical Care Medicine, Charing Cross Hospital, London, United Kingdom

Patel P.
Department of Anesthesiology, Anesthesia Service VA Medical College, University of California, San Diego, California, United States

Pavan F.
Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, University of Udine, Udine, Italy

Pea F.
Institute of Clinical Pharmacology and Toxicology, Department of Experimental and Clinical Pathology and Medicine, University of Udine, Udine, Italy

Pelosi P.
Terapia Intensiva de Marchi, Fondazione Policlinico Mangiagalli Regina Elena, Milan, Italy

Petrini F.
Anestesia e Rianimazione – PO SS.ma Annunziata, Università G. d'Annunzio di Chieti, Pescara, Italy

Piva M.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara University Hospital, Trieste, Italy

Plani F.
Trauma Unit Johannesburg Hospital, Division of Trauma and Critical Care, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Racca F.
Dipartimento di emergenza e accettazione, Azienda Ospedaliera CTO-CRF-ICOR-MA, Turin, Italy

Reis Miranda D.
Department of Anesthesiology, Erasmus Medical Centre, Rotterdam, The Netherlands

Rocco P.R.M.
Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Rodriguez B.
Oxford University Computing Laboratory, Oxford, United Kingdom

Romano S.M.
Department of Critical Care, Internal Medicine and Cardiology, University of Florence, Florence, Italy

Rossi A.
Anaesthesia and Intensive Care Unit, Cardiovascular Department, University Hospital 'Careggi', Florence, Italy

Ruggiero E.G.
Medicina d'Urgenza Ospedale S. Paolo, Naples, Italy

Ruskin K.J.
Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut, United States

Salvo I.
Department of Anesthesia and Intensive Care Unit, Children Hospital V. Buzzi, Milan, Italy

Santamaria L.B.
Department of Neuroscience, Psychiatric and Anesthesiological Sciences, School of Medicine. Policlinico Universitario 'G. Martino', University of Messina, Messina, Italy

Schiraldi F.
Medicina d'Urgenza Ospedale S. Paolo, Naples, Italy

Schmidlin D.
Anaesthesia and Intensive Care, Hirslanden Klinik im Park, Zürich, Switzerland

Schmidt A.P.
Department of Anesthesiology, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil

Scolletta S.
Department of Surgery and Bioengineering, Anaesthesiology and Intensive Care Unit, University of Siena, Italy

Scoponi M.
Anestesia e Rianimazione – PO SS.ma Annunziata, Università G. d'Annunzio di Chieti, Pescara, Italy

Semeraro F.
U.O. Anestesia e Terapia Intensiva, Ospedale Maggiore, Bologna, Italy

Signore M.
Department of Haematology, Oncology and Molecular Medicine, Biotecnology Division, Istituto Superiore di Sanità, Rome, Italy

Singer P.
General Intensive Care Department, Rabin Medical Center, Campus Beilinson, Petah Tikva; The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Sorbara C.
Anaesthesia and Intensive Care Unit, Cardiovascular Department, University Hospital 'Careggi', Florence, Italy

Sorbello M.
Anestesia e Rianimazione – PO SS.ma Annunziata, Università G. d'Annunzio di Chieti, Pescara, Italy

Souza-Fernandes A.B
Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Spiss C.
Department of Anesthesiology and General Intensive Care, Medical University of Vienna, Vienna, Austria

Spöhr F.
Department of Anaesthesiology, University of Heidelberg, Heidelberg, Germany

Stadler M.
Department of Anesthesia CHU-Charleroi, Charleroi, Belgium

Sterz F.
Department of Emergency Medicine, Vienna General Hospital, Vienna, Austria

Stortecky S.
Department of Anesthesiology and General Intensive Care, Medical University of Vienna, Vienna, Austria

Terzi R.G.G.
Faculdade de Ciências Médicas – UNICAMP – Universidade Estadual de Campinas, Campinas, SP, Brazil

Trevisanuto D.
Paediatric Department,Medical School, Padua University,Padua,Italy

Tulli G.
Department of Anaesthesia and Intensive Care,Hospital Nuovo San Giovanni di Dio,Florence,Italy

Ungerstedt U.
Department of Clinical Science,Division of Neurosurgery,University Hospital, Lund,Sweden

Van der Linden P.
Department of Anesthesiology,CHU Brugmann - HUDERF,Brussels,Belgium

Vincent J.-L.
Department of Intensive Care,Erasme Hospital,Free University of Brussels, Brussels,Belgium

Wolfler E.A.
Department of Anesthesia and Intensive Care Unit,Children Hospital V.Buzzi, Milan,Italy

Zin W.A.
Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics,Federal University of Rio de Janeiro, Rio de Janeiro,Brazil

List of Abbreviations

ACC	American College of Cardiology
ACEI	Angiotensin-Converting Enzyme Inhibitors
ACP	American College of Physicians
ACS	American College of Surgeons
AD	Antiarrhythmic Drugs
ADH	Antidiuretic Hormone
AED	Automated External Defibrillators
AF	Atrial Fibrillation
AFV	Aortic Flow Variation
AG	Anion Gap
AHA	American Heart Association
AHCPR	Agency for Health Care Policy and Research
ALI	Acute Lung Injury
AMI	Acute Myocardial Infarction
AOR	Adjusted Odd Ratio
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Pain Service
AR	Adrenoreceptor
ARAS	Ascending Reticulate Activating System
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
ASA	American Society of Anesthesiologists
AT	Anaerobic Threshold
ATLS	Advanced Trauma Life Support
AV	Atrioventricular
AVJT	Atrioventricular Junctional Tachycardia
AVM	Arteriovenous Malformations
BAEP	Brainstem Auditory Evoked Potential
BAER	Brainstem Auditory Evoked Response
BALF	Bronchoalveolar Lavage Fluid
BB	Buffer Base
BBB	Blood-Brain Barrier
BCT	Blunt Cardiac Trauma
BIVAD	Biventricular Assist Device
BMC	Bone Marrow Cells
BMI	Body-Mass Index
BNP	Brain Natriuretic Peptide
BSAC	British Society for Antimicrobial Chemotherapy
BSI	Bloodstream Infection
BVP	Biventricular Pacing

CA	Combined Anaesthesia
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CAD	Coronary Artery Disease
cAMP	Cyclic Adenosyne Monophosphate
CAP	Community Acquired Pneumonia
CARE-HF Study	Cardiac Resinchronisation in Heart Failure Study
CARP	Coronary Artery Revascularization Prophylaxis
CAST	Cardiac Arrhythmia Suppression Trial
CBF	Cerebral Blood Flow
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CCE	Cardiac Cycle Efficiency
CCO	Continuous Cardiac Output
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHF	Congestive Heart Failure
CI	Cardiac Index
CICD	Caspase-Independent Cell Death
Cl	Clearance
CMAP	Compound Muscle Action Potential
CMR	Cerebral Metabolic Rate
CNS	Central Nervous System
COP	Colloid Oncotic Pressure
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPC	Cerebral Performance Category
CPO	Cardiogenic Pulmonary Oedema
CPP	Cerebral Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CPRC	Cardiopulmonary-Cerebral Resuscitation
CRI	Chronic Renal Insufficiency
CRRT	Continuous Renal Replacement Therapy
CRT	Cardiac Resinchronisation Therapy
CT	Computed Tomography
CUSUM	Cumulative Sum Chart
CV	Cardioversion
CVC	Central Venous Catheter
CVP	Central Venous Pressure
CVVHDF	Continuous Veno-Venous Haemodiafiltration
DAD	Diffuse Alveolar Damage
DAG	Diacylglycerol
DEX	dexmedetomidine
DF	Defibrillation
DHP	Dehydropeptidase
DicBP	Dicrotic Blood Pressure
DIPOM	Danish Diabetic Postoperative Mortality and Morbidity
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic Acid
DO_2	Oxygen Delivery

DSD	Delayed Spontaneous Depolarisation
DSTC	Definitive Surgical Trauma Care
EAST	Eastern Association for the Surgery of Trauma
EBM	Evidence Based Medicine
ECD	External Cardioverter Defibrillator
ECF	Extracellular Fluid
ECG	Electriocardiogram
ECM	Extracellular Matrix
ECoG	Electrocorticography
ED	Emergency Department
e-DISTRICT CiPro	European Distance Training Interactive and Collaborative Tools for the Civil Protection
EDRF	Endothelium-Derived Relaxing Factor
EDV	End Diastolic Volume
EDVI	End Diastolic Volume Index
EEG	Electroencephalogram
EELV	End-Expiratory Lung Volume
EF	Ejection Fraction
EGF	Epidermal Growth Factor
ELISA	Enzyme-Linked Immunosorbent Assay
EMDM	European Master in Disaster Medicine
EMI	Electromechanical Interference
EMT	Electro-magnetic Tomography
EP	E Prostanoid
ERK	Extracellular Signal-Regulated Kinase
ESIMC	European Society of Intensive Care Medicine
ESPVR	End-Systolic Pressure-Volume Relationship
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAC	Focal Adhesion Complex
FAK	Focal Adhesion Kinase
FAST	Focused Abdominal Sonograph for Trauma
FES	Functional Electrical Stimulation
FEV	Forced Expiratory Volume
FFP	Fresh Frozen Plasma
FFT	Fast Fourier Transform
FGF	Fibroblast Growth Factor
FIESTA	Fast Imaging Employing Steady-State Acquisition
FiO_2	Fraction of Inspired Oxygen
FRC	Functional Residual Capacity
FVC	Functional Vital Capacity
GA	General Anaesthesia
GABA	Gamma-Amino-Butyric Acid
GAG	Glycosaminoglycans
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
GNB	Gram-Negative Bacteria
GR	Glucocorticoid Receptor
GSW	Gunshot Wound
HAP	Hospital Acquired Pneumonia
HCMV	Human Cytomegalovirus
HDP	Hospital Disaster Preparedness

HDR	Host Defence Response
HES	Hydroxyethyl Starch
HF	Heart Failure
HGF	Hepatocyte Growth Factor
HHS	Hypertonic-Hyperoncotic Solution
HMG	High Mobility Group
HOC	Hypertrophic Obstructive Cardiomyopathy
HPV	Hypoxic Pulmonary Vasoconstriction
HR	Heart Rate
HRQOL	Health Related Quality of Life
HS	Hypertonic Solution
HU	Hounsfield Unit
I2R	Imidazoline 2 Receptor
IATSIC	International Association for the Surgery of Trauma and Surgical Intensive Care
ICC	Intracellular Compartment
ICD	Internal Cardioverter Defibrillator
ICH	Intracerebral Haemorrhage
ICT	Isovolumetric Contraction Time
ICU	Intensive Care Unit
IFN-gamma	Interferon Gamma
IGF	Insulin-Like Growth Factor
IHD	Ischaemic Heart Disease
I-HSA	Iodinated Human Serum Albumin
iNO	Inhaled Nitric Oxide
IPM	Intraperitoneal Microdyalisis
IRT	Isovolumetric Relaxation Time
ISE	Ion Selective Electrode
I-SEE	Interactive Simulation Exercise for Emergencies
ISF	International Sepsis Forum
ISS	Interstitial Space
ITBV	Intrathoracic Blood Volume
IVS	Intravascular Space
IVT	Idioventricular Tachycardia
JAK-2	Janus-Activated Kinase 2
KGF	Keratinocyte Growth Factor
LaSRS	Late Steroid Rescue Study
LBB	Left Bundle Branch
LBBB	Left Bundle Branch Block
LED	Light-Emitting Diode
LIP	Lower Inflection Point
LIS	Locked-in Syndrome
LMA	Laryngeal Mask
LOD	Logistic Organ Dysfunction
LOS	Low Output Syndrome
LOS	Low Output Syndrome
LPS	Lipopolysaccharide
LQTS	Long QT Syndrome
LV	Left Ventricular
LVAD	Left Ventricular Assist Device

LVEDA	Left Ventricular End-Diastolic Area
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
LVP	Left Ventricular Pacing
MAP	Mean Arterial Pressure
MAPK	MItogen-Activated Protein Kinase
MCGs	Multiplayer Computer Games
MCS	Mechanical Circulatory Support
MCW	Medical College of Winsconsin
MD	Microdyalisis
MEG	Magnetencephalography
MEP	Motor Evoked Potential
MEP	Motor Evoked Potential
MET	Medical Emergency Team
MFI	Microvascular Flow Index
MI	Myocardial Infarction
MIC	Minimum Inhibitory Concentration
MIF	Macrophage Inhibitor Factor
MIGET	Multiple Inhert Gas Elimination Technique
MMP	Matrix Metalloproteinases
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ Failure
MONARCS Trial	Monoclonal Anti-TNF: A Randomized Controlled Sepsis Trial
MPI	Mannheimer Peritonitis Index
MPTP	Mitochondrial Permeability Transition Pore
MRI	Magnetic Resonance Imaging
MS	Molar Substitution
NCCLS	National Committee for Clinical Laboratory Standards
NHE-1	Sodium-Hydrogen Exchanger Isoform-1
NIPS	Neonatal Infant Pain Scale
NIV	Non-Invasive Ventilation
NLM	National Library of Medicine
NMDA	N-Methyl-D-Aspartate
NMDAR	NMDA Receptor
NMEP	Neurogenic Motor Evoked Potential
NNPO	Negative Pressure Pulmonary Oedema
NO	Nitric Oxide
NPO	Neurogenic Pulmonary Oedema
NPPV	Non-Invasive Positive Pressure Ventilation
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
NSVT	Non-Sustained Ventricular Tachycardia
NVEs	Networked Virtual Environments
NYHA	New York Heart Association
OLC	Open Lung Concept
OLT	Orthotopic Liver Transplantation
OPS	Orthogonal Polarisation Spectral
OR	Odds Ratio
PA	Pulmonary Artery
PAC	Pulmonary Artery Catheters

PAC	Pulmonary Artery Catheter
PAC	Pulmonary Artery Catheter
PAE	Post Antibiotic Effect
PAI	Plasminogen Activator Inhibitor
PAMP	Preload-Adjusted Maximal Power
PAOP	Pulmonary Artery Occlusion Pressure
PAP	Pulmonary Arterial Pressure
PAPP	Preload-Adjusted Peak Power
PAR	Protease-Activated Receptor
PASE	Pacing Stress Echocardiography
PC/RSC	Posterior Cingulate/Retrosplenial Cortex
PCA	Patient Controlled Anaesthesia
PCM	Pulse Contour Method
PCR	Polymerase Chain Reaction
PCWP	Pulmonary Capillary Wedge Pressure
PDGF	Platelet Derived Growth Factor
PE	Pulmonary Embolism
PEA	Pulseless Electrical Activity
PEEP	Positive End-Expiratory Pressure
PEEPi	Intrinsic Positive End-Expiratory Pressure
PET	Positron Emission Tomography
PGE_2	Prostaglandin E2
PGF	Placental Growth Factor
PGI_2	Prostacyclin
PI	Pulsatility Index
PICU	Paediatric Intensive Care Unit
PIM	Paediatic Intex of Mortality
PIP	Peak Inspiratory Pressure
PK/PD	Pharmacokinetic/Pharmacodynamic
PKC	Protein Kynase C
PM	Pacemaker
PMVT	Polymorphic Ventricular Tachycardia
PNS	Peripheral Nervous System
POP	Postoperative Pneumonia
PPHN	Persistent Pulmonary Hypertension of the Newborn
PPI	Pulse Power Index
PPV	Pulse Pressure Variation
PRAM	Pressure Recording Analytical Method
PTHrP	Parathyroid Hormone-Related Peptide
PTK	Protein Tyrosine Kynases
PTSD	Posttraumatic Stress Disorder
PTT	Pulse Transit Time
PVR	Pulmonary Vascular Resistance
PWA	Pulse Wave Analysis
QOL	Quality of Life
RA	Regional Anaesthesia
rAAV	Recombinanta Adeno-Associated Virus
RAP	Right Atrial Pressure
RAS	Renin-Angiotensin-Aldosterone System
rAV	Recombinant Adenovirus

RBB	Righ Bundle Branch
RBC	Red Blood Cells
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
REM	Rapid Eye Movements
rFVIIa	Recombinant Activated Factor VIIa
rhACP	Recombinant Human Activated Protein
RNA	Ribonucleic Acid
RNAi	RNA Interference
ROSC	Return of Spontaneous Circulation
RPA	Rnase Protection Assay
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
RVEDV	Right Ventricle End-Diastolic Volume
RVEF	Right Ventricular Ejection Fraction
RVESV	Right Ventricle End-Systolic Volume
S	Sieving Coefficient
SA	Sinoatrial
SAPK	Stress-Activated Protein Kynase
SBE	Standard Base Excess
SCCM	Society of Critical Care Medicine
SCD-HeFT Trial	Sudden Cardiac Death - Heart Failure Trial
SCI	Spinal Cord Injured
SCLC	Small Cell Lung Cancer
SD	Standard Deviaton
SDF	Sidetream Darkfield Imaging
SEP	Sensory Evoked Potential
SID	Strong Ion Difference
SIDa	Apparent Strong Ion Difference
SIDe	Effective Strong Ion Difference
SIG	Strong Ion Gap
SIRS	Systemic Inflammatory Response Syndrome
SISPE	Società Italiana Sepsi Pediatrica
SMART	Sensor Modality Assessment and Rehabilitation Technique
SMS	Simple Motif Search
SOFA	Sepsis-Related Organ Failure Assessment
SP-D	Surfactant Protein-D
SPV	Systolic Pressure Variation
SRE	Stretch Response Elements
SSEP	Somatosensory Evoked Potential
SSRE	Shear Stress Response Elements
STAT	Signal Transducer and Activators of Transcription
SvO_2	Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
SVT	Supraventricular Tachycardia
SVV	Stroke Volume Variation
SWS	Slow Wave Sleep
TAA	Thoraco-Abdominal Aneurysm
TAP	Transoesophageal Atrial Pacing
TCD	Transcranial Doppler Sonography
TDI	Tissue Doppler Imaging

TDM	Therapeutic Drug Monitoring
TdP	Torsades de Pointes
TEE	Transoesophageal Echocardiography
TF	Tissue Factor
TFA	Trifluoroacetyl Halide
TG	Triglycerides
TGF	Transforming Growth Factor
TIMPs	Tissue Inhibitors of Metalloproteinases
TMJ	Temporomandibular Joint
TNFR	Tumour Necrosis Factor Receptor
TOECV	Transoesophageal Cardioversion
TROICA	Thrombolysis in Cardiac Arrest
UMLS	Unified Medical Languange System
V/Q	Ventilation/Perfusion Ratio
VAP	Ventilator-Associated Pneumonia
VAS	Ventricular Assist System
Vd	Volume of Distribution
VEGF	Vascular Endothelial Growth Factor
VEP	Visual Evoked Potential
VEP	Virtual Electrode Polarisation
VES	Ventricular Extrasystoles
VF	Ventricular Fibrillation
VILI	Ventilator-Induced Lung Injury
VO_2	Oxygen Consumption
VO_2/DO_2	Oxygen Consumption/Oxygen Delivery
VP	Virtual Patient
VR	Virtual Reality
VT	Ventricular Tachycardia
V_T	Tidal Volume
VT/VF	Ventricular Tachycardia/Fibrillation
VV-ECMO	Venovenous Extracorporeal Membrane Oxygenation
VW	Vulnerable Window

BASICS IN CRITICAL CARE

Chapter 1

Cellular response to mechanical stress

C.S.N.B. Garcia, P.R.M. Rocco, M.M. Morales

Acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury, is a common severe inflammatory disease of the lungs and has a mortality rate of at least 30% [1–4]. Mechanical ventilation is a critical component of the treatment of patients with ARDS and is often lifesaving for these patients. However, its improper use can worsen, or even cause lung injury, in a condition referred to as ventilator-induced lung injury (VILI).

There are four basic mechanisms that can lead to the development of VILI, including gross air leaks (barotrauma) [5], diffuse alveolar injury due to overdistension (volutrauma) [6–8], injury to repeated cycles of recruitment/derecruitment of distal lung units (atelectrauma) [9, 10], and the most subtle form of injury, due to release of mediators from the lung (biotrauma). VILI is determined by the dynamic and continuous interaction between the morphologic and mechanical characteristics of the lung and the ventilator settings. Lungs of patients with ARDS are heterogeneously damaged; hence, mechanical ventilation with normal or even low tidal volumes [11, 12] and application of positive end-expiratory pressure (PEEP) levels can lead to regional lung injury.

Cells comprising the lung parenchyma, airways, and pulmonary and bronchial vascular system are normally subjected to a variety of passive and active mechanical forces associated with lung inflation and vascular perfusion as a result of the dynamic nature of lung function. Abnormal physical forces applied on lung tissues play a critical role in many pathological situations, such as ARDS and VILI. However, how mechanical forces induce their deleterious effects needs to be clarified. Over the past few years, interest in mechanical stimulation and its role in the regulation of cell structure, function, and metabolism has been increased. In vitro studies have shown that cells subjected to stress or strain exhibit a diverse and extensive range of responses, including proliferation, differentiation, gene expression, and synthesis and secretion of proteins. Furthermore, both the pattern and the degree of stretch are important in determining cellular responses.

In the present review, the current basic and clinical status of the mechanisms of sensing and converting inappropriate mechanical stretch into cytotoxic and inflammatory mediators, and extracellular matrix (ECM) remodelling are discussed, giving emphasis to VILI and ARDS. The focus of the discussion is the modulation of intracellular pathways by mechanical forces. A better understanding of the key players at the cellular and molecular levels may allow identification of targets for the treatment of patients with ARDS and for the prevention of VILI.

Mechanical stimulus

Although physical forces are often designated by imprecise terms, such as 'stretch' or 'distension,' they are more accurately defined as follows: 'stress' (force per unit of area) or 'strain' (any forced change in length in relation to the initial length). When the forces are parallel to the plane, the stress is called 'shear stress;' when the stress is directed toward the part on which it acts it is called 'compressive stress,' whereas when it is directed away from the part on which it acts it is called 'tensile stress.' Shear, compressive, and tensile stresses, respectively, resist the tendency of the parts to slide, approach, or separate under the action of applied forces. A stretch is a 'tensile strain,' a shortening is a 'compressive strain,' and an angular distortion is a 'shear strain' [13].

In the lung, strain may be more prominent in cells of the alveolar epithelium during breathing. In pathophysiological states, such as ARDS, as a consequence of increased lung elastic recoil and the heterogeneity of alveolar ventilation, the magnitude of the mechanical strain is altered and cell distortion is increased [14]. Shear stress mainly occurs in conducting airways due to airflow, and in the vascular system as a consequence of blood flow [14, 20]. However, the endothelium may also be subjected to strain and hydrostatic pressure. Elevated transmural pressure in extra-alveolar vessels can result from an increase in lung volume, as a consequence of lung interdependence—assuming that the luminal pressure remains constant [15–17]—whereas increased filtration across alveolar microvessels may be consequent to surfactant inactivation [18, 19]. Additionally, shear stress may act in other cells, e.g. the effects of pleural fluid on pleural mesothelial cells and the fluid layer on airway and alveolar epithelial cells [20]. Shearing forces can also potentially occur in alveoli under pathophysiological conditions, such as in ARDS in which oedema fluids flood the air space. The repetitive opening of distal lung units during inspiration and their collapse again during expiration also results in high shear stress [9, 10]. High inspiratory airflow enhances tensile stress across alveolar surfaces, resulting in greater transmission of kinetic energy to underlying structures [21]. Elevated airflows also increase the shear stress parallel to the surface of the airways and alveolar walls [21, 22]. Finally, strain can be generated by cytoskeletal rearrangements (such as actin contraction), leading to the transmission of tension throughout the cell, including the nucleus [20].

In addition, the types of physical forces also differ depending on the part of the cell where they act. For example, the fluid layer applies pressure on the airway and alveoli, and fluid shear stress applies pressure on the apical surface of epithelium, whereas distension of the basement membrane results in stretching of the basolateral surface of epithelial cells. These different types of physical forces acting on the same cell may activate different signal transduction pathways that mediate diverse biological functions.

Putative mechanisms for mechanotransduction

Mechanotransduction means the conversion of mechanical stimuli into intracellular biochemical and biomolecular alterations. How cells sense (mechanosensors) and convert mechanical forces into biological and biochemical signals to cause changes in gene expression and cell metabolism remains poorly understood. Common mechanosensors include stretch-sensitive ion channels [23], integrin receptors and focal adhesion complexes [24–27], and growth factor receptors. These mechanosensors subsequently activate and interact with various intracellular events, including: (1) generation of second-messenger molecules; (2) activation of specific protein kinases; (3) phosphorylation and activation of participating signalling molecules; (4) amplification through enzymatic cascades; and (5) modulation of gene expression. In the nucleus, physical forces can exert their effects by influencing expression of immediate early-response genes [c-*fos,* c-*jun,* c-*myc, JE,* ETS-like protein (ELK)-1, activation protein (AP)-1, specificity protein (SP)-1, nuclear factor (NF)-κB, and early growth response (Egr)-1], which encode proteins related to transcriptional factors and signal transduction [28]. Transcriptional factors are DNA-binding proteins that regulate gene expression. Of these, NF-κB has received especial attention. Several in vivo and in vitro studies have shown that lung-tissue stretching up-regulates NF-κB [29–32]. Current evidence suggests that the activation and control of NF-κB play a critical role in the generation and propagation of the cytokine response in VILI. NF-κB itself contains a DNA shear-stress response element at its promoter region, and NF-κB protein binds to several inflammatory mediators, such as interleukin (IL)-6, IL-8, IL1-β, and tumour necrosis factor (TNF)-α [33], thereby perpetuating inflammatory processes. NF-κB is likely important in the generation of inflammatory responses that occur in patients with ARDS [34].

Due to the complexity of the pulmonary structure, the possible mechanisms of mechanical stimulation and the potential cellular responses may vary extensively. There are a diversity of cell types and physical forces to which cells are exposed. Furthermore, different types of stimuli may use the same signalling pathway to coordinate cell activity.

Mechanically activated ion-channels pathway

Calcium represents one of the most common molecules that mediate the intracellular signalling initiated by mechanical stress. Mechanical stretch increases Ca^{2+} influx via a mechanosensitive cation channel that might be inhibited by gadolinium (a nonselective inhibitor of stretch-activated ion channels) and verapamil (a blocker of Ca^{2+} channels) [35–37]. This stretch-induced change in Ca^{2+} homeostasis has been demonstrated in cultured pulmonary arterial smooth muscle cells [35], arterial endothelial cells [38], airway epithelial cells [39], and foetal rat lung cells [36]. Mechanical stretch also commandeers protein tyrosine kinases (PTK), which activate phospholipase C-γ (PLC-γ) via tyrosine phosphorylation. PLC-γ mediates the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce inositol

1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilises Ca^{2+} from intracellular storage. DAG, in the presence of intracellular and extracellular Ca^{2+}, activates protein kinase C (PKC). PKC and other signals are able to activate transcriptional factors (c-*fos*) that bind to special response elements, such as stretch response elements (SRE), shear-stress response elements (SSRE) [40] and 12-O-tetradecanoylphorbol 13-acetate (TPA)-responsive elements (TRE) [41], thus increasing gene expression (Fig. 1). A 6-bp element, sensitive to various types of mechanical forces, constitutes the SSRE core. The shear TRE, a divergent phorbolester tissue-responsive element, exhibits the ability to transduce mechanical signals to transcriptional events. Amplified gene expression and other pro- and anti-inflammatory molecules control the pathogenesis of VILI and ARDS (Fig. 1).

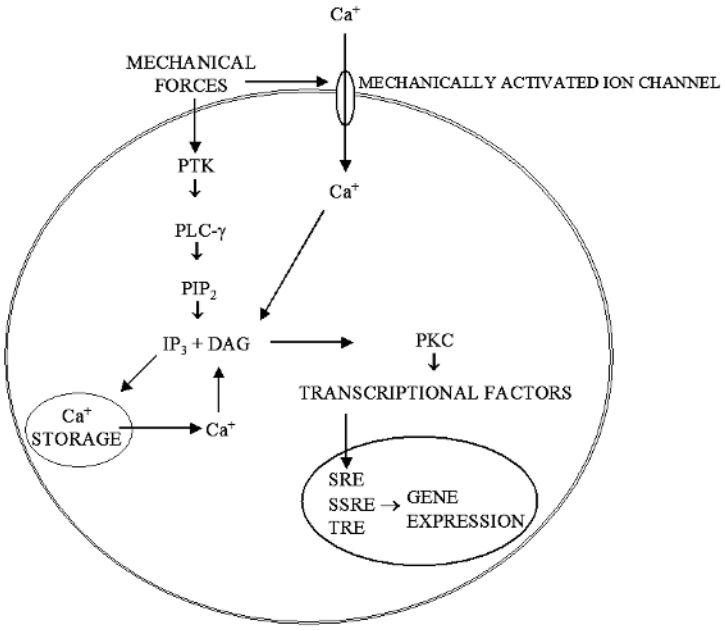

Fig. 1. Summary of the mechanically activated ion-channel pathway. Mechanical forces induce Ca^{2+} influx via a mechanically activated ion channel. Mechanical stretch also activates protein tyrosine kinases (*PTK*) that activates phospholipase C-γ (*PLC*-γ) via tyrosine phosphorylation. PLC-γ mediates the hydrolysis of phosphatidylinositol 4,5-bisphosphate (*PIP_2*) to produce inositol 1,4,5-trisphosphate (*IP_3*) and diacylglycerol (*DAG*). IP_3 mobilises Ca^{2+} from intracellular storage sites. DAG, in the presence of intracellular and extracellular Ca^{2+}, activates protein kinase C (*PKC*). PKC and other signals activate transcription factors (c-*fos*) that bind to special response elements, such as stretch response elements (*SRE*), shear-stress response elements (*SSRE*), and the shear TRE element, thereby boosting gene expression

Plasma membrane stress-disruption pathway

Plasma membrane disruption has been demonstrated by a number of mechanisms, including laser confocal microscopy, electron microscopy, and up-take of high-molecular-weight fluorescent dextran [42–44]. The maintenance of plasma membrane integrity undoubtedly plays an important role in intracellular signalling pathways. Structural damage to cells leads to an elevation in intracellular free Ca^{2+} concentrations, leading to the influx of extracellular Ca^{2+} and to the release of intracellular Ca^{2+} stores [45]. Changes in Ca^{2+} homeostasis can affect signalling pathways and induce PKC activation. Traumatic breaks in the plasma membrane in response to mechanical stress [46] and changes in Ca^{2+} concentration [47] can induce an increase in c-*fos* expression. Plasma-membrane stress disruption also induces the translocation and activation of NF-κB into the nucleus [46]. PKC, activated NF-κB, and c-*fos* can induce transcription of early-response genes and bind to SRE to activate gene transcription [48].

Matrix-integrin-cytoskeleton pathway

Cells are attached to neighbouring cells and to the ECM via transmembrane receptors of the cadherin and integrin families, respectively. On the cytoplasmic face of the cell membrane, these receptors are coupled, either directly or indirectly, to a large number of cytoskeletal plaque proteins, which, as a group, form the focal adhesion complex (FAC). This complex provides a structural connection to allowing signal transmission from the ECM to cells [49]. The tensegrity model, proposed by Ingber [50], predicts that cells are hard-wired to respond immediately to mechanical stresses transmitted over cell-surface receptors that physically couple cytoskeleton to extracellular matrix (e.g. integrins). The FAC serves as a macromolecular scaffold that mechanically couples the cytoplasmic portion of integrins to the actin cytoskeleton. The FAC contains various types of molecules, including those associated with actin (e.g. vinculin, talin, paxilin, and α-actin), focal adhesion kinase (FAK), kinases of the Src family, oncogene products, signalling molecules (e.g. tyrosine and serine protein kinases, and inositol lipid kinases), and some growth factor receptors. These molecules represent key candidates for transforming mechanical stimuli into biochemical signals. Cell stretch increases total protein tyrosine kinase activity, and induces an association of the activated signalling intermediate $pp60^{src}$ with the cytoskeleton [51]. Mechanical stimulation may also directly alter the activity of receptor tyrosine kinases, such as Flk-1, thereby changing the association of integrins with Shc, activating Ras and downstream extracellular-signal-regulated protein kinase (ERK) and c-Jun amino-terminal kinase (JNK) pathways, which in turn lead to transcriptional activation of AP1-TRE-mediated gene expression [52]. A series of non-identified pathways activate subgroups of the mitogen-activating protein kinases [(MAPK), p38 kinase, stress-activated protein kinase (SAPK), JNK, and ERK ½] [53], and transcription factors, such as Egr-1 and SP-1 [54, 55]. Subsequently, this diversity of molecules may activate NF-κB and/or, through other mechanisms, gene transcription. Mem-

bers of the integrin family can also regulate NF-κB action through activation of an inhibitor of NF-κB kinase (IKK). This, in turn, mediates the release of NF-κB from an inhibitor of NF-κB (IκB) by phosphorylation, and the subsequent translocation of NF-κB to the nucleus. Activation of members of the MAPK family and NF-κB induces transcription of early-response genes and binding to SRE to activate transcription [48]. Thus, amplified gene expression and other pro- and anti-inflammatory molecules control the pathogenesis of VILI and ARDS (Fig. 2).

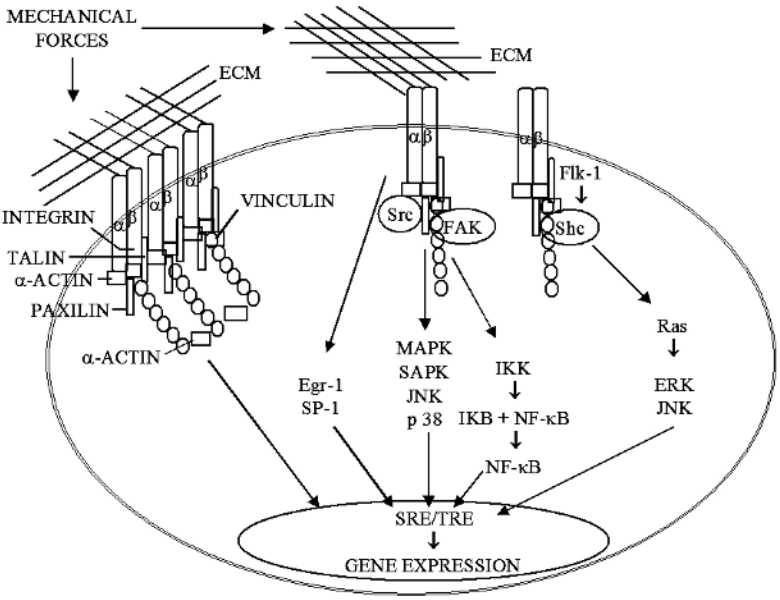

Fig. 2. Extracellular matrix (*ECM*)-integrin-cytoskeleton pathway. Integrins maintain a close relationship with ECM, actin-associated molecules (e.g. vinculin, talin, paxilin, and α-actin), focal adhesion kinase (*FAK*), kinases from Src family, oncogene products, signalling molecules (e.g. tyrosine and serine protein kinases, and inositol lipid kinases), and some growth factor receptors. Mechanical forces may alter the activity of receptor tyrosine kinases (*Flk-1*), changing the association of integrins with Shc, activating Ras and downstream ERK and JNK pathways. These events, in turn, lead to gene expression mediated by TPA-responsive elements (*TRE*). Through a series of non-identified pathways, MAPK, p38 kinase, stress-activated protein kinase (*SAPK*), c-Jun amino-terminal kinase (*JNK*), and transcription factors [early growth response (*Egr*)-1, specificity protein (*SP*)-1] are activated. Subsequently, these molecules may activate nuclear factor (*NF*)-κB and/or, through other mechanisms, gene expression. Members of the integrin family can also regulate NF-κB action by means of the activation of an inhibitor of NF-κB kinase (*IKK*) that mediates the release of NF-κB from the inhibitor of NF-κB (*IκB*), and the subsequent translocation of NF-κB to the nucleus. Activation of members of the MAPK family and NF-κB can induce transcription of early-response genes and bind to stretch response elements (*SRE*) to activate transcription

The cytoskeleton elements can be reorganised to increase the efficiency of transmitting signals from ECM into the cell interior. The pulling of integrins by micropipettes reoriented cytoskeleton filaments, distorted nuclei, and redistributed nucleoli along the axis of the applied tension [56]. Mechanical-stress-induced changes in the cytoskeleton may alter the function of structural molecules that comprise the cytoskeleton and nucleus, including some critical regulatory proteins [57]. Changing structural arrangements within the cytoskeleton and nuclear matrix may expose or obscure internal molecular binding sites, release mechanical constraints for molecular remodelling, or change the porosity of the network [57]. This ECM-integrin-cytoskeleton interconnectedness could be very important for cells adapting to changes in their external environment.

Cell-cell interaction

Mechanical-force-initiated intercellular signalling is transmitted through several types of intercellular communication, which may involve autocrine, paracrine, and juxtacrine interactions. Cells commonly use cytokines, growth factors, and other small soluble factors for communication [58–63]. Messages can also be transmitted directly from one cell to another through cellular junctions [64–67] or by cell-matrix interaction [68–70].

Soluble factors

Autocrine and paracrine mechanisms of cell-cell interactions are important for mechanical-force-initiated signalling. There is evidence of hormone production by lung cells under mechanical stimulation. Mechanical stretch applied to cultured foetal lung epithelial cells stimulates the expression and production of a differentiation factor, parathyroid hormone-related peptide (PTHrP). Torday et al. [58] observed an increased responsiveness of foetal lung fibroblasts to PTHrP. PTHrP is released by type II cells and specifically bind to its receptor on contiguous fibroblasts, stimulating cAMP as a second messenger, which subsequently induces specific functions of foetal lung fibroblasts. This paracrine mechanism is putatively involved in augmenting glucocorticoid binding, increasing metabolic activities (such as lipoprotein lipase elaboration and triglyceride uptake), and stimulating production of cytokines (such as IL-6 and IL-11). These cytokines molecules can act as intercellular mediators, thereby increasing the synthesis of surfactant phospholipids and surfactant proteins from alveolar epithelial cells.

Growth factors constitute another type of commonly used soluble factors for intercellular communication. The strain-induced growth-promoting effect on foetal lung cells appears to be mediated by increased production of endogenous growth factors, including platelet-derived growth factor (PDGF)-B [59]. Mechanical strain increases both gene and protein expression of PDGF-B and its receptor (PDGFR). Additionally, blockade of the receptor by a PTK inhibitor or with antisense PDGF-B oligonucleotides abolishes the strain-induced stimulatory effect

on foetal lung cell proliferation [59]. Another evidence of strain-induced growth-promoting effect is the reduction of insulin-like growth factor gene expression, the abolition of foetal lung breathing movements [60], and changes in foetal sheep lung volume owing to either tracheal obstruction or liquid drainage [61]. These findings agree with foetal breathing movements controlling foetal lung growth via activation of growth factor expression.

As previously reported, many studies using cultured lung cells have focused on the activation of MAPKs, ERK, JNK, and p38 by stretch [30, 62, 71–73]. One interesting pathway that might lead to activation of MAPK is autocrine activation of the epidermal growth factor (EGF) receptor [62, 63].

Intercellular junctions

Tight-junction barrier formation and gap-junctional communication represent two functions directly attributable to cell-cell contact sites. Epithelial and endothelial tight junctions constitute critical elements of the permeability barrier required to maintain discrete compartments in the lung. Gap junctions also enable a tissue to act as a cohesive unit by permitting metabolic coupling and facilitating the direct transmission of small cytosolic signalling molecules from one cell to another. Secondary messengers are probably transmitted across epithelial-cell gap junctions and perhaps between different cell types [64]. Additionally, the intracellular cytoskeleton interconnects neighbouring cells through FACs at specialised junctional complexes [26]. Tight and gap junctions do not act individually, like other junctional elements; instead, adherens junctions and desmosomes help to regulate barrier function and intercellular communication [65]. Intercellular adhesions in alveoli transmit force by connecting epithelial cells in a sheet, with the help of intermediate filaments. Adherens junctions probably act as mechanosensors. The mechanical stimulation of n-cadherin in intercellular adherens junctions in fibroblasts causes gadolinium-sensitive calcium influx and induces actin polymerisation at those sites where force was applied [66]. Additionally, the expression of connexin proteins, the constituents of gap junctions in rat type-2 cells, is modulated by the matrix protein fibronectin, which is abundant in the airspace after alveolar injury [67].

Cell-matrix interaction

The importance of cell-ECM interactions was demonstrated by stretching cells cultured on different ECM substrata [68, 69]. ECM modifies the ability of the cell to adhere to a surface and influences cell shape. For example, contact with various ECM proteins modulates the ability of a mechanical signal to alter type I procollagen gene expression [68]. Strained fibroblasts cultured on laminin or elastin, but not on fibronectin, expressed type I procollagen. These three ECM molecules form some of the main support structures in the lung that could represent load-bearing elements resistant to tissue stretch.

Glycosaminoglycans (GAGs) also participate in cell-matrix interactions by effectively modulating the cellular phenotype via high-affinity binding sites. GAGs interact with other ECM proteins influencing the macromolecular organisation and also regulate collagen fibrillogenesis. GAGs modulate steady-state mRNA expression levels: (1) in a cell-type-specific manner; and (2) in that different GAGs selectively modulate cell-matrix interactions [70].

As previously reported, specific focal adhesions at the cell surface allow mechanical stretch generated in the system to be transduced to the cytoskeletal network. Thus, the cell constitutes an integrated system in terms of mechanical force transduction. A change in the cytsokeletal architecture is transmitted to the nuclear matrix, ultimately allowing the expression of a subset of gene products [56].

Mechanical-force-induced production of inflammatory mediators

The inflammatory response seems to depend on the type of injurious stimulus and follows different molecular pathways. During the past several years, considerable attention has focused on the release of inflammatory mediators from lung cells exposed to mechanical forces. In this context, cell culture models have been employed to examine the stretch-induced inflammatory response [30, 71, 74–76].

Cytokine release in vitro

The pivotal role of IL-8 as an early mediator of the inflammatory cascade was confirmed in vitro by stretching lung cell cultures. Human macrophages, under a strain induced by a 12% increase in surface area at 20 cycles/min, produce IL-8 via NF-κB [30]. However, the same stretch regimen applied to human lung epithelial A549 cells did not elevate IL-8 content. In contrast, A549 lung epithelial cells submitted to a strain of 30% at a frequency of 20 or 40 cycles/min augmented IL-8 after 12–48 h [71]. IL-8 content also rose when A549 epithelial cells were exposed to 40% strain [76]. Thus, the release of IL-8 depends on the magnitude of the cyclic strain on alveolar cells.

Additional in vitro studies have emphasised the importance of the association of a subjacent inflammatory injury and a mechanical deformation to induce the release of cytokines. In this context, Tsuda et al. observed that stretch alone did not affect IL-8 production after 8 h; however, in the presence of glass fibres or crocidolite asbestos, stretch significantly increases IL-8 production in cultured A549 cells [74]. Similarly, mechanical stretch applied to primary cultured foetal rat lung cells increases mRNA levels of macrophage inflammatory protein-2 (MIP-2, the rodent equivalent of human IL-8) only after LPS stimulation [75].

Cytokine release in vivo

Experimental studies have concluded that injurious ventilation results in the production of many cytokines. An ex vivo rat lung ventilation model demonstrated that injurious ventilation regimens increase the bronchoalveolar fluid concentrations of several cytokines, including TNF-α, IL1-β, IL-6, IL-10, MIP-2, and interferon-γ [77]. An isolated-perfused mouse lung model demonstrated hyperventilation-induced release of TNF-α and IL-6 from the lung into to the perfusate [78].

However, the concept that overinflation induces proinflammatory cytokines has been challenged by others. Using the same ELISA kit and the same modality of lung ventilation, Ricard et al. [79] failed to observe any significant release of TNF-α or IL-8 in the absence of lipopolysaccharide (LPS) challenge in an attempt to reproduce the findings of Tremblay et al. [77]. These different results might be related to different initial steady states in the lung, such as the presence of an underlying injury caused by a pathogen [77].

It was recently shown that only 30 min of injurious ventilation (tidal volume of 25 ml/kg body weight) were sufficient to specifically up-regulate ten genes encoding transcriptional factors, stress proteins, and inflammatory mediators, and to specifically down-regulate 12 genes mainly encoding metabolic enzymes [80]. Such early activation took place in the absence of any histological or mechanical signs of injury. Thus, the occurrence of phenotypic activation, even of short duration, should be emphasised. In this context, interventions of very short duration, such as recruitment manoeuvres, could be potentially dangerous.

Prostaglandin synthesis

The alteration of physical forces represents an important factor in lung inflammatory diseases. The synthesis of biologically active eicosanoids by lung cells contributes to the regulation of smooth muscle tone and inflammatory responses. Prostaglandin synthesis in response to mechanical forces may vary with the type of cell and stimuli. For example, cyclic stretch down-regulates the synthesis of prostaglandins (PGs), including PGE_2, prostacyclin (PGI_2), and thromboxane A2 in cat and human airway epithelial cells [81]. This inhibitory effect seems to result from the inactivation of cyclooxygenase. In contrast, shear stress increases the production of PGI_2 by lung endothelial cells [82] and mechanical strain induces a rapid release of PGI_2 by foetal rat lung cells [83].

Mechanical-force-induced extracellular matrix expression

The ECM transmits essential information to pulmonary cells, thereby regulating their proliferation, differentiation, and organisation [84]. ECM components can be divided into four broad categories: collagen, noncollagenous glycoproteins (such as fibronectin and laminin), GAGs, and proteoglycans, and elastic fibres [84]. Cells continuously remodel their microenvironment by changing the components and

structure of the ECM. Most cell types in lung tissue contribute to bringing about dynamic changes in the ECM. Regulation of ECM dynamics is complicated, involving a balance between synthesis and deposition of ECM molecules as well as their degradation. A family of secreted proteases, matrix metalloproteinases (MMPs), plays a role in ECM turnover [85, 86]. Hanseneen et al. [87] demonstrated the existence of a relation between stretched endothelial cells and lung remodelling by release of MMP-1 and MMP-2, both of which are activated through a membrane type-1 MMP (MT1-MMP) pathway. MMP activity is regulated by a variety of mechanisms, including synthesis, secretion, and inhibition by a stoichiometrically complex array of tissue inhibitors of metalloproteinases (TIMPs) [86, 88].

In the past two decades, it has been well-established that cells are sensitive to mechanical forces and can change their phenotype and surrounding ECM in response to changes in their mechanical environment. Mechanical forces alter gene expression and protein synthesis of several lung ECM molecules, such as collagen, GAGs and proteoglycans. Cells can directly remodel their local matrix in response to mechanical stress [89, 90]. An intermittent mechanical strain may diversely regulate gene and protein expression of lung ECM molecules [91]. Differences in the regional distribution of mechanical stress or in the extent of injury generate diverse patterns of matrix protein expression [92]. Epithelial-fibroblast communication is also critical in the regulation of matrix production in the lung [93, 94]. Moreover, the increase in matrix accumulation seems to be mainly related to a higher rate of ECM synthesis, instead of to the activities of degradative enzymes [91].

Mechanical forces increase procollagen fibre expression [68, 91, 92], and the exact role of physical forces on type III procollagen expression has been recently elucidated. In this context, Garcia et al. analysed lung mechanical stretch induced by different levels of stress and strains. They observed that there is a threshold stress above which lung cells express mRNA for procollagen type III [95].

Intermittent mechanical strain, simulating foetal breathing movements, also induces the secretion of GAGs and proteoglycans. Mechanical strain appears mainly to affect the distal part of the secretory pathway, i.e. GAGs and proteoglycans trafficking from *trans*-Golgi to the cell-surface membrane. Strain-enhanced GAG release was partially blocked by BAPTA/AM (an intracellular calcium chelator) and completely abolished by gadolinium (a stretch-activated ion channel blocker). These results suggest that calcium influx, rather than calcium mobilisation from intracellular stores, represents the most important trigger for mechanical-strain-induced GAG exocytosis in foetal lung cells [96].

Stretch-induced synthesis of hyaluronan, a component of the ECM, increases proinflammatory cytokines in VILI [97]. IL-8 production may be stimulated by stretch-induced release of hyaluronan from fibroblasts; a pathway probably mediated by Janus-activated kinase 2 (JAK-2)-dependent transcription of hyaluronan synthase 3 [97]. Hyaluronan released after lung injury can stimulate endothelial cells to produce cytokines by activation of a Toll-like-receptor-4-dependent mechanism [98].

Conclusions

Although mechanical ventilation is lifesaving for patients with ARDS, it can cause VILI. Physical forces provided by mechanical ventilation affect both the function and phenotype of cells in the lung. Impropriate mechanical forces observed during mechanical ventilation of heterogeneously damaged lungs, such as occurs in ARDS, might result in the expression and secretion of inflammatory mediators as well as remodelling of the ECM. The cellular to mechanical forces are a result of the cell's ability to sense and transduce these stimuli. Many studies have focussed on the molecular mechanisms implicated in mechanotransduction. A better understanding of the mechanisms by which lung cells transduce physical forces into biochemical and biological signals is of key importance for identifying targets for the treatment of acute lung injury and for prevention of VILI.

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References

1. Reynolds HN, McCunn M, Borg U et al (1998) Acute respiratory distress syndrome: estimated incidence and mortality rate in a 5-million-person population base. Crit Care 2:29–34
2. Pola MD, Navarrete-Navarro P, Rivera R et al (2000) Acute respiratory distress syndrome: resource use and outcomes in 1985 and 1995, trends in mortality and comorbidities. J Crit Care 15:91–96
3. Brun-Buisson C, Minelli C, Bertollini G et al (2004) Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 30:51–61
4. Misset B, Gropper MA, Wiener-Kronish JP (2003) Predicting mortality in acute respiratory distress syndrome: circulatory system knows best. Crit Care Med 31:980–981
5. Macklin MT, Macklin CC (1944) Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory disease and other conditions: an interpretation of clinical literature in the light of laboratory experiment. Medicine 23:281–352
6. Dreyfuss D, Soler P, Basset G et al (1988) High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164
7. Carlton DP, Cummings JJ, Scherer RG (1990) Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. J Appl Physiol 69:577–583

8. Hernandez LA, Peevy KJ, Moise A et al (1989) Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66:2364–2368
9. Dreyfuss D, Saumon G (1993) Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 148:1194–1203
10. Muscedere JG, Mullen JBM, Gan K et al (1994) Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 149:1327–1334
11. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
12. Gattinoni L, Carlesso E, Cadringher P et al (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. Eur Respir J 47:15S–25S
13. Roark RJ (1954) Formulas for stress and strain. McGraw-Hill, New York
14. Schumacker PT (2002) Straining to understand mechanotransduction in the lung. Am J Physiol Lung Cell Mol Physiol 282:L881–L882
15. Mead J, Takishima T, Leith D (1970) Stress distribution n lungs: a model of pulmonary elasticity. J Appl Physiol 33:14–21
16. Howell JBL, Permutt S, Proctor DF et al (1961) Effect of inflation of the lung on different parts of pulmonary vascular bed. J Appl Physiol 16:71–76
17. Benjamin JJ, Murtagh PS, Proctor DF et al (1974) Pulmonary vascular interdependence in excised dog lobes. J Appl Physiol 37:887–894
18. Webb HH, Tierney DF (1974) Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565
19. Albert RK, Lakshminarayan S, Hildebrandt J et al (1979) Increased surface tension favors pulmonary edema formation in anesthetized dogs' lungs. J Clin Invest 63:1015–1018
20. Wirtz HR, Dobbs LG (2000) The effects of mechanical forces on lung functions. Resp Physiol 119:1–17
21. Kotani M, Kotani T, Li Z et al (2004) Reduced inspiratory flow attenuates IL-8 release and MAPK activation of lung overstretch. Eur Respir J 24:238–246
22. Nucci G, Suki B, Lutchen K (2003) Modeling airflow-related shear stress during heterogeneous constriction and mechanical ventilation. J Appl Physiol 95:348–356
23. Sackin H (1995) Mechanosensitive channels. Annu Rev Physiol 57:333–353
24. Wang N, Butler JP, Ingber DE (1993) Mechanotransduction across the cell surface and through the cytoskeleton. Science 260:1124–1127
25. Banes AJ, Tsuzaki M, Yamamoto J (1995) Mechanoreception at the cellular level: the detection, interpretation, and diversity of responses to mechanical signals. Biochem Cell Biol 73:349–365
26. Ingber DE (1997) Tensegrity: the architectural basis of cellular mechanotransduction. Annu Rev Physiol 59:575–599
27. Chiquet M (1999) Regulation of extracellular matrix gene expression by mechanical stress. Matrix Biol 18:417–426
28. Komuro I, Katoh Y, Kaida T et al (1991) Mechanical loading stimulates cell hypertrophy and specific gee expression in cultured rat cardiac myocytes. J Biol Chem 266:1265–1268
29. Schwartz MD, Moore EE, Moore FA et al (1996). Nuclear factor-κB is activated in alveolar macrophages from patients with acute respiratory distress syndrome. Crit Care Med 24:1285–1292
30. Pugin J, Dunn I, Jolliet P et al (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol Lung Cell Mol Physiol 275:L1040–L1050

31. Lentsch AB, Czermak BJ, Bless NM et al (1999) Essential role of alveolar macrophages in intrapulmonary activation. Am J Respir Crit Care Med 20:692–698
32. Uhlig U, Fehrenbach H, Lachmann RA et al (2004) Phosphoinositide 3-OH kinase inhibition prevents ventilation-induced lung cell activation. Am J Respir Crit Care Med 169:201–208
33. Blackwell TS, Christman JW (1997) The role of nuclear factor-κB in cytokine gene regulation. Am J Respir Cell Mol Biol 17:3–9
34. Moine P, McIntyre R, Schwartz MD et al (2000) NF-kappaB regulatory mechanisms in alveolar macrophages from patients with acute respiratory distress syndrome. Shock 13:85–91
35. Bialecki RA, Kulik TJ, Coluci WS (1992) Stretching increases calcium influx and efflux in cultured pulmonary arterial smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 263:L602–L606
36. Liu M, Xu J, Tanswell AK et al (1994) Inhibition of strain-induced fetal lung cell proliferation by gadolinium, a stretch-activated channel blocker. J Cell Physiol 161:501–507
37. Parker JC, Ivey CL, Tucker JA (1998) Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. J Appl Physiol 84:1113–1118
38. Winston FK, Thibault LE, Macarak EJ (1993) An analysis of time-dependent changes in intracellular calcium concentration in endothelial cells in culture induced by mechanical stimulation. J Biomech Eng 115:160–168
39. Boitano S, Sanderson MJ, Dirksen ER (1994) A role for Ca^{2+}-conducting ion channels in mechanically-induced signal transduction of airway epithelial cells. J Cell Sci 107:3037–3044
40. Resnick N, Collins T, Atkinson W et al (1993) Platelet-derived growth factor B chain promoter contains a cis-acting fluid shear-stress-responsive element. Proc Natl Acad Sci U S A 90:4591–4595
41. Shyy JY, Lin MC, Han J et al (1995) The cis-acting phorbol ester '12-O-tetradecanoyphorbol 13-acetate'-responsive element is involved in shear stress-induced monocyte chemotactic protein 1 gene expression. Proc Natl Acad Sci USA 92:8069–8073
42. McNeil PL, Steinhardt RA (1997) Loss, restoration, and maintenance of plasma membrane integrity. J Cell Biol 137:1–4
43. Terasaki M, Miyake K, McNeil PL (1997) Large plasma membrane disruptions are rapidly resealed by Ca^{2+}-dependent vesicle-vesicle fusion events. J Cell Biol 139:63–74
44. West JB (2000) Pulmonary capillary stress failure. J Appl Physiol 89:2483–2489
45. Hinman LE, Beilman GJ, Groehler KE et al (1997) Wound-induced calcium waves in alveolar type II cells. Am J Physiol Lung Cell Mol Physiol 55:131–138
46. Grembowicz KP, Sprague D, McNeil PL (1999) Temporary disruption of the plasma membrane is required for c-fos expression in response to mechanical stress. Mol Biol Cell 10:1247–1257
47. Bajpai A, Andrews GK, Ebner KE (1989) Induction of c-fos mRNA in rat lymphoma Nb-2 cells. Biochem Biophys Res Commun 165:1359–1363
48. Dos Santos CC, Slutsky AS (2000) Invited Review: Mechanisms of ventilators-induced lung injury: a perspective. J Appl Physiol 89:1645–1655
49. Juliano RL, Haskill S (1993) Signal transduction from the extracellular matrix. J Cell Biol 120:577–585
50. Ingber DE (1993) The riddle of morphogenesis: a question of solution chemistry or molecular cell engineering. Cell 75:1249–1252
51. Liu M, Qin Y, Liu J et al (1996) Mechanical strain induces pp60src activation and

translocation to cytoskeleton in fetal rat lung cells. J Biol Chem 271:7066–7071
52. Chen KD, Li YS, Kim M et al (1999) Mechanotransduction in response to shear stress. Roles of receptor tyrosine kinases, integrins and Shc. J Biol Chem 274:18393–18400
53. Quinn D, Tager A, Joseph PM et al (1999) Stretch-induced mitogen-activated protein kinase activation and interleukin-8 production in type II alveolar cells. Chest 116:89S-90S
54. Lin MC, Almus-Jacobs F, Chen H-H (1997) Shear-stress induction of the tissue factor gene. J Clin Invest 99:737–744
55. Silverman ES, Khachigian LM, Lindner V et al (1997) Inducible PDGF-A-chain transcription in smooth muscle cells is mediated by Egr-1 displacement of Sp1 and Sp3. Am J Physiol 273:H1415–H1426
56. Maniotis AJ, Chen CS, Ingber DE (1997) Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure. Proc Natl Acad Sci U S A 94:849–854
57. Ingber DE (1991) Integrins as mechanochemical transducers. Curr Opin Cell Biol, 3:841–848
58. Torday JS, Liu M, Liu J et al (1998) Mesenchymal determination of mechanical strain-induced fetal lung cell proliferation. Am J Physiol Lung Cell Mol Physiol 275:L545–L550
59. Liu M, Liu J, Buch S et al (1995) Antisense oligonucleotides for PDGF-B and its receptor inhibit mechanical strain-induced fetal lung cell growth. Am J Physiol Lung Cell Mol Physiol 269:L178–L184
60. Harding R, Hooper SB, Han VKM (1993) Abolition of fetal breathing movements by spinal cord transection leads to reductions in fetal lung liquid volume, lung growth, and IGF-II gene expression. Pediatr Res 34:148–153
61. Harding R, Han VKM, Hooper SB (1993) Changes in lung expansion alter pulmonary DNA synthesis and IGF-II gene expression in fetal sheep. Am J Physiol Lung Cell Mol Physiol 265:L403–L409
62. Correa-Meyer E, Pesce L, Guerrero C et al (2002) Cyclic stretch activates ERK1/2 via G proteins and EGFR in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 282:L883–L891
63. Tschumperlin DJ, Shively JD, Swartz MA et al (2002) Bronchial epithelial compression regulates MAP kinase signaling and HB-EGF-like growth factor expression. Am J Physiol Lung Cell Mol Physiol 282:L904–L911
64. Adamson IY, Young L, King GM (1991) Reciprocal epithelial: fibroblast interactions in the control of fetal and adult rat lung cells in culture. Exp Lung Res 17:821–835
65. Boitano S, Safdar Z, Welsh DG et al (2004) Cell-cell interactions in regulating lung function. Am J Physiol Lung Cell Mol Physiol 287:L455–L459
66. Ko KS, Arora PD, McCulloch CA (2001) Cadherins mediate intercellular mechanical signaling in fibroblasts by activation of stretch-sensitive calcium-permeable channels. J Biol Chem 276:35967–35977
67. Guo Y, Martinez-Williams C, Yellowley CE et al (2001) Connexin expression by alveolar epithelial cells is regulated by extracellular matrix. Am J Physiol Lung Cell Mol Physiol 280:L191–L202
68. Breen EC (2000) Mechanical strain increases type I collagen expression in pulmonary fibroblasts in vitro. J Appl Physiol 88:203–209
69. Liu M, Xu J, Tnaswell AK et al (1995) The effect of mechanical strain on fetal rat lung cell proliferation: comparison of two- and three-dimensional culture systems. In Vitro Cell Dev Biol Anim 31:858–866
70. Schaefer T, Roux M, Stuhlsatz HW et al (1996) Glycosaminoglycans modulate cell-ma-

trix interactions of human fibroblasts and endothelial cells in vitro. J Cell Sci 109:479–488
71. Vlahakis NE, Schroeder MA, Limper AH et al (1999) Stretch induces cytokine release by alveolar epithelial cells in vitro. Am J Physiol 277:L167–L173
72. Oudin S, Pugin J (2002) Role of MAP kinase activation in interleukin-8 production by human BEAS-2B bronchial epithelial cells submitted to cyclic stretch. Am J Respir Cell Mol Biol 27:107–114
73. Li LF, Ouyang B, Choukroun G et al (2003) Stretch-induced IL-8 depends on c-Jun NH2-terminal and nuclear factor-κB-inducing kinases. Am J Physiol Lung Cell Mol Physiol 285:L464–L475
74. Tsuda A, Stringer BK, Mijailovich SM et al (1999) Alveolar cell stretching in the presence of brous particles induces iterleukin-8 responses. Am J Respir Cell Mol Biol 21:455–462
75. Mourgeon E, Isowa N, Keshavjee S et al (2000) Mechanical stretch stimulates macrophage in ammatory protein-2 secretion from fetal rat lung cells. Am J Physiol Lung Cell Mol Physiol 279:L699–L706
76. Yamamoto H, Teramoto H, Uetani K et al (2001) Stretch induces a growth factor in alveolar cells via protein kinase. Respir Physiol 127:105–111
77. Tremblay L, Valenza F, Ribeiro SP et al (1997) Injurious ventilatory strategies increase cytokines and c-fos mRNA expression in an isolated rat lung model. J Clin Invest 99:944–952
78. von Bethmann AN, Brasch F, Nusing R et al (1998) Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med 157:263–272
79. Ricard JD, Dreyfuss D, Saumon G et al (2001) Production of inflammatory cytokines in ventilator-induced lung injury: a reappraisal. Am J Respir Crit Care Med 163:1176–1180
80. Copland IB, Kavanagh BP, Engelberts D et al (2003) Early changes in lung gene expression due to high tidal volume. Am J Respir Crit Care Med 168:1051–1059
81. Savla U, Sporn PH, Waters CM (1997) Cyclic stretch of airway epithelium inhibits prostanoid synthesis. Am J Physiol Lung Cell Mol Physiol 273:L1013–L1019
82. Reeves JT, van Grodelle A, Voelkel NF et al (1983) Prostacyclin production and lung endothelial cell shear stress. Prog Clin Biol Res 136:125–131
83. Skinner SJM, Somervell CE, Olson DM (1992) The effects of mechanical stretching on fetal rat lung cell prostacyclin production. Prostaglandins 43:413–433
84. Guzowski DE, Blau H, Bienkowski RS (1989) Extracellular matrix in developing lung. In: Scarpelli E (ed) Pulmonary physiology of fetus, child and adolescent. Lea and Febiger, Philadelphia, pp 83–105
85. Alexander CM, Werb Z (1991) Extracellular matrix degradation. In: Hay ED (ed) Cell biology of extracellular matrix. Plenum Press, New York, pp 255–301
86. Murphy G, Dockery AJ (1992) The matrix metalloproteinases and their inhibitors. Am J Respir Cell Mol Biol 7:120–125
87. Hanseneen NA, Vaday GG, Zucker S et al (2003) Mechanical stretch induces MMP-2 release and activation in lung endothelium: role of EMMPRIN. Am J Physiol Lung Cell Mol Physiol 284:L541-L547
88. Rifas L, Halstead LR, Peck WA et al (1989) Human osteoblasts in vitro secrete tissue inhibitor of metalloproteinases and gelatinase but not interstitial collagenase as major cellular products. J Clin Invest 84:686–694
89. Burger EH, Klein-Nutend J (1998) Microgravity and bone cell mechanosensitivity. Bone 22:127S–130S
90. Sadoshima J, Izumo S (1997) The cellular and molecular response of cardiac myocytes to mechanical stress. Annu Rev Physiol 59:551–557

91. Xu J, Liu M, Post M (1999) Differential regulation of extracellular matrix molecules by mechanical strain of fetal lung cells. Am J Respir Cell Mol Biol 276:L728–L735
92. Parker JC, Breen EC, West JB (1997) High vascular and airway pressures increase interstitial protein mRNA expression in isolated rat lungs. J Appl Physiol 83:1697–1705
93. Mio T, Liu X, Adachi Y et al (1998) Human bronchial epithelial cells modulate collagen gel contraction by fibroblasts. Am J Physiol 274:L119–L126
94. Infeld MD, Brennan JA, Davis PB et al (1993) Human fetal lung fibroblasts promote invasion of extracellular matrix by normal human tracheobronchial epithelial cells in vitro: a model of early airway gland development. Am J Respir Cell Mol Biol 8:69–76
95. Garcia CSB, Rocco PRM, Facchinetti LD et al (2004) What increases type III procollagen mRNA levels in lung tissue: stress induced by changes in force or amplitude? Respir Physiol Neurobiol 144:59–70
96. Xu J, Liu M, Liu J et al (1996) Mechanical strain induces constitutive and regulated secretion of glycosaminoglycans in fetal lung cells. J Cell Sci 109:1605–1613
97. Mascarenhas MM, Day RM, Ochoa CD et al (2004) Low molecular weigh hyaluronan from stretched lung enhances interleukin-8 expression. Am J Respir Cell Mol Biol 30:51–60
98. Taylor KR, Trowbridge JM, Rudisill JA et al (2004) Hyaluronan fragments stimulate endothelial recognition of injury trough TLR4. J Biol Chem 279:17079–17084

Chapter 2

Molecular biology: from the bench to clinical application

M.M. Morales

Many centuries passed without an understanding of why children resembled their parents. People were able to cross animals or plants in order to generate more resistant or stronger offspring without knowing how information could pass from one generation to the other. It took almost 100 years after Gregor Mendel revealed the concept of phenotype inheritance [1] to convince the scientific community that DNA was the molecule responsible for carrying heredity information [2], and to unravel its double-helix structure [3, 4]. Fifty-two years after Watson and Crick's finding, the study of the molecular basis of life, including the role of genes and their evolution, is progressing much faster, which has led to a wider understanding of how organisms function.

Molecular genetics technology has made astonishing advances during the last 20 years. As a result, many genes involved in a wide variety of disorders have been identified and many other diseases have been characterised at the molecular level. Nonetheless, the impact on medicine of all these discoveries has been minimal, although scientists continue to predict that molecular biology will dominate clinical studies and revolutionise their present concepts and treatment strategies.

Molecular biology is sustained by the concept that all living creatures depend on the production of proteins codified by genes contained within DNA. The genes are transcribed into messenger ribonucleic acid (mRNA) by a RNA polymerase that binds to DNA at a nucleotide promoter sequence, located in close proximity to the gene. The promoter can be regulated in order to allow or inhibit gene expression. mRNA is processed inside the nucleus, and then exported to the cytoplasm, where a complex involving ribosomes, transporter RNA, and free amino acids give origin to a new protein.

From the sum of this information arises the 'central dogma' of molecular biology: DNA is transcribed into mRNA which is translated into protein. Knowledge of this chain of events has guided careful study of the participating molecules and of its variance under different conditions and in a large number of species. Analysis of each of the molecules involved in transcription and translation has offered new perspectives on the central dogma. In this article, we provide an overview of the importance of each of these molecules, the most common methods employed in molecular studies of respiratory physiology, and potential molecular genetic strategies in the treatment of lung disease.

Deoxyribonucleic acid

DNA is located in the cell nucleus and contains the genetic information. It is composed of nucleotide subunits, each of which is made up of a sugar, a phosphate, and a nitrogen-containing base. Four different bases can be found in a DNA molecule: the purines adenine and guanine, and the pyrimidines cytosine and thymine. It is well-known that in DNA the number of purine bases equals the number of pyrimidine bases [5]. The structure of DNA is two helical chains, each coiled around the same axis and running in opposite directions. The bases are located on the inside of the helix and the phosphates on the outside [3].

DNA sequencing

The molecular biology technique of DNA sequencing was responsible for the first step made by the scientific community to reveal the genetic code. Nowadays, the complete genome of many species has been totally mapped, including that of humans. DNA sequencing is a simple reaction based on the addition of either radiolabelled or fluorescently labelled dideoxynucleotides [6] (adenosine, guanine, cytosine, and thymine) to a single-stranded DNA replication reaction. These dideoxynucleotides are modified nucleotides, also called terminators, that prevent the addition by a DNA polymerase of new nucleotides to the DNA strand. This results in the generation of DNA fragments of different sizes, which can be separated by gel electrophoresis to reveal the DNA sequence. Nowadays, DNA automatic sequencing is available, in which a fluorescence reader provides the results of these reactions in a rapid and dynamic fashion.

DNA sequencing led to insights into many genetic disorders, by determining mutations or nucleotide deletions in certain genes. For example, cystic fibrosis (CF), which is the most common lethal genetic disease in the Caucasian population, is caused by the failure of the CFTR (cystic fibrosis transmembrane conductance regulator) chloride channel to function properly, resulting in general, exocrine pancreatic dysfunction, gastrointestinal disorders, infertility. In the lungs, there is reduced fluid secretion, which leads to accumulation of thick, dehydrated mucus in the airways and thus high susceptibility to bacterial lung infections, mainly by *Pseudomonas aeruginosa* and *Staphylococcus aureus* [7], which ultimately causes pulmonary fibrosis. The autosomal genetic defect is in the CFTR gene is the consequence in 70% of patients of a deletion of three nucleotides that code for phenylalanine at position 508 (ΔF508) of the CFTR sequence. This information could only be revealed by DNA sequencing of tissue samples from many CF patients. The ΔF508 mutation leads to misprocessing and subsequent degradation of the mutant protein in the endoplasmatic reticulum, preventing CFTR from reaching the cell membrane [8–11].

Knockout animal models

After the whole genome has been sequenced, the second step is to identify the exact functions of the component genes. For this purpose, molecular biology uses an important tool, called the knockout technique, which allows manipulation of the genotype of animals either by removal of a gene or by mutation of a target genes. The absence or mutation of a gene makes possible an understanding of its functions inside the organisms, or produces a model for studying mutations that occur frequently in humans, such as those giving rise to genetic diseases. The process of homologous recombination, which is the basis of the knockout technique, allows scientists to trade a whole gene in its locus for an engineered construct, which can also be the same gene but in mutated form (gene targeting). By mechanisms that are poorly understood but are similar to what occurs during meiosis and mitosis, when homologous chromosomes align along the metaphase plane, the engineered construct, which includes flanking DNA identical in sequence to that of the targeted locus, finds the targeted gene and recombination takes place within the homologous sequence. Embryonic stem cells that suffered ablation or targeted mutation of the gene of interest are selected and injected into blastocysts, producing chimeras. These are crossed with each other to yield knockout or targeted homozygous offspring.

In the long-living CFTR knockout mouse model constructed by Durie et al., the animals have symptoms similar to those found in the human form of cystic fibrosis, such as lung interstitial thickening and fibrosis, liver disease with hepatosteatosis, pancreatic acinar atrophy, and adherent fibrillar material in ileal lumen and crypts. These animals could be used for testing drugs and therapies for their safety and efficacy in CF patients [12]. Another example, in lung is the work that described the importance of surfactant protein-D (SP-D), which also used SP-D knockout mice model. In those animals, delayed clearance of *Pneumocystis carinii* infection, increased lung inflammation, and altered metabolism of nitric oxide were observed [13]. These are some examples of how powerful molecular biology knowledge can be and how much it can add to understanding lung physiology and the origin of diseases in other organs.

Gene transfection

Another common instrument to study gene function is cloning, which allows the expression of a gene product outside the genome. Cloning begins with the insertion of a gene in small circular molecules of DNA called plasmids, which are found in bacteria and are separate from the bacterial chromosome. Plasmids usually carry only one or a few genes, have a single origin of replication, and are used as vectors to deliver the studied gene. Other vectors, such as cosmids or retroviruses, can be used for the same purpose. Plasmids are a very interesting tool due to their ability to be overexpressed in bacteria and transfected into cells lines in vitro or into organisms in vivo, permitting the expression of foreign genes. Wild-type CFTR and CFTR genes containing mutations frequently found in CF patients (ΔF508, G551D,

R334W, R347P, A455E) were transfected into IB3 cells (a human bronchial epithelial cell line derived from a CF patient) and into *Xenopus* oocytes. Expression of the wild-type and foreign genes allowed the characteristics of the mutated chloride channels to be compared with those of wild-type CFTR using electrophysiological methods [14, 15].

Polymerase chain reaction

The polymerase chain reaction (PCR) revolutionised molecular biology and greatly facilitated the study of DNA. A pair of oligonucleotides, called primers, each one complementary to a strand of DNA and comprising a known portion of DNA, are incubated with the DNA samples of interest, free nucleotides, and DNA polymerase in a thermal cycler. Repeated cycles of 1 min or less at 94°C denatures the DNA strands, while a temperature in the range of 50–60°C is used for primer annealing, and extension of the new formed strands by DNA polymerase is carried out at 72°C. PCR results in the exponential amplification of the known portion of the DNA. The technique made it possible to amplify genes specifically and to use the amplified samples for sequencing, and further research, including of genetic disorders. The amplified PCR products can also be inserted into vectors, such as plasmids, for cloning, sequencing, or gene targeting. PCR is very useful in the detection of mutations and of infectious agents, such as human cytomegalovirus (HCMV), in different diseases. For example, low levels of HCMV were identified in idiopathic interstitial pneumonia, which occurred after allogenic bone marrow transplantation [16].

Currently, research advances have produced real-time PCR, which uses fluorescently labelled primers or nucleotides that, once incorporated into the new strand, release their fluorescence. This allows the amplification to be followed cycle by cycle, and is a more accurate technique. The diagnostic application of this technique has brought about the rapid identification of organisms of clinical and epidemiological importance. *Streptococcus pneumoniae,* the leading cause of community-acquired pneumonia, is a lung infectious agent that can be specifically and rapidly identified using real-time fluorescence PCR [17].

Ribonucleic acid

Besides DNA, other molecules can be studied in order to understand the molecular basis of life. mRNA differs from DNA mainly in its structure and composition: (a) a single-stranded polymer of ribonucleic acids, instead of deoxyribonucleic acids; (b) uracil instead of thymine. mRNA levels reflect cellular gene expression patterns, which allows the different expression characteristics of a cell, tissue, or organism under different conditions to be analysed. Such studies yield insight into the events taking place at the molecular level that are responsible for generating a specific phenotype.

Reverse transcription followed by PCR

Reverse transcription followed by PCR (RT-PCR) is the most frequently used tool to study mRNA expression. Basically, in order to carry out PCR, mRNA needs to be converted into a DNA strand. The addition to the reaction of reverse transcriptase, which is a retroviral DNA polymerase capable of using RNA templates, results in the transformation mRNA into complementary single-stranded DNA (cDNA). The mRNA is primed with oligonucleotide dTs (oligo-dTs) that bind to the poly-A tail (only present in mRNA). cDNAs can subsequently be used in PCRs with specific primers of the studied gene to amplify the mRNA of interest.

RT-PCR can, in fact, indirectly identify the expression of specific genes, as was the case for verifying placental growth factor (PGF) expression in small-cell lung cancers (SCLC) and non-small-cell lung cancers (NSCLC). PGF gene expression was identified in these cell lines and was higher in SCLC than in NSCLC cell lines [18], demonstrating the medical importance of this gene as a tumour marker.

Other molecules can also signal the presence of lung disease. In the airway epithelia of CF patients, an increase in IL-8 mRNA expression, early in the disease, was demonstrated using real time RT-PCR, showing the importance of this method as a diagnostic instrument [19].

RNase protection assay

Another important technique to quantify RNA is the RNase protection assay (RPA), which consists of the *in vitro* transcription of radiolabelled antisense RNA probe complementary to the mRNA of interest. The reaction consists of free nucleotides, including labeled UTP or CTP, RNA polymerase, and a plasmid carrying the template DNA fragment needed to synthesise the RNA probe. After purification of the newly generated antisense RNA probes, they are incubated with the RNA samples for 12–16 h, during which time complementary RNA anneals to the probe. Subsequently, the samples are digested with RNase, which cleaves single-stranded molecules, while target mRNA is protected from degradation by probe annealing. The nondigested samples are separated by denaturating urea gel electrophoresis and exposed to autoradiographic films, where the intensity of the signal from the labeled probe will be relative to the quantities of target mRNA. This technique was used by Murray et al. to elucidate the role of the CLC-2 chloride channel in lung embryology. The gene was shown to be highly expressed in foetal lung and down-regulated after birth [20].

RNA interference

A very recent technique used to study the role of gene expression is RNA interference (RNAi), which allows the silencing of specific genes. RNAi consists of the cellular delivery of long double-stranded RNAs (dsRNAs ~200 nt) that are processed into small interfering RNAs (siRNAs), 20–25 nucleotides long, by an enzyme called DICER (RNase III-like enzyme). The siRNAs are assembled into complexes

called RNA-induced silencing complexes (RISCs), which are responsible for the cleavage of complementary mRNA molecules. Since the presence within cells of long dsRNA initiates a potent antiviral response, which leads to the inhibition of protein synthesis and RNA degradation, siRNAs are now introduced directly into cells. Antisense oligonucleotides are commonly used to anneal to their complementary mRNAs. This causes degradation of the complex, and thus silencing of the target gene. This technique can be adjusted for gene therapy in the lung. For example, it was already shown that ZEB1 (a transcription repressor) suppression by RNAi leads to E-cadherin induction in different lung cancer cell lines. The loss of E-cadherin is associated with cancer de-differentiation, invasion, and metastasis [21].

DNA arrays

Most experiments in molecular biology involve the analysis of one gene in one experiment. A recent technique, called DNA array, uses chips to screen a biological sample for the presence of many genetic sequences at once. The principle of this tool is simple base-pairing or hybridisation. Arrays simultaneously show interactions among thousands of genes, and allow researchers to identify specific sequences (for example, genes) or to determine the expression levels of genes.

The construction of a DNA array consists, first, of immobilisation of known DNA onto a solid surface, such as glass or nylon substrates, using automated spotting. Arrays are used to detect the presence of mRNAs transcribed from different genes. cDNA labeled with fluorescent tags pairs to the spot at which the complementary DNA is affixed. The spot can then be visualised, indicating that cells in the sample had recently transcribed a gene that contained the probed sequence. The intensity of the fluorescence depends on how many copies of a particular mRNA were present in the sample, and thus roughly indicates the expression level of that gene. Arrays also show which genes in the genome are active in a particular cell type under a particular condition. Two cDNA samples tagged with different fluorochromes can reveal which genes were transcribed in two different situations.

DNA array has been very important in the detection of different expression patterns in many situations and in the identification of mutations. In a study by Sougakoff et al., various *rpoB* (associated with antibiotic resistance) gene mutations were detected in clinical isolates of *Mycobacterium tuberculosis* conferring rifampicim resistance [22]. Another important aspect of DNA array is that it can be used to widely screen for expression of a certain gene, as observed in a gene expression study in the small intestine of CF mice. The results of the DNA array analysis revealed up-regulation of innate immune response genes and down-regulation of transport and lipid metabolism genes [23].

Protein

mRNA levels do not always directly reflect the translation activity of a cell, since processing can lead to a minor quantity of translated protein, even with initially high levels of mRNA. That is why it is necessary to also study the protein products of genes.

Western blotting

Many techniques have been developed to study protein expression, the most common being Western blotting, which is an adaptation of one of the first approaches to studying DNA and RNA, i.e. Southern and Northern blotting, respectively. Western blotting involves the separation of sample proteins by size on a polyacrylamide gel and then transferring those proteins to a nitrocellulose membrane, which is then incubated with a primary antibody against the target protein and a secondary antibody that recognises the primary antibody and is conjugated to a detection molecule, for example alkaline phosphatase or peroxidase. This technique allows researchers to detect specific proteins in different tissues or cells, and/or evaluate protein expression under a variety of conditions.

Western blots have proven to be a useful tool in establishing or excluding the diagnosis of bacterial or fungal pneumonia. Expression of the soluble protein TREM-1 by phagocytes is specifically up-regulated by microbial products [24]; thus, the presence of soluble TREM-1 protein (triggering receptor expressed in myeloid cells) in bronchoalveolar lavage fluid, especially from patients receiving mechanical ventilation, may be an indicator of pneumonia.

Immunolocalisation

Fixation of tissues or of a cell monolayer allows the in situ localisation of proteins, and their traffic in the cytoplasm or inside organelles. This approach provides an accurate picture of what is happening inside the cell. Immunohistochemistry (for tissues analysis) and immunocytochemistry (for cells analyses) involve incubating cryostat or paraffin sections of tissue or cells with primary antibodies raised against the target proteins and then with a second antibody conjugated to flourophores or enzymes, such as peroxidase or alkaline phosphatase. The primary antibody can be conjugated to the detection molecules as well.

Diagnosis can be facilitated by immunohistochemistry, since it shows protein markers in their exact location throughout the tissue, as was the case in distinguishing between mesothelioma and renal cell carcinoma [25]. Studies using these techniques have also increased our understanding of the physiology of lung disease. Lauredo et al. found that monocytes, neutrophils and alveolar macrophages contribute to increasing the activity of lung tissue kallikrein (TK), which is a serine protease important in the pathophysiology of asthma, and responsible for the generation of kallidin and bradykinin, mediators that contribute to airway hyper-

responsiveness. Identification of the cell types responsible for the production of TK in the airways could be important in elucidating the mechanisms of inflammation that contribute to the pathophysiology of asthma, and may help in the development of new therapies to control the disease [26].

Protein array

A recently developed technique in protein detection is protein array, which allows the detection of target proteins, monitoring of their expression levels, and analysis of their interactions and functions. Together with DNA array, efficient and sensitive high-throughput protein analysis is possible, based on the ability to carry out a large number of determinations in parallel using automated means. Protein array is central to proteomics technology, since the human proteome is much more complex than the genome, considering that many proteins can be derived from the same gene by alternative gene splicing, and that proteins can undergo posttranslational modifications.

Protein array consists of assay systems using proteins immobilised on surfaces such as glass and membranes. Binding reagents, which may be antibodies, proteins, or nucleic acids, are incubated with chips to reveal affinity spots. Proteins other than the specific binders can be used for in vitro functional interaction screenings between two proteins, protein and DNA, protein and drugs, etc. The software for data analysis, as well as the hardware and detection system, can be easily adapted from that used for analysing DNA arrays. With this technology, the expression of several proteins and a large number of samples from different source can be evaluated at the same time, avoiding the time-consuming limitations of individual analysis.

Many diagnoses are made using blood or urine samples and immunoassays such as ELISA (enzyme-linked immunosorbent assay), which is capable of identifying proteins in complex protein samples by using antibodies specific to the target protein. This kind of diagnosis can be done, for example, for HIV, pregnancy (chorionic gonadotrophin), or even pulmonary tuberculosis [27]. It is expected that microarray ELISA-style assays will accelerate immunodiagnostics significantly.

Regarding lung physiology, there have been very few studies using protein array, since this technique is very recent. Nonetheless, Chen et al. used protein array to identify proteins associated with the survival of patients with lung adenocarcinoma. Morphologic assessment of lung tumours is informative but insufficient to adequately predict patient outcome. These studies identified new prognostic biomarkers and indicated that protein expression profiles can predict the outcome of patients with early-stage lung cancer [28].

Gene therapy

The most promising application of molecular biology is gene therapy, in which defective genes responsible for disease development are corrected or compensated

for. The most common approach is the insertion of a normal gene into a nonspecific location within the genome to replace a nonfunctional gene, but there are other approaches, such as exchanging the abnormal gene for a normal one by homologous recombination, repairing the abnormal gene by selective reverse mutation, or even altering the regulation (degree of transcription) of certain genes. The vectors used to deliver the gene targeted for insertion into the patients' cells also vary. The most commonly used vectors are viruses, which have developed a way of encapsulating their genes and delivering them to human cells, often with pathologic consequences. By manipulating the viral genome, scientists can remove disease-causing genes and insert therapeutic genes. Many strains of viruses can be used in gene therapy: retroviruses, e.g. HIV, can create double-stranded DNA copies of their RNA genomes that are subsequently integrated into the chromosomes of host cells [29]. Adenoviruses have double-stranded DNA genomes [30] and cause respiratory, intestinal, and eye infections in humans. Adeno-associated viruses are small, single-stranded DNA viruses that can insert their genetic material at a specific site on chromosome 19 [31]. Herpes simplex viruses are double-stranded DNA viruses that mainly infect neurons [32]. The major problem in using viruses is that they present a variety of potential problems to the patient, like toxicity and immune and inflammatory responses [33]. In addition, there is always the fear that the viral vector, once inside the patient, will recover its ability to cause disease. Thus, as an alternative to virus-mediated gene-delivery systems, several non-viral vectors have been developed. The simplest method of vector delivery is the direct introduction of therapeutic DNA into target cells [34], or insertion of oligonucleotide complexes capable of correcting the abnormal gene into cells containing deletion mutations, thereby restoring the normal cell genotype [35]. In addition, it is also possible to create artificial lipid spheres, with an aqueous core [36], that carried the therapeutic DNA (liposome/DNA complex) and is capable of passing the DNA through the target cell membrane. Despite being less immunogenic vectors, liposome/DNA complexes have a low-level correction component and their survival in the cells is extremely transient.

Besides the immune system barrier, there are also physical barriers that influence the effectiveness of gene therapy. For instance, the normal human airway surface reduces liposomal/DNA-complex-mediated gene delivery more than 25-fold [37], while thick inflammatory secretions from CF patients block and/or inactivate the transduction of recombinant adenoviruses (rAV), liposome/DNA complexes [37–39], and recombinant adeno-associated virus (rAAV) in cells in vitro [40]. Gene therapy also has other limitations, such as: a) the short lived nature of the therapeutic effect, because integrating therapeutic DNA into the genome together with the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits; b) multigene disorders, since some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes, making the respective diseases especially difficult to treat effectively using gene therapy.

Among lung genetic disorders, CF has been one of the most extensively studied

regarding the success of gene therapy. Clinical trials started in 1993, using rAV delivered to the nasal epithelium of CF patients. The transduced gene partially corrected transient chloride transport defects [41], but other authors found that rAV-mediated delivery of CFTR to the nasal epithelium of CF patients failed to produce functional correction [42]. Adenoviral-mediated delivery to the airways seems to result in low-level gene transfer (~1%), while high doses are associated with inflammatory responses to rAV [33, 43, 44]. Liposome/DNA complex vectors have also been tested in CF patients, and the first clinical trial demonstrated 20% restoration of transepithelial potential difference (PD) [45]. However, four of eight patients developed reactions such as fever, myalgias and anthralgia, which were associated with increased IL-6 expression [46].

rAAV type-2, delivered by aerosol administration, lacked toxicity. Vector genomes were quantified at 0.6 and 1 copy per cell at 14 and 30 days, respectively. Despite these promising results, no vector-derived mRNA could be detected at any time point [47], similar to previous in vitro studies of human airway epithelium [48]. More recent clinical trials revealed advances in the tolerance to rAAV-2-mediated CFTR gene therapy and improvement in the pulmonary function of patients with CF [49].

Conclusions

As discussed in this article, molecular biology has already played a major role in several fields of medicine, such as disease characterisation, identification, and diagnosis. Advances in gene therapy suggest that the molecular biology provides information that can radically change medical treatment of genetic disorders. The improvements that studies of the molecular basis of life can bring to medical science are enormous, which justifies that these two areas of science continue to interact closely in order to improve the quality of life.

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References

1. Peter JA (1959) Mendel's experiments in plant hybridizations. In: Classic Papers in Genetics. Prentice-Hall, New Jersey
2. Hershey AD, Chase M (1952) Independent functions of viral protein and nucleic acid in growth of bacteriophage. J Gen Physiol 36:39–56
3. Watson JD, Crick FHC (1953) Molecular structure of nucleic acids: a structure for deoxyribonucleic acid. Nature 171:737–738
4. Watson JD, Crick FHC (1953) Genetic implications of the structure of deoxyribonucleic acid. Nature 171:964–967
5. Chargaff E (1951) Structure and function of nucleic acids as cell constituents. Fed Proc 10(3):654–659
6. Sanger F, Nicklen S, Coulson AR (1977) DNA sequencing with chain termination inhibitors. Proc Natl Acad Sci USA 74:5463–5468
7. Morales MM, Capella MA, Lopes AG (1999) Structure and function of the cystic fibrosis transmembrane conductance regulator. Braz J Med Biol Res 32(8):1021–1028
8. Dalemans W, Barbry P, Champigny G et al (1991) Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature 354:526–528
9. Cheng SH, Gregory RJ, Marshall J et al (1990) Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. Cell 63:827–834
10. Kartner N, Augustinas O, Jensen TJ et al (1992) Mislocalization of delta F508 CFTR in cystic fibrosis sweat gland. Nat Genet 1:321–327
11. Kopito RR (1999) Biosynthesis and degradation of CFTR. Physiol Rev 79:S167-S173
12. Durie PR, Kent G, Phillips MJ, Ackerley CA (2004) Characteristic multiorgan pathology of cystic fibrosis in a long-living cystic fibrosis transmembrane regulator knockout murine model. Am J Pathol 164(4):1481–1493
13. Atochina EN, Gow AJ, Beck JM et al (2004) Delayed clearance of pneumocystis carinii infection, increased inflammation, and altered nitric oxide metabolism in lungs of surfactant protein-D knockout mice. J Infect Dis 189(8):1528–1539
14. Schwiebert EM, Morales MM, Devidas S et al (1998) Chloride channel and chloride conductance regulator domains of CFTR, the cystic fibrosis transmembrane conductance regulator. Proc Natl Acad Sci USA 95(5):2674–2679
15. Fulmer SB, Schwiebert EM, Morales MM et al (1995) Two cystic fibrosis transmembrane conductance regulator mutations have different effects on both pulmonary phenotype and regulation of outwardly rectified chloride currents. Proc Natl Acad Sci USA 92(15):6832–6836
16. Jiwa M, Steenbergen RD, Zwaan FE et al (1990) Three sensitive methods for the detection of cytomegalovirus in lung tissue of patients with interstitial pneumonitis. Am J Clin Pathol 93(4):491–494
17. McAvin JC, Reilly PA, Roudabush RM et al (2001) Sensitive and specific method for rapid identification of Streptococcus pneumoniae using real-time fluorescence PCR. J Clin Microbiol 39(10):3446–3451
18. Woo IS, Park MJ, Byun JH et al (2004) Expression of placental growth factor gene in lung cancer. Tumour Biol 25(1–2):1–6
19. Muhlebach MS, Reed W, Moah TL (2004) Quantitative cytokine gene expression in CF airway. Pediatr Pulmonol 37 (5):393–399
20. Murray CB, Morales MM, Flotte TR et al (1995) CIC-2: a developmentally dependent chloride channel expressed in the fetal lung and downregulated after birth. Am J Respir Cell Mol Biol 12(6):597–604

21. Ohira T, Gemmill RM, Ferguson K et al (2003) WNT7a induces E-cadherin in lung cancer cells. Proc Natl Acad Sci USA 100(18):10429–10434
22. Sougakoff W, Rodrigue M, Truffot-Pernot C et al (2004) Use of a high-density DNA probe array for detecting mutations involved in rifampicin resistance in Mycobacterium tuberculosis. Clin Microbiol Infect 10(4):289–294
23. Norkina O, Kaur S, Ziemer D, De Lisle RC (2004) Inflammation of the cystic fibrosis mouse small intestine. Am J Physiol Gastrointest Liver Physiol 286(6):G1032–G1041
24. Gibot S, Cravoisy A, Levy B et al (2004) Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 350(5):451–458
25. Ordonez NG (2004) The diagnostic utility of immunohistochemistry in distinguishing between mesothelioma and renal cell carcinoma: a comparative study. Hum Pathol 35(6):697–710
26. Lauredo IT, Forteza RM, Botvinnikova Y, Abraham WM (2004) Leukocytic cell sources of airway tissue kallikrein. Am J Physiol Lung Cell Mol Physiol 286(4):L734–L740
27. Meyer G, Roy PM, Sors H, Sanchez O (2003) Laboratory tests in the diagnosis of pulmonary embolism. Respiration 70(2):125–132
28. Chen G, Gharib TG, Wang H et al (2003) Protein profiles associated with survival in lung adenocarcinoma. Proc Natl Acad Sci USA 100(23):13537–13542
29. Kobinger GP, Weiner DJ, Yu QC, Wilson JM (2001) Filovirus-pseudotyped lentiviral vector can efficiently and stably transduce airway epithelia in vivo. Nat Biotechnol 19(3):225–230
30. Song JS, Kim HP (2004) Adenovirus-mediated HSV-TK gene therapy using the human telomerase promoter induced apoptosis of small cell lung cancer cell line. Oncol Rep 12(2):443–447
31. Auricchio A, O'Connor E, Weiner D et al (2002) Noninvasive gene transfer to the lung for systemic delivery of therapeutic proteins. J Clin Invest 110(4):499–504
32. Natsume A, Wolfe D, Hu J et al (2003) Enhanced functional recovery after proximal nerve root injury by vector-mediated gene transfer. Exp Neurol 184(2):878–886
33. Joseph PM, O'Sullivan BP, Lapey A et al (2001) Aerosol and lobar administration of a recombinant adenovirus to individuals with cystic fibrosis. I. Methods, safety, and clinical implications. Hum Gene Ther 12(11):1369–1382
34. Yoshida M, Iwasaki Y, Asai M et al (2004) Gene therapy for central diabetes insipidus: effective antidiuresis by muscle-targeted gene transfer. Endocrinology 145(1):261–268
35. Zamecnik PC, Raychowdhury MK, Tabatadze DR, Cantiello HF (2004) Reversal of cystic fibrosis phenotype in a cultured Delta508 cystic fibrosis transmembrane conductance regulator cell line by oligonucleotide insertion. Proc Natl Acad Sci USA 101(21):8150–8155
36. Li HY, Neill H, Innocent R et al (2003) Enhanced dispersibility and deposition of spray-dried powders for pulmonary gene therapy. J Drug Target 11(7):425–432
37. Kitson C, Angel B, Judd D et al (1999) The extra- and intracellular barriers to lipid and adenovirus-mediated pulmonary gene transfer in native sheep airway epithelium. Gene Ther 6:534–546
38. Stern M, Caplen NJ, Browning JE et al (1998) The effect of mucolytic agents on gene transfer across a CF sputum barrier in vitro. Gene Ther 5:91–98
39. Perricone MA, Rees DD, Sacks CR et al (2000) Inhibitory effect of cystic fibrosis sputum on adenovirus-mediated gene transfer in cultured epithelial cells. Hum. Gene Ther 11:1997–2008
40. Virella-Lowell I, Poirier A, Chesnut KA et al (2000) Inhibition of recombinant adeno-associated virus (rAAV) transduction by bronchial secretions from cystic fibrosis patients. Gene Ther 7:1783–1789

41. Zabner J, Couture LA, Gregory RJ et al (1993) Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. Cell 75:207–216
42. Knowles MR, Hohneker KW, Zhou Z et al (1995) A controlled study of adenoviral-vector-mediated gene transfer in the nasal epithelium of patients with cystic fibrosis. N Engl J Med 333:823–831
43. Zuckerman JB, Robinson CB, McCoy KS et al (1999) A phase I study of adenovirus-mediated transfer of the human cystic fibrosis transmembrane conductance regulator gene to a lung segment of individuals with cystic fibrosis. Hum Gene Ther 10:2973–2985
44. Bellon G, Michel-Calemard L, Thouvenot D et al (1997) Aerosol administration of a recombinant adenovirus expressing CFTR to cystic fibrosis patients: a phase I clinical trial. Hum Gene Ther 8:15–25
45. Caplen NJ, Alton EW, Middleton PG et al (1995) Liposome-mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis. Nat Med 1:39–46
46. Ruiz FE, Clancy JP, Perricone MA et al (2001) A clinical inflammatory syndrome attributable to aerosolized lipid-DNA administration in cystic fibrosis. Hum Gene Ther 12:751–761
47. Aitken ML, Moss RB, Waltz DA et al (2001) A phase I study of aerosolized administration of tgAAVCF to cystic fibrosis subjects with mild lung disease. Hum Gene Ther 12:1907–1916
48. Duan D, Yue Y, Yan Z et al (2000) Endosomal processing limits gene transfer to polarized airway epithelia by adeno-associated virus. J Clin Invest 105:1573–1587
49. Moss RB, Rodman D, Spencer LT et al (2004) Repeated adeno-associated virus serotype 2 aerosol-mediated cystic fibrosis transmembrane regulator gene transfer to the lungs of patients with cystic fibrosis: a multicenter, double-blind, placebo-controlled trial. Chest 125(2):509–521

ADVANCES IN CRITICAL CARE

Chapter 3

Autologous bone marrow cells transplantation in ischaemic cardiomyopathy: initial clinical results

S. Almeida de Oliveira, L. Henrique, W. Gowdak, J.E. Krieger

During the past few years, tremendous advances have been made in surgical and interventional revascularisation in the treatment of atherosclerotic coronary artery disease (CAD). Additionally, life-style modifications and new pharmacological agents have been added to the therapeutic arsenal to relieve patients from angina pectoris. Still, there is an increasing number of patients with CAD whose symptoms are unresponsive to conventional medical therapy and revascularisation procedures, a condition frequently referred to as refractory angina [1]. The severity and extent of the disease preclude complete myocardial revascularisation. Instead, affected patients undergo 'incomplete' coronary artery bypass grafting (CABG), in which one or more diseased vessels are left without being grafted. Although there is usually improvement in the symptoms for variable periods of time after surgery, many patients continue to experience angina in their daily activities, thus rendering this approach only partially effective. Alternative therapies for refractory angina include transcutaneous electrical nerve stimulation [2], enhanced external counterpulsation [3], and transmyocardial laser revascularisation [4]. In the last decade, gene therapy for ischaemic vascular disease has slowly made its way to the clinical stage, with promising results [5].

Cell therapy represents a novel therapeutic strategy for treating cardiac diseases including ischaemic heart disease (IHD) and heart failure. As our understanding of the biology of stem cells grows, new opportunities for tissue repair are being created. It is widely accepted now that bone-marrow-derived cells functionally play a role in the induction of angiogenesis in different conditions, such as wound healing and limb ischaemia [6, 7], postmyocardial infarction [8, 9], and endothelialisation of vascular grafts [10]. Results from animal models of IHD have shown that pluripotent stem cells have the potential to differentiate in both contractile tissue and blood vessels in ischaemic tissues [11, 12]. Early reports of improvement in myocardial perfusion and segmental contractility in acute [13] and chronic [14] IHD in small series of patients have initially established the safety and feasibility of transplantation of bone marrow cells (BMC) for treating IHD.

This study was designed to test the hypothesis that intramyocardial injection of autologous BMC combined with CABG for treating severe IHD is safe and well-tolerated, and may help to increase perfusion as well as the number of viable cells in the ischaemic myocardium of patients undergoing 'incomplete' myocardial revascularisation for diffuse CAD.

Methods

This prospective, nonrandomised, open-label, phase I clinical study was approved by the Institutional Ethics Committee (Heart Institute, InCor, University of São Paulo Medical School, São Paulo, Brazil) and was conducted in accordance with the federal guidelines of the Brazilian National Research Ethics Council.

Patient selection

From August 2002 to July 2003, ten patients were enrolled after providing written informed consent. Patients had to meet all of the following criteria for enrolment: (1) age between 18 and 80 years; (2) presence of limiting angina (class III–IV as defined by the CCS [15]) despite maximally tolerated medical therapy; (3) multivessel CAD as assessed by angiography; (4) not to be an optimal candidate for a complete CABG due to the extent and severity of the obstructive lesions, as assessed by an expert panel; (5) to have at least one non-bypassable coronary artery associated with an area of viable ischaemic myocardium. Patients were excluded if any of the following criteria was met: (1) the presence of any medical condition associated with a life expectancy below 1 year; (2) past or current history of neoplasia; (3) no objective evidence of myocardial ischaemia even in the presence of severe CAD; (4) primary haematological disease; (5) associated cardiomyopathy of other aetiologies. Table 1 shows the selected population demographics.

Table 1. Patient population demographics

	Patients (n = 10)
Age (years)	59 ± 6
Males (n)	8
Diabetes (n)	6
Hypertension (n)	9
Hypercholesterolemia (n)	6
Smoking (n)	3
Previous myocardial infarction (n)	10
Previous percutaneous coronary intervention (n)	1
Previous CABG (n)	0

Study protocol

At baseline and 30 and 90 days after surgery, all patients were subjected to a clinical evaluation (history/physical), laboratory tests (biochemical/haematological), resting and 24-h ambulatory ECG, and dobutamine stress echocardiography; myocardial perfusion was assessed (at rest and after pharmacological vasodilatation) with ^{201}Tl scintigraphy with single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI).

Dobutamine stress echocardiography

Dobutamine stress echocardiography was carried out as previously described [16], with an infusion of intravenous atropine at intermediate doses of dobutamine (20 $\mu g\ kg^{-1}\ min^{-1}$). Tests were administered and reviewed by the same blinded observer. A 16-segment left ventricular (LV) wall motion model was used; images were displayed side-by-side in a quad-screen format to compare resting, low-dose dobutamine, peak, and recovery stages. Commercial equipment (Hewlett Packard 5500, equipped with 2.5- and 3.5-MHz transducers, Andover, MA, USA) was employed and all echocardiograms were recorded on standard VHS tape for 'off-line' analysis. Wall motion was assessed by visual interpretation for each myocardial segment and scored as described elsewhere [17].

^{201}Tl scintigraphy (gated SPECT)

At baseline and at 30 days after surgery, dipyridamole stress and SPECT imaging were carried out using the same protocol. Studies were read by two blinded observers. After the patient had fasted for 3 h, approximately 111 MBq of ^{201}Tl were injected at peak pharmacological stress with dipyridamole. Stress SPECT images were acquired within 10 min, and redistribution images were obtained 3–4 h later. After reinjection of 55 MBq of ^{201}Tl at rest, images were acquired 12 h later.

SPECT studies were acquired with the use of a dual-head camera (Adac Vertex-Plus, Phillips Medical Systems, Andover, MA, USA), with rectangular detectors, equipped with a low-energy general purpose collimators (Rembrandt Low Energy Vertex General Purpose, Phillips Medical Systems). Images were acquired using a 64×64 matrix, 32 projections, and 180° circumferential orbit from right anterior to left-posterior oblique views for classical orthogonal tomography slice construction.

For assessment of segmental wall motion, gated perfusion images were displayed in cine mode, and a qualitative wall motion score was attributed. In addition, left ventricular ejection fraction (LVEF) was estimated by automatic processing with Quantitative Gated SPECT (QGS) software.

Magnetic resonance imaging

All patients were subjected to MRI using a 1.5 T GE CV/i System (GE Medical Systems, Waukesha, WI, USA). Patients were placed in the supine position, with a surface phased array (four elements) cardiac coil applied at the left thoracic wall (two posterior and two anterior elements). ECG triggering was obtained by four leads placed at the left anterior thoracic wall. Eight to ten short-axis slices, enough to cover the entire LV from apex to base, and four long-axis slices were acquired. Three pulse sequences were used for data acquisition. A gradient-echo in steady-state acquisition (FIESTA, fast imaging employing steady-state acquisition) was done for LV function evaluation. End-diastolic volume and systolic volumes and LVEF were calculated on the FIESTA images using Simpson's rule on short-axis cine images.

A fast-gradient-echo-EPI pulse sequence was used to assess myocardial perfusion during stress with dipyridamole and at rest, after injection of gadolinium (0.05 mM kg^{-1}). A gradient-echo with an inversion-recovery preparatory pulse was used to determine myocardial delayed enhancement, 10–20 min after bolus injection of 0.2 mM gadolinium kg^{-1}. For comparison, short and long-axis slices were acquired precisely at the same locations by both pulse sequences.

Preparation of BMC

After induction of anaesthesia and immediately prior to surgery, 100 ml of bone marrow from the patient's right posterior iliac crest were aspirated and heparinised. Mononuclear cells were isolated by density gradient centrifugation on Ficoll-Paque Plus (Amersham Biosciences, Piscataway, NJ, USA). These cells were washed with heparinised saline, resuspended in 5 ml normal saline, and placed in five 1-ml syringes ready for injection. A 1-ml sample of the cell suspension was used for cell counting and sorting by flow cytometry using leukocyte differentiation markers. Trypan blue exclusion test showed viability to be more than 90% in the cell suspension.

The BMC suspension was treated with human IgG polyclonal antibody and incubated with the following monoclonal antibodies conjugated with fluorescein isothiocyanate (Pharmigen, San Diego, CA, USA), phycoerythrin (PE), PerCP or CyChrome: anti-CD19 (clone HD-37) as a pan-B cell marker (Pharmigen); anti-CD10 (clone HI10a), CALLA marker (Becton Dickson, BD, USA); anti-CD4 (clone MT310) as a T-helper cell marker (Pharmigen); anti-CD8 (clone DK25) as a T-supressor cell marker (Pharmigen); anti-CD3 (clone HI3a) as a pan-T-cell marker (Pharmigen); anti-CD56 (clone BI59) as a NK-cell marker (Pharmigen); anti-CD13 (clone WM-47) as a myeloid cell marker (DAKO); anti-CD15 (clone BI59) as a myeloid cell marker (Pharmigen); anti-CD14 (clone TUK-4) as a monocyte marker (Pharmigen); anti-CD45 (clone 2D1) as a pan-leukocyte marker (BD); anti-CD34 (clone HPCA-2) as a haematopoietic progenitor marker (BD); and anti-CD38 (clone HB27) as an activated lymphocyte and plasma cell marker (BD). Erythrocytes were lysed after staining with Becton Dickinson lysis buffer according to the manufacturer's instructions. Data acquisition and analyses were done on a three-colour immunofluorescent fluorescent-activated cell sorter (FACS SCAN) with CellQuest 3.1 software (BD).

Coronary artery bypass grafting and injection of BMC

CABG was done during cardiopulmonary bypass and warm blood cardioplegic arrest. Once all bypasses had been completed, the BMC were implanted into the myocardial tissue. Approximately 25 samples of cell suspension (0.2ml each) were injected into the ischaemic non-bypassable area of myocardium using a 22-gauge hypodermic needle. After the injections were done, the heart was reperfused, and the operation completed as usual. Patients were transferred to and stayed at the Cardiac Surgery Recovery Unit for 1 ± 1 day.

Statistical analysis

Results are shown as mean ± standard deviation. The paired Student's *t* test was used for comparisons between time points (before and 30 days after surgery). Statistical significance was set at $P < 0.05$.

Results

Procedural data

The total procedural time for the operation and intramyocardial injection was 5 h and 30 min ± 30min and the 'on-pump' time was 64 ± 5 min. Patients received an average of 2.6 ± 0.2 grafts and were injected with approximately $13 \pm 2 \times 10^7$ cells. Selected cell populations are shown in Table 2. Injected segments included the inferior ($n = 7$), anterior ($n = 2$), septal ($n = 1$), apical ($n = 1$), and lateral ($n = 1$) walls. Note that two patients were injected in two different myocardial segments, so that 12 segments were injected in ten patients.

Table 2. Selected cell population (%) after flow cytometry

CD14+	CD38+CD34+	CD38—CD34+	CD34+
4.87 ± 0.50	1.41 ± 0.19	0.19 ± 0.05	1.30 ± 0.13

In-hospital morbidity and mortality: clinical follow-up

All patients survived the procedure. Complications not related to the intramyocardial injection included pulmonary infection ($n = 2$) and acute decompensation of heart failure ($n = 1$). Those complications were managed clinically and resolved within a few days. No significant abnormalities were seen in biochemical/haematological tests. No changes in hepatic or renal function were observed. Mean in-hospital period was 11 ± 2 days. During the first month of follow-up, all patients remained free of angina.

Cardiac arrhythmias

The mean heart rate significantly increased from 69 ± 3 bpm in the baseline to 78 ± 4 bpm 30 days after surgery (P 0.02), which is a frequent finding in patients after cardiac surgery. However, there was no increase in the number of supraventricular (6 ± 4/h vs 5 ± 2/h; P = ns) or ventricular (6 ± 5/h vs 8 ± 3/h; P = ns) premature beats. No patient presented life-threatening arrhythmias, such as sustained ventricular tachycardia.

Transthoracic stress-echocardiogram

No structural abnormalities were seen on 2D Doppler echocardiograms at any time point after the procedure. As expected, LV function analysis showed that, compared to baseline, there was a significant decrease in the mean LV end-diastolic diameter (B = 52.6 ± 1.8 vs 30D = 50.5 ± 1.4 mm vs 90D = 47.3 ± 1.3 mm; $P < 0.0001$) and in the mean end-diastolic volume (B = 150.3 ± 16.6 vs 30D = 131.7 ± 11.1 vs 90D = 107.3 ± 8.6 ml; $P < 0.0001$). Overall, there was a significant increase in the mean LVEF (B =0.53 ± 0.05 vs 30D = 0.60 ± 0.04 vs 90D = 0.61 ± 0.04; $P < 0.0001$). The ischaemic score as assessed by stress-echo significantly decreased in all patients from an average of 1.7 ± 0.12 at baseline to 1.43 ± 0.07 after 30 days.

^{201}Tl scintigraphy

At baseline, myocardial perfusion defects were seen in 31 segments by ^{201}Tl scintigraphy, including the 12 segments injected with BMC. Overall, a comparison of the results at 30 days with the baseline values showed that perfusional defects were improved in 16 (52%), normalised in eight (26%) and unchanged in seven (22%) myocardial segments. Specifically, in the 12 injected segments, there was either improvement ($n = 6$; 50%) or normalisation ($n = 3$; 25%) of perfusional defects compared to baseline. In three (25%) of the injected segments, there was no evidence of improvement in myocardial perfusion.

Magnetic resonance imaging

As expected after CABG, the LV ischaemic score significantly decreased from 0.64 ± 0.14 (baseline) to 0.15 ± 0.08 (30 days) to 0.22 ± 0.09 (90 days) ($P = 0.0013$) (Fig. 1a). More interestingly, the ischaemic score of the injected area also significantly decreased from 1.16 ± 0.17 (baseline) to 0.29 ± 0.21 (30 days) to 0.42 ± 0.25 (90 days) *(P* = 0.0001) (Fig. 1b). No structural abnormalities were seen on MRI after the procedure.

Discussion

The results of the present study show the feasibility and safety of intramyocardial injection of autologous BMC combined with CABG in patients suffering from diffuse CAD who were not optimal candidates for complete surgical myocardial revascularisation.

The majority of patients with mild to moderate angina can be treated adequately with anti-anginal medications [18]. However, as life expectancy increases and the mortality rate due to acute coronary syndromes decreases, there is a growing population of patients with CAD for whom medical therapy is only partially effective. Many of them have already undergone multiple percutaneous coronary interventions (PCIs) or previous surgical revascularisation and hence are not 'ideal'

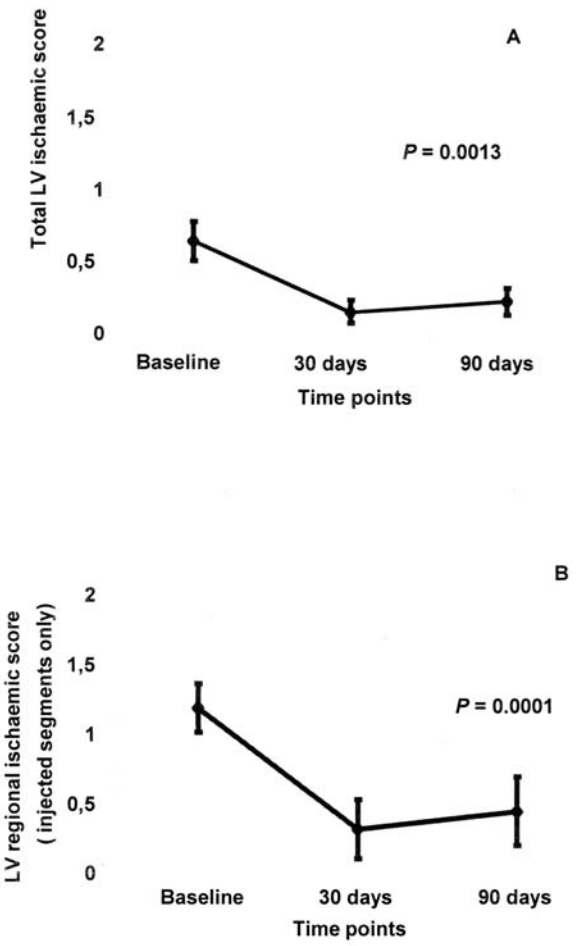


Fig. 1. Total (**A**) and regional (**B**) left ventricular (LV) ischaemic score as assessed by MRI at baseline, 30 days, and 90 days after injection of BMC

candidates for additional procedures. It is clear that new therapeutic strategies must be sought to treat those patients.

In chronic IHD, privation of oxygen and nutrients to myocytes might be an important factor in the death of otherwise viable myocardium, which could lead to cell replacement by fibrous tissue deposition and further impairment of LV function. Neoangiogenesis, a multifactorial process involving complex interactions between inflammatory cells, cytokines, and many extracellular matrix proteins, is a crucial step in preserving cardiomyocytes from death [19]. Usually, when extensive myocardial ischaemic injury occurs, the contribution of neoangiogenesis to the ischaemic capillary network is insufficient to keep pace with the tissue demands

and, therefore, normal contractility of ischaemic but viable myocardium cannot be sustained [20].

Experimental evidence suggests that bone-marrow-derived elements have the potential to induce therapeutic angiogenesis of ischaemic tissues [21]. It has been shown that, after vascular injury, endothelial progenitor cells are naturally mobilised from the bone marrow to the circulation, along with haematopoietic stem cells and haematopoietic progenitor cells. The physiological role of co-recruitment of haematopoietic stem and progenitor cells in the formation of long-lasting functional neovessels remains to be determined [22].

Based on the initial reports of successful transplantation of progenitor cells in patients with acute or chronic coronary artery disease [12–14], we conducted this phase-1, open-label, nonrandomised trial and were able to show that intramyocardial injection of autologous BMC combined with CABG is feasible, safe and well-tolerated. Moreover, there is preliminary evidence that significant improvement in perfusion and contractility occurred in the injected myocardial segments.

Regarding the safety issues of the protocol within the first 30 days, we observed no deaths or other major complications related to the procedure. The duration of surgery, 'on-pump' time, and hospitalisation were not increased compared to isolated CABG. There was a small but significant increase in heart rate 30 days after surgery compared to baseline. This is not unusual after cardiac surgery and may reflect sympathetic hyperactivity related to incisional pain, anxiety, anaemia, or even mild pericarditis. There was no detectable increase in the number of ectopic beats, either supraventricular or ventricular. No life-threatening arrhythmias were detected. In the clinical follow-up, all patients remained free of angina. Cardiac imaging showed neither evidence of scar tissue formation in the injection sites nor structural abnormalities related to the procedure, such as pericardial effusion.

Although this was basically a safety study, we also collected functional data especially regarding myocardial perfusion and contractility. Analysis of echocardiogram showed that, following the procedure, there was a significant decrease in the mean LV end-diastolic diameter and volume, with a corresponding significant increase in the mean LVEF. The overall improvement in LV function reflects the recovery of ischaemic viable (hibernating) myocardium normally seen after CABG. Corroborating that, there was a significant decrease in the mean LV ischaemic score as assessed by stress-echo. Therefore, as perfusion in ischaemic viable myocardium is restored, myocardial function improves.

Cardiac scintigraphy showed that there was an overall improvement or normalisation of perfusional defects in the majority (78%) of the segments analysed after CABG. Specifically, in the injected and non-revascularised myocardial segments, there was a similar pattern of either improvement or normalisation (75%) seen 30 days after the procedure.

Additionally, MRI showed a significant decrease in the LV ischaemic score after the procedure, similar to what was seen with echo. Interestingly, the ischaemic score in the injected and non-revascularised areas also significantly decreased. Taken together, these data suggest that there was improvement in myocardial perfusion in the injected but non-grafted areas. Even though an indirect effect for this improve-

ment from the grafts placed in the adjacent areas cannot be ruled out, it is tempting to speculate that the transplanted cells may have contributed to this response.

Angiogenesis may be the main mechanism by which myocardial perfusion was improved in the injected areas. In this study, we purposefully injected BMC in areas of myocardium defined as hibernating, in which restoration of myocardial function is possible once ischaemia is reverted. The presence of a sustained ischaemic background may play an important role in cell engraftment (homing) necessary for the therapeutic effect of any cell-based strategy [23]. Currently, we can only speculate that angiogenesis is the result not only of transdifferentiation of transplanted cells [24] but also the action of cytokines and growth factors [25]. In this regard, an additional contribution to myocardial perfusion and cell survival in injected sites could have arisen from the distant grafted coronary arteries, in which blood flow was restored. Finally, an inflammatory response caused by the intramyocardial injections per se could have stimulated the release of angiogenic factors that ultimately led to blood vessel growth. Identification of the specific mechanisms underlying the improvement in myocardial perfusion observed in the study patients was beyond the scope of this study. An alternative or additional explanation for improvement in contractility could be differentiation of the injected cells into cardiomyocytes. Further studies are obviously needed to answer this question.

Recently, a work by Kocher et al. [9] showed that bone marrow from adult humans contains endothelial precursors with phenotypic and functional characteristics of embryonic haemangioblasts, and that these can be used to directly induce new blood vessel formation in the infarct bed (vasculogenesis) as well as proliferation of preexisting vasculature (angiogenesis) after experimental infarction. Neoangiogenesis resulted in decreased apoptosis of hypertrophied myocytes in the peri-infarct region, long-term salvage and survival of viable myocardium, reduction in collagen deposition, and sustained improvement in cardiac function. Similarly, Orlic et al. [8] demonstrated that locally delivered BMC can lead to myocyte and vasculature proliferation, thus generating de novo myocardium and ameliorating the outcome of CAD.

In a study similar to ours, Stamm et al. [26] injected BMC into the infarct border zone in six patients who had experienced myocardial infarction and undergone CABG. Their work showed that, 3–9 months after surgery, LV function was enhanced in four patients, and infarct tissue perfusion had improved strikingly in five patients.

The major limitations of our study include the small number of patients enrolled, the short period of follow-up, and the study protocol itself, which was designed for safety and did not allow any definite conclusion about the efficacy of cell transplantation, although there was evidence for myocardial perfusion improvement in injected segments.

The effectiveness of cell transplantation in improving myocardial perfusion and contractility in patients with advanced CAD is a question to be addressed in controlled studies with a larger series of patients and longer follow-up. The initial reports of successful and safe transplantation of stem and progenitor cells are

encouraging, and further efforts to develop this alternative therapeutic approach are merited. We are now conducting a prospective, randomised, double-blind, placebo-controlled trial in a large number of patients (60 patients). This study will permit more detailed observations about the efficiency of BMC transplantation into the ischaemic myocardium.

References

1. Kim MC, Kini A, Sharma SK (2002) Refractory angina pectoris—mechanism and therapeutic options. J Am Coll Cardiol 39:923–934
2. Hautvast RW, DeJongste MJ, Staal MJ et al (1998) Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am Heart J 136:1114–1120
3. Urano H, Ikeda H, Ueno T et al (2001) Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. J Am Coll Cardiol 37:93–99
4. Frazier OH, March RJ, Horvath KA (1999) Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. N Engl J Med 341:1021–1028
5. Udelson JE, Dilsizian V, Laham RJ et al (2000) Therapeutic angiogenesis with recombinant fibroblast growth factor-2 improves stress and rest myocardial perfusion abnormalities in patients with severe symptomatic chronic coronary artery disease. Circulation 102:1605–1610
6. Luttun A, Carmeliet G, Carmeliet P (2002) Vascular progenitors: from biology to treatment. Trends Cardiovasc Med 12:88–96
7. Takahashi T, Kalka C, Masuda H et al (1999) Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med 5:434–438
8. Orlic D, Kajstura J, Chimenti S et al (2001) Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci USA 98:10344–10349
9. Kocher AA, Schuster MD, Szabolcs MJ et al (2001) Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat Med 7:430–436
10. Noishiki Y, Tomizawa Y, Yamane Y et al (1996) Autocrine angiogenic vascular prosthesis with bone marrow transplantation. Nat Med 2:90–93
11. Orlic D, Kajstura J, Chimenti S et al (2001) Bone marrow cells regenerate infarcted myocardium. Nature 410:701–705
12. Hamano K, Li TS, Kobayashi T et al (2002) Therapeutic angiogenesis induced by local autologous bone marrow cell implantation. Ann Thorac Surg 73:1210–1215
13. Assmus B, Schachinger V, Teupe C et al (2002) Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 106:3009–3017
14. Perin EC, Dohmann HF, Borojevic R et al (2003) Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 107:2294–2302

15. Campeau L (1976) Grading of angina pectoris. Circulation 54:522–523
16. Herpner AM, Bach DS, Armstrong WF (1997) Early chronotropic incompetence predicts the need for atropine during stress echocardiography. Am J Cardiol 79:365–366
17. Smart SC, Sawada S, Ryan T et al (1993) Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. Circulation 88:405–415
18. Gibbons RJ, Abrams J, Chatterjee K et al (2003) American College of Cardiology; American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). J Am Coll Cardiol 41:159–168
19. Kalkman EA, Bilgin YM, van Haren P et al (1996) Determinants of coronary reserve in rats subjected to coronary artery ligation or aortic banding. Cardiovasc Res 32:1088–1095
20. Braunwald E, Rutherford JD (1986) Reversible ischemic left ventricular dysfunction: evidence for the 'hibernating myocardium.' J Am Coll Cardiol 8:1467–1470
21. Kalka C, Masuda H, Takahashi T et al (2000) Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci USA 97:3422–3427
22. Rafii S, Lyden D (2003) Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. Nat. Med 9:702–712
23. Shintani S, Murohara T, Ikeda H et al (2001) Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. Circulation 103:2776–2779
24. Goodell MA, Jackson KA, Majka SM et al (2001) Stem cell plasticity in muscle and bone marrow. Ann. N. Y. Acad. Sci 938:208–218
25. Carmeliet P (2003) Angiogenesis in health and disease. Nat Med 9:653–660
26. Stamm C, Westphal B, Kleine HD et al (2003) Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 361:45–46

Chapter 4

Haemorrhagic shock

J. Boldt

Bleeding resulting in (severe) hypovolaemia is often present in surgical, trauma, and intensive care patients. Adequate volume restoration in this situation appears to be essential to stave off noncompensatory, irreversible shock and subsequently to avoid development of multiple organ dysfunction syndrome (MODS). In a prospective review of more than 100 consecutive patients who died in hospital after admission for treatment of injuries, the most common defects in patient management were related to inadequate volume resuscitation [1]. Thus, vigorous optimisation of the circulation is a prerequisite in managing these patients. This manoeuvre is aimed at guaranteeing stable macro- and microhaemodynamics while avoiding excessive fluid accumulation in the interstitial tissue. The choice of fluid for this purpose engenders the most controversy and there is still a dispute over the beneficial and adverse effects of each type of volume replacement strategy. In recent years, the crystalloid/colloid dispute has been enlarged to a colloid/colloid debate because aside from the natural colloid albumin, several synthetic colloids are increasingly used as plasma substitutes in the haemorrhagic shock patient.

Haemorrhagic shock and the trauma patient

Aggressive prehospital volume administration ('in the field') has been common practice for more than 25 years in trauma patients. Some recent studies, however, have shown that early volume restoration before definite haemostasis has been performed may result in accelerated blood loss, hypothermia, and dilutional coagulopathy in certain types of trauma [2]. Thus, it has been recommended that volume replacement should not be started early (concept of 'permissive hypotension'; 'scoop and run' principle) [3]. The present article does not intend to intensify the controversy between delayed volume resuscitation and early (field) volume replacement.

Trauma is often associated with blood loss. Management of haemorrhage-related hypovolaemic shock after trauma can be divided into three phases [4]:

- Phase I: The period from injury to surgery for control of bleeding (pre-definite care)
- Phase II: The period immediately during and after the operation
- Phase III: The period during which the trauma patient is on the intensive care unit (post-definite care).

General considerations of hypovolaemic shock

Hypovolaemia secondary to bleeding may be associated with flow alterations that are inadequate to fulfil the nutritive role of the circulation. Many of the manifestations of organ failure after successful primary resuscitation may result from peripheral (micro-) circulatory derangements. In spite of achieving 'normal' systemic haemodynamics, it is not guaranteed that perfusion in all organs and tissues is maintained as well. During low-output syndrome (LOS), the organism tries to compensate perfusion deficits by redistribution of flow to vital organs (e.g. heart, brain), resulting in an underperfusion of other organs (splanchnic bed, kidney). Various inflammatory mediators and vasopressors are released in this situation and are of particular importance for the development of impaired perfusion.

Recent evidence suggests that the endothelium is not only a passive barrier between the circulating blood and the tissue, but may also be markedly involved in the regulation of microcirculatory blood flow by producing important regulators of vascular tone (e.g. prostaglandins, nitric oxide, endothelins, angiotensin II). The regional regulation of blood flow is likely to reflect a balance between systemic mechanisms (e.g. the autonomous nervous system) and other, more locally active blood flow regulators. One important approach to improve perfusion in this situation is the use of sufficient amounts of volume.

Principles of volume replacement in the hypovolaemic patient

The primary goal of volume administration is to guarantee stable systemic haemodynamics and microcirculation by rapidly restoring the volume of the intravascular compartment. Excessive fluid accumulation, particularly in the interstitial tissue, should be avoided. The infused fluid may stay in the intravascular compartment or equilibrate with the interstitial/intracellular fluid compartments (Fig. 1). Different mechanisms are involved in the control of volume and composition of each compartment, including the antidiuretic hormone (ADH) system and the renin–angiotensin system (RAS). The principal action of these systems is to retain water in order to restore water or intravascular volume deficits, to retain sodium in order to restore the intravascular volume, and to increase hydrostatic perfusion pressure by vasoconstriction. Enhanced activity of these systems is known to occur in stress situations, e.g. during haemorrhage. If water or intravascular volume deficits and the stress-related stimuli are additive, volume therapy may inhibit this process through counter-regulatory mechanisms. ADH production is dependent on maintenance of the extracellular volume, especially in the intravascular compartment. Administration of a restricted amount of crystalloids may replace a previous water deficit, but replacement of an intravascular volume deficit would require much more volume to inhibit activation of this system. Thus, it can be expected that replacement of only water will not inhibit the normal responses of the ADH system and of the RAS, whereas administering a combination of crystal-

Changes in compartments during fluid infusion

Compartment	Glucose 5%	NaCl 0.9%	Colloids
intravascular	↑	↑	↑↑↑
interstitial	↑↑	↑↑	—
intracellular	↑↑↑		—

Fig. 1. Changes of the different volume compartments by the different volume replacement strategies

loids and colloids (replacement of the water deficit and simultaneous guarantee of a sufficient intravascular volume) may achieve this goal.

One important aspect of volume therapy in the haemorrhagic shock patient is the risk of inducing interstitial oedema. Tissue oedema is related to an imbalance in the sum of the Starling forces across capillary membranes or an increase in protein permeability, by which an increase in fluid flux to the interstitial space is promoted. A decrease in membrane integrity, an increase in hydrostatic pressure, and a decrease in intravascular colloid oncotic pressure (COP) will induce fluid movement across the microvascular membrane and may produce interstitial tissue fluid accumulation (e.g. pulmonary oedema). Moreover, endothelial swelling may also occur, by which tissue perfusion is further disturbed in association with the risk of developing organ dysfunction (Fig. 2).

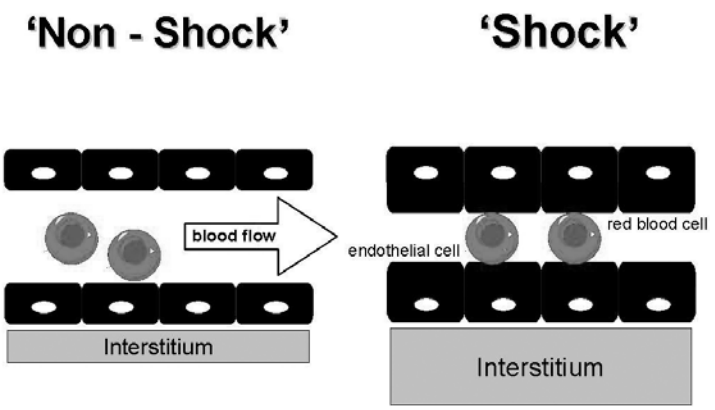


Fig. 2. Endothelial swelling secondary to haemorrhagic shock

Volume replacement strategies for treating haemorrhagic shock

Due to their different physicochemical characteristics, the various volume-replacement solutions differ in their haemodynamic efficacy. After infusion, crystalloids rapidly shift from the intravascular to the interstitial compartment and subsequently possess only a limited volume-replacing capability. Consequently, if haemodynamic stability is to be guaranteed, crystalloids have to be administered at three to five times the volume lost. Due to the subsequent interstitial dilution, the interstitial COP decreases, resulting in the formation of interstitial oedema. According to their widely differing colloid oncotic pressures, colloids are separated into hypooncotic (e.g. 3.5% gelatin and 4% albumin), isooncotic (e.g. all 6% hydroxyethyl starch preparations) and hyperoncotic (e.g. 10% hydroxyethyl starch, 10% dextran, and 20% human albumin).

Allogenic blood/blood components

The inherent risk of transmission of viral and immunological diseases has forced us to reduce the use of allogenic blood and blood products. As shown by various studies, the reduction in haematocrit and in arterial oxygen content is not deleterious since compensating mechanisms are able to guarantee tissue oxygenation and systemic oxygen transport. When non-blood plasma substitutes are used to replace volume deficits, the margin of safety may become compromised, especially in patients with significant coronary obstruction. There is an increasing risk of a discrepancy between myocardial oxygen requirements and available subendocardial oxygen supply, which may result in deterioration of myocardial performance. The 'optimal' haemoglobin level for patients with sepsis or septic shock is still undetermined. Transfusion of allogenic blood in the patient with a haemoglobin level of 8–10 g/dl appears to be without benefit with regard to tissue perfusion or oxygenation [5]. Elevating haemoglobin levels higher than 7–10 mg/d has also been shown to be without any benefit in outcome [5]. Blood transfusions may even have detrimental effects on organ perfusion, oxygenation (e.g. of the splanchnic circulation), and immune function [6, 7]. Thus, it is generally accepted that the use of allogenic blood should be restricted to those patients requiring augmentation of their haemoglobin level. Fresh frozen plasma (FFP) should be used only for treating the bleeding patient showing coagulopathy.

Crystalloids

Hypotonic (e.g. dextrose in water), isotonic (e.g. Ringer's solution), and hypertonic (e.g. 7.5% saline solution) crystalloids have to be distinguished when using crystalloids for volume replacement. Crystalloids are freely permeable to the vascular membrane and are therefore distributed mainly in the interstitial and/or intercellular compartments. Only 25% of the infused crystalloid solution remains in the intravascular space, whereas 75% extravasates into the interstitium [8, 9]. Dilution

of plasma protein concentration may also be accompanied by a reduction in plasma COP, leading to tissue oedema. It has been shown in animal experiments that even a massive crystalloid resuscitation is less likely to achieve adequate restoration of microcirculatory blood flow compared to a colloidal-based volume replacement strategy [10]. In an experimental trauma–haemorrhage model, either colloids (dextran) or crystalloids (Ringer's acetate) were used to replace blood loss after surgical trauma [11]. The crystalloid group showed significantly larger amounts of tissue water in muscle and jejunum than the colloid-treated group of animals. Administration of large amounts of normal saline should be avoid because of producing hyperchloraemic acidosis [12, 13].

Colloids

Albumin

Albumin is a naturally occurring plasma protein. The molecular mass of albumin is approximately 69 kDa. Albumin is derived from pooled human plasma, heated, and sterilised by ultrafiltration. Thus, albumin is generally accepted to be safe in terms of transmission of infectious diseases. Albumin may have some additional specific effects aside from its volume-replacing properties. The importance of albumin may be related to its transport function for various drugs and endogenous substances, e.g. bilirubin, free fatty acids. Albumin has also been reported to possess beneficial effects on membrane permeability secondary to free-radical scavenging. These effects, however, have only been shown experimentally, and no clinical study has demonstrated any of these beneficial effects in comparison with synthetic plasma substitutes. There appears to be no reason to treat haemorrhage-related hypovolaemia with albumin, because albumin can easily be replaced by other, less expensive plasma substitutes.

Dextran

Dextran is a glucose polymer that is available in two preparations of different molecular masses and concentrations: 6% dextran 70 (average molecular mass 70 kDa) and 10% dextran 40 (average molecular mass 40 kDa). Increases of plasma volume after infusion of 1000 ml of dextran 70 ranged from 600 to 800 ml. Negative side effects of dextrans have been well-described and include severe coagulation abnormalities resulting in increased bleeding tendency and severe life-threatening hypersensitivity reactions.

Gelatins

Gelatins are modified beef collagens. Due to their low average molecular mass (approximately 35 kDa), the intravascular half-life of infused gelatin is short (ap-

proximately 2 h) and gelatins are thus the least effective colloids. This disadvantage is balanced by the absence of a dose-limitation with gelatins, which are listed by the World Health Organisation as an essential drug. In the USA, however, gelatins were abandoned in 1978 due to a high incidence of hypersensitivity reactions.

Hydroxyethyl starch

Hydroxyethyl starch (HES) is a high polymeric glucose compound that is manufactured through hydrolysis and hydroxyethylation from the highly branched starch amylopectin. Polymerised d-glucose units are joined primarily by 1–4 linkages with occasional 1–6 branching linkages. The degree of branching is approximately 1:20, which means that there is one 1–6 branch for every 20 glucose monomer units. Natural starches cannot be used as plasma substitutes because they are unstable and rapidly hydrolysed by circulating amylase. Substituting hydroxyethyl for hydroxyl groups results in a highly increased solubility and retards enzymatic hydrolysis of the compound, thereby delaying its breakdown and elimination from the blood. The hydroxyethyl groups are introduced mainly at carbon positions C_2, C_3, and C_6 of the anhydroglucose residues. The pharmacokinetics of HES preparations are further characterised by the pattern of hydroxyethylation, in particular by the molar substitution and by the degree of substitution. The molar substitution (MS) is computed by counting the total number of hydroxyethyl groups present and dividing the number by the quantity of glucose molecules. The available HES preparations are characterised by concentration (low: 3%; medium: 6%; high: 10%), degree of substitution (DS) (low: 0.4; medium: 0.5; high: 0.62 and 0.7), and the mean molecular mass [low-molecular mass (LMM)-HES: 70 kDa; medium-molecular mass (MMM)-HES: 130–260 kDa; high-molecular mass (HMM)-HES: > 450 kDa]. Current evidence indicates that the ratio of C_2:C_6 hydroxyethylation is another important aspect for pharmacokinetic effects as well as side-effects (e.g. accumulation, bleeding complications). Several different HES preparations are available commercially in Europe, whereas in the USA only the first generation HMM-HES (Hetastarch; concentration: 6%; 450 kDa; DS: 0.7) is approved for volume replacement.

Hypertonic solutions

Enthusiasm has been expressed for hypertonic solutions (HS) or hypertonic-hyperoncotic solutions (HHS) especially in the treatment of severe haemorrhagic shock in trauma patients. HS appear to improve cardiovascular function on multiple levels:

- Displacement of tissue fluid into the blood compartment
- Direct vasodilatory effects in the systemic and pulmonary circulation
- Reduction in venous capacitance
- Positive inotropic effects through direct actions on myocardial cells

The main mechanism of action of hypertonic solutions is the rapid mobilisation

of endogenous fluid and subsequent plasma volume expansion. Due to the hypertonicity of the solutions, only a small volume of fluid (approximately 4ml/kg) is necessary to effectively restore cardiovascular function ('small volume resuscitation'). The initial improvement in cardiovascular function (e.g. increase in cardiac output) seems to be mediated by the hypertonicity of the solution, whereas the solute composition does not seem to be important. Since the beneficial effects of hypertonic saline solution have been reported to be rather transient, hypertonic solutions are often mixed with colloids (dextran or HES); these solutions showed a significant prolongation of efficacy (Fig. 3). Several studies using HS for treating hypovolaemia reported beneficial effects on microcirculation or organ perfusion. Hypertonic volume replacement may additionally correct perfusion deficits due to a significant increase in perfusion pressure, improvement in capillary flow distribution, endothelial de-swelling effects, and concomitant haemodilution [14, 15]. As endothelial swelling aggravates microvascular function in low perfusion states, the de-swelling effects of hypertonic fluid therapy can be beneficial in this situation (Fig. 4). Shrinkage of the endothelium increases the inner diameter of the capillaries, resulting in decreased resistance [16]. The fluid shift into the intravascular space secondary to hypertonic volume replacement also induces haemodilution and a decrease in viscosity—beneficial effects for microcirculatory perfusion. Animal studies have supported improvement in renal, intestinal, pancreatic, and myocardial flows after administration of hypertonic solutions [14–19], whereas standard colloid or crystalloid volume therapy failed to achieve these effects [14].

Characteristics of hypertonic-colloid solutions

	HyperHaes™ (Fresenius-Kabi, Germany)	RescueFlow™ (BioPhausia, Sweden)
Electrolyte concentration	7.2% NaCl	7.5% NaCl
Sodium	1,232 mmol/l	1,283 mmol/l
(theoretical) Osmolarity	2,464 mosmol/l	2,567 mosmol/l
Colloid	hydroxyethyl starch	dextran
Colloid concentration	6%	6%
Mean molecular weight (kD)	200	70
Indication	severe volume deficit	severe volume deficit

Fig. 3. Characteristics of the two available hypertonic solutions

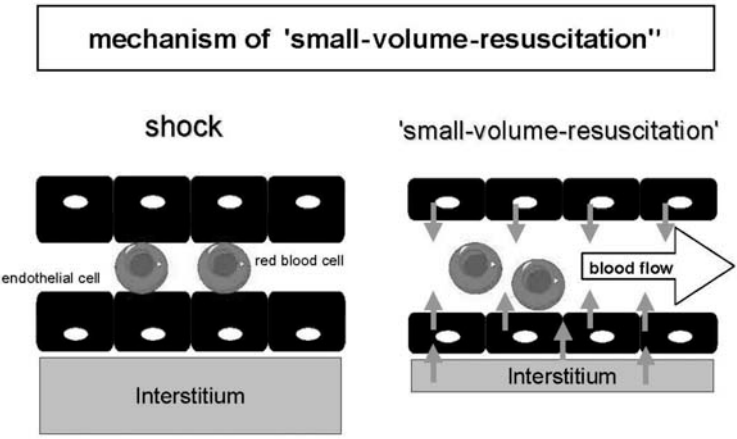


Fig. 4. Hypertonic solutions reduce endothelial swelling and thus improve tissue perfusion

Guiding volume therapy

Evaluation of volume deficit and guiding adequate volume therapy remain a challenge. The aim of appropriate monitoring is to avoid insufficient fluid infusion as well as fluid overload. Standard haemodynamic monitoring, such as measuring blood pressure and heart rate (HR), are often inaccurate to detect volume deficits or to guide volume therapy. In spite of negative data on the value of pulmonary artery catheters (PAC) in the critically ill, PAC are still widely used for this purpose. However, cardiac filling pressures (e.g. central venous pressure and pulmonary artery occlusion pressure) are often misleading surrogates for assessing optimal left-ventricular loading conditions. Cardiac filling pressures are influenced by several factors other than blood volume, including alterations in vascular or ventricular compliance and intrathoracic pressure.

Measurement of intrathoracic blood volume (ITBV) has been reported to be a more reliable method to monitor volume therapy in this situation [20]. ITBV monitoring was associated with a reduction in ICU and hospital stay, and even mortality was demonstrated to be reduced [21].

Echocardiography, especially transoesophageal echocardiography (TEE), is the most specific monitoring instrument to evaluate cardiac filling. However, due to its high costs it is not available to every ICU patient. Moreover, TEE is an intermittent rather than a continuous monitoring device and thus may be unreliable to guide volume therapy.

Perturbations of organ perfusion are thought to be of fundamental importance in the pathogenesis of organ dysfunction in the critically ill [22]. The importance of occult hypovolaemia for the development of organ perfusion deficits has been

supported by several studies [23, 24]. There still does not exist an optimal protocol for routine clinical monitoring to detect perfusion deficits. Haemodynamic parameters, such as cardiac output, VO_2, and DO_2, are not regarded as optimal measures for assessing the adequacy of regional or microcirculatory perfusion [25]. The haemorrhagic shock patient is at risk of experiencing splanchnic hypoperfusion with subsequent development of translocation and systemic inflammatory response syndrome (SIRS) [26]. Abnormalities of splanchnic perfusion may coexist with normal systemic haemodynamic and metabolic parameters. Non-invasive, continuous tonometry measuring gastric mucosal partial pressure of carbon dioxide (gastric pCO_2) may be an attractive option for diagnosis and monitoring of splanchnic hypoperfusion. In patients undergoing major non-cardiac surgery, maintaining haemodynamic stability was no guarantee of an adequate splanchnic perfusion and could not definitely protect against significant postoperative complications [27]. Although this monitoring instrument has produced some promising results, it is far from being the new 'gold standard' for guiding volume management of the critically ill [28].

Conclusions

In the severely hypovolaemic (haemorrhagic) patient, adequate volume restoration is essential to treat noncompensatory, irreversible shock. Lengthy uncorrected hypovolaemia will jeopardise survival by the continuous stimulation of various vasopressive and immune cascades, and prolonged underresuscitation of the hypovolaemic patient may have fatal consequences for organ function. Thus, vigorous optimisation of the circulating volume is a prerequisite to avoid development of MODS in the haemorrhagic patient. It is time to leave emotions aside when discussing the most appropriate volume replacement strategy in the haemorrhagic patient and to concentrate on the available scientific evidence. What have we learned from the past concerning the management of the haemorrhagic shock patient?

- Allogenic blood should be avoided as far as possible; it cannot, however, be completely eliminated from our strategy to manage the haemorrhagic shock patient (Fig. 5).
- There is convincing evidence that blood volume is restored more rapidly with colloids than with crystalloids. In addition, colloids are more efficient resuscitative fluids than crystalloids, and offer a more efficient regimen to guarantee microcirculatory flow. However, crystalloids are often recommended as the first choice to treat haemorrhage: The American College of Surgeons Classes of Acute Haemorrhages specified four classes of acute haemorrhage using a blood loss ranging from up to 750 ml to 2000 ml [29]. Fluid replacement should be performed with crystalloids exclusively (3:1 rule)—there is no place for infusing (synthetic) colloids (Tab. 1).
- Certain colloids (e.g. HES) are associated with beneficial effects on microperfusion, capillary integrity, inflammatory response, and endothelial activa-

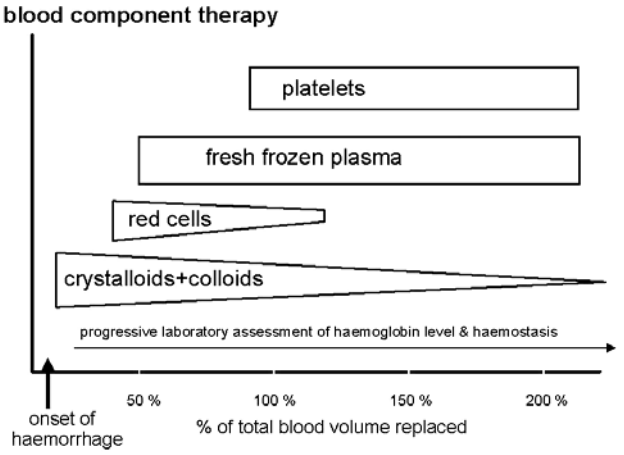


Fig. 5. Management of severe haemorrhage

Table 1. Management of the bleeding patients according to the American College of Surgeons Classes of Acute Haemorrhage (modified from [33])

Factors	I	II	III	IV
Blood loss, ml	< 750	750-1500	1500-2000	> 2000
Blood loss, %BV	< 15	15-30	30-40	> 40
Puls, BPM	> 100	> 100	> 120 >	140
Blood pressure	Normal	Normal	Decreased	Decreased
Puls pressure (mmHg)	Normal/ increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiration per min	14-20	20-30	30-40	> 35
Urine output, ml/hr	30 or more	20-30	5-15	Negligible
CNS (mental status)	Slightly anxious	Midly anxious	Anxious confused	Confused lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid +blood	Crystalloid +blood (3:1 rule)

tion/integrity, but they are still underused in the severely ill haemorrhagic patient.

– The most beneficial effects in animals have been shown with the use of hypertonic solutions, but this strategy is far from being widely accepted in treating the haemorrhagic shock patient.

What endpoints should be chosen when guiding volume replacement? Although often used, 'clinical signs' of hypovolaemia are non-specific and insensitive. Most studies on volume replacement were not focused on outcome. It remains unclear whether mortality is an appropriate endpoint when assessing the benefit of different volume replacement strategies [30, 31]. New insights into

treating hypovolaemia, such as the risk of development of systemic inflammatory response syndrome (SIRS) and post-haemorrhagic organ dysfunction (e.g. renal or pulmonary insufficiency), should change this point of view. We need improved monitoring technologies that will help us to better guide volume therapy and improved 'point-of-care' markers that will help us to better assess whether volume therapy is appropriate to sufficiently restore hypovolaemia-associated alterations.

References

1. MacKenzie EJ, Morris JA Jr, Smith GS et al (1990) Acute hospital costs of trauma in the United States: implications for regionalized systems of care. J Trauma 30:1096–1103
2. Deane SA, Gaudry PL, Woods P et al (1988) The management of injuries - a review of deaths in hospital. Aust NZJ Surg 58:463–469
3. Deakin CD (1994) Early fluid resuscitation in haemorrhagic shock. Eur J Emerg Med 1:83–85
4. Bickell WH (1993) Are victims of injury sometimes victimized by attempts at fluid resuscitation? Ann Emerg Med 22:225–226
5. Lucas CE (1990) Update on trauma in Canada. 4. Resuscitation through the three phases of hemorrhagic shock after trauma. Can J Surg 33:451–456
6. Hebert P, Wells G, Blajchman A et al (1999) A multicenter randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 340:409–417
7. Marik P, Sibbald W (1993) Effect of stored-blood transfusion in oxygen delivery in patients with sepsis. JAMA 269:3024–3029
8. Landers DF, Hill GE, Wong KC et al (1996) Blood transfusion-induced immunomodulation. Anesth Analg 82:187–204
9. Norberg A, Brauer K, Prough DS et al (2005) Volume turnover kinetics in fluid shifts after hemorrhage, fluid infusion, and the combination of hemorrhage an fluid infusion in sheep. Anesthesiology 102:985–994
10. Vaupshas HJ, Levy M (1990) Distribution of saline following acute volume loading: postural effects. Clin Invest Med 13:165–177
11. Funk W, Baldinger V (1995) Microcirculatory perfusion during volume therapy. A comparative study using crystalloid or colloid in awake animals. Anesthesiology 82:975–982
12. Schött U, Lindbom LO, Sjöstrand U (1988) Hemodynamic effects of colloid concentration in experimental hemorrhage: a comparison of Ringer's acetate, 3% dextran-60 and 6% dextran-70. Crit Care Med 16:346–352
13. Kellum JA (2002) Saline-induced hyperchloremic metabolic acidosis. Crit Care Med 30:259–261
14. Prough DS (2000) Acidosis associated with perioperative saline administration. Anesthesiology 93:1184–1187
15. Kreimeier U, Messmer K (1987) New perspectives in resuscitation and prevention of multiple organ system failure. In: Baethmann A, Messmer K (eds) Surgical Research: Recent Concepts and Results. Springer, Berlin, pp 39–50
16. Whinney RR, Cohn SM, Zacur SJ (2000) Fluid resuscitation for trauma patients in the 21st century. Curr Opin Crit Care 6:395–400
17. Virlos I, Siriwardena AK (2000) Hypertonic saline attenuates end-organ damage in an experimental model of acute pancreatitis. Br J Surg 87:1336–1340

18. Oi Y, Aneman A, Svensson M et al (2000) Hypertonic saline-dextran improves intestinal perfusion and survival in porcine endotoxin shock. Crit Care Med 28:2843–2850
19. Vollmar MD, Preissler G, Menger MD (1996) Small-volume resuscitation restores hemorrhage-induced microcirculatory disorders in rat pancreas. Crit Care Med 24:445–450
20. Mazzoni MC, Borgstrom P, Arfors KE et al (1988) Dynamic fluid redistribution in hyperosmotic resuscitation of hypovolemic hemorrhage. Am J Physiol 255:H629-H637
21. Sakka SG, Bredle DL, Reinhardt K et al (1999) Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. J Crit Care Med 14:78–83
22. Mitchell JP, Schuller D, Calandrino FS et al (1992) Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 145:990–998
23. Pittard AJ, Hawkins WJ, Webster NR (1994) The role of the microcirculation in the multi-organ dysfunction syndrome. Clin Intensive Care 5:186–190
24. Fiddian-Green RG (1990) Gut mucosal ischaemia during cardiac surgery. In: Taylor K (ed) Seminar of Cardiovascular Surgery. Saunders, Philadelphia, pp 1–11
25. Mythen MG, Webb AR (1994) The role of gut mucosal hypoperfusion in the pathogenesis of postoperative organ dysfunction. Intensive Care Med 20:203–209
26. Gutierrez G, Bismar H, Dantzker DR et al (1992) Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. Crit Care Med 20:451–457
27. Mythen MG, Webb AR (1995) Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Ann Surg 130:423–429
28. Marik PE, Iglesias J, Marini B (1997) Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aortic aneurysm repair. J Crit Care 12:51–55
29. Bams JL, Mariani MA, Groneveld ABJ (1999) Predicting outcome after cardiac surgery: comparison of global haemodynamic and tonometric variables. Br J Anaesth 82:33–37
30. Miller RD (1999) Update on blood transfusions and blood substitutes. Anesth Analg 88:71–78
31. Cook D, Guyatt G (2001) Colloid use for fluid resuscitation: Evidence and spin. Ann Intern Med 2001 135:205–208
32. Astiz ME, Rackow EC (1999) Crystalloid-colloid controversy revisited. Crit Care Med 27:34–35

Chapter 5

Microdialysis: principles and techniques

C.-H. Nordström, U. Ungerstedt

The technique of microdialysis provides the opportunity for continuous monitoring of metabolic changes in the tissue before they are reflected in peripheral blood chemistry or in systemic physiological parameters. The method was developed more than 30 years ago for monitoring chemical events in the animal brain [1, 2] and has become an accepted scientific standard technique. Altogether there have been about 10 000 published studies reporting the use of microdialysis. In the late 1980s, the possibilities for monitoring the human brain were first explored [3], and microdialysis has since then been used for biochemical monitoring of most human tissues. Clinical application of the technique was, however, delayed due to lack of instruments suitable for clinical routine use, including bedside monitoring of relevant biochemical variables.

In 1995, CMA Microdialysis (Stockholm, Sweden) introduced a sterile microdialysis catheter, a simple microdialysis pump, and a bedside biochemical analyser. The instrumentation was originally intended for subcutaneous and intramuscular use but with slight modification of the microdialysis catheter it has been used also intracerebrally as an integrated part of routine multi-modality monitoring. In this short review, some of the principles and limitations of the microdialysis technique will be discussed and data from experimental studies in animals and clinical experiences from various human tissues will be presented.

The microdialysis technique

The basic idea of microdialysis is to mimic the function of a blood capillary by positioning a thin dialysis tube in the tissue (Fig. 1). The membranous wall of the tube allows free diffusion of water and solutes between the surrounding interstitial fluid and the perfused solution (perfusate). The concentration gradients between the interstitial fluid and the perfusate constitute the driving force for diffusion. The molecular masses of the molecules being sampled is limited by the pore size of the dialysis membrane (cut-off). The perfusate flows along the dialysis membrane slowly and at a constant speed and the sample (dialysate) is collected and analysed biochemically.

The achieved concentration of the analytes in the dialysate is dependent upon the degree of equilibration between the perfusate and the interstitial fluid. This is termed relative recovery (recovery) and is defined as the dialysate/interstitial concentration ratio, expressed as a percentage [4]:

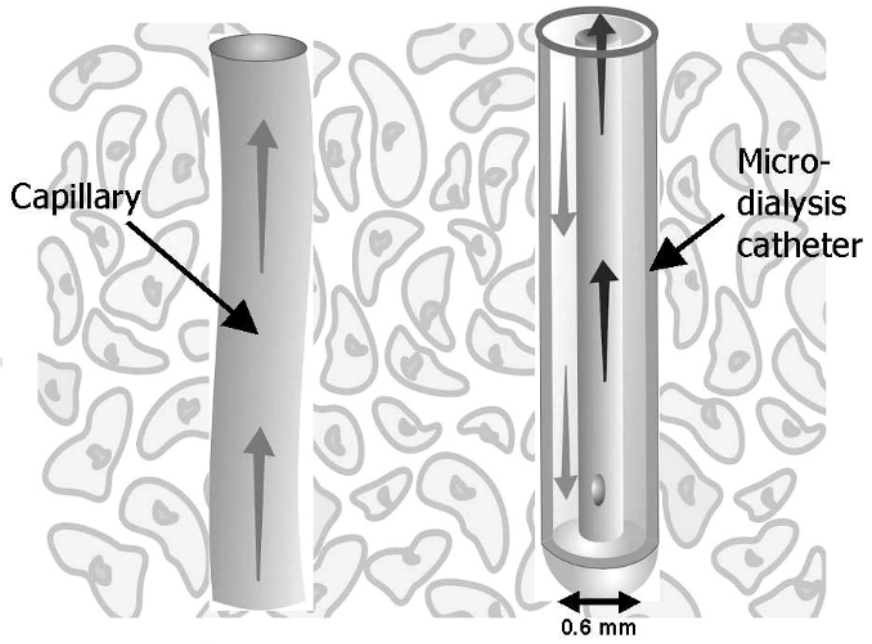


Fig. 1. The microdialysis technique mimics the function of a blood capillary by positioning a thin dialysis tube in the tissue

$$\text{Recovery} = \frac{\text{Conc}_{\text{tissue}}}{\text{Conc}_{\text{dialysate}}}$$

Accordingly, the microdialysis technique does not usually give the absolute concentration of the studied biochemical variables unless it is calibrated in vivo. When clinical microdialysis is performed as a standardised routine technique, this limitation is mostly without significance. However, some of the factors determining the recovery are important to recognise.

Factors affecting recovery in vivo

The three most important factors affecting recovery in vivo are: the area of the semi-permeable membrane, the perfusion flow rate, and the diffusion in the surrounding interstitial fluid. A schematic illustration of the effects of changes in perfusion flow rate and the length of the microdialysis membrane is given in Fig. 2. Recovery increases in proportion to the dialysis membrane area [5]. Compared to dialysis membranes used in most experimental studies, the microdialysis catheters intended for clinical purposes are very large. The CMA/60 catheter, which is used, for example, in subcutaneous tissue, has a 30-mm-long dialysis membrane, and the CMA/70 catheter used in the brain has a membrane length of 10 mm. The

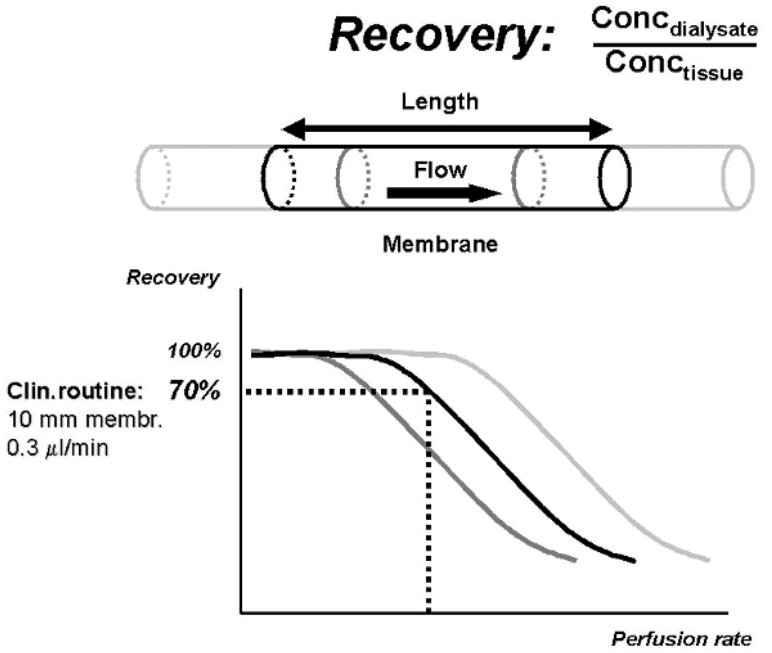


Fig. 2. The effects of changes in perfusion flow rate and length of the dialysis membrane on (relative) recovery. For intracerebral routine use, a 10-mm microdialysis microdialysis catheter is perfused at 0.3 µl/h, which gives a (relative) recovery of approximately 70 %

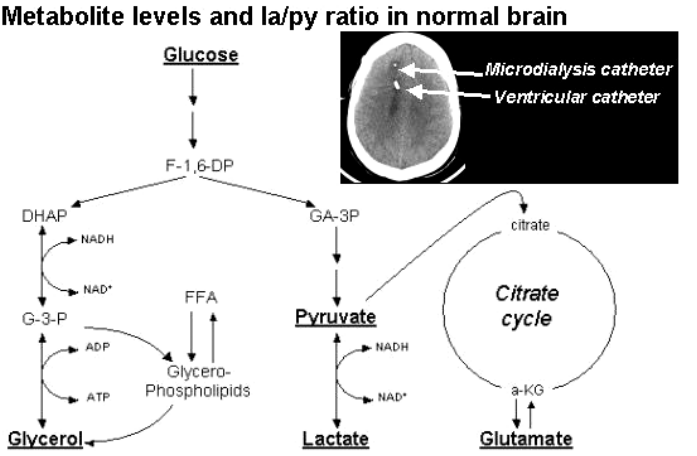
diameter of both probes is about 0.6 mm and the standard cut-off of the dialysis membrane (during clinical routine) is 20 kDa. For special purposes (monitoring of large molecules, e.g. cytokines) microdialysis catheters with 100-kDa cut-off are available for clinical routine applications [6].

The standard perfusion flow rate employed during clinical routine is 0.3 ml/min, which allows sampling every 30 min. Due to the slow perfusion rate and the large dialysis membrane, recovery is high: the in vivo recovery for the intracerebral (CMA/70) catheter is approximately 70% for the biochemical variables used routinely (see below) [7] while for the longer CMA/catheter recovery approaches 90%. If the perfusion rate is increased to permit more frequent sampling, recovery decreases to about 30% at 1 µl/min [7].

The diffusion rate in the surrounding interstitial space is of importance and varies with the molecular masses of the studied analytes and the size and tortuosity of the interstitium (prolongation of diffusion pathways due to cell membranes). Recovery may thus vary between tissues and changes with the pathophysiological conditions. The problem is without significance for clinical routine but is very relevant, for example, when microdialysis is used for quantitative pharmacokinetic studies [8, 9]. The importance of the diffusion limitation of the surrounding interstitial space also explains why it is useless to perform in vitro calibration to compensate for the recovery in vivo.

Biochemical variables monitored during clinical routine

The biochemical variables used for routine monitoring during clinical conditions were chosen to cover important aspects of cerebral energy metabolism and to indicate the extent of degradation of cellular membranes (Fig. 3). In Fig. 3, reference levels for normal human brain (during wakefulness) and piglet brain (during general anaesthesia) are given [10, 11].



Perfusion rate **0.3** µl/min	Glucose mmol/L	Lactate mmol/L	Pyruvate µmol/L	La/py ratio	Glutamate µmol/L	Glycerol µmol/L
Human brain (wakefulness)	**1.7 ± 0.9**	**2.9 ± 0.9**	**166 ± 47**	**23 ± 4**	**16 ± 16**	**80 ± 40**
Piglet brain (anaesthesia)	1.8 ± 0.7	2.0 ± 0.8	124 ± 94	18 ± 5	7 ± 6	35 ± 11

Fig. 3. Simplified diagram of intermediary metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids and to the citric acid cycle. Fructose-1,6-diphosphate (*F-1,6-DP*), dihydroxyacetone-phosphate (*DHAP*), glyceraldehyde-3-phosphate (*GA-3P*), glycerol-3-phosphate (*G-3-P*), free fatty acids (*FFA*), triglycerides (*TG*), α-ketoglutarate *(α-KG*). *Underlined* metabolites are measured at the bedside with enzymatic techniques. Reference levels for normal human brain (during wakefulness) and piglet brain (during general anaesthesia) are also given [10, 11]

Under normal conditions, glucose is the sole substrate for cerebral energy metabolism. In the cytosol it is degraded to pyruvate (glycolysis) with a net yield of 2 ATP for each molecule of glucose. Due to the redox conditions, part of the pyruvate (py) is converted to lactate (la). The la/py ratio reflects the cytoplasmic redox state, which can be expressed in terms of the lactate dehydrogenase equilibrium:

$$\frac{[NADH]\,[H^+]}{[NAD^+]} = \frac{[Lactate]}{[Pyruvate]} \times K_{LDH}$$

The la/py ratio thus gives information about tissue oxygenation. The major part of pyruvate enters the citric acid cycle in the mitochondria with a net yield of another 36 ATP. The relation between the citric acid cycle and the important excitatory transmitter glutamate is shown in Fig. 3. However, the glutamate level obtained by microdialysis does not exclusively reflect liberation of the transmitter. The intracellular concentration of glutamate is high and the concentration in the interstitial fluid probably often reflects release from leaky cells.

Since the brain does not contain any triglycerides (TG), a high level of intracerebral glycerol is considered to be a reliable indicator of degradation of the glycerophospholipids of cellular membranes and thus of cell damage [12, 13]. In other tissues, and in particular in fat tissue, glycerol is mainly obtained from the degradation of TG. Lipolysis is under sympathetic control through catecholamine receptors on adipocytes, which are stimulated by circulating catecholamines as well as by local noradrenergic nerve endings. The glycerol level in subcutaneous fat tissue may be used as an indicator of physical as well as mental stress [14].

During clinical routine, biochemical variables are analysed with a CMA 600 Microdialysis Analyser (CMA Microdialysis, Stockholm, Sweden). This analyser uses enzymatic and colorimetric techniques. The reagent enzymatically oxidises the substrate, and hydrogen peroxide is formed. Peroxidase then catalyses the reaction between hydrogen peroxide, 4-amino-antipyrine, and either phenol 3,5-dichloro-2-hydroxy-benzene sulfonic acid (in the case of glycerol) or *N*-ethyl-*N*-(2-hydroxy-3-sulfonylpropyl)-*m*-toluidine (in the case of pyruvate) to form red-violet quinoneimine or quinonediimine. The rate of coloured substance formation is proportional to the substrate concentration, which is photometrically measured at 546-nm wavelength.

Clinical microdialysis

The microdialysis technique has been used in most human tissues. In the following, a brief review of data from the tissues shown in bold in Fig. 4 is provided. Since microdialysis is an invasive technique, tissue damage caused by the catheter and the possible complications are of special importance. These risks may be most obvious during intracerebral microdialysis, and the brain is also the organ where we have most clinical experience.

It is essential that the blood–brain barrier (BBB) remains intact during microdialysis, and many experimental studies have shown that this is the case [15, 16]. The initial tissue damage causes a disruption of the BBB that is visible ~ 10 min after probe insertion but the BBB appears to again be intact after 30 min [17]. Histological examinations have described the tissue reactions in the rat brain surrounding the microdialysis probe [18]. Within the first 2 days the neuropil was normal and only occasional haemorrhage surrounded the probe. On the third day, an astrocytic reaction was seen using antiserum against glial fibrillary acidic protein. Fourteen days after implantation, layers of reticulin-positive fibres surrounded the dialysis membrane. Similar reactions may occur in the human brain but it should be

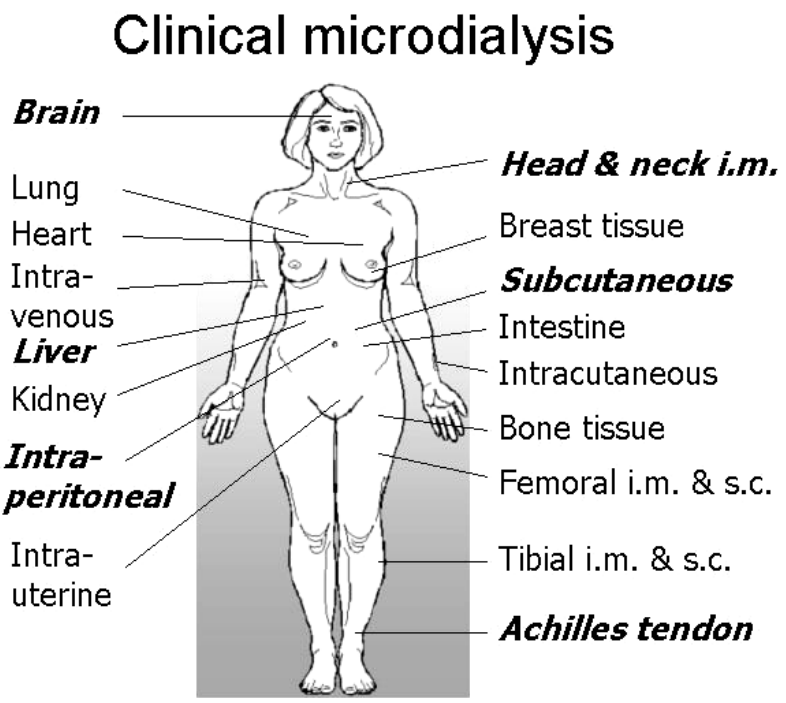


Fig. 4. Human tissues that have been studied using the microdialysis technique. Tissues shown in *bold* are discussed in the text

underlined that, in contrast to the experimental situation, during clinical conditions the catheters and all surgical procedures are performed under sterile conditions. In addition, the relation between the size of the brain and the probe is very different for the rat and the human brain, and large species variations exist, e.g. regarding the proportions of neurons to astrocytes.

We have used intracerebral microdialysis as a clinical routine monitoring technique in more than 300 patients (most of them with multiple intracerebral catheters) and we have not noted any complications caused by the microdialysis technique.

Subcutaneous and myocutaneous microdialysis

Since the glucose concentration in the extracellular space of the subcutaneous adipose tissue closely mirrors the blood glucose concentration, microdialysis might be an ideal technique for frequent analysis of the glucose level. Subcutaneous or myocutaneous microdialysis may also be used for tissue monitoring after plastic surgery.

Subcutaneous microdialysis

A reliable method for long-term, continuous in vivo monitoring of blood glucose concentrations in insulin-dependent diabetes has been sought for several decades. In 1993, Bolinder et al. [19] suggested subcutaneous microdialysis as a solution to this problem. Their studies showed that microdialysis could be used for continuous, long-term monitoring in diabetic patients during ordinary daily life and that the daily glucose profiles could be used for tailoring insulin therapy. In a follow-up study, it was shown that the true diurnal variability was too great to be accurately reflected even by frequent self-monitoring of the blood glucose level [20].

The importance of careful control of the blood glucose level was recently emphasised by the observation that maintenance of a blood glucose level below 6 mmol/l significantly reduced mortality in intensive care patients [21, 22]. To investigate whether the subcutaneous glucose level accurately reflected blood glucose levels also during intensive care, we performed a study in 62 severely head-injured patients (2434 simultaneous analyses of glucose concentration in arterial blood and subcutaneous adipose tissue) [23]. With the techniques used in the study (perfusion flow 0.3 ml/min; membrane length 30 mm), the recovery for glucose from subcutaneous adipose tissue has been shown to be between 0.79 [24] and 0.9 [25]. Since the ratio blood/plasma glucose concentration is approximately 0.9, we would expect that under ideal circumstances the interstitial glucose concentration is equal to blood glucose concentration divided by 0.9 and, since recovery for glucose with the present technique is approximately 0.8, the obtained ratio glucose s.c./glucose blood would be close to 0.9.

In many patients, a very good correlation was obtained, as illustrated by the two cases shown in Fig. 5. However, when comparing the average glucose concentration in blood (mean value ± SEM) and in the interstitial fluid of subcutaneous adipose tissue (mean value ± SEM) in all 62 patients during the first 24 h after start of intensive care (Fig. 6), the glucose s.c. was significantly higher ($P \sim 0.001$) during the period 6–7 h after start than at 1–2 h, although the blood glucose concentration did not change significantly. The ratio glucose s.c./glucose blood increased slowly during the first hours and was approximately 0.85 6–7 h after start of treatment. The ratio continued to increase slowly and was above 0.90 about 60 h after start of treatment.

During the first hours after trauma, many patients were probably under sympathetic stress with peripheral vasoconstriction although their vital functions had been secured. We assume that our anti-stress/anti-hypertensive treatment protocol [26] affected the balance between local consumption rate and delivery of glucose. A close correlation between glucose s.c. and glucose blood, similar to that obtained in diabetic humans under normal conditions [19, 20], was not obtained until the initial stress reaction had been treated, as revealed by the decreases in MAP, lactate s.c., and glycerol s.c. (see [23]).

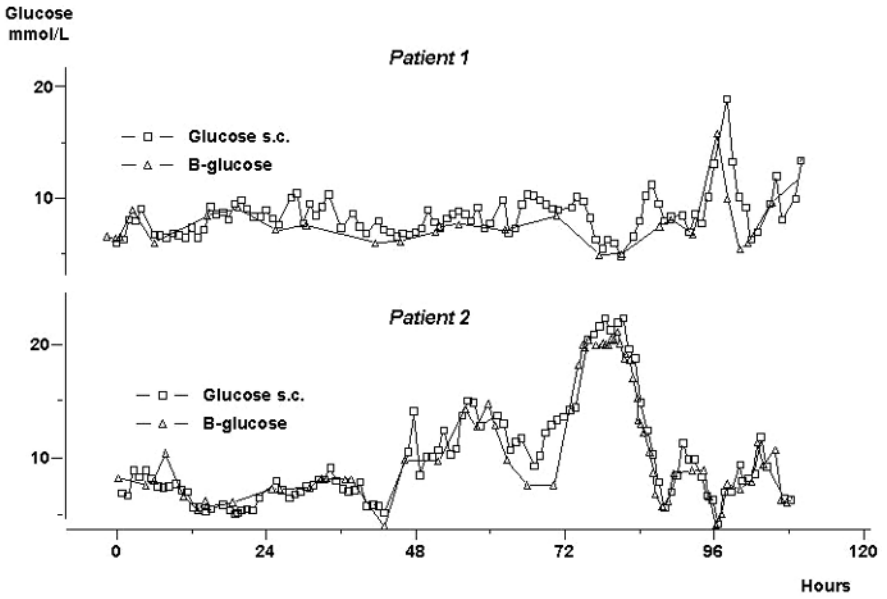


Fig. 5. Comparison of glucose level in subcutaneous fat tissue as measured by microdialysis and the simultaneous blood glucose levels in two patients during intensive care after severe traumatic brain injury [23]

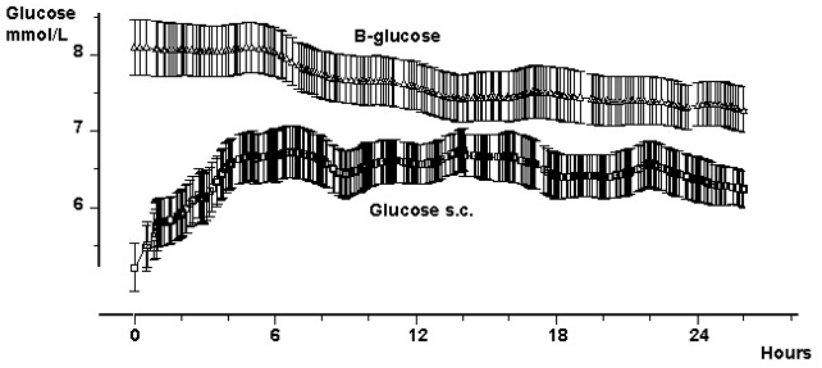


Fig. 6. Average glucose concentration (mean value ± SEM) in blood (B-glucose) and interstitial fluid of subcutaneous adipose tissue (glucose s.c.) in 62 patients during the first 24 h after start of pharmacological treatment to counteract stress reaction and increased intracranial pressure [23]

Myocutaneous microdialysis

Myocutaneous flaps have been increasingly used in reconstructive surgery. Despite technical advances and improved surgical skills, 1–10% of the free flaps are lost, commonly due to postoperative thrombosis of the vascular pedicle. Röjdmark et al. [27] used microdialysis to study the biochemical changes induced during flap transfer. They defined the biochemical changes observed during ischaemia and suggested that the technique might be useful for postoperative flap surveillance. They also conducted a post-operative study of ten women previously treated for breast cancer who underwent reconstruction with transverse rectus abdominis or latissimus dorsi flaps [28]. The postoperative biochemical changes were monitored for 24 h, and the authors concluded that the microdialysis technique seemed to be well-suited for continuous monitoring of tissue metabolism in myocutaneous flaps of different origin.

Recently, a microdialysis study demonstrated the changes of glucose, lactate, and pyruvate in an experimental model of microvascular flap during ischaemia and reperfusion [29]. The authors concluded that decreasing glucose levels and increasing lactate concentrations were associated with arterial and venous occlusions from the first hour of ischaemia. In venous ischaemia, lactate concentrations remained lower than those in arterial ischaemia. The increases in the la/py and lactate/glucose ratios were related to ischaemia and also discriminated arterial occlusion from venous occlusion.

Microdialysis of the liver

After liver transplantation some degree of clinical and biochemical dysfunction invariably occurs. Early detection of vascular complications, such as arterial and portal vein thrombosis, are especially important in the early transplantation period. In an experimental study in the pig, Nowak et al. [30] used intrahepatic microdialysis to study the levels of glucose, pyruvate, lactate, and glycerol before surgery, during cold storage of the liver, and during implantation and recirculation. After cold perfusion, glucose, lactate, and glycerol levels increased whereas pyruvate rapidly decreased. During cold storage, glucose and glycerol levels increased, lactate remained stable, and pyruvate levels were undetectable. After portal reperfusion glucose, lactate, and glycerol continued to increase for about 60 min, thereafter they slowly normalised. The calculated la/py ratio initially increased but remained stable during cold storage. During rewarming, it showed and accelerated increase but after reperfusion the la/py ratio rapidly normalised.

Knowledge of these metabolic patterns during experimental conditions was used to interpret changes observed in ten consecutive patients undergoing whole-organ orthopic liver transplantation [31]. The authors concluded that the microdialysis procedure was easy to perform and safe, and described the metabolic profiles reflecting recovery of the liver graft from ischaemia-reperfusion injury.

Intraperitoneal microdialysis

The intestinal tract and the intra-peritoneal cavity are of considerable interest during intensive care, and a suitable monitoring technique would be valuable not only for diagnosis of disorders of the visceral organs but also for post-surgical surveillance. Also, during shock and multi-organ failure, splanchnic ischaemia is as a major contributing component. Microdialysis of the intestinal wall has been performed in many experimental studies. Most of these experiences were recently reviewed and the data extended in a doctoral thesis [32]. However, microdialysis of the intestinal wall would probably be difficult to perform during clinical conditions.

Based on experimental studies, intraperitoneal microdialysis (IPM) was recently suggested as a possible clinical method [33]. In a pig model, intestinal ischaemia was induced either by occlusion of the superior mesenteric artery or occlusion of arcus vessels supplying a 30-cm-long small bowel segment. The authors concluded that IPM might be a good monitoring technique for the early detection of intestinal ischaemia also under clinical conditions.

The IPM technique was subsequently introduced for biochemical monitoring after major abdominal surgery and the results were presented in a series of publications [34–37]. Although the number of studied patients is still limited and the data must be regarded as preliminary, IPM seems to have the possibility of becoming an important technique for clinical routine monitoring and further clinical scientific investigations.

Intracerebral microdialysis

The majority of clinical studies involving microdialysis have been done in the brain. As mentioned above, the biochemical variables used during routine monitoring were chosen to cover important aspects of cerebral energy metabolism (glucose, pyruvate, lactate), to indicate excessive interstitial levels of excitatory transmitter substance (glutamate), and to give indications of degradation of cellular membranes (glycerol). Most of the basic principles regarding cerebral energy have been known since decades [38]. However, it might be useful to review how the levels of these measured biochemical variables vary during experimental, transient cerebral ischaemia when the microdialysis technique is used for sampling.

Figure 7A shows changes in the intracerebral levels of glucose and lactate as well as the la/py ratio after induction of cerebral ischaemia. In Fig. 7B, changes in the la/py ratio are compared to simultaneous changes in the levels of glutamate and glycerol. In this experimental study, transient brain ischaemia was induced in foetal lambs in utero by occlusion of the umbilical cord followed by resuscitation after cardiac standstill (data from Amer-Wåhlin et al.). The microdialysis technique was identical to that used during clinical conditions but the perfusion rate was increased (1.0 ml/min) to allow frequent sampling (which explains the basal levels of the biochemical variables). Induction of ischaemia caused an almost instanta-

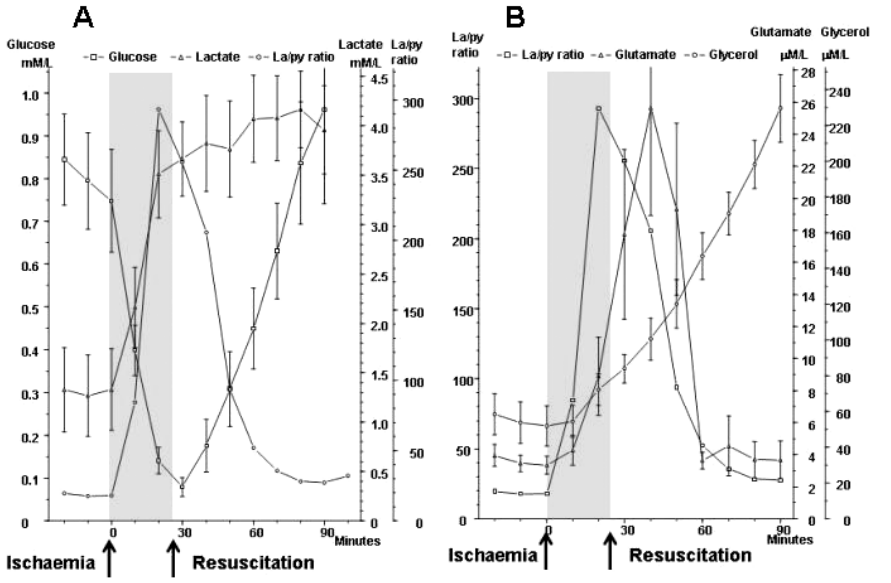


Fig. 7A, B. Changes in intracerebral biochemistry during transient global cerebral ischaemia. **A** Glucose and lactate levels (mean ± SD), and the lactate/pyruvate (*la/py*) ratio. **B** The la/py ratio, as well as the levels of glutamate and glycerol (mean ± SD) are shown

neous increase in the la/py ratio, followed shortly afterwards by an increase of the glutamate level. Glucose, pyruvate, and glutamate rapidly recovered after resuscitation but the levels of lactate and glycerol continued to be elevated.

These data are of importance for the interpretation of our clinical findings. The la/py ratio, reflecting the redox state of the cytoplasm, will increase immediately when delivery of oxygen is insufficient and will rapidly return to close to normal upon re-oxygenation. The lactate level rapidly increases during ischaemia but remains elevated when circulation is restituted. Glycerol, the indicator of degradation of cellular membranes, increases relatively slowly during energy failure and remains elevated for some time when energy metabolism is normalised. The interstitial glucose level, finally, reflects the balance between delivery from the blood capillaries and cellular uptake.

It is important to realise that the microdialysis technique gives biochemical information only concerning a small volume surrounding the catheter. However, the regional differences in blood flow and energy metabolism are considerable in most pathophysiological conditions. The fact that microdialysis is a regional technique may thus be regarded as an advantage, provided the positioning of the catheters can be visualised in relation to the focal injuries. Since the CMA/70 catheter has a thin gold thread placed in the tip of the probe, it may be visualised on routine CT scanning (see Fig. 3). This gold thread does not interfere with MR

scanning (but the perfusion pumps must naturally be disconnected and removed during scanning).

It has been possible to identify the metabolic pattern in various parts of the injured brain by inserting multiple intracerebral microdialysis catheters in patients with severe traumatic brain lesions (Fig. 8). The studies have shown that 'bioche-

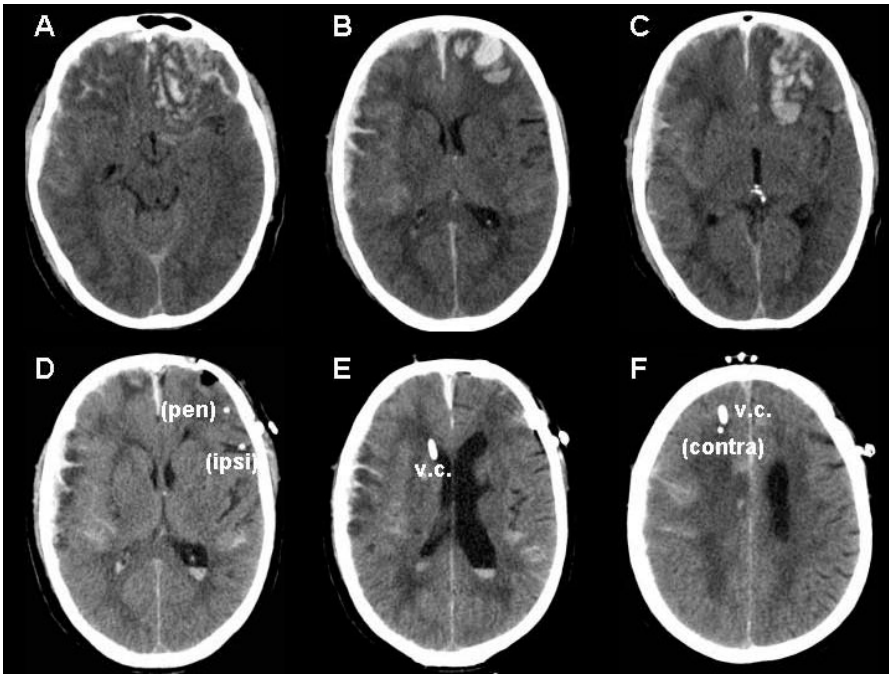


Fig. 8A–F. CT-scanning before (**A–C**) and after (**D–F**) surgical evacuation of a left frontal cerebral contusion. A ventricular catheter (*v.c.*) is positioned in the right frontal horn. One microdialysis catheter is placed in the penumbra zone (*pen*) and one catheter is placed ipsilateral to the evacuated contusion but outside the penumbra zone (*ipsi*). A third microdialysis catheter is positioned in the contralateral, less-damaged hemisphere (*contra*)

mical penumbra zones' surround focal brain lesions and that most adverse secondary events primarily affect these sensitive zones (Fig. 9) [39, 40]. These observations have direct clinical implications. By performing intracerebral microdialysis with bedside biochemical analysis, it will be possible to detect adverse events and to treat them before they have caused cellular degradation or deterioration detected by general physiological variables.

Intracerebral microdialysis has also been used to determine the optimal level of cerebral perfusion pressure (CPP) for the individual patient [41, 42]. This level is of particular importance in patients with an increased intracranial pressure (ICP)

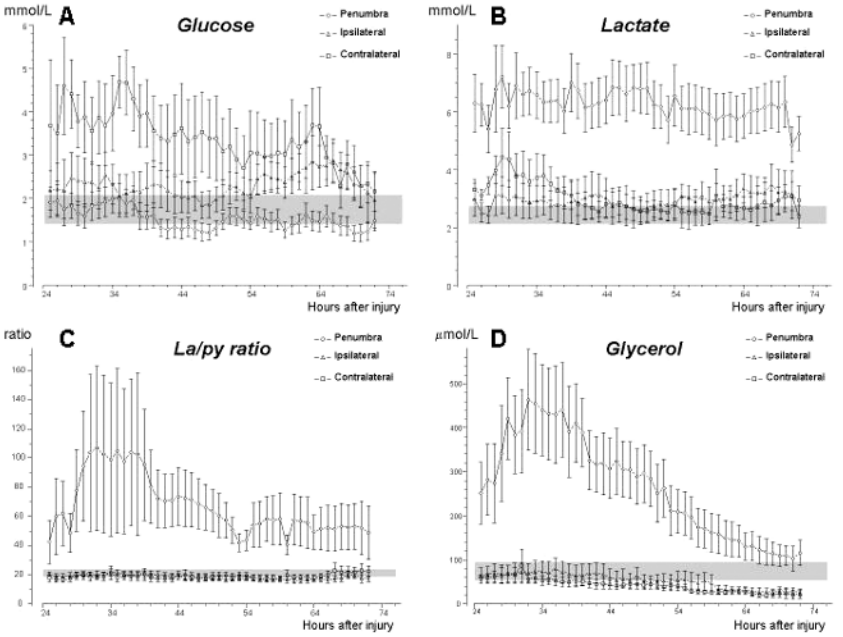


Fig. 9. Intracerebral levels (mean ± S.E.M.) for glucose (**A**), lactate (**B**), la/py ratio (**C**), and glycerol (**D**) levels 24–72 h after injury in the penumbra zone surrounding an evacuated focal brain contusion as well as in ipsilateral and contralateral tissue (see Fig. 8). The level in normal human brain (mean ± S.D.) is marked by the grey fields. (Data from [40])

due to brain oedema (Fig. 10). In these patients, an increase in CPP (and intracapillary hydrostatic pressure) will cause a net transport of water into the brain interstitium and a further increase in ICP [26, 42, 43].

Other aspects of clinical microdialysis and the possibilities of clinical research

As illustrated in Fig. 4, microdialysis has been used in various human tissues. Most frequently, energy metabolism has been monitored as part of clinical routine. However, microdialysis is an open technique permitting sampling of most stable biochemical compounds provided they pass the dialysis membrane. The technique may also be used for delivering substances to the interstitial fluid from the perfusate. For routine purposes, catheters with a membrane cut-off of 20 kDa are used but 100-kDa catheters are available for clinical purposes, which allows the study also of larger molecules (e.g. cytokines). When these catheters are used, some technical precautions, such as addition of colloids to the perfusate, must be taken to avoid interstitial loss of the perusing fluid [6, 44].

The use of the microdialysis technique may sometimes result in quite unex-

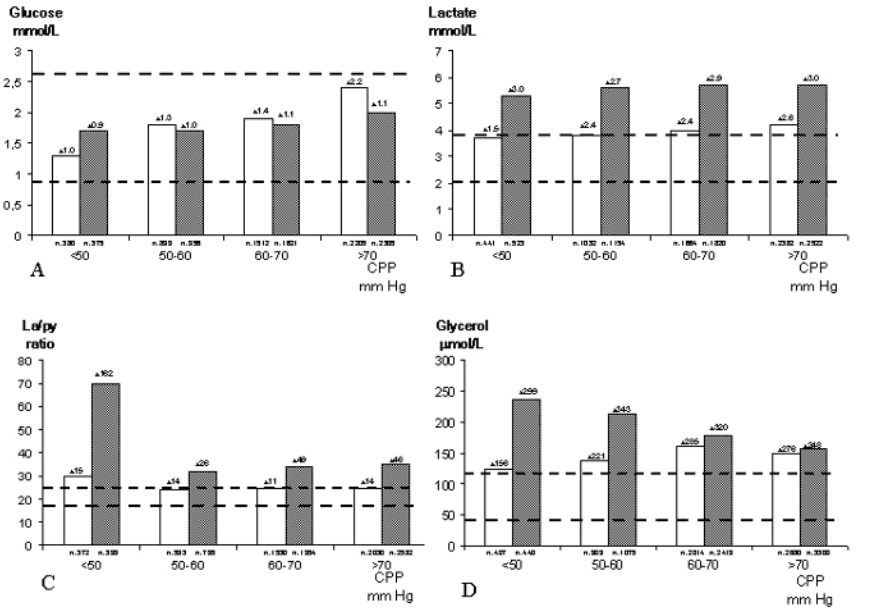


Fig. 10. Mean levels ± S.D. for glucose (**A**), lactate (**B**), la/py ratio (**C**), and glycerol (**D**) in the penumbra zone (*grey bars*) and in the contralateral hemisphere (*open bars*) in relation to four ranges of cerebral perfusion pressure (*CPP*) in 50 patients with severe traumatic brain lesions [41, 42]. The *interrupted lines* indicate the range (mean ± S.D.) in normal human brain during wakefulness. (From [10])

pected clinical discoveries, as illustrated by a study of patients with chronic Achilles tendinosis [45]. In this study, the authors found high levels of glutamate but no sign of inflammation and no increase in prostaglandin E2 in patients with chronic Achilles tendon pain. Surprisingly, a subsequent study showed that eccentric training relieved the pain but did not decrease the glutamate level in the tendon [46].

The microdialysis technique has great potential for clinical scientific studies. This fact is illustrated by the possibilities of measuring the interstitial concentrations of various drugs and even performing quantitative pharmacokinetic studies. The brain may seem to be the most difficult tissue for such investigations, but due to the BBB and the large functional differences in different regions, perhaps also the most challenging target. Two recent publications have shown that such pharmacokinetic studies are possible to accomplish [8, 9].

Conclusions

This presentation has provided a short review of clinical microdialysis and of some of the experimental studies of particular clinical relevance. Since the microdialysis

literature is vast, the selection of references has been quite personal. Microdialysis is now being introduced as a clinical technique in many centres; thus, it is important to recognise its prerequisites and limitations and to take advantage of the fact that it is a regional technique. The experiences reported thus far indicate that it will continue to be a powerful technique for experimental and clinical scientific studies and that it will be incorporated into multi-modality monitoring during qualified intensive care.

References

1. Ungerstedt U, Pycock CH (1974) Functional correlates of dopamine neurotransmission. Bull Schweiz Akad Med Wiss 1278:1–5
2. Ungerstedt U (1991) Microdialysis – principles and application for studies in animal and man. J Intern Med 230:365–373
3. Meyerson BA, Linderoth B, Karlsson H et al (1990) Extracellular measurements in the thalamus of parkinsonian patients. Life Sci 46:301–308
4. Ungerstedt U, Herrera-Marschitz M, Jungnelius U et al (1982) Dopamine synaptic mechanisms reflected in studies combining behavioural recordings and brain dialysis. In: Kotisaka M et al (eds) Advances in dopamine research. Pergamon Press, New York, pp 219–231
5. Ungerstedt U (1984) Measurement of neurotransmitter release by intracranial dialysis. In: Marsden CA (ed) Measurement of neurotransmitter release in vivo. Wiley and Sons, New York, pp 8–107
6. Hillman J, Åneman O, Andersson C et al (2005) A microdialysis technique for routine measurement of macromolecules in the injured human brain. Neurosurgery 56:1264–1270
7. Hutchinson PJ, O'Connell MT, Al-Rawi PG et al (2000) Clinical cerebral microdialysis: a methodological study. J Neurosurg 93:37–43
8. Tunblad K, Ederoth P, Gärdenfors A et al (2004) Altered blood-brain barrier transport of morphine in experimental meningitis studied with microdialysis. Acta Anaesthesiol Scand 48:294–301
9. Ederoth P, Tunblad K, Bouw R et al (2004) Blood-brain barrier transport of morphine in patients with severe brain trauma. Br J Clin Pharmacol 57:427–435
10. Reinstrup P, Ståhl N, Hallström Å et al (2000) Intracerebral microdialysis in clinical practice. Normal values and variations during anaesthesia and neurosurgical operations. Neurosurgery. 47:701–710
11. Gärdenfors A, Nilsson F, Skagerberg G et al (2002) Cerebral physiological and biochemical changes during vasogenic brain edema induced by intrathecal injection of bacterial lipopolysaccharides in piglets. Acta Neurochir 144:601–608
12. Ungerstedt U, Bäckström T, Hallström Å et al (1997) Microdialysis in normal and injured human brain. In: Kinney JM, Tucker HN (eds) Physiology stress and malnutrition. Functional correlates, nutritional intervention. Lippincott – Raven, Philadelphia, pp 361–374
13. Hillered L, Valtysson J, Enblad P et al (1998) Interstitial glycerol as a marker for membrane phospholipid degradation in the acutely injured human brain. J Neurol Neurosurg Psychiatry 64:486–491
14. Hagström-Toft E, Arner P, Wahrenberg H et al (1993) Adrenergic regulation of human

tissue metabolism in situ during mental stress. Endocrinol Metab 76:392–398
15. Blasberg RG, Fenstermacher JD, Patlack CS (1983) Transport of α-aminobutyric acid across brain capillary and cellular membranes. J Cereb Blood Flow Metab 3:8–12
16. Hamberger A, Nyström B (1984) Extra- and intracellular amino acids in the hippocampus during development of hepatic encephalopathy. Neurochem Res 9:1181–1192
17. Benveniste H, Drejer J, Shousboe A et al (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43:1369–1374
18. Benveniste H, Diemer NH (1987) Cellular reactions to implantation of a microdialysis tube in the rat hippocampus. Acta Neuropathol (Berl) 74:234–238
19. Bolinder J, Ungerstedt U, Arner P (1993) Long-term continuous glucose monitoring with microdialysis in ambulatory insulin-dependent diabetic patients. Lancet 342:1080–1085
20. Bolinder J, Hagstrom-Toft E, Ungerstedt U et al (1997) Self-monitoring of blood glucose in type I diabetic patients: comparison with continuous microdialysis measurements of glucose in subcutaneous adipose tissue during ordinary life conditions. Diabetes Care 20:64–70
21. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359–1367
22. Van den Berghe G, Wouters PJ, Bouillon R (2003) Outcome benefit of intensive insulin therapy in critically ill: insulin dose versus glycemic control. Crit Care Med 31:359–366
23. Lourido J, Ederoth P, Sundvall N et al (2002) Correlation between blood glucose concentration and glucose level in subcutaneous adipose tissue evaluated with microdialysis during neuro intensive care. Scand J Clin Lab Invest 62: 285–292
24. Rosdahl H, Hamrin K, Ungerstedt U et al (1998) Metabolite levels in human skeletal muscle and adipose tissue studied with microdialysis at low perfusion flow. Am J Physiol 274:E936-E945
25. Moberg E, Hagstrom-Toft E, Arner P (1997) Protracted glucose fall in subcutaneous adipose tissue and skeletal muscle compared with blood during insulin-induced hypoglycaemia. Diabetologia 40:1320–1326
26. Grände PO, Asgeirsson B, Nordström CH (2002) Volume targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments. Acta Anaesthesiol Scand 46:929–941
27. Röjdmark J, Hedén P, Ungerstedt U (1998) Microdialysis – a new technique for free flap surveillance: methodological description. Eur J Plast Surg 21:344–348
28. Röjdmark J, Blomqvist L, Malm M et al (1998) Metabolism in myocutaneous flaps studied by in situ microdialysis. Scan J Plast Reconstr Hand Surg 32:27–34
29. Setälä LP, Korvenoja EMJ, Härmä MA et al (2004) Glucose, lactate, and pyruvate response in an experimental model of microvascular flap ischemia and reperfusion: a microdialysis study. Microsurgery 24:223–231
30. Nowak G, Ungerstedt J, Wernerman J et al (2002) Metabolic changes in the liver graft monitored continuously with microdialysis during liver transplantation in a pig model. Liver Transpl 8:424–432
31. Nowak G, Ungerstedt J, Wernerman J et al (2002) Clinical experiences in continuous graft monitoring with microdialysis early after liver transplantation. Br J Surg 89:1169–1175
32. Sommer T (2004) Microdialysis in the assessment of regional intestinal ischemia. Doctoral thesis. Center of Sensory-motor Interaction, Aalborg University, Denmark
33. Ungerstedt J, Nowak G, Ericzon BG et al (2003) Intraperitoneal microdialysis (IPM): a

new technique for monitoring intestinal ischemia studied in a porcine model. Shock 20:91–96
34. Jansson K, Ungerstedt J, Jonsson T et al (2003) Human intraperitoneal microdialysis: increased lactate/pyruvate ratio suggests early visceral ischemia. A pilot study. Scand J Gastroenterol 38:1007–1011
35. Jansson K, Redler B, Truedsson L et al (2004) Intraperitoneal cytokine response after major surgery: higher postoperative intraperitoneal versus systemic cytkine levels suggest the gastrointestinal tract as a major source of the postoperative inflammatory reaction. Am J Surg 187:373–377
36. Jansson K, Redler B, Truedsson L et al (2004) Postoperative on-line monitoring with Intraperitoneal Microdialysis (IPM) is a sensitive clinical method for measuring increased anaerobic metabolism that correlates to cytokine response. Scand J Gastroenterol 39:434–439
37. Jansson K, Strand I, Redler B et al (2004) Results of intraperitoneal microdialysis depend on the location of the catheter. Scand J Clin Lab Invest 64:63–70
38. Siesjö BK (1978) Brain energy metabolism. John Wiley & Sons, Chichester New York Brisbane Toronto
39. Ståhl N, Schalén W, Ungerstedt U et al (2003) Bedside biochemical monitoring of the penumbra zone surrounding an evacuated acute subdural haematoma. Acta Neurol Scand 108:211–215
40. Engström M, Polito A, Reinstrup P et al (2005) Intracerebral microdialysis in clinical routine – the importance of catheter location. J Neurosurg 102:460–469
41. Nordström CH, Reinstrup P, Xu W et al (2003) Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. Anesthesiology 98:809–814
42. Nordström CH (2003) Assessment of critical thresholds for cerebral perfusion pressure by bedside monitoring of regional energy metabolism. Neurosurg Focus 15 (6); Article 5
43. Nordström CH (2005) Treatment of increased intracranial pressure: Physiological and biochemical principles underlying volume targeted therapy – the 'Lund concept.' Neurocritical Care 2:83–96
44. Rosdahl H, Hamrin K, Ungerstedt U et al (2000) A microdialysis method for the in situ investigation of the action of large peptide molecules in human skeletal muscle: detection of local metabolic effects of insulin. Int J Biol Macromol 28:69–73
45. Alfredson H, Thorsen K, Lorentzon R (1999) In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain. Knee Surg Sports Traumatol Arthrosc 7:378–381
46. Alfredsson H, Lorentzon R (2003) Intratendinous glutamate levels and eccentric training in chronic Achilles tendinosis: a prospective study using microdialysis technique. Knee Surg Sports Traumatol Arthrosc 11:196–199

Chapter 6

Sidestream dark-field imaging and image analysis of oral microcirculation under clinical conditions

D.M.J. Milstein, J.A.H. Lindeboom, C. Ince

Tissue dysoxia and microcirculatory dysfunction are generally regarded as the primary culprits of organ failure and inadequate wound healing in critically ill patients [1, 2]. Tissue oxygenation is also important for organ function as well as wound healing following trauma or surgery. Proper wound healing and the maintenance of the microcirculation are essential and constitute the ultimate goal of critical care and intensive care medicine. The capillaries in the tissue microcirculation collectively are the final destination in the circulatory trajectory of oxygen transport, in which erythrocytes off-load their oxygen (O_2) to parenchymal cells of the target site. A shift in oxygen supply and tissue oxygen demand must be corrected in order to prevent irreversible organ damage and proper wound healing. An interesting approach in further understanding tissue dysoxia and the proper choice of treatment in critically ill patients is to measure the oxygenation states of the microcirculation and tissue in vivo. This can directly provide useful information by assessing whether the organ in question and related compartments are functioning adequately in meeting the oxygen supply and demand quota in disease and/or the postoperative recovery states of wound healing. Since systemic haemodynamic variables do not provide adequate information about the functional condition of either the microcirculation or the availability of oxygen in the microcirculation and tissue, direct measurements are needed.

The oral and maxillofacial compartments are highly vascularised areas and offer a very approachable site for noninvasively monitoring and assessing the microcirculation and wound healing properties. The biologic advantage in monitoring wound healing and the microcirculation in the buccal area is that it is a place where wounds heal relatively rapidly and the progress of the natural healing process can be monitored noninvasively in its own natural environment. Sublingual measurements using orthogonal polarisation spectral (OPS) imaging have already yielded insightful information on sepsis, its reaction to therapy, and its prognosis [2–6]. New optical techniques have been recently introduced that have, for the first time, allowed detection of microcirculatory properties and determinants of microcirculatory function in internal human organs [7]. These techniques have been applied to the oral cavity because of their relevance to the oral circulation, its approachability, as well as its specific importance, for example in oral disease and therapy [8]. Although these technologies are discussed here in the context of the microcirculation of the buccal cavity, they have been applied to the microcir-

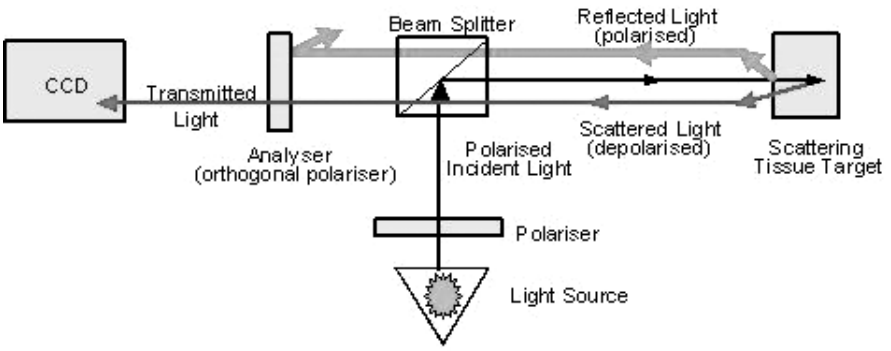
culation in other organ systems [9–11]. In this review, we present an improved method, called sidestream dark-field imaging, to observe the oral microcirculation and a new method for the analysis of the functional morphology of the microcirculation. These methods are applicable to various microcirculatory beds of patients and have the potential to be implemented in software designed for use in bedside quantification.

Sidestream dark-field imaging: an improved method for imaging the oral microcirculation

A well-functioning microcirculation is essential for wound healing following maxillofacial surgery. The rich vasculature of the oral mucosa has made it possible to challenge the thresholds of vascular regeneration and thereby monitor wound healing in oral tissue [12]. Surgical intervention compromises the integrity of the microcirculation and its oxygen distribution by induction of trauma to the immediate mucosal vasculature. This, in turn, can induce hypoxia in tissues surrounding the operative area. Investigating the microcirculation in patients has been difficult in the past simply due to the unavailability of suitable technology. The intravital microscope used in animal experimentation has only been employed in humans in limited locations, such as the skin, lip, and the bulbar conjunctiva [13].

Recently, intravital microscopy has been miniaturised and developed for clinical conditions by the implementation of OPS imaging in a hand-held microscope type device. OPS imaging is a relatively new technology that provides information on the kinetics and architecture of the microcirculation without the need to trans-illuminate. OPS imaging uses 550 ± 70 nm (green) polarised light, which is guided through a series of lenses (Fig. 1A). The green light is absorbed by haemoglobin (Hb) in the erythrocytes, which can then be seen as dark moving structures in the image. Polarisation is maintained when light is reflected from the tissue surface and is filtered by an orthogonally placed polariser situated in front of a video camera. The scattered light inside the tissue loses its polarisation and can then pass through the crossed polariser, allowing observation of flowing erythrocytes in the underlying microcirculation (Fig. 1A) [14]. OPS imaging has been validated against other techniques, such as capillary microscopy and intravital fluorescent microscopy, for its relevance and use in clinical monitoring [15, 16]. A newer and more improved monitoring device in terms of technology and image quality for clinical observation of the microcirculation at the bedside has lately been developed. This technology is known as sidestream dark-field (SDF) imaging [7, 17].

SDF imaging offers better resolution and clarity than its predecessor the OPS imaging device, and the same ease of noninvasive, in vivo, real-time imaging of the microcirculation (Fig. 2). In this method, light-emitting diodes (LEDs) are placed at the tip of a light guide that emits a 540 ± 50 nm (green) light, which is absorbed by Hb in erythrocytes, which in turn appear as clear dark bodies moving through the microcirculation. Unlike the light source of the OPS device, which comes from



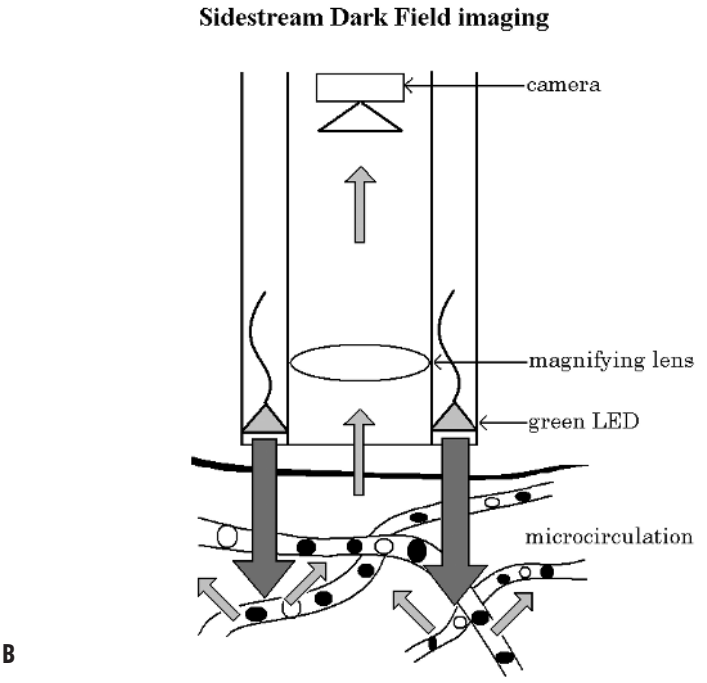


Fig. 1A, B. Orthogonal polarisation spectral (OPS) and sidestream dark-field (SDF) imaging technologies. **A** OPS imaging technology eliminates directly reflected green (550 ± 70 nm) polarised light from tissues surface via an orthogonally placed analyser, thus allowing visualisation of structures below the surface. This consequently results in clear imaging of erythrocytes, shown as dark bodies flowing through the microcirculation. **B** In SDF imaging, green (540 ± 50 nm) light is emitted from light-emitting diodes (LEDs) arranged in a ring around the tip of the light guide and directly illuminating the tissue microcirculation, which is optically isolated from the imaging central core of the light guide. Both techniques implement a light wavelength (green; 540–550 nm) that is absorbed by haemoglobin (Hb) in erythrocytes

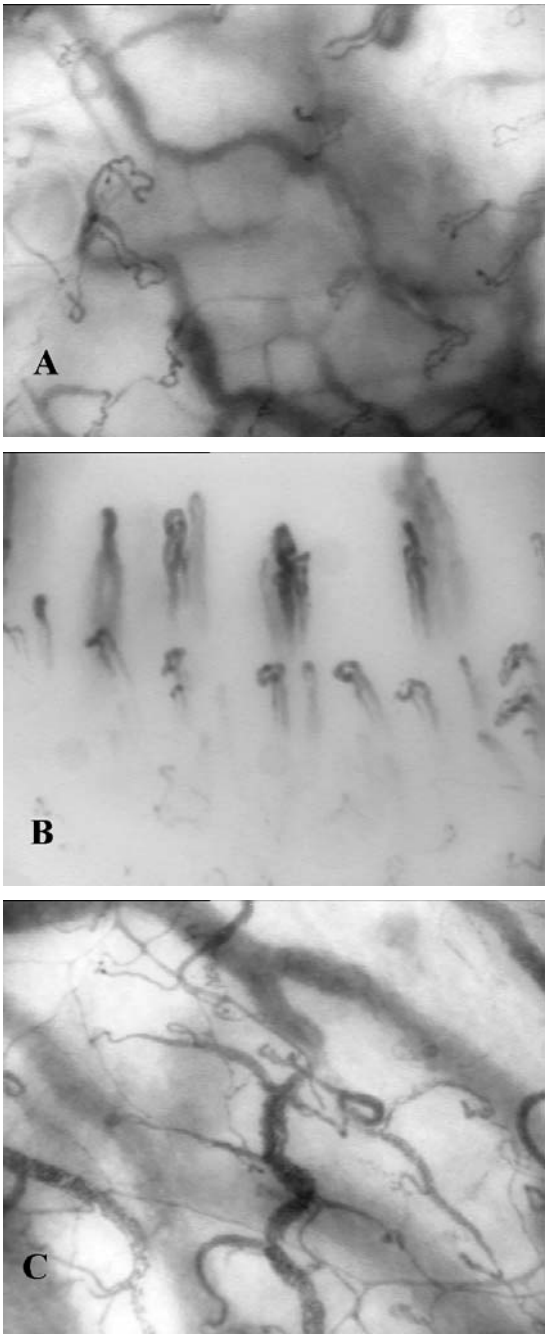


Fig. 2A–C. SDF imaging of the oral microcirculation in a healthy volunteer, **A** labial mucosa, **B** gingiva, **C** sublingual mucosa

inside the probe itself, the SDF device has the LEDs arranged in a ring around the tip of the probe, whereby the illuminating light source is optically isolated from the emission light path in the core of the light guide (Fig. 1B). In this way, the light penetrates deeper into the tissue illuminating the microcirculation from the interior, and the dark-field illumination thus entirely avoids reflections coming from the tissue surface (Fig. 1B). SDF imaging yields a clear image of the microcirculatory components. Erythrocytes and leukocytes flowing in the microvasculature can be observed with higher resolution and deeper monitoring capabilities [5]. Of note, there is no orthogonally placed polariser in this device and further image improvement is achieved by synchronising LED illumination with the video frame rate.

Quantification of the functional morphology of microcirculation

The greatest challenge in assessing imaging footage from OPS and SDF devices has been the setting-up of a standardised systematic approach for analysis of microcirculatory images that allows identification and quantification of microcirculatory abnormalities during critical illness and wound healing. Obstacles that need to be taken into consideration and overcome are movements, resolution, camera, and sample thicknesses of the tissues being monitored. OPS movies have been analysed and quantified by semi-quantitative and semi-automated methods. These have proven to be both practical and highly sensitive in identifying microcirculatory abnormalities in sepsis [2–4].

Currently, OPS and SDF imaging is used on tissues for which no automated analytical software package is available. This presents a problem when trying to analyse and interpret results acquired from the microcirculation. In order to use these devices and yield quantifiable information from the microcirculation of different anatomical tissues, a more flexible and universal methodology is needed to consecutively analyse a variety of microvascular structures independent of their vascular anatomy. We have developed a general consensus with six centres involved in microcirculation research in intensive care regarding the procedure for analysis of OPS and SDF imaging data from patients. The consensus is based on a semi-quantitative method in which the data from these techniques are analysed as follows. First, all video data of the microcirculation should be digitally recorded. In capturing and recording imaging video data, three areas pertaining to the tissue of interest should be selected (left, centre, right) and each area should be recorded for a duration of 2–5 min. Then, once all the video-clip data has been recorded, a selection of the most stable clips with the clearest images should be selected for analysis. It is best to capture at least three clips of 5–10 s for each filmed area. Thus, there should be a total of nine clips (three clips of each area) of 5–10 s.

Heterogeneous blood flow with capillary dysfunction is associated with microvascular alterations during sepsis [18, 19]. In analysing OPS and/or SDF images, our consensus requires images from three different regions of interest of the tissue to be selected, after which each image is then divided into four equal quadrants (I, II, III, IV) for analysis (Fig. 3A). The flow analysis consensus uses a semi-quantitative

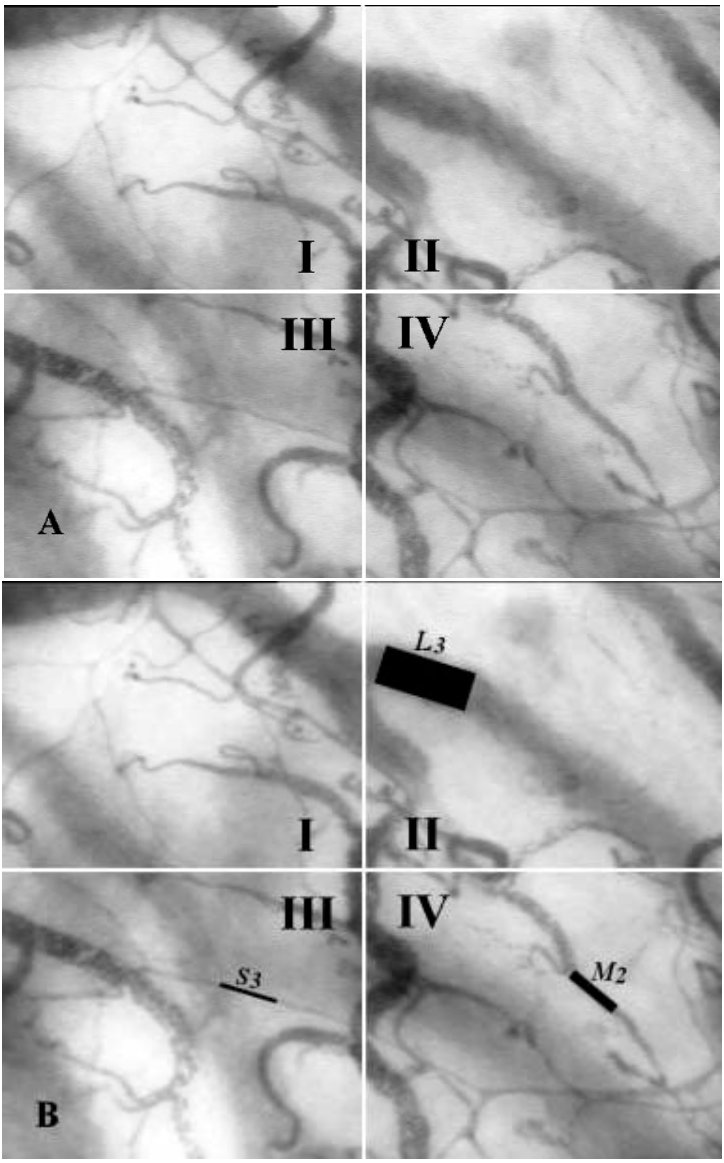


Fig. 3A, B. Semi-quantitative analysis consensus of SDF imaging data. **A** The sample image is divided into four quadrants (*I, II, III, IV*). **B** Analysis of the sample by quantification of the blood vessel diameter, scored as small (*S;* 10–25μm), medium (*M;* 26–50μm), or large (*L;* 51–100μm). Additional quantification of flow properties are scored as no flow (*0*), intermittent flow (*1*), sluggish flow (*2*), and continuous flow (*3*). During actual analysis, as many blood vessels as possible should be counted. Here, three different blood vessels have been selected for explanatory purposes in order to illustrate the semi-quantitative consensus for quantification of microvascular structures

analytical technique consisting of judging microvascular flow characteristics, discriminating between no flow (0), intermittent flow (1), sluggish flow (2), and continuous flow (3). A fifth category, representing hyperdynamic flow properties, could be defined, although currently this is not included in our analysis consensus. Further analytical quantifications consistent with the consensus for flow analysis involve categorising individual blood vessels in each quadrant based on their diameter. The diameter in this case is semi-quantitatively defined by a dimensional constraint, S, M, and L, representing small (10–25 μm), medium (26–50 μm), and large (51–100 μm) vessels, respectively (Fig. 3B). After quantification of vessel diameter and flow, an average score of the total flow is calculated for each group of vessels in each quadrant. This average score is called the microvascular flow index (MFI) for the group of vessels and it is the sum of each quadrant vessel score divided by the number of quadrants in which the vessel type is visible. Thus, in analysing vascular density, the number of each vessel type (small, medium, and/or large) is counted in each quadrant, and an average of each vessel type is calculated for each quadrant. It is recommended, however, due to time and practical considerations, to loop the imaging video clips, and, in case there are different types of flow in one quadrant, average the flow (e.g. for 2 small vessels normal and 5 small vessels moderate, the average would be moderate flow for that quadrant). If software is available to measure the lengths of each segment, then the vascular density is expressed as the length of specific vessels in micrometers (μm) per area (μm^2) of observation.

Analysis software for microcirculation images

We are currently developing software to analyse SDF imaging data. The software is designed to identify microvessel contour in vascular images in an automated fashion. This process is known as skeletonisation or segmentation (Fig. 4A) and is essential for automated recognition of the microcirculation. This procedure has become feasible due to the improved image quality introduced by SDF technology. Once segmentation has been achieved, the software can determine length, width, and blood velocity of individual vessel segments. Velocity is determined semi-automatically after constructing space–time diagrams from the centre-line intensity of vessels in subsequent video frames [20]. Space–time diagrams portray erythrocyte dynamics by plotting the movement of each individual erythrocyte along a segment of a selected blood vessel as a function of time. From the slope of the resulting diagonal lines, erythrocyte velocity is calculated. Such an analysis creates a distinct static image in which erythrocytes appear as dark diagonal bands separated by light bands representing plasma gaps (Fig. 4B). Space–time diagrams provide information relating to erythrocyte velocity, lineal density, and the supply rate [20]. Finally, the software creates a detailed statistical fingerprint of the video sequence containing vascular flow parameters. The software under development is unique because it allows the inclusion of vasculature parameters that were previously not possible and integrates them to create a profile of the microcirculation. It is expected that this software package, in combination with improved image quality provided by

SDF technology, will greatly facilitate evaluation of microcirculatory function during sepsis and wound healing.

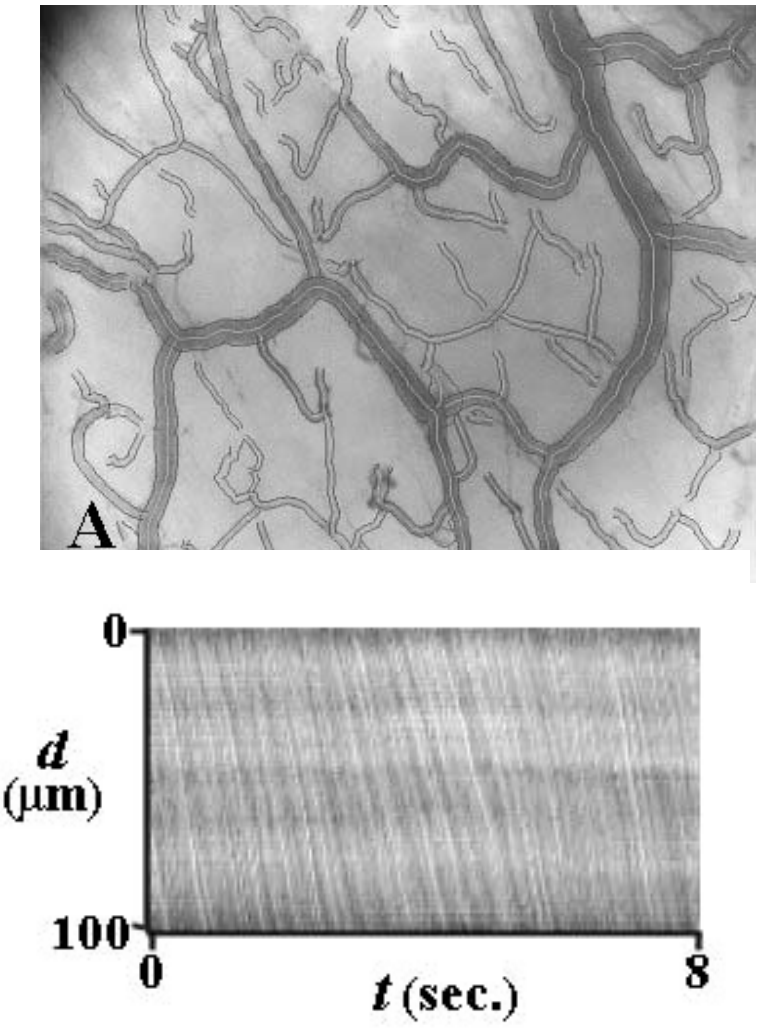


Fig. 4. Sample of the imaging processing software, currently under development, showing semi-automated vessel identification by way of segmentation (**A**). Intravascular erythrocyte dynamics are analysed using space–time diagrams (**B**), where *d* is the distance traveled (μm) within a capillary sample segment and *t* is time, that define the location of the erythrocyte within the selected segment

Conclusions

Tissue dysoxia and microcirculatory dysfunction are major contributors to the progression of organ failure and inadequate wound healing in critically ill patients. The oral and maxillofacial compartments are highly vascularised areas and offer a very approachable site and model for monitoring wound healing and the functional state of the microcirculation in patients. In this chapter, SDF imaging technology and its vascular analytical methods were introduced with regard to quantifying the microcirculation and its architecture. New optical technologies like SDF imaging will allow detailed observation and monitoring of the functional condition of the microcirculation and assessment of the availability of oxygen in the microcirculation and surrounding tissues.

References

1. Hunt TK, Ellison EC, Sen CK (2004) Oxygen: at the foundation of wound healing-introduction. World J Surg 28(3):291–293
2. Sakr Y, Dubois MJ, De Backer D et al (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32:1825–1831
3. De Backer D, Creteur J, Preiser JC et al (2002) Microvascular blood flow is altered inpatients with sepsis. Am J Respir Crit Care Med 166:98–104
4. Spronk PE, Ince C, Gardien MJ et al (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395–1396
5. Siegemund M, Van Bommel J, Ince C (1999) Assessment of regional tissue oxygenation. Intensive Care Med 25:1044–1060
6. De Backer D (2003) OPS techniques. Minerva Anesthesiol 69(5):388–391
7. Ince C (2005) The microcirculation is the motor of sepsis. Crit Care 9(suppl 4):S13-S19
8. Lindeboom JAH, Mathura KR, Ince C (2002) Orthogonal polarization spectral imaging in oral squamous cell carcinomas. AAOM 56:3a (abs)
9. Mathura KR, Bouma GJ, Ince C (2001) Abnormal microcirculation in brain tumors during surgery. Lancet 17:1698–1699
10. Pennings FA, Bouma GJ, Ince C (2004) Direct observation of the human cerebral microcirculation during aneurism surgery reveals increased arteriolar contractility. Stroke 35(6):1284–1288
11. Vollebregt KC, Boer K, Mathura KR et al (2001) Impaired vascular function in women with pre-eclampsia observed with orthogonal polarization spectral imaging. BJOG 108(11):1148–1153
12. Lindeboom JAH, Mathura KR, Ince C (2004) OPS imaging: a new in vivo technique to assess changes in microvascularization in gingival flaps. AO 16:15a (abs)
13. Bollinger A, Fagrell B (eds) (1990) Clinical capillaroscopy: a guide to its use in clinical research and practice. Hogrefe & Huber, Toronto
14. Groner W, Winkelman JW, Harris AG et al (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5(10):1209–1212
15. Mathura KR, Vollebregt KC, Boer K et al (2001) Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation. J Appl Physiol 91(1):74–78
16. Harris AG, Sinitsina I, Messmer K (2002) Validation of OPS imaging for microvascular

measurements during isovolumic hemodilution and low hematocrits. Am J Physiol Heart Circ Physiol 282(4):H1502-H1509
17. Ince C (2005) Sidestream dark-field (SDF) imaging: an improved technique to observe sublingual microcirculation. Crit Care 8(suppl 1):P72
18. Eerbeek O, Milstein DMJ, Ince C (2004) Microcirculatory dysfunction in Langendorff endotoxemic rat hearts. Shock 21:81
19. Ince C, Ashruf JF, Avontuur JA et al (1993) Heterogeneity of the hypoxic state in rat heart is determined at the capillary level. Am J Physiol 263:H294-H301
20. Ellis CG, Ellsworth ML, Pittman RN et al (1992) Application of image analysis for evaluation of red blood cell dynamics in capillaries. Microvasc Res 44(2):214–25

Chapter 7

Perfusion optimisation at the microcirculatory level

D. De Backer

The importance of perfusion optimisation in the early management of severe sepsis was recently highlighted by Rivers et al. [1]. However, microcirculatory alterations can frequently be observed in severe sepsis and shock states, in addition to global and regional haemodynamic alterations. The microcirculation is of particular importance as it is the place where most of the exchanges in oxygen and nutrients between the blood and the tissues occur. The microcirculation differs from the systemic circulation by many aspects. First, capillary PO_2 and haematocrit are much lower than arterial ones and may even behave differently. Second, the control of microvascular blood flow is complex and depends both on local metabolic control and on systemic humoral controls, but capillary perfusion is relatively independent from systemic blood flow and pressure. Thus, interventions affecting the general circulation may have different effects at the microcirculatory level, and may therefore fail to improve tissue perfusion. This review discusses the effects of several interventions on the microcirculation.

Techniques used to investigate the microcirculation

Intravital microscopy is the gold standard technique for studying the microcirculation and is still used in animal studies. This technique can unfortunately not be used in humans, as a large microscope needs to be applied on a fixed tissue preparation while fluorescent dyes are infused. Alternative methods have been used in humans, including phlethysmography, video microscopy of the nailfold area, and laser Doppler technique [2]. Unfortunately these approaches have several limitations that preclude their use in critically ill patients. For example, laser Doppler techniques have been frequently used in critically ill patients, as they have the advantage that they can be used to examine various tissues, including the upper digestive tract, through insertion of a nasogastric tube. Laser Doppler provides measurements of blood flow in relative units (mV); accordingly, only relative changes to baseline can be assessed. However, the major limitation of this technique is that it does not take into account the heterogeneity of microvascular blood flow, since the measured parameter represents the average of the velocities in all the vessels included in the investigated volume (~1 mm^3). Thus, blood flow measured by this technique will be influenced by arteriolar and venular blood flow more than by capillary blood flow. Phlethysmographic techniques have similar limita-

tions, the sampling volume being even larger. In addition, phlethysmography is influenced by microvascular and regional blood flow, and the relative contribution of both factors cannot be delineated. Nailfold videomicroscopy can detect blood flow heterogeneity but the nailfold area is unfortunately very sensitive to changes in temperature and peripheral vasoconstriction.

Orthogonal polarisation spectral (OPS) imaging and side-stream dark-field (SDF) imaging are recently-developed non-invasive techniques that allow direct visualisation of the microcirculation [3, 4]. Both techniques involve the use of a small camera and a few lenses. The devices are small and can easily be used at the bedside. High-contrast images of the microcirculation are formed by absorbing structures (e.g. red blood cells) close to the surface that are illuminated by the light reflected from deeper structures. Due to their specific characteristics, OPS and SDF can be used to visualise the microcirculation in tissues protected by a thin epithelial layer, such as the mucosal surface. In critically ill patients, the sublingual area is the most easily investigated mucosal surface. Other mucosal surfaces include rectal and vaginal surfaces which are of limited accessibility, and ileal or colic mucosa in patients with enterostomies. Images can also be generated in eyelids and in the nailfold [5].

The use of OPS imaging techniques to visualise the microcirculation has been validated against standard techniques. Vessel diameters, functional capillary density, and vessel blood flow were found to be similar with OPS imaging and standard intravital fluorescence videomicroscopy in various animal models [3, 6–8]. In human healthy volunteers, the agreement in the measurement of capillary density and red blood cell (RBC) velocity in the nailfold area was excellent between OPS imaging and capillaroscopy [5]. Unfortunately, a quantitative approach cannot actually be used for observations of the sublingual microcirculation in critically ill patients, due to small movements of the probe (especially respiratory movements). Accordingly, we developed a semi-quantitative method to determine capillary density and the proportion of perfused capillaries [9]. These techniques are particularly helpful to disclose capillary recruitment, but are not able to identify changes in velocities within vessels.

Evidence for alterations in microcirculatory blood flow in sepsis

Numerous experimental studies have observed a decrease in capillary density and the presence of stopped-flow capillaries in close vicinity of well-perfused capillaries (blood flow heterogeneity) [10–12]. Although these alterations can be observed in various conditions, including haemorrhagic shock [10], ischaemia/reperfusion injury [13], and sepsis [11, 12, 14–16], they are more severe in septic than in other insults [17, 18]. Animal studies have clearly shown that similar microvascular alterations can be observed in striated muscles [12, 19], small bowel mucosa [15], liver [20], pancreas [21], and skinfold [13]. The microcirculatory alterations clearly differ from macrocirculatory haemodynamic alterations of sepsis, with vasoconstriction in the microcirculation in opposition to the vasodilatory state with high cardiac output.

We used the OPS technique in the sublingual area of patients in circulatory

failure [9, 22] and observed that microcirculatory alterations are frequent in shock states. Fifty patients with severe sepsis (n = 8) and septic shock (n = 42) were investigated within 48 h of the onset of sepsis [9]. Compared to controls, septic patients presented a decrease in capillary density (vessels containing no RBCs cannot be visualised) and a decrease in the proportion of perfused capillaries. These alterations were more pronounced in nonsurvivors than in survivors. In a second cohort of 49 patients with septic shock, we daily investigated the sublingual microcirculation up to shock resolution or death, and observed that microvascular blood flow rapidly improved (but did not totally resolve) in survivors but remained altered in non survivors, whether these patients died from shock or from multiple organ failure after the shock was resolved [23]. In survivors, microcirculatory alterations improved even though these patients were still on vasopressors for several days. In addition, improvements in microvascular alterations of more than 7.5% within the first 24 h of observation was an excellent predictor of good outcome, and, perhaps more importantly, this was even the most powerful predictor of outcome in these patients, well before improvements in APACHE II score, global haemodynamics, or SOFA score. These data suggest that microvascular blood flow alterations are implicated in the pathophysiological process involved in the development of multiple organ failure and death in septic patients.

What are the implications of microvascular alterations?

Microvascular alterations have major physiopathological implications. The juxtaposition of well-perfused and non-perfused capillaries may be responsible for the sepsis-induced decrease in oxygen extraction capabilities [24–26]. In addition, stopped flow capillaries are associated with zones of tissue hypoxia, as suggested by the decreased intravascular PO_2 [27, 28] Finally, the transient flow observed in some capillaries may lead to focal areas with ischaemia/reperfusion injury.

One major question is whether these microvascular blood flow alterations are the initial mechanism, leading to alterations in tissue metabolism, or are they secondary to cellular events, with flow matching the direct heterogeneous metabolic alterations? It is difficult but important to separate these opposing alternatives. In the first case, interventions improving microvascular perfusion may be beneficial while they would be useless in the second case. Several arguments nevertheless suggest that microcirculatory alterations may be the triggering event. First, in a pivotal study, Ellis et al. [19] reported in a model of peritonitis induced by caecal ligation that heterogeneity of microvascular blood flow increased with an increased number of stopped-flow capillaries (from 10 to 38%) and in the proportion of fast-flow to normal-flow capillaries. Moreover, in well-perfused capillaries, O_2 extraction increased, rather than decreased, and the VO_2 of this segment also increased. These results strongly argue against a sepsis-induced mitochondrial dysfunction, at least in the early phase of sepsis. Indeed, a primary mitochondrial dysfunction would have been accompanied by a decreased VO_2 and O_2 extraction in this segment. Similarly, Ince et al. [27] reported that microvascular PO_2 is

decreased in sepsis, which is incompatible with primary metabolic alterations. These data suggest that the sepsis-induced decrease in extraction capabilities is related to blood-flow heterogeneity but not to impaired capacities of the tissues to use oxygen. Second, we observed that the severity of alterations in the sublingual microcirculation is inversely related with sublingual PCO_2 and that both alterations can be reversed [29]. Of note, tissue PCO_2 does not increase when flow matches metabolism. All together, these observations suggest that microcirculatory alterations are involved in the pathophysiology of sepsis-induced organ dysfunction and that they do not match metabolic alterations, at least in the early phases of sepsis.

Another major question is whether these microvascular blood flow alterations are influenced by systemic factors. If so, monitoring of the microcirculation may be useless, as these alterations may be inferred from more easily applicable monitoring techniques. Since microcirculatory and macrocirculatory alterations usually coexist, it is quite difficult to separate the influence of the two factors. Experimental studies suggest that microcirculatory alterations can occur even when blood flow or perfusion pressure is maintained [17, 18, 30]. Using OPS technique on the sublingual microcirculation in 96 patients with severe sepsis and septic shock, we observed that the severity of microcirculatory alterations was not related to arterial pressure, the use of vasopressors, or the cardiac index [31].

How can microvascular blood flow be manipulated in sepsis?

Focal vasoconstriction, microthombi, and impairment of RBC and white blood cell (WBC) deformability are likely to concur in these microvascular alterations. In view of the severe vasoconstriction observed in some vessels, inflammatory and vasoactive mediators, such as tumour necrosis factor (TNF) [32] and endothelin [33], may play a major pathophysiological role, whereas nitric oxide (NO) may have a protective role [34].

The physiologic characteristics of the microcirculation (importance of rheologic properties, absence of adrenergic receptors on the capillaries but their presence at the precapillary and venular levels) and the mechanisms responsible for the sepsis-induced microvascular alterations (microthrombi, WBC adhesion, vasoconstriction) suggest that fluid resuscitation, vasodilatory compounds, and drugs with anti-inflammatory and anticoagulant activities improve the microcirculation while adrenergic compounds have more limited impact.

Animal experiments have shown that colloid solutions, and especially dextrans and starch solutions, can improve microcirculatory blood flow [35–37] but human data are lacking. The effects of packed RBCs are quite controversial, with some data suggesting that RBC transfusion can improve microcirculation perfusion [38], whereas other studies show the opposite effect [39]. Even if severe anaemia may weaken microcirculatory oxygenation [40], less severe haemodilution may be beneficial so that the effects of RBC transfusions should be analysed according to baseline haematocrit. The effect of storage time and the presence or absence of

residual leucocytes in the transfused products can represent important factors affecting the microvascular response to RBC transfusions.

The role of adrenergic agents is, unexpectedly, less well-defined, although some data are available regarding the role of beta-adrenergic stimulation. Several experimental studies have reported that dobutamine improves microcirculatory blood flow [41, 42], probably via a vasodilatory effect on arterioles. We have recently shown that dobutamine improves the sublingual microcirculation in patients with septic shock, independently of its systemic effects [43]. The effects of alpha-adrenergic agents are less well-understood. Interestingly, while the topical application of norepinephrine induces arteriolar vasoconstriction, intravenous administration of norepinephrine did not affect the rat microcirculation [44]. Human data are lacking regarding the effects of alpha-adrenergic drugs on the microcirculation. Ledoux et al. [45] have reported, using the laser Doppler technique, that norepinephrine-induced increases in mean arterial pressure (MAP) from 65 to 85 mmHg did not affect skin microcirculatory blood flow. However, the small number of patients, the intrinsic limitations of the technique used, and the skin of the forearm as a site of observation are important considerations that can limit definitive conclusions. Aside from the level of pressure, the choice of the drug to be used can also be central. Interestingly, some data highlight the microcirculatory effects of vasopressin in circulatory shock [46, 47]. Albert et al. [46] demonstrated that vasopressin preserved renal blood flow in endotoxaemic rabbits, while Westphal et al. [47] reported a major decline in gut perfusion in rats submitted to caecal ligation. Among other factors, differences in vasopressin doses may explain these conflicting results. Dubois et al. [48] reported that vasopressin did not deteriorate the sublingual microcirculation in patients with severe vasodilatory shock treated with low doses of vasopressin.

Other strategies, and especially vasodilatory agents, can be used to manipulate the microcirculation in sepsis [49]. Among these, NO donors appear promising. Animal data suggest that NO deficiency accentuates microcirculatory alterations [34]. We observed that microvascular alterations were fully reversible after topical application of a high dose of acetylcholine (Fig. 1), suggesting that vasodilators may be of value [9, 22]. This was further corroborated by Spronk et al. [50], who reported that nitroglycerin improved the sublingual microcirculation; unfortunately, it also induced a marked hypotension. In addition, the potential cytotoxic effects of NO donors should not be neglected so that further studies are needed to evaluate the usefulness of these agents in the therapy of septic shock.

Among other therapies, activated protein C is particularly promising. Even though it has been clearly demonstrated that activated protein C improves survival in critical care patients [51], the underlying mechanisms are still not fully understood. Hoffmann et al. [52] described an improved capillary density and a decrease in adherent and rolling leucocytes in rodents submitted to endotoxin and treated with activated protein C. These results were confirmed in other experimental settings [53, 54]. Interestingly, the effects may be independent of the anticoagulatory effects of activated protein C [54]. The effects of activated protein C in patients with septic shock are currently under evaluation.

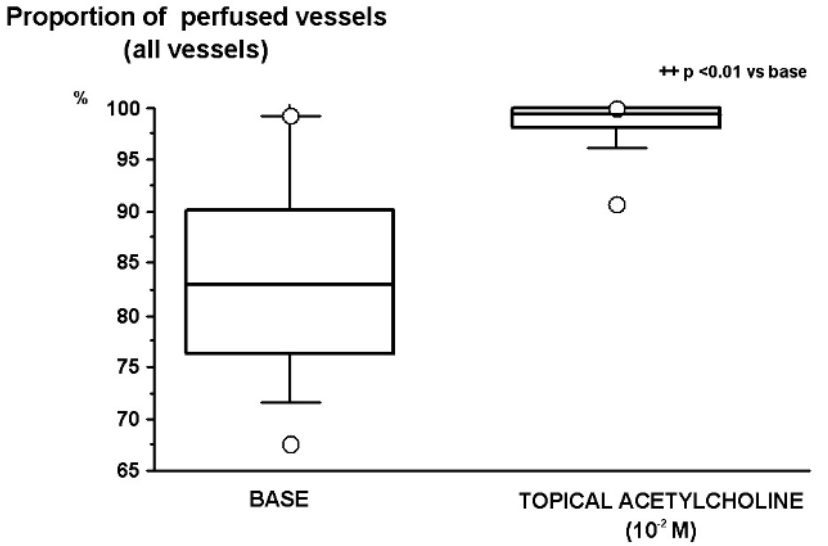


Fig. 1. Effects of topical acetylcholine application on sublingual microcirculation in patients with 11 patients in septic shock. Drawn from data presented in [9]

Conclusions

Microvascular alterations are frequent in patients with septic shock and their severity has been shown to be associated with outcome. These alterations can be improved by topical application of acetylcholine or intravenous administration of nitrates. The microcirculatory effects of other interventions more classically used to improve global oxygen delivery are less well-defined. Fluids, and especially colloids, and dobutamine have been shown to improve the microcirculation, while RBC transfusions have more variable effects. Experimental studies suggest that activated protein C improves the microcirculation in septic patients.

References

1. Rivers E, Nguyen B, Havstadt S et al (2001) Early goal-directed therapy in the treatment of severe sepsis, septic shock. N Engl J Med 345:1368–1377
2. De Backer D, Dubois MJ (2001) Assessment of the microcirculatory flow in patients in the intensive care unit. Curr Opin Crit Care 7:200–203
3. Groner W, Winkelman JW, Harris AG et al (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5:1209–1212
4. Slaaf DW, Tangelder GJ, Reneman RS et al (1987) A versatile incident illuminator for intravital microscopy. Int J Microcirc Clin Exp 6:391–397
5. Mathura KR, Vollebregt KC, Boer K et al (2001) Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation. J Appl Physiol 91:74–78

6. Langer S, von Dobschuetz E, Harris AG et al (2000) Validation of the orthogonal polarization spectral imaging technique on solid organs. In: Messmer K, (ed) Orthogonal polarization spectral imaging. Karger, Basel vol 24, pp 32–46
7. Laemmel E, Tadayoni R, Sinitsina I et al (2000) Using orthogonal polarization spectral imaging for the experimental study of microcirculation: comparison with intravital microscopy. In: Messmer K, (ed) Orthogonal polarization spectral imaging. Karger, Basel vol 26, pp 50–60
8. Harris AG, Sinitsina I, Messmer K (2000) The Cytoscan$^{(TM)}$ Model E-II, a new reflectance microscope for intravital microscopy: Comparison with the standard fluorescence method. J Vasc Res 37:469–476
9. De Backer D, Creteur J, Preiser J C et al (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166:98–104
10. Zhao KS, Junker D, Delano FA et al (1985) Microvascular adjustments during irreversible hemorrhagic shock in rat skeletal muscle. Microvasc Res 30:143–153
11. Cryer HM, Garrison RN, Kaebnick HW et al (1987) Skeletal microcirculatory responses to hyperdynamic Escherichia coli sepsis in unanesthetized rats. Arch Surg 122:86–92
12. Lam CJ, Tyml K, Martin CM et al (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077–2083
13. Dammers R, Wehrens XH, Oude EM et al (2001) Microcirculatory effects of experimental acute limb ischaemia-reperfusion. Br J Surg 88:816–824
14. Baker CH, Wilmoth FR (1984) Microvascular responses to E. coli endotoxin with altered adrenergic activity. Circ Shock 12:165–176
15. Farquhar I, Martin CM, Lam C et al (1996) Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res 61:190–196
16. McCuskey RS, Urbaschek R, Urbaschek B (1996) The microcirculation during endotoxemia. Cardiovasc Res 32:752–763
17. Boczkowski J, Vicaut E, Aubier M (1992) In vivo effects of Escherichia coli endotoxemia on diaphragmatic microcirculation in rats. J Appl Physiol 72:2219–2224
18. Nakajima Y, Baudry N, Duranteau J et al (2001) Microcirculation in intestinal villi. A comparison between hemorrhagic and endotoxin shock. Am J Respir Crit Care Med 164:1526–1530
19. Ellis CG, Bateman RM, Sharpe MD et al (2002) Effect of a maldistribution of microvascular blood flow on capillary O2 extraction in sepsis. Am J Physiol 282:H156-H164
20. Corso CO, Gundersen Y, Dörger M et al (1998) Effects of nitric oxide synthase inhibitors NG-nitro-L-arginine methyl eshter and aminoethyl-isothiourea on the liver microcirculation in rat endotoxemia. J Hepatol 28:61–69
21. Foitzik T, Eibl G, Hotz HG et al (2000) Endothelin receptor blockade in severe acute pancreatitis leads to systemic enhancement of microcirculation, stabilization of capillary permeability, and improved survival rates. Surgery 128:399–407
22. De Backer D, Creteur J, Dubois MJ et al (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91–99
23. Sakr Y, Dubois MJ, De Backer D et al (2004) Persistant microvasculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32:1825–1831
24. Walley KR (1996) Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. J Appl Physiol 81:885–894
25. Humer MF, Phang PT, Friesen BP et al (1996) Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol 81:895–904

26. Drazenovic R, Samsel RW, Wylam ME et al (1992) Regulation of perfused capillary density in canine intestinal mucosa during endotoxemia. J Appl Physiol 72:259–265
27. Ince C, Sinaasappel M (1999) Microcirculatory oxygenation and shunting in sepsis and shock. Crit Care Med 27:1369–1377
28. Zuurbier CJ, van Iterson M, Ince C (1999) Functional heterogeneity of oxygen supply-consumption ratio in the heart. Cardiovasc Res 44:488–497
29. De Backer D, Creteur J, Dubois MJ (2003) Microvascular alterations in patients with circulatory failure. In: Vincent J-L (2003) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin pp 535–544
30. Tugtekin I, Radermacher P, Theisen M et al (2001) Increased ileal-mucosal-arterial PCO_2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 27:757–766
31. De Backer D, Sakr Y, Creteur J et al (2003) Microvascular alterations are independent of systemic factors in patients with septic shock. Intensive Care Med 29:S10
32. Vicaut E, Hou X, Payen D et al (1991) Acute effects of tumor necrosis factor on the microcirculation in rat cremaster muscle. J Clin Invest 87:1537–1540
33. Groeneveld AB, Hartemink KJ, de Groot MC et al (1999) Circulating endothelin and nitrate-nitrite relate to hemodynamic and metabolic variables in human septic shock. Shock 11:160–166
34. Hollenberg SM, Broussard M, Osman J et al (2000) Increased microvascular reactivity and improved mortality in septic mice lacking inducible nitric oxide synthase. Circ Res 86:774–778
35. Singh S, Anning PB, Winlove CP et al (2001) Regional transcapillary albumin exchange in rodent endotoxaemia: effects of fluid resuscitation and inhibition of nitric oxide synthase. Clin Sci 100:81–89
36. Hoffmann JN, Vollmar B, Laschke MW et al (2002) Hydroxyethyl starch (130 kD), but not crystalloid volume support, improves microcirculation during normotensive endotoxemia. Anesthesiology 97:460–470
37. de Carvalho H, Dorigo D, Bouskela E (2001) Effects of Ringer-acetate and Ringer-dextran solutions on the microcirculation after LPS challenge: observations in the hamster cheek pouch. Shock 15:157–162
38. Genzel-Boroviczeny O, Christ F, Glas V (2004) Blood transfusion increases functional capillary density in the skin of anemic preterm infants. Pediatr Res 56:751–755
39. Tsai AG, Cabrales P, Intaglietta M (2004) Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. Transfusion 44:1626–1634
40. Schwarte LA, Fournell A, van Bommel J et al (2004) Redistribution of intestinal microcirculatory oxygenation during acute hemodilution in pigs. J Appl Physiol 98(3):1070–1075
41. Secchi A, Wellmann R, Martin E et al (1997) Dobutamine maintains intestinal villus blood flow during normotensive endotoxemia: an intravital microscopic study in the rat. J Crit Care 12:137–141
42. Secchi A, Ortanderl JM, Schmidt W et al (2001) Effects of dobutamine and dopexamine on hepatic micro- and macrocirculation during experimental endotoxemia: an intravital microscopic study in the rat. Crit Care Med 29:597–600
43. De Backer D, Creteur J, Koch M et al (2004) Changes in microvascular blood flow are not related with changes in cardiac index during dobutamine infusion. Intensive Care Med 30:S26
44. Le Noble LM, Tangelder GJ, Slaaf DW et al (1987) Adrenergic stimulation of the rat

mesenteric vascular bed: a combined micro- and macrocirculatory study. Pflugers Arch 410:250–256
45. LeDoux D, Astiz ME, Carpati CM et al (2000) Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 28:2729–2732
46. Albert M, Losser MR, Hayon D et al (2004) Systemic and renal macro- and microcirculatory responses to arginine vasopressin in endotoxic rabbits. Crit Care Med 32:1891–1898
47. Westphal M, Freise H, Kehrel BE et al (2004) Arginine vasopressin compromises gut mucosal microcirculation in septic rats. Crit Care Med 32:194–200
48. Dubois MJ, De Backer D, Creteur J et al (2003) Effect of vasopressin on sublingual microcirculation in a patient with distributive shock. Intensive Care Med 29:1020–1023
49. Buwalda M, Ince C (2002) Opening the microcirculation: can vasodilators be useful in sepsis? Intensive Care Med 28:1208–1217
50. Spronk PE, Ince C, Gardien MJ et al (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395–1396
51. Bernard GR, Vincent J-L, Laterre PF et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
52. Hoffmann JN, Vollmar B, Laschke MW et al (2004) Microhemodynamic and cellular mechanisms of activated protein C action during endotoxemia. Crit Care Med 32:1011–1017
53. Knock A, Diedrich S, Pavlovic D et al (2005) Activated protein C improves intestinal microcirculation in experimental endotoxemia in the rat. Crit Care 9:S1
54. Ohrum P, Kirschenbaum LA, Reisbeck M et al (2004) Effects of activated protein C (APC) on neutrophil-endothelial cell interactions independent of fibrinogen in septic shock. Crit Care Med 32:A144

Chapter 8

Pacemaker resynchronisation in the treatment of severe heart failure

J.L. Atlee

Patients with heart failure (HF) are at increased risk for hospitalisations, arrhythmias, and mortality. Despite convincing evidence that combined diuretics, angiotensin-converting enzyme inhibitors (ACEI), β-blockers, and aldosterone antagonists (i.e. optimal drug therapy) can reduce hospitalisations and mortality in patients with HF, such life-prolonging therapy continues to be underutilised [1]. More recently, devices for the management of patients with HF, including implantable cardioverter-defibrillators (ICDs) and pacemaker cardiac resynchronisation therapy (CRT)[1] have been shown to result in substantial mortality reduction [2–5]. Thus, CRT is yet another therapy that may be of benefit to selected patients with severe heart failure.

Overview of permanent pacing indications

More than 40 years ago, implanted pacemakers (PM) became the therapy for patients with symptomatic bradycardia due to atrioventricular (AV) block [6]. Subsequently, indications for PM were expanded to include pacing for bradycardia due to sinus node dysfunction, pacing in the hypersensitive carotid sinus syndrome, pacing for neurocardiogenic syncope, and pacing for the prevention or termination of tachyarrhythmias [7]. While pacing indications for children and adolescents are similar, there is less emphasis on the rate criteria for bradycardia; rather, more emphasis has been placed on the correlation of symptoms with conditions amenable to pacing therapy. Also, in addition to the more conventional indications for PM, its use has now been expanded to include other conditions.

Among these is hypertrophic obstructive cardiomyopathy (HOC) with symptoms and with significant resting or drug-provoked (nitroglycerine or isoproterenol) left ventricular (LV) outflow tract obstruction (LVOT). However, such patients must not be candidates for surgery or refractory to drugs (β-blockers, calcium channel blockers). If so, HOC with LVOT forms a class IIb indication for dual-chamber pacing with a short AV delay (< 120 ms) [7]. This will reduce the LVOT gradient in many, but not all patients. Possible beneficial effects of pacing in

[1] Contemporary ICD integrate anti-bradycardia and -tachycardia pacing, and many CRT as well.

patients with LVOT include induced paradoxical septal wall motion, reduced systolic anterior mitral valve motion, increased LVOT diameter, and reduced Venturi forces through the LVOT [8, 9]. The relative importance of other suggested beneficial effects of pacing in HOC, such as improved left ventricular (LV) diastolic function, increased coronary blood flow, and depression of systolic function is unresolved. Further, pacing has not been convincingly shown to reduce mortality in HOC, with or without LVOT.

Pacemaker cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is used to treat advanced heart failure (NYHA Class III or IV; AHA/ACC Stage C or D)[2] and consists of biventricular pacing (BVP) or LVP to synchronise ventricular contractions in patients with advanced HF. Commonly, such patients have abnormal ventricular activation or electrical dyssynchrony [10, 11]. The latter is manifest as QRS interval prolongation (often, with a left bundle branch block) and is associated with cardiac dysfunction [12, 13] and increased mortality [10]. The following discussion is organised under four headings: (1) physiology of CRT, (2) pacing site selection, (3) haemodynamic and other observations pertinent to CRT, and (4) clinical evidence for efficacy of CRT in HF.

Physiology of CRT

Abnormal electrical timing in heart failure

Key targets of CRT are the LV activation pattern and atrioventricular (AV) delay [14]. The LV usually contracts synchronously, with little more than 40-ms variation in the timing of electrical or mechanical systole throughout the wall. Mechanical synchrony produces more effective and energetically efficient LV ejection. With premature stimulation of a portion of the ventricles, e.g., with left bundle-branch block (LBBB) or right ventricular (RV) pacing, the activation sequence changes. This generates regions of early (RV) and delayed (LV) contraction. Furthermore, early shortening at the stimulation site (RV) is wasted work. The RV filling pressure is still low, so little ejection occurs. Moreover, delayed LV activation occurs at higher wall stress, because the ventricular septum has already developed tension.

[2] NYHA (New York Heart Association) functional classification of HF: Class I - symptoms at rest; Class II - symptoms with usual exertion; Class III - symptoms with < ordinary exertion; and Class IV - symptoms at rest. The ACC/AHA (American College of Cardiology/American Heart Association) emphasises the evolution and progression of HF: Stage A: high risk for HF, but without evident structural heart disease (SHD); Stage B: with SHD, but without HF symptoms; Stage C: with SHD and past or current symptoms of HF; Stage D: with end-stage SHD and need for advanced therapy (i.e. positive inotropes, mechanical circulatory support, cardiac transplantation, or hospice care).

Finally, this is wasted work, because any previously activated myocardium may undergo paradoxical stretch. The net result is a decline in systolic function of about 20%, with reduced cardiac output and efficiency, increased end-systolic volume and wall stress, and delayed relaxation.

Mechanical dysfunction secondary to intrinsic LV conduction delay (i.e. LBBB, wide QRS rhythm) vs single-site RV pacing is not necessarily equivalent [14]. The former has an even greater adverse impact on contraction, as a larger territory of myocardium may be prematurely activated.

Finally, the AV delay also influences net LV chamber mechanics [14]. Too short or too long delays result in suboptimal LV filling and may cause mitral regurgitation (MR). Translating this behaviour to patients with HF is non-trivial, because the failing heart must operate at high filling pressures. This reduces diastolic LV filling during atrial systole, even if atrial and ventricular contractions are properly synchronised.

Optimisation of AV delay: AV resynchronisation

There is conflicting evidence for the efficacy of AV resynchronisation with VDD or DDD pacing in patients with LV dysfunction or advanced HF. Hochleiter et al. noted symptomatic improvement with DDD pacing and a short AV delay (100 ms) in 16 patients with advanced HF [15]. This benefit persisted at 1 year, but the incidence of sudden death (presumably, arrhythmic) increased at 2 years [16]. Brecker et al. assessed the effect of variable AV delay on symptoms and exercise tolerance in patients with dilated cardiomyopathy and reduced ventricular filling times due to AV valvular regurgitation [17]. Cardiac output, exercise duration, and maximum O_2 consumption increased with shorter AV delays. Also, the exercise-limiting symptom changed from breathlessness to leg fatigue.

In contrast, Linde's group found no improvement in NYHA functional class, stroke volume, ejection fraction, or quality of life 1, 3, and 6 months after physiologic pacing with optimised AV delay in ten patients with advanced HF secondary to ischaemic or dilated cardiomyopathy [18]. There was, however, short-term improvement in stroke volume and cardiac output. Similarly, Gold et al. found no improvement in haemodynamic, clinical or echocardiographic variables with VDD pacing and short AV delays in 12 patients with severe HF [19]. While Nishimura's group did find differences in response to dual-chamber pacing with optimised AV delay in patients with dilated cardiomyopathy and severe LV dysfunction, these were based on the PR interval at rest [20]. Patients with PR intervals > 200 ms had significant improvement in cardiac output, LV end-diastolic pressure, diastolic filling time, and less MR during pacing. With normal PR intervals, diastolic filling time was unchanged, but cardiac output decreased with pacing. Finally, Sack et al. found no variables that consistently predicted a beneficial response to dual-chamber pacing with optimised AV delay [21]. However, patients could be stratified into 'responders' and 'non-responders' based on acute haemodynamic assessment.

Thus, individual patient testing is the only way to distinguish patients who might benefit from optimising the AV delay in right-sided dual-chamber pacing

[22]. Controlled studies that link short-term to long-term benefits in significant numbers of patients are currently lacking.

Optimal ventricular activation in heart failure

Wiggers first recognised the importance of synchronised ventricular contractions [23]. He described LV contraction as a 'series of sequential fractionate contractions of muscle bundles,' and proposed that a disturbance in the temporal sequence of LV contraction might be caused by interspersed areas of ischaemia or fibrosis. Nearly 40 years later, Harrison noted 'disorganised contraction' (termed 'asynergy') on kinetocardiograms of patients with coronary heart disease [24]. Shortly thereafter, Herman and colleagues correlated the presence of LV asynergy with clinical HF [25]. Some 16 years later, the impact of rate-dependent LBBB on LV function was analysed during exercise radionuclide angiography [26]. In subjects with rate-dependent LBBB, but without demonstrable coronary artery disease (CAD), there was an abrupt decrease in LV function with exercise. In contrast, in controls (without CAD), LV function increased by 26%. Moreover, LV wall motion analysis revealed that onset of LBBB coincided with development of asynchronous LV contraction. Similarly, Grines et al. observed striking delays between LV systolic and diastolic events in patients with isolated LBBB [12]. They hypothesised that altered ventricular activation with LBBB led to delayed LV contraction, RV–LV dyssynchrony, lower LV ejection fractions, abnormal interventricular septal motion, and shortened diastolic filling times. Much later, Amitzur's group compared the effects of different pacing sites (i.e. surrogates for conduction abnormalities) on blood flow velocities in the left anterior descending (LAD) and left circumflex (LCX) coronary arteries [27]. LCX flow velocities were not affected by multisite pacing; however, LAD flow velocities decreased with pacing from the right RVA or mid-RV vs with RA or LV pacing. It was speculated that the differences were due to earlier activation of LAD-perfused territories (especially, the interventricular septum) with right-sided pacing. In contrast, with left-sided pacing, there was nearly simultaneous activation of both the LAD- and LCX-perfused territories, excluding both from the effects of an early activation state. Finally, Xiao et al. examined the effects of abnormal ventricular activation (prolonged QRS) on the time course of the LV pressure pulse waveform in patients with dilated cardiomyopathy [28]. QRS prolongation reduced peak dP/dt, and increased the time to peak dP/dt, relaxation times, and overall duration of the LV pressure pulse waveform. The authors postulated that if QRS duration were reduced, possibly by pacing, then improved inotropy might result.

Pacing site selection

Right ventricular apex

When transvenous endocardial leads were first used for permanent pacing, the RVA was the choice lead position [9]. It was relatively easy to obtain stable RVA lead positions with good pacing and sensing characteristics, and an acceptable incidence of lead dislodgement. Since then, there have been advances in lead technology (e.g. tined, active fixation, and steroid-eluting leads). Also, pacing from other parts of the ventricles is possible. However, AAI pacing with intact AV conduction still leads to higher cardiac outputs and ejection fractions vs RVA DDD pacing [29]. Thus, the normal pattern of ventricular activation is important. In patients with normal LV function, cardiac output with DDD pacing is often adequate. Thus, there was little impetus to explore other pacing sites [9]. However, now there is potential to further optimise LV function with pacing to normalise the pattern of ventricular activation in selected patients with HF, despite optimal drug therapy. Thus, pacing to achieve this goal now has a higher priority.

RV apex vs RV outflow tract pacing and dual-site RV pacing

Usually, permanent ventricular pacing is with electrode(s) at the RV apex (RVA). Permanent pacing from the RV outflow tract (RVOT) is also feasible [30]. Several small trials have provided conflicting results regarding the efficacy of RVOT pacing in HF. Giudici et al. found that VVI pacing from the RVOT improved cardiac output vs RVA pacing in patients receiving DDD pacemakers for sinus node dysfunction [31]. However, pacing sites were not randomised, cardiac output measurements were unblinded, RVOT pacing was tested in some patients with normal sinus node function, and the trial was not restricted to patients with HF. Thus, these findings require confirmation. Victor et al. compared RVOT to RVA pacing in ten patients with complete heart block or chronic atrial fibrillation and normal LV function [32]. Each received a DDD pacemaker with one lead in the RVOT and another at the RVA. Pacing was randomised between sites. There was no difference between RVOT and RVA pacing for effect on haemodynamics or exercise tolerance. Two prospective, randomised trials, one with VDD [33] and the other with DDD pacing [34], confirmed no beneficial haemodynamic effect of RVOT vs RVA pacing in HF patients. Therefore, the pacing mode, not the RV pacing site, appears to have a greater effect on haemodynamics in patients with HF.

Finally, Buckingham et al. tested whether simultaneous RVA and RVOT (dual-site) pacing would narrow the QRS and improve haemodynamics during a clinical electrophysiological study [35]. The QRS narrowed (130±110 ms) with dual-site pacing, but there was no significant change in cardiac output. In their sequel report, this group tested dual-site RV pacing to improve LV systolic function in patients with reduced LV ejection fractions [36]. There was no significant effect of dual-site pacing on any measured parameters of LV function. Thus, it appears that dual-site RV pacing has little potential to improve haemodynamics in patients with HF.

Biventricular pacing

In patients with HF and LBBB or intraventricular conduction delay (QRS ≥ 0.13 s), pacing to synchronise RV and LV contractions (i.e. BVP) will narrow the QRS and has potential to improve ventricular interdependence and haemodynamics more than single- or dual-site pacing from the RV. Early evidence supporting BVP was limited to small, uncontrolled, observational studies with short follow-up. For example, Cazeau et al. studied eight patients with NYHA Class IV HF (despite maximal medical therapy) and widened QRS complexes, who had refused or were ineligible for heart transplantation [37]. Each patient underwent baseline haemodynamic evaluation with temporary pacing leads for RV apex, RVOT and LV pacing, or BVP between the RVOT or RV apex and the LV. Based on the baseline results, lead placement of an existing pacemaker were modified or a new system was implanted for BVP. For patients in sinus rhythm, atrial-triggered BVP increased cardiac index (CI) by 25%, and reduced pulmonary capillary wedge pressure (PCWP) by 17%. In four patients who survived 3 months, NYHA functional class improved to Class II. Leclercq et al. assessed the acute haemodynamic benefit of BVP with optimised AV delay in 18 patients with drug-refractory, advanced HF and mean QRS = 170 ms [38]. PCWP and CI were measured during AAI pacing (control), again during single-site RV DDD pacing, and during BVP (simultaneous LV with RV apex or RVOT pacing). PCWP and CI were significantly increased with BVP. Kass et al. reported the acute haemodynamic effects of BVP vs VDD pacing from the RV mid-septum or apex in 18 patients with dilated cardiomyopathy, prolonged QRS, and advanced HF [39]. Pacing from the LV free-wall site with the greatest conduction delay (i.e. single-site LV pacing) was also examined. LV dP/dt_{max} and pulse pressure increased most with single-site LV pacing. BVP caused a more modest (but still significant) increase in LV dP/dt_{max}. Pacing from the RVA or septum had negligible effects on LV systolic function.

Haemodynamic and other observations pertinent to CRT

BVP is mainly restricted to patients with advanced HF due to dilated cardiomyopathy, a low ejection fraction (usually ≤ 35%), and LBBB or intraventricular conduction delay (QRS = 0.13 s) [8, 14]. In such patients, observational studies show significant haemodynamic improvement: (1) increased cardiac output, ejection fraction, and blood pressure; (2) reduced pulmonary capillary wedge pressure and MR; (3) enhanced LV systolic function (i.e. maximum LV dP/dt and/or LV pressure-volume loops); and (4) improved magnitude and synchronisation of LV contraction. Also, either BVP or single-site LV pacing improves LV function without increasing O_2 consumption, thereby increasing myocardial efficiency [40, 41]. Further, BVP or single-site LV pacing vs RV apex pacing reduces sympathetic activity and increase arterial pressure [42]. These latter effects were attributed to stimulation of arterial or cardiopulmonary baroreceptors with vasodepression or cardioinhibition, respectively.

LV pacing site affects BVP efficacy

Studies of acute pacing in HF have revealed findings that relate primarily to LV pacing site selection [14]. First, the acute effects of single-site LV pacing are often similar or even more prominent than those of BVP. To date, BVP has involved simultaneous stimulation of the RV and LV, which may not be optimal in HF. While single-site LV pacing pre-excites the LV lateral wall, and would seemingly shift electrical delay to the RV, mechanical effects likely differ. This may relate to intramyocardial spread of excitation from a single LV pacing site vs fascicular conduction from the right bundle branch. Furthermore, BVP causes simultaneous RV–LV stimulation, which does not mimic normal activation, and may be suboptimal. Second, modifying the AV delay influences the net systolic response to single-site LV or BVP, but this is a more modest effect vs that of the LV pacing site per se. For AV delays of 110–140 ms, the mechanical responses to single-site LV or BVP appear similar, with both greater than with single-site RV pacing [39, 42]. Third, studies of the acute effects of single-site LV or BVP vs single-site RV pacing have not revealed benefits or detriments on cardiac diastolic function (i.e. isovolaemic relaxation time-constant or diastolic pressure–volume curve). Fourth, CRT with LV free- vs anterior-wall stimulation significantly improves LV systolic performance [43].

Identification of patients most likely to respond to CRT

Today, CRT is advised (Class IIb indication) only for selected patients with idiopathic dilated or ischaemic cardiomyopathy and medically refractory advanced HF [7]. In addition, the QRS duration must be $\geq$ 130 ms, LV end-diastolic diameter $\geq$ 55mm, and ejection fraction $\leq$ 35%.

Even so, a central issue has been the identification of patients most likely to benefit from CRT [14]. The primary variable for patient selection has been QRS duration, an electrical marker for spatially dispersed mechanical activation. It has been shown that patients with wider QRS complexes have greater immediate mechanical responses to CRT [39, 42, 43]. Also, the worse the cardiodepression, perhaps itself reflecting LV electrical dyssynchrony, the greater the CRT response [14]. Thus, regardless of the methods used to measure mechanical dysfunction due to electrical dyssynchrony or the response to CRT (e.g. LV ejection fraction, LV dP/dt, Doppler flow assessment), any of these most strongly correlate with responsiveness to CRT [44]. Finally, there is also controversy as to whether the amount of QRS narrowing with CRT is predictive of efficacy [14]. Short-term studies have not confirmed this, although one longer-term study suggests such correlation [45].

Clinical evidence for efficacy of CRT in HF

Until now, we have looked only at the acute haemodynamic effects of CRT. Is there evidence for longer-term efficacy? The first positive evidence comes from meta-analysis of randomised trials of CRT. Other evidence comes from ongoing or

completed, multicentre prospective trials of CRT: the MIRACLE, VIGOR, PATH-CHF, MUSTIC and COMPANION trials.

Meta-analysis of CRT trials

Bradley et al. [46] searched several databases and other sources[3] with the terms 'pacemaker,' 'pacing,' 'HF,' 'dual-site,' 'multisite,' 'biventricular,' 'resynchronisation,' and 'LV preexcitation.' Eligible were reports that included death, hospitalisation for HF, or ventricular arrhythmias as outcomes. Of 6883 potentially relevant reports initially identified, 11 reports of four randomised trials with 1634 total patients were included in the meta-analysis. Follow-up for these trials was from 3 to 6 months. Significant findings from pooled data were that CRT reduced death from progressive HF by 51% vs controls. Mortality due to HF was 1.7% for CRT vs 3.5% for controls. CRT also reduced HF hospitalisation by 29%, and showed a trend toward reducing all-cause mortality. There was no statistically significant effect of CRT on non-HF mortality. For a subset of patients with ICD, CRT had no clear impact on ventricular tachyarrhythmias. These findings would suggest that CRT has a substantial impact on the most common mechanism of death (progressive HF) in patients with advanced HF.

Desai et al. [4] carried out a similar meta-analysis to determine whether ICD therapy reduces all-cause mortality in patients with nonischaemic cardiomyopathy. Interestingly, four out of five primary prevention trials (total of 1854 patients) showed a statistically nonsignificant effect of ICD over medical therapy for all-cause mortality. Only the COMPANION trial (1520 patients, discussed below), in which a cardiac rhythm management device with both ICD and CRT capabilities was used, showed a statistically significant reduction in all-cause mortality with ICD over optimal medical therapy [3].

Prospective, randomised CRT trials

MIRACLE

In the first report from the MIRACLE[4] ICD trial investigators, 453 patients with advanced HF (ejection fraction < 35%; QRS ≥ 130 ms) were randomised to CRT or no CRT [47]. However, conventional HF drug therapy was maintained in both groups. Patients with CRT experienced significant improvement in 6-min walk distance, NYHA functional status, quality of life, treadmill time during exercise testing, and ejection fraction. Also, fewer CRT patients required hospitalisation for

[3] MEDLINE (1966–2002), EMBASE (1980–2002), the Cochrane Controlled Trials Register (2nd Quarter 2002), the National Institutes of Health Clinical Trials.gov database, the US Food and Drug Administration Web site, and reports presented at scientific meetings (1994–2002).

[4] Multicenter InSync RAndomized CLinical Evaluation Trial

HF. In the second report, 369 patients requiring ICD therapy were randomised to CRT or no CRT [2]. Except for the inclusion of ICD, the criteria were similar to the previous trial [47]. At 6 months, patients with CRT had greater improvement in median quality of life score and functional class. Also, peak O_2 consumption and treadmill exercise time increased significantly with CRT. However, there was no change in 6-min walk distance. There were no significant differences between test groups for LV size or function, HF status, survival, or rates of hospitalisation. No proarrhythmia were observed. Importantly, ICD tachyarrhythmia termination capabilities were not impaired.

VIGOR

In this trial, patients with LV HF and LBBB ($n = 53$) received BVP as CRT [48]. Echocardiograms were acquired at randomisation and after 6 and 12 weeks of BVP. Heart rate, QRS duration, and serum norepinephrine values were unchanged, and left atrial and LV end-systolic volume. LV end-systolic and end-diastolic dimensions were reduced. After 12 weeks of BVP, there was significant improvement in measures of systolic function, including LV outflow tract and aortic velocity time integrals, and myocardial performance indices.

PATH-CHF

The first report from these investigators described the impact of 6 months of CRT on echocardiographic variables of LV function [49]. For 25 patients with advanced HF (ischaemic or idiopathic dilated cardiomyopathy) and increased QRS duration, CRT significantly reduced LV end-diastolic and end-systolic diameter and volume, and increased ejection fraction. Concerning LV volume reduction, 'non-responders' had significantly higher baseline LV end-diastolic volume than 'responders.' Overall, there was only mild baseline MR, which according to semi-quantitative analysis, was reduced only slightly by CRT. The second PATH-CHF report compared short- and long-term effects of atrial synchronous, single-site ventricular pacing (LVP) or BVP [50]. Forty-one patients were randomised to 4 weeks with LVP or BVP, then to 4 weeks without treatment, and finally to 4 weeks with the alternative treatment (BVP or LVP). The best CRT method (LVP or BVP) was then continued for 9 months. Primary end points were exercise capacity measures. Single-site pacing (LVP) was selected for longer-term CRT in the majority ($n = 36$) of patients. However, the early clinical effects of LVP and BVP for CRT were not statistically significantly different, so that trial results were pooled to assess early sequential treatment effects. Oxygen uptake at both the anaerobic threshold and peak exercise level during bicycle exercise testing was significantly increased with both treatments. Also, the 6-min walk distance increased with both treatments. Finally, these improvements persisted after 12 months of CRT. Thus, for the short-term, any differences between LVP and BVP for effect on the primary end-points (measures of exercise capacity) appear small with short-term CRT.

MUSTIC

Three reports have come from the MUSTIC investigators. The first was a single-blind, randomised, controlled crossover study comparing exercise and other responses to BVP in 67 patients with advanced HF due to LV systolic dysfunction and with QRS > 150 ms [51]. Patients were randomised to 3 months of inactive pacing (VVI at 40 bpm) or BVP, and then crossed over to the other mode. The primary end point was 6-min walk distance. Secondary end points included quality of life, peak exercise O_2 consumption, hospitalisations for HF, treatment preference (active vs inactive pacing), and mortality. Nine patients were withdrawn from the study before randomisation, and ten failed to complete both study periods. Significant findings (active vs inactive pacing) in 48 patients who completed both study phases were a 22% increase in 6-min walk distance, 32% improvement in quality-of-life score, 8% increase in peak O_2 uptake, and a 67% reduction in hospitalisations. Also, active pacing was preferred by 85% of patients. The second MUSTIC report assessed whether the benefits of BVP observed during the aforementioned crossover phase were sustained over 12 months [52]. Patients (n = 131) in sinus rhythm (SR) or atrial fibrillation (AF) were assessed for 6-min walk distance, peak O_2 uptake, quality-of-life score, NYHA functional class, echocardiographic variables, and ejection fraction. After 12 months, all patients with SR and 88% with AF were programmed to BVP. Compared to baseline, significant findings were: 20% (SR) and 18% (AF) increased 6-min walk distance; 11% (SR) and 9% (AF) increased peak O_2 consumption; 36% (SR) and 32% (AF) improvement in quality of life; 25% (SR) and 27% (AF) improvement in NYHA functional class; and, 5% (SR) and 4% (AF) improvement in ejection fraction. MR decreased by 45% (SR) and 50% (AF). A more recent report from the MUSTIC investigators confirmed the BVP quality-of-life benefit in patients with NYHA Class III HF and intraventricular conduction delay [53].

VENTEK-CHF

It is well-established that both acute and chronic HF contribute to the need for antitachycardia (AT) therapy in patients with ICDs. The VENTEK-CHF trial reviewed the frequency of the need for ICD therapy in 54 patients with triple-chamber BVP ICDs. ICDs had transvenous RV and epicardial LV pacing leads [54]. Thirty-two patients completed 3-month, randomised, blinded periods of BVP (VDD) or no pacing. Of these, 13 received appropriate AT therapy for ventricular arrhythmias at least once in the 6-month post-implant period. Five had at least one episode of AT therapy while programmed to BVP, whereas 11 had at least one episode while programmed to no pacing. Three patients received ICD AT therapy during both pacing periods. The decrease in AT therapy during the BVP period was statistically significant, and may have been related to haemodynamic improvement with BVP.

COMPANION

This trial was terminated prematurely after the recruitment of 1600 patients [55]. A total of 1520 patients with NYHA Class III or IV HF due to ischaemic or nonischaemic cardiomyopathies, and a QRS interval of ≥ 0.12 s were randomly assigned in a 1:2:2 ratio to receive optimal drug therapy (see Introduction) for HF alone or in combination with CRT with either a PM or PM-ICD. The primary composite end point was time to death from or hospitalisation for any cause. As compared with optimal drug therapy alone, pacemaker CRT decreased the risk of the primary composite end point (hazard ratio, 0.81; $P = 0.014$), as did CRT with a PM-ICD (hazard ratio, 0.80; $P = 0.01$). The risk of the combined end point of death from or hospitalisation for heart failure was reduced by 34% for the PM group ($P < 0.002$) and by 40% in the PM-ICD group ($P \sim 0.001$) as compared to the group with optimal drug therapy for HF alone. Finally, a PM reduced the risk of the secondary end-point (death from any cause) by 24% ($P = 0.059$), and a PM-ICD reduced this risk by 36% ($P = 0.003$).

Conclusions

Pacemaker CRT is a novel adjunct therapy for the treatment of severe HF, but it does not replace the need for optimal drug therapy (see Introduction). In patients with, or susceptible to malignant ventricular arrhythmias (the latter based on clinical electrophysiological testing), CRT is combined with an ICD (ICD-CRT). Of course, all ICDs implanted today are also PMs, and may incorporate adaptive-rate pacing and other capabilities as well. Importantly, not only does CRT improve haemodynamics, exercise tolerance, and quality of life for patients with severe HF over the short term, it also appears to confer a longer-term survival benefit. Based on the COMPANION trial results, this may be even greater for patients with ICD-CRT vs PM-CRT. However, CRT therapy is costly, and it seems unlikely that CRT for severe HF will be affordable for all nations for some time. Even so, CRT ± ICD may yet be shown to reduce the need for even more costly HF therapies (e.g. a ventricular assist device; total artificial heart; heart transplant).

References

1. Fonarow GC (2005) Strategies to improve the use of evidence-based heart failure therapies. Rev Cardiovasc Med 6:S32–S42
2. Young JB, Abraham WT, Smith AL et al (2003) Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 289:2685–2694
3. Bristow MR, Saxon LA, Boehmer J et al (2004) Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
4. Desai AS, Fang JC, Maisel WH et al (2004) Implantable defibrillators for the prevention

of mortality in patients with nonischaemic cardiomyopathy JAMA 292:2874–2879
5. McAlister FA, Ezekowitz JA, Wiebe N et al (2004) Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Int Med 141:381–390
6. Furman S (2000) Introduction: History of cardiac pacing. In: Ellenbogen KA, Kay GN, Wilkhoff BL (eds) Clinical cardiac pacing and defibrillation, 2nd edn. Saunders, Philadelphia, pp 1–13
7. Gregoratos G, Abrams J, Epstein AE et al (2002) ACC/AHA/NASPE 2002 Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. Circulation 106:2145–2161
8. Sweeney MO, Ellenbogen KA (2002) Implantable devices for the electrical management of heart disease: overview of indications for therapy and selected advances. In: Antman EM (ed) Cardiovascular therapeutics. Saunders, Philadelphia, pp 503–528
9. Gold MR, Peters RW (2000) Pacing in patients with heart failure. In: Ellenbogen KA, Kay GN, Wilkhoff BL (eds) Clinical cardiac pacing and defibrillation, 2nd edn. Saunders, Philadelphia, pp 497–507
10. Baldasseroni S, Opasich C, Gorini M et al (2002) Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J 143:398–405
11. Farwell D, Patel NR, Hall A et al (2000) How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 21:1246–1250
12. Grines CL, Bashore TM, Boudoulas H et al (1989) Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 79:845–853
13. Murkofsky RL, Dangas G, Diamond JA et al (1998) A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction J Am Coll Cardiol 32:476–482
14. Leclercq C, Kass DA (2002) Retiming the failing heart: Principles and current clinical status of cardiac resynchronization. J Am Coll Cardiol 39:194–201
15. Hochleitner M, Hortnagl H, Ng CK et al (1990) Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. Am J Cardiol 66:198–202
16. Hochleitner M, Hortnagl H, Hortnagl H et al (1992) Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. Am J Cardiol 70:1320–1325
17. Brecker SJ, Xiao HB, Sparrow J et al (1992) Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. Lancet 340:1308–1312
18. Linde C, Gadler F, Edner M et al (1995) Results of atrioventricular synchronous pacing with optimized delay in patients with severe congestive heart failure. Am J Cardiol 75:919–923
19. Gold MR, Feliciano Z, Gottlieb SS et al (1995) Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. J Am Coll Cardiol 26:967–973
20. Nishimura RA, Hayes DL, Holmes DR Jr et al (1995) Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. J Am Coll Cardiol 25:281–288
21. Sack S, Franz R, Dagres N et al (1999) Can right-sided atrioventricular sequential pacing provide benefit for selected patients with severe congestive heart failure? Am J Cardiol 83:124D-D129
22. Dresing TJ, Natale A (2001) Congestive heart failure: the pacing approach. In: Goldstein

S, Sabbah HN (eds) Heart failure reviews, vol. 6. Dordrecht, The Netherlands, Kluwer Academic, pp 15–25
23. Wiggers C (1926) Are ventricular conduction changes important in the dynamics of left ventricular contraction? Am J Physiol 74:12–30
24. Harrison T (1965) Some unanswered questions concerning enlargement and failure of the heart. Am Heart J 69:100–115
25. Herman MV, Heinle RA, Klein MD et al (1967) Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. N Engl J Med 277:222–232
26. Bramlet DA, Morris KG, Coleman RE et al (1983) Effect of rate-dependent left bundle branch block on global and regional left ventricular function. Circulation 67:1059–1065
27. Amitzur G, Manor D, Pressman A et al (1995) Modulation of the arterial coronary blood flow by asynchronous activation with ventricular pacing. Pacing Clin Electrophysiol 18:697–710
28. Xiao HB, Brecker SJ, Gibson DG (1992) Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. Br Heart J 68:403–407
29. Rosenqvist M, Isaaz K, Botvinick EH et al (1991) Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 67:148–156
30. Buckingham TA (1997) Right ventricular outflow tract pacing. Pacing Clin Electrophysiol 20:1237–1242
31. Giudici MC, Thornburg GA, Buck DL et al (1997) Comparison of right ventricular outflow tract and apical lead permanent pacing on cardiac output. Am J Cardiol 79:209–212
32. Victor F, Leclercq C, Mabo P et al (1999) Optimal right ventricular pacing site in chronically implanted patients: a prospective randomized crossover comparison of apical and outflow tract pacing. J Am Coll Cardiol 33:311–316
33. Gold MR, Shorofsky SR, Metcalf MD et al (1997) The acute hemodynamic effects of right ventricular septal pacing in patients with congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 79:679–681
34. Gold MR, Brockman R, Peters RW et al (2000) Acute hemodynamic effects of right ventricular pacing site and pacing mode in patients with congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 85:1106–1109
35. Buckingham TA, Candinas R, Schlapfer J et al (1997) Acute hemodynamic effects of atrioventricular pacing at differing sites in the right ventricle individually and simultaneously. Pacing Clin Electrophysiol 20:909–915
36. Buckingham TA, Candinas R, Attenhofer C et al (1998) Systolic and diastolic function with alternate and combined site pacing in the right ventricle. Pacing Clin Electrophysiol 21:1077–1084
37. Cazeau S, Ritter P, Lazarus A et al (1996) Multisite pacing for end-stage heart failure: early experience. Pacing Clin Electrophysiol 19:1748–1757
38. Leclercq C, Cazeau S, Le Breton H et al (1998) Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 32:1825–1831
39. Kass DA, Chen CH, Curry C et al (1999) Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation. 99:1567–1573
40. Nelson GS, Berger RD, Fetics BJ et al (2000) Left ventricular or biventricular pacing improves cardiac function at diminished energy costs in patients with dilated cardiomyopathy and left bundle branch block. Circulation 102:3053–3059

41. Ukkonen H, Beanlands, RSB, Burwash IG et al (2003) Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation 107:28–31
42. Auricchio A, Stellbrink C, Block M et al (1999) Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation. 99:2993–3001
43. Butter C, Auricchio A, Stellbrink C et al (2001) Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 104(25):3026–3029
44. Nelson GS, Curry CW, Wyman BT et al (2000) Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 101:2703–2709
45. Alonso C, Leclercq C, Victor F et al (1999) Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol. 84:1417–1121
46. Bradley DJ, Bradley EA, Baughman KL et al (2003) Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. JAMA 289:730–740
47. Abraham WT, Fisher WG, Smith AL et al (2002) Multicenter InSync Randomized Clinical, Evaluation Cardiac resynchronization in chronic heart failure. N Engl J Med 346:1845–1853
48. Saxon LA, De Marco T, Schafer J et al (2002) Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling. Circulation 105:1304–1310
49. Stellbrink C, Breithardt OA, Franke A et al (2001) Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 38:1957–1965
50. Auricchio A, Stellbrink C, Sack S et al (2002) Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 39:2026–2033
51. Cazeau S, Leclercq C, Lavergne T et al (2001) Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 344:873–880
52. Linde C, Leclercq C, Rex S et al (2002) Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation In Cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 40:111–118
53. Linde C, Braunschweig F, Gadler F et al (2003) Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC) Am J Cardiol 91:1090–1095
54. Higgins SL, Yong P, Sheck D et al (2000) Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol 36:824–827
55. Salukhe TV, Francis DP, Sutton R (2003) Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial terminated early; combined biventricular pacemaker-defibrillators reduce all-cause mortality and hospitalization. Int J Cardiol 87:119–120

Chapter 9

The importance of guidelines in airway management

F. Petrini, M. Sorbello, M. Scoponi

'Though this be madness, yet there is method in 't'
(Hamlet - Act II, Scene II)

The structure and organisation of health care delivery are in the midst of rapid change. Increases in health care costs, competition and regulation are prompting health care providers from a variety of disciplines to define their practice in measurable ways and to identify the outcomes to which they contribute and aspire.

This is true also for anaesthesia, and particularly for airway management, which is one of the most discussed topics of anaesthesia care for potentially life-threatening problems and implications.

With the aim of defining the importance of airway management guidelines, just like trying to answer a question from *Hamlet*, we may discuss them in a 'literary way', through Sir William Shakespeare's comedies.

'The Tempest'

The unanticipated difficult airway can be considered a clinical problem potentially encountered by all anaesthesiologists, and is recognised as one of the most important causes of major anaesthesia-related morbidity [1, 2]. Nowadays, it is well known that approximately one third of all adverse anaesthetic outcomes are related to respiratory problems, and almost one third of all anaesthetic-related deaths result from an inability to manage the difficult airway [3].

Statistics are difficult to perform in the field of airway management for several reasons; the lack of common definitions and of common measuring instruments for near misses and adverse events makes it difficult to put all the data together and to compare them. Another important problem is represented by the 'iceberg effect': hard outcomes are so rare and may only represent the tip of the difficult airways potential risks, so that in some aspects it is really underestimated, while some others could be overestimated [4, 5]. Finally, literature suffers from the problem of near-miss accidents and from the possibility of several clinicians 'selecting' (often unconsciously) the type of outcomes and adverse events they are collecting [6].

This is the epidemiological 'tempest' of airway management and this is the field in which practical guidelines should be applied.

'As you Like it'

The first practical consequence of the above-described situation in the early 1990s was the general trend of all anaesthetists to act based on personal experience in the face of all kinds of problems, especially those concerning airways management. There was no major attention to preventive strategies and difficult intubation predictors, except for what might have been suggested by personal attitude. Several devices were available for difficult management, such as the laryngeal mask airway (LMA) or emergency tracheal access, the first being considered unsafe to trust in compared with classical intubation, and the second considered as the nightmare, the forsaken situation that was best not mentioned. Airway management education and teaching could be considered as 'first-line fighting', and learning was the classical 'attempts and mistakes' method, everything to be played on clinicians' responsibilities and patients' morbidity.

'The Comedy of Errors'

This Shakespeare comedy title could be one of the closed claims projects sponsored by the American Society of Anesthesiologists (ASA) in the early 1990s: airway management difficulties were one of the leading causes of anaesthesia-related deaths and morbidity, representing the most expensive field for insurance refunds, especially in some settings such as emergency or obstetrics and gynaecology [2]. In 1993, the ASA issued the first version of the guidelines for difficult airways management, including a decisional algorithm, recommendations and equipment based upon literature reviews, experts' opinions and the Consensus Conference. Ten years later, the ASA reviewed the guidelines, and since 1993 many other documents on airway management have been written by enthusiastic international expert groups such as the Canadian Society of Anesthesiologists, the French Society of Anaesthesia and Intensive Care, the Italian Society of Anaesthesia, Resuscitation and Intensive Therapy (SIAARTI), and the Difficult Airway Society [5, 7, 8].

The ASA guidelines were the first attempt to put some order, in a typical American way, into such a difficult field, reinforcing the necessity for short and clear protocols to act in the few moments available for interventions during airway emergency. The key role played by the ASA guidelines was to move the matter of the difficult airway from the dark side of the moon, underlining both the dimensions of the problem and the necessity for protocols and commercial devices to reduce the likelihood of adverse outcomes.

'The Merchant of Venice'

The widespread diffusion of guidelines and research to improve them resulted in a major challenge and in fascinating commercial possibilities for manufacturers of airways devices. An important editorial by Cook underlines that in the late 1980s

'the options for maintaining the airway during anaesthesia were limited to the tracheal tube or the face mask combined with an oropharyngeal airway'. New devices, among which the LMA obviously plays a key role, have been developed, tested and applied, resulting on several occasions in a safe bridge for ventilation or a precious device that has saved more than one patient's life [9].

Undoubtedly, only the best devices can survive daily clinical practice and the severe refereeing of clinical trials or prospective studies: on the one hand, this phenomenon represented an advantage for the anaesthesist and for patients' safety, while on the other it was a course for guideline redactors. It may be difficult to recommend a certain device over another while guidelines are in preparation; sometimes insufficient data are available not only to validate a new device, but also to contraindicate its use in clinical practice.

The 2005 SIAARTI guidelines overcame the taxonomic problem of the bewildering variety of suprapharyngeal, extrapharyngeal, oropharyngeal and oesophageal devices, just indicating them as 'LMA and other extraglottic devices', on the principle that none of them go through the vocal cords and the glottic opening. As the number of devices grows, it is not the same for the scientific papers (correctly) validating their role in difficult airway management, while the LMA and the Combitube are the most widely recommended devices in clinical practice [9]. Last but not least, we must not forget that a possible role of airways management guidelines should be accounted for by costs: today the cost of a dedicated chart, including all useful devices in available sizes, may be expensive although somewhat 'mandatory', and its absence could be considered faulty in litigation [7]. On the other hand, the widespread diffusion of guidelines has caused a wider diffusion of certain 'economic' devices, and it may push manufacturers to introduce low-price (disposable) devices or to lower the cost of specific instruments, e.g. fibre-optic devices and fibrescopes.

'Measure to Measure'

'Nothing can be improved if it can't be measured' (Leonardo Da Vinci): in effect this was surely the first need felt by all researchers in the field of airway management. Guidelines gave a sudden acceleration to this need. Measuring was the key to success.

Measuring patients' anthropometric features was—correctly—intended as the only way to assess and preliminarily manage patients with difficult airways; measuring instruments and devices produced new sizes for widespread applications. Measuring data coming from clinical studies was considered to be the only way to validate protocols, instruments and devices. Stronger than before was the need to discuss clearly and compare clinical trial results: the era of evidence-based medicine (EBM) was also beginning for anaesthesia and airway management [1, 10–12]. Evaluation of evidence-based outcome and utilisation of clinical practice guidelines may be considered as methods to determine and implement optimal practices and to improve patient safety. In this sense practice guidelines are systematically

structured recommendations that assist practitioners and patients in making decisions about health care.

But we may ask: is it always possible to measure? And is it always correct to measure? Airway management represents a hard challenge for statistics: it is often impossible or difficult to perform randomised controlled trials in certain settings, and similarly it is difficult to equalise some variables such as individual experience or the feedback coming from other colleagues during difficulties [10, 13]. The paper from Yentis and Lee [11] represents a cornerstone for what concerns difficulty measuring, with a new laryngoscopic grading system (also adopted in the last SIAARTI document); the same author 2 years later asks 'Predicting difficult intubation: worthwhile exercise or pointless ritual?', putting in doubt both predictive tests and the value of statistics in certain fields [12].

Furthermore, do we always need to measure? In a fascinating paper by Smith and Pell we can read: 'As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence-based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute' [14].

Beyond the excesses, verisimilarly EBM could exist with observational data too, and in certain fields it may also benefit from experts' opinions and consensus conference results. This is particularly true whenever data may not be collected in a prospective way, and, moreover, if data are not fully compared, as suggested by Kunz and Oxman or Moher and co-workers, resulting in misleading conclusions or under/over-estimating results [15, 16].

The new 2005 SIAARTI 'Recommendations for airway control and difficult airway management' recognised the importance of the opinion of the SIAARTI task force, calling these specialists 'expert witnesses' with the critical role of deciding the strength of recommendations in the 'grey zone' of EBM [5, 7, 17, 18].

When writing guidelines, all these arguments should be taken into account; Shekelle and co-workers provided a very exhaustive paper concerning guidelines development, pointing out that the methods development should ensure that treating patients according to the guidelines will achieve the outcomes that are desired [19]. In the authors' opinion, this may only be possible by following a precise flow chart: the first step is prioritising topics of interest and refining the subject area (if reported as airways problems this should not be so difficult). The second step is convening and running guideline development groups: in some fields (such as paediatric, emergency or obstetrics and gynaecology airways management), expert opinion may count as 'scientific data', especially if evidence or studies are lacking. The third step should be to consider systematic review of all available data and evidence grading: as stated before, this is not always possible for airways management. Of the more than 800 studies included in the 2005 SIAARTI guidelines, many were graded as level III or IV on the Delphi modified scale, and some of the level II studies could be affected by statistical or procedural bias [5].

The next step is translating the evidence into recommendations for clinical practice, accounting for the existing differences between clinical attitudes, and availability of devices and instruments, and trying to minimise the gap between theory and practice. Graded recommendations should finally be evaluated, reviewed and constantly updated. The same steps are suggested by the Italian higher agencies for health care (Ministero della Salute and FISM) [20, 21].

In conclusion, much work is involved in publication of guidelines, and even more when clear data and precise measurements are missing in situations such as difficult airways.

'Midsummer Night's Dream'

According to previous considerations, we must admit that the ideal airway management guidelines are really difficult to realise, and, in any case, they would never fit into daily clinical practice, taking account of scientific evidence on the one side and reality on the other. Is their real importance thus a 'midsummer night's dream'? Not at all. Guidelines for the management of difficult airways have changed the way of considering anaesthesia practice, leading clinicians and researchers to a more careful evaluation of both clinical practice and research. In addition, the institution of clinical trials, the evaluation of new devices, the more careful evaluation of patients and the prudential approach to predicted borderline or severe difficulties have led to an increase in patients' safety *(primum non nocere)*.

A recent paper published by Peterson and co-workers shows how real guidelines are and how important they might be. The authors examine what changed in the field of airway management-related accidents after the introduction of the 1993 ASA guidelines through the investigation of closed claims in the USA [22]. While considering this paper, one of the first attempts to provide a clinical evaluation of the guidelines, it is important to underline that after their introduction something changed in the daily practice of anaesthesia in the USA. The bridge between theory and clinical practice may be represented by the result that while nothing changed for the incidence of accidents during anaesthesia maintenance, extubation and recovery, the incidence of fatal accidents or permanent brain damage associated with anaesthesia induction was clearly reduced after 1993. Some theoretical aspects, e.g. the number of laryngoscopic attempts, became clinical effects: the incidence of accidents was linearly related to the number of attempts in case of difficulty (such as strictly recommended in the 2005 SIAARTI document) [5].

Probably as a result of penetration of the guidelines, the wider diffusion of 'prudent' techniques such as awake intubation, or the presence of LMA as 'a bridge to secure ventilation' or of introducers and tube-exchangers on anaesthesia carts may account for the almost one quarter reduction in the odds of death or brain damage recorded by the investigators [22].

Furthermore, according to a recently published analysis from the ASA Committee on Professional Liability Closed Claims Project, severe anaesthesia-related injuries are becoming less frequent in the reports to insurance carriers. Moreover,

claims for respiratory-damaging events (inadequate ventilation, oesophageal or difficult intubation) decreased significantly in the 1990s compared to the 1980s [2, 22].

These data, together with (still little) evidence regarding the lack of safety of loco-regional anaesthesia as an alternative to difficult intubation, the risks of emergency and out-of-hospital settings, and the importance of 'trained' early emergency tracheal access, were all considered, reported and recommended in the 2005 SIAARTI guidelines [8]. Unfortunately, in Italy there is no possibility of similar data accessing (insurance and/or litigations registers).

Literature and observational data, together with a rational implementation of expert opinion approved by scientific societies may lead to suggested recommendations, not dreams: according to Shakespeare, '*The course of true love never did run smooth' (Act I, Scene I).*

'Much Ado About Nothing'

We may then conclude that all problems regarding the importance of guidelines may be considered as the title of Shakespeare's famous comedy. But, as usual, *in medio stat virtus*. Guidelines represent a cornerstone for daily practice, the behavioural gold standard for the different situations that may be encountered. At the same time there are limits in different situations, because of penetration and acceptance of guidelines, and because some fields lack sufficient data to allow a strictly scientific elaboration of guidelines. This may be the case in airway management for NORA, thoracic surgery, paediatric anaesthesia, the intensive care unit or out-of-hospital emergency settings. In such fields, guidelines should also take account of logistic difficulties, non-elective conditions, which are well known to be associated with unplanned difficulties, and higher rates of fatal accidents and differences of skills [23]. The contribution of board-certified anaesthesiologists in the improvement of emergency and perioperative care and outcome must not be forgotten [24].

Furthermore, much has yet to be done to improve the guidelines themselves, because of both the technological race and continuous attempts to improve quality. Many efforts are currently being made for evaluation of clinical practice guidelines [17, 20], possibly through dedicated instruments (AGREE Collaboration) and to find the best compromise between theory and practice, in the effort to provide correct evidence evaluation and grading strength of recommendations [25, 26]. In this setting, the 2005 SIAARTI guidelines are also attempting quality improvement, stating important quality points for guidelines self-assessment, data recording, equipment storage and disinfection, teaching and learning, multidisciplinary cooperation, diffusion and acceptance. The SIAARTI Task Force is compiling a national data collection on diffusion and penetration of guidelines through a questionnaire published on the SIAARTI website (www.siaarti.org 'Gruppi di Studio' section) and on the Gruppo di Studio Vie Aeree Difficili webpage (www.vieaereedifficili.org).

Finally, the 1993 ASA guidelines were discussed in litigation in only 18% of

claims in a 7-year period: really not *'much ado'*! This limited importance in the litigation processes may be due to the reflection of the ASA guidelines in usual and standard practice patterns [22]. In any case, we must not forget that guidelines have often been considered a two-way street in legal settings, as they might both strengthen and weaken the defence of the practitioner. In Branthwaite and Beresford we can read that: '…(Protocols and guidelines) … are best considered indicative of an accepted course of practice rather than the final arbiter of professional standards. However if legal action is brought because harm results from transgression of guidelines and protocols 'without good reason' the claimant is very likely to succeed' [13, 22, 27, 28].

'All's Well that Ends Well'

Considering that airway management problems are the first cause of anaesthesia-related accidents, we can say that airway management guidelines play a key role in both practitioner and patient safety, probably being one of the most important for anaesthestic practice, having focused attention on the 'airways problem', and having really changed clinical practice, with important effects on patient survival. They introduced in some way the 'culture of prediction' (even though we must not forget that predictive elements for difficult ventilation and intubation may be present in as few as one third of patients who end up being really difficult to manage), breaking up the 'cannot intubate fear': first of all encouraging the 'call for help' and subsequently inducing clinicians to plan strategies for predicted and unpredicted difficulties, also fulfilling the need of a quick and practical behavioural model in case of difficulties [5, 23, 29, 30].

In a recent paper, 10% of anaesthetists in the Oxford region admitted not having a personal plan for an alternative emergency airway management: also for these reasons SIAARTI underlined that guidelines, once developed and acquired, should be made available to practitioners in a user-friendly format at the bedside [4, 5, 31].

Moreover, guidelines invited anaesthetists to set up their difficult airways cart, making a larger number of clinicians familiar with prediction of difficulties and previously 'elitary' techniques and devices such as awake intubation and the fibrescope, and taking away the mythological image of techniques such as early tracheal emergency access, no more a 'nightmare' but a 'dream' for young residents and skilled clinicians, who would like to perform it on mannequins and simulations in order to be ready to do it whenever it may be needed (in one case in a million, maybe) [13, 23, 32].

Surely much work has yet to be done: recommendations may be adopted, modified, or rejected according to clinical needs and constraints, also considering that guidelines are not intended to be standards or absolute requirements. Their application cannot guarantee any specific outcome, and no guideline can ever be specific enough to be applied in all situations [33, 34]. Furthermore, guidelines have illuminated the problem of learning and training in a field that must be considered central to the practice of anaesthesiology, while young practitioners frequently feel

poorly trained in this area [35]. A large range of skills needs to be acquired, and guidelines may be considered a kind of template for training purposes, further representing the first attempt to institutionalise this aspect of learning and teaching. That is particularly true for airway management guidelines; nevertheless, for several years it has been emphasised that strict adherence to a predefined strategy could decrease respiratory catastrophes and specific anaesthesia-related morbidity and mortality. Some events, such as the dramatic cannot ventilate/cannot intubate scenario and the difficult or crucially impossible ventilation [36, 37], are (fortunately) rare in the clinical setting, but contemporarily they are (unfortunately) so rare as not to be systematically studied and their management will never be truly evidence based [38]. Guidelines considered these situations, forcing anaesthetists to think of this rare possibility and of the way they would act, leading them to consider that the only way to obtain skills would be by simulation. Several papers have been written and ever more realistic and sophisticated mannequins have been realised on the 'long wave' of guidelines.

Unfortunately, this theoretically good teaching tool is not always simple to translate into training efficacy: the guidelines in anaesthesia training of the European Board of Anaesthesiology Reanimation and Intensive Care are vague and much less specific on airway management topics than on other topics, as are the latest USA guidelines [39, 40]. When surveyed 2 years after publication of the first ASA guidelines, most American anaesthesiology residency training programmes did not include formal training on these topics [41]. Twelve years later, when the ASA guidelines were updated, the educational approach in this area remained the same, and a similar informal and poor approach on airway management teaching is common, from the east (Japan) to the west (European countries) [41, 42]. The Royal College of Anaesthetists seems to have made a positive effort, and its suggestions are well integrated with the Difficult Airway Society guidelines [43], but a lot of work has to be done during continuing medical education (CME) programmes in basic and advanced airway management for skills in which anaesthesiologists can be involved as experts. Mannequin practice, case presentation, problem-based learning, discussion and crisis resource management have been SIAARTI objectives for CME since 1998 [8].

In conclusion, airway management guidelines may become a fundamental part of quality improvement pathways, a strong effort towards quality of research, thus becoming a powerful instrument to defend practitioners during litigation processes.

According to these reflections, we may move the title's question towards the question proposed by Hung and Murphy in a recent editorial: 'Changing practice in airway management: are we there yet?', answering, with Shakespeare's words, 'all's well that ends well' [44].

References

1. Cheney FW (1999) The American Society of Anesthesiologists Closed Claims Project: what have we learned, how has it affected practice, and how will it affect practice in the future? Anesthesiology 91:552–556
2. Cheney FW (2002) Changing trends in anaesthesia-related death and permanent brain damage. ASA Newsletter 66(6) http://asahq.org/newsletter/2002 /6_02/cheney.html
3. Reed AP (2002) Recent advances in airway management. The Mountsinai Journal of Medicine 69:78–82
4. Alberti KJ (2001) Medical errors: a common problem. BMJ Editorial 322:501–502
5. Gruppo di Studio SIAARTI Vie Aeree Difficili (2005) Raccomandazioni per il controllo delle vie aeree e la gestione delle difficolta'. Minerva Anestesiol (in press)
6. Haller G, Myles P (2005) Learning from incidents and near misses reports. Anesthesiology 102:1287–1291
7. ASA Task Force on Management of the Difficult Airway (2003) Practice guidelines for management of the difficult airway. Anesthesiology 98:1269–1277
8. Petrini F (2005) Vie aeree difficili in anestesia. Minerva Anestesiol 71(suppl 1, no 6):68–72
9. Cook TM (2003) Novel airway devices: spoilt for choice? Anaesthesia 58:107–110
10. Myles PS, Bain DL, Johnson F et al (1999) Is anaesthesia evidence based? A survey of anaesthetic practice. BJA 82(4):591–595
11. Yentis SM, Lee DJH (1998) Evaluation of an improved scoring system for the grading of direct laryngoscopy. Anaesthesia 53:1041–1044
12. Yentis SM (2002) Predicting difficult intubation: worthwhile exercise or pointless ritual? Anaesthesia 57:105–109
13. Henderson J, Cook TM, Watts JC et al (2004) Difficult Airway Society Guidelines. Anaesthesia 59:1242–1255
14. Smith GCS, Pell JP (2003) Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 327:1459–1461
15. Kunz R, Oxman AD (1998) The unpredictability paradox: review of empirical comparisons of randomised and non randomi sed clinical trials. BMJ 317:1185–1190
16. Moher D, Cook DJ, Eastwood S et al for the QUOROM Group (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet 354:1896–1900
17. Kish MA (2001) Guide to development of practice guideline. CID 32:851–854
18. IDSA (2005) Guidelines for infectious diseases specialists serving as expert witnesses. CID 40:1393–1394
19. Shekelle PG, Woolf SH, Eccles M et al (1999) Developing guidelines. BMJ 318:593–596
20. Istituto Superiore Sanità (2004) Piano Nazionale Linee Guida (PNLG). Manuale Metodologico. (ASSR Eds) Arti Grafiche Passoni, Milano, pp 1–86 www.pnlg.it/doc/pnlg/dnecess.htm
21. Gruppo Italiano per la Medicina Basata sulle Evidenze (GIMBE) (1996-2004) Introduzione di Linee Guida in un'organizzazione sanitaria. http://www.gimbe.org
22. Peterson GN, Domino KB, Caplan RA et al (2005) Management of the difficult airway. A closed claims analysis. Anesthesiology 103:33–39
23. Henderson J, Popat MT, Latto IP, Pearce AC (2004) Difficult Airway Society (DAS) guidelines for management of the unanticipated difficult intubation. Anaesthesia 59:675–694

24. Melloni C (2005) Morbidity and mortality related to anesthesia outside the operating room. Minerva Anestesiol 71:325–334
25. AGREE Collaboration (2003) Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 12:18–23
26. GRADE Working Group (2004) Grading quality of evidence and strength of recommendations. BMJ 328:1–8
27. Hyams AL, Braidenburg JA, Lipsitz SR et al (1995) Practice guidelines and malpractice litigation: a two way street. Ann Intern Med 122:450–455
28. Hyams AL, Shapiro DW, Brennan TA (1996) Medical practice guidelines in malpractice litigation: an early retrospective. J Health Polit Policy Law 21:289–313
29. Cattano D (2004) Risk assessment of the difficult airway: an Italian survey of 1956 patients. Anesth Analg 99:1774–1779
30. Scoponi M, Dell'Atti I, Petrini F (2005) Airway management: routine use of an assessment form. Proceedings, AIRWAY 05, Abano Terme P26
31. Bockari BSW, Popat MT (2004) Management of unanticipated difficult intubation: a survey of current practice in the Oxford region. EJA 21:123–127
32. Chambers WA (2004) Difficult airways—difficult decision: guidelines for publication? Anaesthesia 59:631–635
33. Lohr KN, Field MJ (1992) A provisional instrument for assessing clinical practice guidelines. In: Field MJ, Lohr KN (eds) Guidelines for clinical practice. From development to use. National Academy Press, Washington DC
34. Hayward RSA, Wilson MC, Tunis SR et al for the Evidence Based Medicine Working Group (1995) Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? JAMA 274:570–574
35. Stringer KR, Bajenov S, Yentis SM (2002) Training in airway management. Anaesthesia 57(10):967–983
36. Langeron O, Masso E, Huraux C et al (2000) Prediction of difficult mask ventilation. Anesthesiology 92:1229–1236
37. Gautam P, Gaul TK, Lathra N (2005) Prediction of difficult mask ventilation. EJA 22:638–640
38. Yarrow S (2004) Trends in tracheal intubation: emphasis on the difficult airway. Curr Opin Anesthesiol 17:485–486
39. EBA for UEMS (2001) Guidelines in Anaesthesia Training of the European Board of Anaesthesiology, Reanimation and Intensive Care. EJA 18:563–571
40. Anaesthesiology Residency Review Committee (2004) Programs requirements for graduate medical education in anaesthsiology. http://www.acgme.org/downloads/RRC
41. Swchwartz AJ (2004) Difficult airway management needs to be difficult! BJA 17:477–478
42. Hagberg CA, Greger J, Chely JE et al (2003) Instruction of airway management skills during anesthesiology residency training. J Clin Anesth 15:149–153
43. Royal College of Anaesthetists (RCA) (2000) Competency based specialist registrar years 1 and 2. www.rcoa.ac.uk
44. Hung O, Murphy M (2004) Changing practice in airway management: are we there yet? Can J Anaesth 51(10):963–968

Chapter 10

BioGrid: a collaborative environment for Life Science Research[1]

C.-H. Huang

Background

Health-care-related research and practice often produce tremendous amounts of data. These are usually geographically distributed among hospitals, clinics, research labs, radiology centres, etc. For research, training, or clinical purposes, physicians and medical researchers often need to consult and analyse medical data from distributed sites. An efficient software and hardware infrastructure to support on-demand information extraction as well as automated data integration and analysis in a real-time manner would provide significant convenience and is therefore increasingly needed. However, due to the sensitive nature of these data and the lack of an effective integration approach, medical data are often stored and archived within individual sites and are usually disconnected from the outside network in order to enforce security issues.

A typical clinical example, among many others, that could benefit from such an infrastructure is remote intensive care. According to reports by the Leapfrog Group, a nonprofit coalition of businesses and other groups working to improve hospital operations, there has been a severe shortage of intensive care specialists in the United States—fewer than 6 000 at a time when nearly 5 million patients are admitted to ICUs each year. Typically, hospitals rely on nurses to notice a problem with a patient. The nurse then pages a physician, who runs to the ICU to check on the patient. With monitoring devices and in-room cameras connected to the infrastructure, physicians can check the patient's ventilator, intravenous medication, and anything else, anywhere and anytime. This allows critical care doctors and nurses to monitor dozens of patients at different hospitals simultaneously, much as an air traffic controller keeps track of several aeroplanes. Professionals watching from afar alert those on duty at the respective hospitals to changes or problems through videoconferencing equipment located at the nurses' stations. This greatly enhances the quality of intensive care in a way that could not be equalled, even with double or triple the on-site staffing, by enabling hospitals to make the best use of a limited number of intensive care doctors.

In addition, a large number of data-intensive or computation-intensive appli-

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cations arising from the life sciences, ranging from genetic and proteomic informatics, clinical practice on individuals to social health care, will greatly benefit from an infrastructure offering on-demand information extraction, automated data integration, and analysis. Specific examples include the following.

- Molecular modelling for drug design
- Computational genomics/proteomics
- Genetic linkage analysis
- Molecular sequence analysis
- Phylogeny reconstruction
- Determination of protein structures
- Identification of genes and regulatory patterns
- Biological information retrieval
- Genetic/biochemical networks
- Biomedical modelling and simulation
- Biomedical image simulation
- Distributed medical database management and integration
- Biomedical image processing
- Integration of biological information
- Data mining and visualisation of biomedical data
- Text mining of biomedical information bases
- Telesystems for diagnostic, prognostic, and therapeutic applications
- Health data storage and retrieval
- Medical imaging (management, analysis, processing and simulation)
- Social healthcare
- Pharmaceutics and clinical trials
- Computerised epidemiology
- Collaborative and proprietary health networks
- Integrative bioinformatics and medical informatics systems.

Grid: a potential solution

Among the efforts toward finding a solution infrastructure, grid technology has gradually proved to be a promising one. The grid represents a rapidly emerging and expanding technology that allows geographically distributed resources (CPU cycles, data storage, sensors, visualisation devices, and a wide variety of Internet-ready instruments), which are under distinct control, to be linked together in a transparent fashion [1, 2]. The aggregate computing power, data storage, network bandwidth, and user friendliness all contribute to the prosperity of this new information technology. The potentials of the grids to serve as a general-purpose research platform can also be attributed to the following facts, as pointed out in [3]:

1. The Internet is reasonably mature and able to serve as fundamental infrastructure
2. Network bandwidth has increased to the point of being able to provide efficient and reliable services

3. Storage capacity has now reached commodity levels, where one can purchase a terabyte of disk for roughly the same price as a high-end PC
4. More and more instruments are becoming Internet-aware
5. Clusters, supercomputers, storage, and visualisation devices are becoming more easily accessible
6. Applications have been parallelised
7. Collaborative environments are moving out of the alpha phase of implementation.

Challenges ahead

Despite the layers of security, data encryption, and certificate authorities provided by grid-enabling toolkits such as Globus, issues of interoperability, security, performance, management, and privacy need to be carefully considered. The compatibility of diverse security models and the translation of different high-level protocols, which specify actions in the grid, are the critical elements for interoperability. Besides, data management and replication mechanisms [4] proposed by current grid-enabling toolkits mainly deal with flat files. Data access control is handled at a file level. When it comes to the sharing and exploitation of large amounts of globally distributed data and information repositories in the health sector, such primitive mechanisms are not sufficient for use.

The UConn Health-Grid Initiatives

The UConn Bio-Grid Initiatives were launched in 2003. This project investigates the infrastructure needed for high-performance, automated integration and analysis of information from a wide spectrum of life science research and practice. The project will establish a grid-enabled network throughout the UConn campus in support of: (1) on-campus interdisciplinary health-care-related research projects, (2) regional collaborative health-care projects by research institutes and health-care providers in Connecticut, and (3) a 'virtual' health-care data repository and computation centre for use nationally and internationally.

Specifically, the first aim is to build a campus-wide computational and data grid, the Bio-Grid, that allows distributed Internet-aware resources, such as computers, sensors, and visualisation devices, etc. While under distinct control, these resources will be transparently linked, thereby offering aggregate computing power, storage capacity, network bandwidth, and ease of use to health-care-related research and practice at the University of Connecticut. This will be the first large-scale computational and data grid in Connecticut. Initially, the Bio-Grid will provide a test-bed for on-campus interdisciplinary health-care-related research projects. The Bio-Grid will incorporate research institutes and health-care providers in Connecticut in order to gradually establish a regional translational health-care research centre. The second aim of this project is to provide robust middleware support, on top of the Bio-Grid infrastructure, for secure retrieval and efficient integration of

sensitive clinical and health information. This enhanced middleware support will, for example, allow physicians to have secure access to their patients' images and to send hybrid requests over distributed data bases, which otherwise could not be easily reached. Another example is for radiologists from geographically dispersed hospitals to compare diagnoses by sharing standardised mammograms over the Bio-Grid, and to perform sophisticated epidemiological studies across national boundaries, all in a timely and on-demand manner. For global compatibility, the integration tests involve two international research teams.

The third aim, in conjunction with the research enterprise, is to establish a Bio-Grid Consortium. This involves ongoing efforts of several educational development programs and the establishment of annual scientific meeting on Bio-Grid-related research. Specifically, a series of cross-disciplinary e-Health courses (short-term and semester-long) are being developed at the University of Connecticut as part of a new, self-contained e-Health minor, open to students and professionals of educational institutes and to health-care providers in Connecticut. This program will produce software engineers who are prepared to formalise and solve emerging medical and health applications, as well as clinical scientists and professionals with extensive knowledge regarding information-processing. In addition, an annual international workshop (The Bio-Grid Workshop) was initiated in 2003 to reinforce and promote awareness of the possibilities and advantages linked to grid technologies in bioinformatics, clinical informatics, bio-imaging, and public health informatics. The project will eventually promote the UConn Bio-Grid as a 'virtual' healthcare data repository and computation centre for use nationally and internationally.

Current work

The first phase of our ongoing work involves the setup of a regional computational and data grid, a task to be coordinated with research and medical institutes in Connecticut, such as Yale University, Wesleyan University, the Connecticut State University System, Trinity College, Hartford Hospital, and Connecticut Children's Hospital, as well as with a few regional medical resource networks, and biotech and pharmaceutical companies in Connecticut. The second phase is, in addition to the Bio-Grid infrastructure, to develop middleware support for secure and automated integration of health data. Augmented with customised web portals and application interfaces, the middleware support will be general-purpose for use in a wide variety of applications.

The details of the grid setup, middleware infrastructure, and hardware/software interface are elided to better the readability of this paper, factoring in the nature of the APICE conference. Therefore, in the following we discuss three specific projects, conducted by researchers at the University of Connecticut, that are currently being grid-enabled.

Genomic knowledge inference

It is crucial that the massive amount of genomic data produced are well-represented so that useful biological information may be efficiently extracted or inferred. A useful tool for effective knowledge representation is the *semantic network* system [5]. This is a conceptual model for knowledge representation in which the knowledge entities are represented by nodes (or vertices), while the edges (or arcs) are the relations between entities. A semantic network is an effective tool, serving as the backbone knowledge representation system for genomic, clinical, and medical data. Usually, these knowledge bases are stored at locations geographically distributed. This highlights the importance of an efficiently distributed semantic network system enabling distributed knowledge integration and inferences. Note that the semantic network is a key component of the *Unified Medical Language System* (UMLS) project, which was initiated in 1986 by the U.S. National Library of Medicine (NLM). The goal of the UMLS is to facilitate associative retrieval and integration of biomedical information so that researchers and health professionals can use such information from different (readable) sources [6]. The UMLS project consists of three core components: (1) the *Metathesaurus,* providing a common structure for more than 95 source biomedical vocabularies. It is organised by concept, which is a cluster of terms, e.g., synonyms, lexical variants, and translations, with the same meaning; (2) the *Semantic Network,* categorising these concepts by semantic types and relationships; and (3) the *SPECIALIST* lexicon and associated lexical tools, containing over 30 000 English words, including various biomedical terminologies. Information for each entry, including base form, spelling variants, syntactic category, inflectional variation of nouns and conjugation of verbs, is used by the lexical tools [5].

The 2002 version of the Metathesaurus contains 871 584 concepts named by 2.1 million terms. It also includes inter-concept relationships across multiple vocabularies, concept categorisation, and information on concept co-occurrence in MEDLINE.

Our research team has developed a distributed semantic network system, based on a task-based and message-driven model to exploit both task and data parallelism while processing queries [8]. Our system also features *multi-threading* and *task migration* to support communication latency hiding and load balancing, respectively. In the task-based message-driven model, queries are decomposed into tasks and distributed among processors for execution. Other system support activities are also decomposed into system tasks and distributed as well. When a task is completed, a message is generated to either spawn new tasks or trigger further processing, depending on the property and current status of the task. This process is carried out by two collaborating components: the host system (Fig. 1) and the slave system (Fig. 2). The host system interacts with the user and processes the information for the slave system, while the slave system performs task execution.

This task-based and message-driven system is particularly suitable for grid environments. The next phase of this project is to test the knowledge reasoning efficiency of the grid-enabled distributed semantic network system on the Bio-Grid.

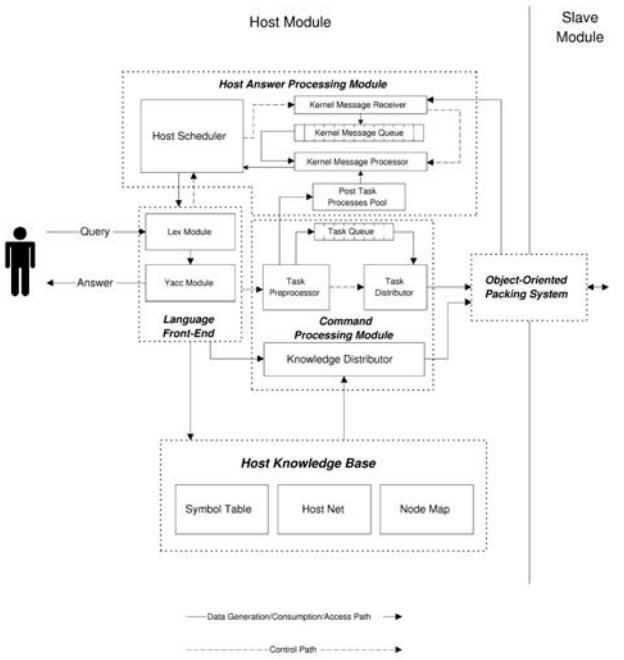

Fig. 1. Host architecture

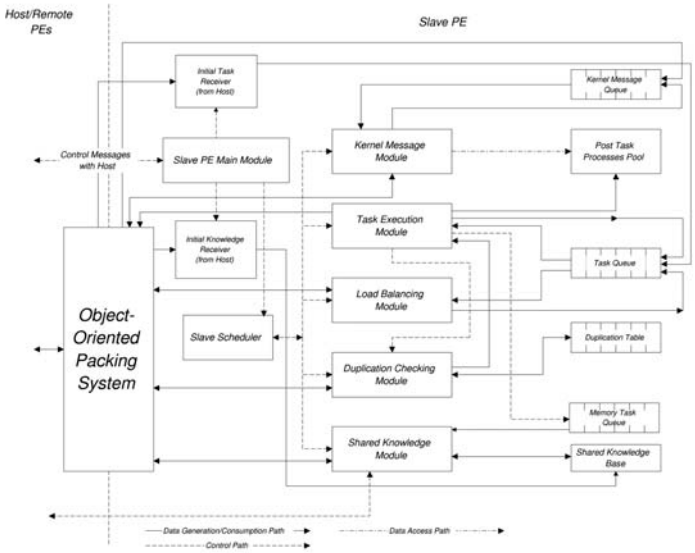

Fig. 2. Slave architecture

Study of protein functions

The complete sequencing of numerous genomes raises the next major challenge in biology, to understand the function of genes contained within these genomes. To date, scientists have only unravelled the functions of a small percentage of the encoded proteins. Protein functions are often ascribed to recurring sub-structural *motifs* (or *mini-motifs*, as they often contain less than 15 amino acids), which usually present specific positional characteristics in the protein sequences. Devising efficient models, computationally or stochastically, to identify potentially *functional motifs* is the first essential step toward realising protein function.

There are numerous databases containing small collections of mini-motifs that are mostly defined by a function, such as glycosylation or phosphorylation. Thus, in order to determine whether a protein contains consensus motifs for these functions, one must know the function that is being searched. This approach is not conducive to identifying new functions of proteins. Since so many mini-motifs have been identified, most scientists are familiar with only a subset of the broad functional range of these motifs. This is a current limitation in the study of protein functions. Analogous to one of the protein domain databases (Pfam, CDD, or Swissprot) that contain nearly all known protein domains, we have generated a database of mini-motifs in proteins having a broad functional spectrum.

We searched the scientific literature using Pubmed and several existing databases and collected 312 consensus mini-motifs that target proteins for a specific biological function. From the frequency of papers identifying a mini-motif, as determined based on a sample of randomly selected papers from Pubmed, it can be roughly estimated that 2 500 mini-motifs have been reported in the literature. So far, most entries in our database are for intracellular mini-motifs in eukaryotes. We will continue to expand the categories as well as the database, adding receptor/adhesion molecular ligand-binding motifs, and motifs from plant, archaebacteria, bacteria, fungi, and viruses.

This project, led by Dr. Sanguthevar Rajasekaran (CSE, UConn) and Dr. Marty Schiller (Neuroscience, UConn Health Center), with the participation of Drs. M. Gryk, M. Maciejewski (Neuroscience, UConn Health Center) and C.-H. Huang (CSE, UConn), has yielded a web-based program (SMS, simple motif search) [9] to search the proteome database for the presence of mini-motifs in protein queries. The SMS downloads our mini-motif database and several other NCBI databases (RefSeq, LocusLink, HomoloGene, Taxonomy, Pfam, and dbSNP databases) as the input and analyses for potentially functional mini-motifs.

The SMS program has searched proteins for the presence of the 312 mini-motifs in our mini-motif database. A proteome enrichment factor for each mini-motif is calculated by dividing the observed number of occurrences of a mini-motif in a proteome by the predicted number, which is based on the probability and the amino-acid frequencies in each proteome. We used the SMS to analyse several proteomes. Statistics show that several mini-motifs are enriched in the human proteome and that the Abelson tyrosine kinase (Abl) SH3 domain ligand mini-motif is the most enriched mini-motif, at 673 368-fold. Of the 312 motifs examined,

eight mini-motifs are more than 100-fold enriched and 28 mini-motifs are more that five-fold enriched. The highly enriched mini-motifs represent a broad range of functional categories and are not limited to one or few functions. These results suggest that the functions of these mini-motifs are commonly used in proteins. While one may expect evolutionary selection against mini-motifs in proteins where they are non-functional, analysis of the eukaryotic proteomes shows this is not the case. Only 15 of the 312 mini-motifs examined in the human proteome are less that 0.75-fold enriched, which is also representative of the six other species (mouse, rat, fly, rice, watercress, and yeast) examined [10].

The project is currently in the phase of further developing effective computation models and efficient novel computational techniques to select computationally significant mini-motifs in protein databases. In addition, a unified scoring scheme, incorporating probabilistic analysis, homology analysis, subcellular localisation analysis, domain linker region analysis, and protein surface analysis, is being devised to reduce false-positives. This is an important step toward experimentally validating the biological significance of the selected mini-motifs and further unravelling protein functions. The unified filtering scheme will also consider the *known biology* of a protein, while selecting mini-motifs for experimental verification. For example, Grb2 is an adaptor that links receptor tyrosine kinases to signalling in the mitogen activated kinase (MAPK) pathway. In these cases, identifying an Erk docking site and a 14–3–3 binding site on Grb2 is of interest concerning its functions, because these motifs bind Shc, Raf, and Erk, important proteins in the MAPK signalling pathway. This project will result in a follow-up collaborative research project with biologists to experimentally verify the functionalities of the selected mini-motifs, which will be of essential importance to deciphering gene functions, investigating protein functions, and to identifying novel targets for the development of insecticides, antibiotics, antiviral drugs, and health-related drugs.

Dozens of publicly accessible protein databases are available worldwide and are actively curated and updated. To facilitate cross-species, cross-domain, and integrated protein data analysis, the project will use the Bio-Grid to automatically integrate and analyse those target download sites. The monitoring server of the Bio-Grid will constantly probe database download sites for information update so that the database is complete and up-to-date.

Ergometric bike design

Led by researchers from the School of Allied Health (Dr. Pouran Faghri) and Computer Science and Engineering (Dr. Sanguthevar Rajasekaran) at the University of Connecticut, the project aims to develop a real-time learning system that will be embedded into a functional electrical stimulation (FES)-induced leg cycling system to provide highly efficient cycling performance in people with disability. The learning model will be person-specific and will involve novel real-time (continuous) person-specific learning algorithms that incorporate physiological data from the subject and history data from developed (discrete) musculoskeletal

models to provide proper sequencing of FES to appropriate muscle groups to obtain the most efficient function (hybrid learning system). For this project, we will use FES-induced leg cycle ergometry as a test bed and provide optimal FES timing and sequencing to leg muscles for the most efficient cycle ergometry. This FES-induced leg cycling system will offer additional flexibility by adjusting control parameters to cater to the rider, allowing target cycling speed to be user-defined, and the timing and magnitude of stimulation to be adjusted during and between exercise training. To develop the model, we will collect physiological, kinetic, and kinematic data from a group of spinal-cord-injured (SCI) individuals during FES-induced leg cycle ergometry at different electrical stimulation intensities and flywheel resistances, as well as from a group of able-bodied individuals during different flywheel resistances without FES. A forward dynamic musculoskeletal model of semi-reclined FES-induced leg cycling will be developed to determine ways to improve cycling performance, defined by minimising individual muscle force requirements to turn the pedal crank with maximal power output while delaying the onset of muscle fatigue. We will then incorporate the forward dynamics model as a discrete compartment of the novel, embedded hybrid learning system that will adapt stimulation parameters and sequencing of different muscles, resulting in efficient cycle ergometry for a given individual.

Conclusions

A large number of data-intensive or computation-intensive applications arising from a wide spectrum of life science research, ranging from genetic and proteomic informatics, clinical practice on individuals to social health-care, will greatly benefit from the infrastructure for on-demand information extraction, automated data integration, and analysis. Grids are a step towards bridging the gap between modern information technology and life science. The Bio-Grid initiatives will spark the interest of this inter-disciplinary research and, hopefully, bring life science research and practice into a new era.

References

1. Berman F, Fox G, Hey T (2003) Grid computing: making the global infrastructure a reality. John Wiley & Sons, Brisbane
2. Foster I, Kesselman C (1999) The grid: blueprint for a new computing infrastructure. Morgan Kaufmann, San Francisco
3. Green M, Miller R (2004) Molecular structure determination on a computational and data grid. Proc 4-th IEEE/ACM Symposium on Cluster Computing and the Grid – BioGrid Workshop, CD-ROM
4. Stockinger H, Samar A, Allcock B et al (2001) File and object replication in data grids. Proceedings of 10th IEEE Symposium on High Performance and Distributed Computing (HPDC)
5. Lee C-W, Huang C-H, Rajasekaran S (2003) TROJAN: a scalable parallel semantic

network system. Proceedings of the 15th IEEE International Conference on Tools with Artificial Intelligence, pp 219–223
6. Lindberg D, Humphreys B, McCray A (1993) The unified medical language system. Methods Inf Med 32(4):281–291
7. McCray A, Srinivasan S, Browne A (1994) Lexical methods for managing variation in biomedical terminologies. Proc Annual Symposium Compu Appl Med Care, pp 235–239
8. Lee C-W, Huang C-H, Yang L et al (2004) Path-based distributed knowledge inference in semantic networks, J Supercomputing 29(2):211–227
9. Balla S, Thapar V, Huang C-H et al (2005) SMS: A new tool for investigating protein functions. Nat Methods (In press)
10. Butler R, Engert D, Foster I et al (2000) A national-scale authentication infrastructure. IEEE Transactions on Computer 33(12):60–66

ANTIBIOTICS

Chapter 11

The classifications of antibiotics

R. De Gaudio

The performance of antimicrobial therapy depends on the drug, the host, and the infecting agent [1]. In the clinical setting, the interactions between these three factors are complex and they result in a dose–response relationship that is difficult to predict [2]. However, the choice of the appropriate drug at the appropriate dosage is fundamental for therapeutic success and for avoiding the emergence of resistant strains [3].

Classical chemical classification

The classical chemical classification of systemic antibiotics that is used in the ICU setting, i.e. beta-lactams, aminoglycosides, fluoroquinolones, macrolides, glycopeptides, polymixins, oxazolidones, and streptogramins, remains useful at the beginning of the complex strategy leading to the appropriate antibiotic therapy in the specific clinical situation [3]. Even though more recent classifications based on susceptibility tests and pharmacodynamic–pharmacokinetic interactions have made this approach obsolete [4, 5], it at least suggests when a class of antibiotics should not be used because of the natural resistance of the microorganism implicated in the specific infection [3]. For example, gram-negative strains are naturally resistant to glycopeptides, and intracellular pathogens are naturally resistant to beta-lactams [3]. Selection of the appropriate antimicrobial drug cannot be based only on natural resistance of the specific bacterial strain, but must also consider possible acquired resistances that are becoming widespread across every classical chemical class of antibiotic [6].

Classification based on pharmacokinetic–pharmacodynamic models: the MIC approach

Since some acquired resistances are difficult to predict, the selection of an antimicrobial drug based solely on the classical chemical classification without susceptibility tests is often misleading and even dangerous for the outcome of the infected patient. The purpose of susceptibility tests is to evaluate the drug potency against a population of potential pathogens [7]. Usually, the susceptibility test parameter most important for dose and drug selection is the minimum inhibitory concentra-

tion (MIC), which is the lowest concentration that completely inhibits visible growth of the organism as detected by the unaided eye after an 18- to 24-h incubation period with a standard inoculum of approximately 10 0000 CFU/ml [8]. Therefore, MIC is a static in vitro parameter.

The interactions between antibiotic pharmacokinetics and pharmacodynamics have been studied using MIC-based models that try to adjust the doses of antibiotic therapy to achieve antibiotic plasma concentrations above MIC for the respective pathogen throughout the dosing interval. In these approaches, the pharmacokinetic parameter is usually the serum concentration of the anti-infective agent, and the pharmacodynamic parameter is usually MIC [9–11]. The parameters developed by studying these models include time above the MIC (t > MIC), the ratio of peak concentration and MIC (C_{max}/MIC), and the ratio of 24-h area under the curve and MIC (AUC/MIC) [12, 13].

Classification of antibiotics in time-dependent (concentration-independent) and concentration-dependent groups derives from the MIC approach [1, 2]. Time-dependent antibiotics, including beta-lactams, glycopeptides, clindamycin, streptogramins, natural macrolides, and linezolid, have a therapeutic performance that depends on the length of time that the drug is in contact with the bacteria. Their effect will increase with increasing concentrations until a finite point (the maximum kill rate) is reached. After that point, increasing concentrations will not produce a corresponding increase in the effect; therefore, high peak concentration will not help. Maximum killing generally occurs at concentrations approximately four to five times the MIC [14]. The parameter that has been most often used to assess the efficacy of time-dependent antibiotics is the time that the antibiotic plasma concentration exceeds the MIC for a particular microorganism, i.e. the t MIC, which should be 40–100% of the interval between two consecutive doses [15–18]. Concentration-dependent antibiotics, including aminoglycosides, fluoroquinolones, and metronidazole, exhibit a bacterial rate of killing that increases with increasing concentrations of the antibiotic. The goal in this case is to maximise the drug concentration. The parameters that are most currently used are those that reflect an increase in drug concentration, i.e. C_{max}/MIC and AUC/MIC. C_{max}/MIC should be above 10 and AUC/MIC above 100–175 [1, 3].

However, the pharmacodynamic effect in vivo results from a dynamic exposure of the infective agent to the antibiotic drug at the effect site [6, 9]. Static parameters obtained in vitro, such as MIC, give partial and sometimes misleading information about the dynamic situation at the infection site under in vivo conditions [1]. Moreover, pharmacokinetics derived from serum concentrations do not reflect the effective concentrations at the infection site [6, 20]. Therefore, models based on the MIC have several disadvantages, both pharmacokinetic and pharmacodynamic, while the main advantage is that MIC is a well-established laboratory parameter routinely determined in microbiology for the evaluation of efficacy of anti-infective agents. From the pharmacokinetic point of view, the MIC approach compares the MIC to measurements obtained from the concentration–time curve measured in plasma, not considering protein binding and tissue distribution [21]. Protein binding is relevant because only the drug that is unbound from plasma proteins

will be available to exert a pharmacological effect [3]. Tissue distribution also needs to be taken into account, given that most infections occur not in plasma, but in the interstitial space of tissues.

From a pharmacodynamic point of view, the MIC approach provides only limited information on drug action. For instance, MIC does not provide information on the rate of bactericidal activity and whether increasing antimicrobial concentrations can increase this rate [1]. Since MIC determination depends on the number of bacteria at a single time point, many different combinations of growth and kill rates can result in the same MIC. Moreover, MICs are conventionally measured for constant antibiotic concentrations and therefore represent threshold concentrations. This implies the existence of an all-or-nothing concentration–effect relationship. All concentrations below MIC are treated equally. Similarly, no quantitative distinction is made for all concentrations above MIC, whereas concentrations just below it show some anti-infective activity. Moreover, concentrations just above MIC do not show the maximum effect, which is only achieved with higher concentrations [1, 22]. Concluding, static MIC approaches do not reflect the in vivo scenario, in which bacteria are not being exposed to constant but to constantly changing antibiotic concentrations.

From MIC to breakpoint MIC

To overcome some of these disadvantages linked to the MIC approach, the concept of breakpoint MIC has been recently developed [5, 23, 24]. Breakpoint MIC considers the relationship between drug potency, as expressed by MIC, and the pharmacokinetics of the antimicrobial drug in the light of clinical experience [5, 24]. Breakpoints are discriminatory antimicrobial concentrations used in the interpretation of results of susceptibility testing to classify isolates as susceptible, intermediate, or resistant [5, 24]. Classification based on breakpoint MIC takes into account the pathogens but at the same time it tries to give the most relevant classification for an antibiotic drug by separating drugs that are effective against specific pathogens from those that are ineffective [23, 24]. Clinical, pharmacological, and microbiological considerations are all important in different ways in setting MIC breakpoints. Different countries have different approaches to this problem, and these have been coordinated in Europe by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and in the USA by the National Committee for Clinical Laboratory Standards (NCCLS) [8, 23].

Breakpoints MIC is now available for penicillins, cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones [5, 23, 24]. The original formula developed by the British Society for Antimicrobial Chemotherapy (BSAC) is [5, 24]:

$$\text{Breakpoint concentration} = C_{\max} f s / e t$$

where $C_{\max}$ is maximum serum concentration following a stated dose at steady state (1 h post-dose), e is the factor by which the $C_{\max}$ should exceed the MIC. Normally a value of 4 is used, but this may be less for compounds that achieve high

tissue concentrations in relation to their serum levels. *f* is a factor related to protein binding: for protein binding < 70%, *f* = 1; for protein binding 70–90%, *f* = 0.5; and for protein binding > 90%, *f* = 0.2. *t* is a factor (normally 1) related to serum elimination half-life. For a serum elimination half-life between 1 and 3 h, *t* = 1; if it is > 3 h, *t* = 0.5; or if it is < 1 h, *t* = 2. *s* is a shift factor usually equal to 1 and ranging between 0.5 and 2.

The rationale for determining a breakpoint MIC is that a 'susceptible' organism should respond to the standard dose of the agent. A 'resistant' organism should not respond and an 'intermediate' one may or may not respond to standard doses, yet would have an increased chance of responding to a greater dose if the infection is at a site where the antimicrobial is actively concentrated

From the MIC approach to the time-killing curves approach

To overcome the pharmacodynamic disadvantages of the MIC approach, the dynamic relationship between pharmacokinetic and pharmacodynamic factors of antibiotic drugs have been recently faced from a different point of view [1, 25, 26]. In fact, dosages and dosing intervals of antimicrobial agents can now be evaluated with reference to dynamic pharmacokinetic and pharmacodynamic parameters using models based on time-kill curves that evaluate microbial killing and growth as a function of both time and antibiotic concentration [25, 26]. Antibiotic concentration can either be held constant or changed to mimic an in vivo concentration profile, be it in plasma or at the infection site [1]. Kill curves investigate the time course of the antibacterial effect. In vitro models include those with constant antibiotic concentrations, which study the effects of a constant concentration of drug against bacteria as a function of time; and those with variable antibiotic concentrations, in which the antibiotic concentrations fluctuate by dilution or diffusion [1, 25, 26]. Curves in the presence (kill curves) and absence (growth curves) of antibiotic can be compared [1]. According to methods analysing time-killing curves at constant antibiotic concentrations, Garrett [27] grouped the interactions between antibiotic concentration and growth-rate constant of the bacterial population into four classes: Class I interactions are characterised by a linear relationship between the growth-rate constant and the antibiotic concentration. Class II interactions occur when increasing antibiotic concentrations determine a decrease of the growth-rate constant to approach zero. Class III interactions exhibit class I behaviour at low concentrations, which turns into class II behaviour at high concentrations. Class IV interactions are characterised by S-shaped plots of the growth-rate constant vs antibiotic concentrations that may be due to binding of the drug to nutrients at low concentrations [27]. A disadvantage of these approaches is that they do not reflect the clinical situation in which drug concentrations fluctuate. Models with changing antibiotic concentrations try to simulate in vivo concentration-time profiles using human pharmacokinetic parameters in order to assess the antibacterial effect. Changing concentrations can be produced either by dilution or diffusion.

The main concern with dilution models is that the bacterial inoculum is diluted together with the antibiotic. Recently, a simple one-compartment in vitro model was developed to study the pharmacodynamic effect of concentrations of piperacillin against *Escherichia coli*, following administration of constant or fluctuating concentrations [28]. The free interstitial concentrations of the drug reached in humans after different doses and dosing regimens were simulated.

Complex diffusion models to simulate two-compartment pharmacokinetics have been also described [29]. Serially placed bacterial compartments, representing extravascular infection sites, interface with a central compartment through artificial capillaries. The porous capillary walls allow for bidirectional passage of antibiotics but are impermeable to bacteria. Such models can be used for simulation of both continuous and intermittent drug administration [30].

In vitro models were also developed to simulate in vivo conditions in specific infection sites or conditions, such as the bladder [31], bacterial cystitis [32], otitis medium [33], endocarditis [35], chronic pneumonia [36], infected fibrin clots [37], and implant-related infections [38].

Several mathematical models have been proposed to analyse the data derived from experimental kill curves that enable a dynamic interpretation of drug–bacteria interactions. These mathematical models are useful to simulate different dosing scenarios and may be concentration-based, AUC-based, or dose-based. Zhi et al. published the mathematical solutions for linear nonsaturable and nonlinear saturable possible pharmacodynamic interactions between beta-lactam antibiotics and microorganisms. The equations were derived for different dosage regimens, such as single and multiple intravenous bolus and constant infusion at steady state. The authors applied the model to the activity of piperacillin against *Pseudomonas aeruginosa* and concluded that the saturable nonlinear model was appropriate.

A similar approach for concentration-based pharmacokinetic–pharmacodynamic analysis is based on an E_{max} model, where E_{max} is the maximum bacterial killing rate for a certain antibiotic. Such models have been demonstrated to be particularly useful for beta-lactam antibiotics. Firsov et al. used a two-compartment in vitro dynamic model with antibiotic and bacterial dilution to study the effect of antibiotics, and suggested two integral parameters to characterise antimicrobial effect duration (TE) and intensity (IE). TE is the time from the moment of antibiotic administration to the moment when the bacterial count reaches its initial level again, and IE is the area between the microbial growth curves in the presence and absence of an antibiotic [36]. Commonly used predictors of antimicrobial effect (AUC/MIC and $t >$ MIC) were examined for pharmacokinetically different quinolones. Linear correlations were established between IE and log AUC/MIC and log $t >$ MIC [38–42].

A sigmoid dose–response model was used by Craig et al. to characterise the in vivo antimicrobial activity in an animal model. This dose-based method considers also E_{max}. A general disadvantage of AUC- and dose-based analyses is related to the fact that the parameters AUC and dose merely reflect single integrated parameters and not the dynamic profile of the drug concentration in vivo.

Conclusions

The classic chemical classification of antibiotics is still useful in the initial selection of the antibiotic drug. However, since it is a single, static in vitro parameter, the MIC may be useful in dose and drug selection in antimicrobial therapy. Clinically, an in vivo antimicrobial effect is the result of a dynamic exposure of the infective agent to the unbound antibiotic drug fraction at the relevant effect site. Therefore, dynamic pharmacokinetic–pharmacodynamic approaches have been developed to evaluate the dynamic relationship between bacteria and antibiotics. The kill curve approaches followed by pharmacokinetic–pharmacodynamic analysis may provide more meaningful information about the interaction between bacteria and antibiotics because they are functions of concentration and time.

References

1. Mueller M, De la Pena A, Derendorf H (2004) Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. Antimicrobial agents and chemotherapy 48:369–377
2. Craig WA (1998) Choosing an antibiotic on the basis of pharmacodynamics. Ear Nose Throat J 77:7–11
3. Van Saene HKF, Silvestri L, De la Cal MA (2005) In: Gullo A (ed) Infection control in the intensive care unit, 2nd edn. Springer, Milan, pp 91–155
4. Derendorf H, Meibohm B (1999) Modeling of pharmacokinetic/pharmacodynamic (pharmacokinetic-pharmacodynamic) relationships: concepts and perspectives. Pharm Res 16:176–185
5. Mouton JW (2002) Breakpoints: current practice and future perspectives. Int J Antimicrob Agents 19:323–331
6. Liu P, Muller M, Derendorf H (2002) Rational dosing of antibiotics: the use of plasma concentrations versus tissue concentrations. Int J Antimicrob Agents 19:285–290
7. Drusano GL, Preston SL, Hardalo C et al (2001) Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob Agents Chemother 45:13–22
8. National Committee for Clinical Laboratory Standards (1997) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 4th edn. Approved Standard. NCCLS Publication No. M7–A4. National Committee for Clinical Laboratory Standards, Villanova, Palermo, Italy
9. Schentag JJ (1999) Pharmacokinetic and pharmacodynamic surrogate markers: studies with fluoroquinolones in patients. Am J Health Syst Pharm 56:S21–S24
10. Li RC, Zhu M, Schentag JJ (1999) Achieving an optimal outcomein the treatment of infections. The role of clinical pharmacokinetics and pharmacodynamics of antimicrobials. Clin Pharmacokinet 37:1–16
11. Schentag JJ (1999) Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. J. Chemother 11:426–439
12. Madaras-Kelly KJ, Ostergaard BE, Hovde LB et al (1996) Twenty-four-hour area under the concentration-time curve/MIC ratio as a generic predictor of fluoroquinolone antimicrobial effect by using three strains of Pseudomonas aeruginosa and an in vitro pharmacodynamic model. Antimicrob. Agents Chemother 40:627–632

13. Mouton JW, Punt N (2001) Use of the t > MIC to choose between different dosing regimens of beta-lactam antibiotics. J Antimicrob Chemother 47:500–501
14. Nightingale C (1980) Pharmacokinetics of the oral cephalosporins in adults. J Int Med Res 8:2–8
15. Drusano GL (1990) Human pharmacodynamics of beta-lactams, aminoglycosides and their combination. Scand J Infect Dis Suppl 74:235–248
16. Craig WA, Redington J, Ebert SC (1991) Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. J Antimicrob Chemother 27:29–40
17. Vogelman B, Gudmundsson S, Leggett J et al (1988) Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 158:831–847
18. Turnidge JD (1998) The pharmacodynamics of beta-lactams. Clin Infect Dis 27:10–22
19. Drusano GL, Craig WA (1997) Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. J Chemother 9(Suppl 3):38–44
20. Andes D, Craig WA (2002) Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents 19:261–268
21. Derendorf H (1989) Pharmacokinetic evaluation of beta-lactam antibiotics. J Antimicrob Chemother 24:407–413
22. Bouvier d'Yvoire MJY, Maire PH (1996) Dosage regimens of antibacterials. Clin Drug Investig 11:229–239
23. Kahlmeter G, Brown DFJ, Goldstein FW (2003) European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. J Antimicrob Chemother 52:145–158
24. Dudley MN, Ambrose PG (2000) Pharmacodynamics in the study of drug resistance and establishing in vitro susceptibility breakpoints: ready for prime time. Curr Opin Microbiol 3:515–521
25. Guerillot F, Carret G, Flandrois JP (1993) Mathematical model for comparison of time-killing curves. Antimicrob Agents Chemother 37:1685–1689
26. Mueller M, de La Peña A, Derendorf H (2004) Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. Antimicrob Agents Chemother 48:369–377
27. Garrett, ER (1978) Kinetics of Antimicrobial Action. Scand J Infect Dis 14:54–85
28. Nolting A, Dalla Costa T, Rand T et al (1996) Pharmacokinetic-pharmacodynamic modeling of the antibiotic effect of piperacillin in vitro. Pharm Res 13:91–96
29. Blaser J, Stone BB, Zinner SH (1985) Two compartment kinetic model with multiple artificial capillary units. J Antimicrob Chemother 15: 131–137
30. Blaser J, Stone BB, Zinner SH (1985) Efficacy of intermittent versus continuous administration of netilmicin in a two-compartment in vitro model. Antimicrob Agents Chemother 27:343–349
31. Greenwood D, O'Grady F (1978) An in vitro model of the urinary bladder. J Antimicrob Chemother 4:113–120
32. Greenwood D (1985) An in-vitro model simulating the hydrokinetic aspects of the treatment of bacterial cystitis. J Antimicrob Chemother 15:103–109
33. Vance-Bryan K, Larson TA, Garrison MW et al (1992) An in vitro pharmacodynamic model to simulate antibiotic behavior of acute otitis medium with effusion. Pharm Res 9:920–924
34. McGrath BJ, Kang SL, Kaatz GW et al (1994) Bactericidal activities of teicoplanin, vancomycin, and gentamicin alone and in combination against Staphylococcus aureus

in an in vitro pharmacodynamic model of endocarditis. Antimicrob Agents Chemother 38:2034–2040
35. Kutlin A, Roblin PM, Hammerschlag MR (1999) In vitro activities of azithromycin and ofloxacin against Chlamydia pneumoniae in a continuous-infection model. Antimicrob Agents Chemother 43:2268–2272
36. Palmer SM, Rybak MJ (1997) An evaluation of the bactericidal activity of ampicillin/sulbactam, piperacillin/tazobactam, imipenem or nafcillin alone and in combination with vancomycin against methicillin-resistant Staphylococcus aureus (MRSA) in time-kill curves with infected fibrin clots. J Antimicrob Chemother 39:515–518
37. Darouiche RO, Dhir A, Miller AJ et al (1994) Vancomycin penetration into biofilm covering infected prostheses and effect on bacteria. J Infect Dis 170:720–723
38. Blaser J, Vergeres P, Widmer AF et al (1995) In vivo verification of in vitro model of antibiotic treatment of device-related infection. Antimicrob Agents Chemother 39:1134–1139
39. Firsov AA, Shevchenko AA, Vostrov SN et al (1998) Interand intraquinolone predictors of antimicrobial effect in an in vitro dynamic model: new insight into a widely used concept. Antimicrob Agents Chemother 42:659–665
40. Firsov AA, Vostrov SN, Shevchenko AA et al (1998) A new approach to in vitro comparisons of antibiotics in dynamic models: equivalent area under the curve/MIC breakpoints and equiefficient doses of trovafloxacin and ciprofloxacin against bacteria of similar susceptibilities. Antimicrob Agents Chemother 42:2841–2847
41. Firsov AA, Vasilov RG, Vostrov SN et al (1999) Prediction of the antimicrobial effects of trova-floxacin and ciprofloxacin on staphylococci using an in-vitro dynamic model. J Antimicrob Chemother 43:483–490
42. Firsov AA, Vostrov SN, Kononenko OV et al (1999) Prediction of the effects of inoculum size on the antimicrobial action of trovafloxacin and ciprofloxacin against Staphylococcus aureus and Escherichia coli in an in vitro dynamic model. Antimicrob Agents Chemother 43:498–502

Chapter 12

An overview of antibiotic pharmacokinetics

M. Palazzo

Although it would seem obvious that antibiotics benefit patients with infection, the high hospital mortality associated with antibiotic-treated sepsis in critically ill patients suggests otherwise. The success of antibiotics is influenced by immunocompetence, severity of insult, timing of treatment, and physiological reserve. McCabe and Jackson provided the first convincing study assessing the efficacy of antibiotics in patients with gram-negative bacteraemia [1]. They classified patients according to their underlying condition as rapidly fatal, ultimately fatal, or non-fatal. Among those with a rapidly or ultimately fatal condition, as might be expected there was no impact of antibiotics on mortality. However, for those with a non-fatal condition appropriate antibiotics made a highly significant difference. In addition, it has been shown that prompt administration of empirical antibiotics reduces the frequency of shock associated with bacteraemia [2]. More recent intensive care studies have re-emphasised the importance and impact of early administration and appropriate antibiotic use on hospital mortality, with appropriateness based on in vitro sensitivities [3–5].

Although the choice of an antibiotic is clearly important, the dose, method of administration, and consequent pharmacokinetics are also relevant and are the subject of this review.

Measurement of antibiotic activity

Quantification of microorganism susceptibility to antibiotics has classically been measured by in vitro minimum inhibitory concentration (MIC). Unfortunately, MIC fails to reflect in vivo activity partly due to the failure to account for variation in organism growth phases, antibiotic tissue penetration, or protein binding. To provide clinicians with more useful measures of susceptibility, many institutes, such as NCCLS (National Committee for Clinical Laboratory Standards, USA) and BSAC (British Society for Antimicrobial Chemotherapy, UK), have suggested the use of breakpoint minimum inhibitory antibiotic concentrations (breakpoint MIC) for susceptibility testing. Breakpoint MIC is based on known pharmacokinetic and pharmacodynamic data for each combination of antibiotic and organism [6]. Organisms are classified as susceptible (sensitive), resistant, or intermediate susceptible to an antibiotic at breakpoint concentrations. Intermediate susceptibility implies that, although standard antibiotic dosing may not be effective, in some

circumstances higher doses might. Most laboratories have now automated breakpoint-based antibiotic susceptibility testing.

There is good evidence in immunocompetent patients that antibiotic concentrations in excess of susceptibility breakpoint concentrations correlate well with in vivo responses [7, 8]. However, in conditions such as endocarditis, cystic fibrosis, meningitis, and osteomyelitis, in which tissue penetration might be limited, breakpoint MIC has not proved to be as predictive of in vivo outcome as time-kill studies. The latter measure the rate of killing over 48 h with a particular antibiotic concentration.

Concentration-dependent, time-dependent, post-antibiotic effect of antibiotics

The efficacy of some antibiotics is closely related to the peak concentration above breakpoint (concentration-dependent activity), while for others it is better related to the length of time concentrations of the drug sustained above breakpoint MIC (time-dependent activity).

Soon after Florey's introduction of penicillin in 1940, Eagle showed that therapeutic outcome was determined by the aggregate time that penicillin remained above bactericidal levels [9]. A number of investigators have since confirmed that β-lactam efficacy is closely related to the time its concentration remains above MIC [10–12]. Penicillins, cephalosporins, macrolides, carbapenems, clindamycin, linezolid, and glycopeptides are all characterised by time-dependent killing, although glycopeptides may also show concentration-dependent properties.

The precise concentration target above the MIC for time-dependent antibiotics remains a matter of controversy and may also depend on host factors. It is generally thought that concentrations should be four to six times the MIC [13–15]. There is no evidence that even higher concentrations above MIC add to microorganism kill rates [10]. In fact, an interesting observation was made by Eagle in 1948 in this regard. While β-lactams have time-dependent activity, aminoglycosides, fluoroquinolones, amphotericin B, and metronidazole typically exhibit concentration-dependent killing [16].

To quantify the likely effectiveness of antibiotics, various relationships between drug concentration and MIC have been proposed. Concentration-dependent antibiotics are best monitored by the ratio of peak serum antibiotic concentration to MIC, or the ratio of area under the concentration time curve (AUC) to MIC (AUC/MIC), while time-dependent drugs should be evaluated by the time that the serum concentration exceeds MIC (T > MIC) [17].

A number of antibiotics demonstrate the ability to suppress bacterial re-growth after their concentrations have fallen below MIC. This post-antibiotic effect (PAE) has been mostly demonstrated in vitro and should not be confused with the effects caused by sub-minimum inhibitory concentrations (sub-MIC). The latter describes antibiotic concentrations that have failed to exceed MIC at any stage during treatment. Sub-MIC concentrations produce morphological and surface adherence changes and toxin release without inhibiting growth or killing the organism. With the exception of the carbapenems, β-lactams have modest PAE against gram-positive bacteria and little or

no PAE against gram-negative bacteria [18–22]. However, other time-dependent agents, such as macrolides and glycopeptides, may have PAE of up to 6 h against some gram-positive bacteria, such as *Staphylococcus aureus* [18].

Concentration-dependent antibiotics including aminoglycosides and fluroquinolones, show consistent PAE lasting several hours against gram-negative and gram-positive organisms. Metronidazole, clindamycin, and chloramphenicol also have PAE against gram-negative anaerobes. It would appear that, in general, antibiotics with nucleic-acid or protein-synthesis inhibitory activity tend to have PAE.

The antifungal agents amphotericin B and 5-fluorocytosine also have significant in vitro PAE, lasting up to 10 and 7 h, respectively, against *Candida* species [23]. In contrast, imidazoles have little in vitro but significant in vivo PAE [23, 24].

The importance of antibiotics showing PAE, particularly those drugs with time-dependent activity, is that they may be given for sensitive organisms on an intermittent bolus basis without concern for therapeutic failure.

Table 1 outlines details of antibiotics, including their pharmacokinetic properties, frequently used in treating the critically ill. Further data on maximum plasma concentrations following typical dosing and their relationship to MIC has been comprehensively detailed elsewhere [6].

Table 1. Mode of activity and approximate pharmacokinetic values for some antibiotics used in treating the critically ill[a]

Antibiotic (molecular mass)	Action	PAE	PB (%) (l/kg)	App Vd	Metabolism (%)	Renal excretion (% unchanged)
Amoxicillin (419)	T	N	18	0.21	10	60
Cefotaxime (477)	T	N	38	0.3	40	60
Cefuroxime (424)	T	N	33	0.2	None	95
Ceftriaxone (598)	T	N	90	0.14	40	60
Ceftazidime (546)	T	N	17	0.25	None	90
Erythromycin (733)	T	N	18	0.72	65	15
Imipenem (317)	T	Y	20	0.26	25[c]	70
Cilastatin (380)						
Meropenem (437)	T	Y	2	0.3	75	25
Benzyl Penicillin (334)	T	N	60	0.2	20	80
Teicoplanin (1875–1891)	T	Y	89	1.0	2–3	97
Vancomycin (3300)	T	Y	50	0.8	None	100
Linezolid (337)	-T	-N	31	40	65	30
Gentamicin (463)	C	Y	<10	0.3	None	95
Tobramycin (467)	C	Y	<10	0.3	None	95
Piperacillin (539)	T	N	2631	0.2	6	
Tazobactam			26	50	26	
Ciprofloxacin (331)	C	Y	40	2.1	30	50
Clindamycin (461)	T	N	90	1.2	90	10
Metronidazole (171)	C	Y	20	0.8	60	20
Amphotericin B (liposomal)	C	Y	90	131	NK	NK
Fluconazole (306)	T	Y	11	1.0	11	80

[a]The dosing goal for concentration dependent drugs is to maximise concentrations estimated by peak/MIC or AUC/MIC. The goal for time dependent drugs with little PAE is to prolong the time above 4 times MIC. The goal for time dependent drugs with significant PAE is to maximise AUC (area under time concentration curve). A comprehensive list of typical peak concentration following standard dosing is outside the scope of this table but available from other sources [6]

[b] Concentrated in liver then excreted by bile in active form

[c]Metabolised in kidney by dehydropeptidase (DHP). Cilastatin blocks renal DHP

App Vd, Apparent volume of distribution; *T1/2*, elimination half life; *PAE*, significant post antibiotic effect > 2h where known; *PB*,; *T*, time-dependent activity; *C*, concentration-dependent activity; *NK*, not known

Critical illness and pharmacokinetic changes: general considerations

While many drugs, such as inotropes and sedatives, can be titrated with immediate effects, antibiotics have a long lead time and their effectiveness may not be apparent for at least 2 days. Critical illness alters volume distribution while hepatic and renal dysfunction make antibiotic kinetics and effectiveness unpredictable. A clinician faced with a patient failing to respond to treatment has to differentiate between several possibilities, e.g. insufficient antibiotic concentrations, changes in in-vivo organism susceptibility, and the presence of a new pathogen, to explain why in vitro sensitivity is not matched by clinical progress.

As a general rule, volume distribution is greater than normal in critically ill patients. Therefore, for a given patient and antibiotic dose, peak concentrations are lower. This is a good reason for monitoring aminoglycoside peak concentrations at least once in some patients; there should be as much concern for insufficient dose and antibiotic failure as there is for overdosing and toxicity. Volume distribution has a significant effect on antibiotic half-life. If antibiotic clearance (Cl) remains unchanged, the increased volume distribution (Vd) will also proportionally decrease the elimination rate constant (Ke), since clearance = Vd × Ke. Ke is related to half-life ($T_{1/2}$) by Ke = ln2/$T_{1/2}$, and assuming no change in clearance, a rise in Vd prolongs $T_{1/2}$. An increase in Vd that prolongs $T_{1/2}$ might be a useful effect for time-dependent antibiotics but a major disadvantage for concentration-dependent agents that might achieve lower peaks.

Hepatic dysfunction and antibiotic concentrations

The pharmacodynamic effects of antibiotics related to hepatic function are well known. For example, erythromycin, clarithromycin, ciprofloxacin, isoniazid, fluconazole, and itraconazole are potent enzyme inhibitors. Ciprofloxacin and erythromycin inhibit CYP1A2 and thus interfere with theophylline metabolism, which can lead to theophylline toxicity. Other antibiotics are enzyme inducers and may also cause problems. For example, rifampicin induces cytochrome P450 (CYP3A and other families) and may thus result in the failure of concomitantly administered warfarin and HIV protease inhibitors.

The effect of liver dysfunction on antibiotic concentrations is less well-defined. The overall effect of changes in protein binding, apparent volume of distribution, hepatic blood flow, extent of hepatic extraction, enzyme induction, and functional hepatic mass is potentially complex.

Albumin concentrations fall with hepatic and catabolic states, while α-1-acid glycoproteins concentrations rise with inflammatory processes. Albumin, the most abundant protein, binds to acidic drugs and a fall in albumin potentially increases free drug. An increase in α-1-acid glycoproteins, which bind basic drugs, would reduce free drug concentration. Although reduced albumin binding results in more free drug, the latter leads to greater tissue distribution thereby reducing plasma drug concentrations. Concomitant rises in bilirubin concentration displace anti-

biotics from albumin-binding sites, further increasing the free drug concentration and apparent volume distribution. Such changes would normally expose the drug to further hepatic metabolism. The activity of cytochrome P450 may be unchanged, increased, or decreased due to hepatocellular loss, or enzyme induction or inhibition. These numerous interactions restrict the prescription of antibiotics to an individual patient basis.

Fortunately, for the majority of antibiotics hepatic metabolism is limited and antibiotic protein binding is low enough to make no difference regarding their effectiveness. There is therefore little need to alter doses. However patients with severe hepatic disease would require some lowering of drug doses for the few antibiotics metabolised by the liver (chloramphenicol, clindamycin, metronidazole, nafcillin, tetracycline, cefotaxime, and erythromycin).

Renal dysfunction and antibiotic concentrations

Most antibiotics are removed from the body largely unchanged in urine; consequently, oliguria potentially leads to drug accumulation. An increased Vd due to critical illness and fluid overload at the onset of oliguria, however, would dictate that the normal loading doses of antibiotic should at least remain unchanged if not increased, while subsequent doses are given less frequently, particularly in patients with a reduced glomerular filtration rate (GFR) receiving no support. However, patients supported by continuous renal replacement therapy (RRT) could have a GFR ranging from 15 to 60 ml/min, which results in the clearance of antibiotics in a similar manner to a native kidney once clearance rates approximate 35 ml/min. These patients may need no reduction in dosage; in fact, underdosing may lead to some confusion when a patient fails to respond to an apparently appropriate drug. Therefore a clinical judgement must be made that weighs the value of obtaining microbiological control with perhaps slightly elevated concentrations against the risk of toxicity (in most cases, seizures or enzyme changes). Underdosing has the greater risk of ineffective treatment. One approach to estimating whether β-lactams are being administered at effective doses would be to use the surrogate behaviour of aminoglycoside or glycopeptide concentrations under the same circumstances to estimate whether dosing is likely to be too low. Patients receiving intermittent dialysis have average urea clearances over a week of 15 ml/min. Most of the recommendations for reduced dosage are based on this level of renal function.

In very severe infections, such as endocarditis and meningococcal septicaemia, treated with penicillin, the narrow line between ensuring effectiveness and toxicity particular in those with supported acute renal failure is best managed by introducing synergy with a low dose of a second antibiotic, usually an aminoglycoside.

Guidance on antibiotic dosage intervals is based on estimations of $T_{1/2}$, which is related to clearance and volume of distribution by $T_{1/2} = \ln 2\ Vd/Cl$. The clearance of an antibiotic while receiving RRT will be the sum of the clearance by dialysis plus clearance by non-renal means (hepatic metabolism and/or loss through biliary excretion). Clearance by dialysis is usually less than that by fully functioning

normal native kidneys; thus, $T_{1/2}$ will be prolonged and dosage intervals need to be increased in dialysis patients. Typically, penicillins, aminoglycosides, cephalosporins, carbapenems, glycopeptides, and fluconazole have a prolonged $T_{1/2}$ in patients on RRT and need increased dosage intervals. By contrast, chloramphenicol, ceftriaxone, clindamycin, erythromycin, metronidazole, itraconazole, amphotericin B, acyclovir, rifampicin, and to a lesser extent ciprofloxacin have substantial non-renal clearances and $T_{1/2}$ during RRT is only marginally increased.

Clearance on RRT depends on the mode of RRT, flow of filtrate or dialysate, antibiotic molecular mass, and sieving coefficients. Continuous veno-venous haemofiltration (CVVHF) antibiotic clearance is by convection. For this process, the sieving coefficient and ultrafiltration rate are considerably more important than molecular size. On the other hand, continuous haemodialysis (CVVHD), an entirely diffusive process, is molecular-weight-sensitive and better suited to the removal of small molecules below 500 Da. Consequently, the clearance of some antibiotics, such as glycopeptides with molecular masses in excess of 1100 Da is more efficient with CVVHF than with CVVHD.

The sieving coefficient (S) is the fraction of a substance that passes through the filter and is calculated as S = antibiotic concentration in filtrate/[0.5 (antibiotic concentration in afferent + efferent blood)].

For a given haemofiltration rate, clearance is most efficient for those antibiotics with the highest sieving coefficients. These include aminoglycosides, carbapenems, metronidazole and vancomycin, all of which have sieving coefficients between 0.9 and 1. Cefuroxime, cefotaxime, and ceftazidime also have moderately high sieving coefficients (0.9, 0.62, and 0.86, respectively) and are efficiently cleared by haemofiltration. However, drugs with the highest sieving coefficients are also those most influenced by changes in the filtration rate. When the filtration rates are kept high, i.e. 35 ml/min, the tendency to accumulation is small.

Most antibiotics other than vancomycin and teicoplanin are of low molecular mass and thus are easily removed by diffusion during CVVHD.

For this reason, most antibiotics are readily cleared by CVVHDF, and once urea clearances exceed 35 ml/min, there is little need to alter standard dosages or intervals for fear of toxicity. Clearly, a continuous filtration system that is constantly interrupted or used in an intermittent fashion to accommodate investigations or procedures will mimic the lower average clearances of an intermittent dialysis technique in which dosing intervals need to be prolonged. Glycopeptide and aminoglycoside antibiotics can additionally be monitored and provide an indication of what is likely to be happening to other, similar antibiotics.

As a general rule, severely infected patients on intermittent dialysis should initially receive normal antibiotic doses followed by smaller doses given much less frequently. Aminoglycoside measurements that are made post-dialysis determine the troughs, so that non-renal toxicity can be avoided while those made post-administration (off dialysis) are useful to ensure peaks that are appropriate for a concentration-dependent drug.

Antibiotic distribution in tissues

Successful eradication of deep-seated infections depends on achieving bactericidal concentrations at the infection source. The infecting agent may be either within cells, extracellular, or both. *Mycobacteria*, *Salmonella*, *Listeria*, *Legionella*, *Chlamydia*, and *Mycoplasma* species are found mainly in cells, while pyogenic bacteria locate primarily in the extracellular space. The ability of antibiotics to penetrate such sites is related to the type of antibiotic, protein binding, tissue characteristics, and method of antibiotic administration.

Type of antibiotic

β-Lactams and aminoglycosides distribute primarily to the extravascular fluid, although aminoglycosides eventually accumulate by a process of endocytosis in cells and may thus reach two- to four-fold higher intracellular concentrations; however, their intracellular activity is limited. Macrolides, lincosamides (mainly clindamycin), and fluoroquinolones are heavily concentrated in cells through a mechanism of simple diffusion, with partition based on differences in intracellular and extracellular pH, and in the cases of lincosamides and macrolides an active transport system. Macrolides have significant intracellular activity, which makes them potent agents for combating obligate intracellular organisms such as *Legionella*. Lincosamides, however, fail to have enhanced intracellular activity despite achieving high intracellular concentrations. Therefore, the degree of intracellular penetration is not necessarily correlated with antibiotic activity, probably because the subcellular location of antibiotic may not match that of the organism. Equally, while agents with poor cellular penetration are likely to have limited activity against intracellular infections, when higher extracellular concentrations are achieved and time is allowed, treatment can be effective. An example of this would be the use of ampicillin to treat infection with *Listeria monocytogenes* [25].

Influence of protein binding

Antibiotics principally bind to albumin and an equilibrium is established between bound and free antibiotic. Free antibiotic is able to diffuse into tissue and microbes. In vitro and in vivo studies suggest that high intravascular protein binding limits free antibiotic accessibility to tissues and reduces effectiveness [26–28]. Given the mode of action of time-dependent antibiotics with no PAE, which rely on free concentrations to be consistently above MIC, it would seem more prudent to choose a poorly rather than highly bound antibiotic. In an in vivo study, Wise demonstrated the advantage of amoxicillin over flucloxacillin in a blister penetration model. However, he cautioned that the effect of protein binding was not so relevant when the choice was between drugs of relatively low protein binding, i.e. < 70% [27]. Most β-lactams are time-dependent with no PAE and are moderately

bound (10–30%), but ceftriaxone and flucloxacillin are over 80% bound. Other antibiotics, such as ciprofloxacin, vancomycin, tetracycline, and chloramphenicol, are significantly bound (40–60%) while aminoglycosides are poorly bound (<10%). Consequently, for the majority of drugs, protein binding is sufficiently low to not pose a problem of tissue antibiotic availability; however, therapeutic failure of a highly bound agent has been reported [29].

Differences between tissues

The disposition of antibiotics has traditionally been studied by comparing tissue to serum concentration ratios in infected and non-infected tissues. However, differing doses, administration methods, and processing of specimens has resulted in wide variations in estimates of tissue distribution. Notwithstanding, some broad trends can be observed. For example, antibiotic concentrations in ascitic fluid are about 50% those in serum, peak concentrations being achieved some hours after those in serum. A major determinant of relative antibiotic concentrations in serum and fluid filled cavities is the ratio of cavity surface area (SA) to cavity volume (V). High SA/V ratios more closely follow serum concentration fluctuations, while low SA/V ratios typically have dampened peaks and higher troughs [30].

The relative antibiotic concentrations achieved in bronchial secretions, sputum, and lung tissue are of particular interest. For most antibiotics, the concentration achieved in sputum is very low while lung tissue concentrations are considerably higher. Opinion is divided as to whether sputum concentrations are of any importance [31, 32]. Antibiotics, such as ciprofloxacin, cefotaxime, and erythromycin, are concentrated in the lung to concentrations considerably higher than those in plasma and would thus seem to be ideal agents for pulmonary infections. Cruciani reported that while single large doses of vancomycin achieved lung tissue concentrations between 25 and 40% those in blood, by 12 h 43% of patients failed to have any detectable vancomycin in lung tissue [33]. Although one might expect a correlation between higher tissue concentrations and infection cure rates, there remains little data for most antibiotics other than ciprofloxacin [34–37].

Mode of administration and antibiotic availability

Many authors have proposed that β-lactam tissue availability might be better served by continuous infusions rather than intermittent dosing [13, 38–43]. Animal and human studies have explored these proposals. Although the animal studies showed little methodological consistency, the balance of opinion is that continuous infusions are slower to achieve target concentrations but result in a higher average antibiotic tissue concentration over time [44–46]. While the speed of achieving target concentrations is easily resolved with a loading dose, the clinical question remains whether this results in better treatment of infection. Roosendaal attempted to answer this with a series of rat studies using ceftazidime against *Klebsiella pneumoniae* infections [45]. She initially observed that continuous infusion (without a loading dose) did not

produce a significantly better response than intermittent treatment. However, further studies comparing normal and leucopaenic rats infected with *Klebsiella pneumoniae* showed that while continuous infusions were equally effective in both groups of animals, intermittent doses were considerably less effective in the leucopaenic rats. There is evidence that for many antibiotics prediction of clinical outcome with respect to blood antibiotic concentrations seems to be best correlated with the 24-h AUC/MIC ratio, otherwise known as AUIC [47, 37].

Clinical evidence of pharmacokinetic changes in the critically ill

Time-dependent antibiotics

The importance of appropriate antibiotic administration was first alluded to in 1946 by Jawetz, who suggested that the newly discovered penicillin was being given infrequently and at too low a dose, probably because of its wartime scarcity [48]. Except for aminoglycosides and glycopeptides, for which blood concentrations can be routinely measured, inadequate concentrations of other antibiotics can go unrecognised and potentially give rise to a clinical dilemma, i.e. is failure to respond to therapy due to development of resistance, emergence of another organism, or an inadequate dose of the right drug for the original pathogen?

The effects of simple illness on the pharmacokinetics of ceftazidime was studied by Ljungberg in ten febrile but otherwise healthy 80-year-old men [49]. Acute infection was found to be associated with an increase in Vd and renal clearance. In the following year, Shikuma examined piperacillin kinetics in 11 critically ill patients with previously normal renal and hepatic function, and observed a large variation in clearance, $T_{1/2}$ and Vd. The latter varied from 0.1 to 1.3 l/kg (normal value 0.18 ± 0.03 l/kg) and clearance ranged from 7.3–56.4 l/h [50]. The expanded Vds were thought to be due to the requirement for volume expansion therapy and changes in protein concentrations.

In a recent study of critically ill patients receiving recommended doses of ceftazidime, Gomez found that 50% of patients had concentrations four times below the MIC_{90} for *Pseudomonas aeruginosa* for a substantial period of the dosing interval; this was attributed to larger than expected Vd [51]. Lipman reported similar findings using standard doses of the new cephalosporin cefepime and suggested that a 50% increase in dosage (1 g every 4 h) would result in trough concentrations three times the MIC_{50} for *P. aeruginosa* and perhaps be more effective [52]. Similar problems have been noted among severe burns patients, in whom low antibiotic concentrations are sometimes difficult to correct even with higher doses [53–55].

Many investigators feel that antibiotic blood concentration should be at least four to five times the MIC in order to control serious infections [13, 14, 39, 43, 56]. In view of the documented increases in Vd, there is concern that patients might become particularly vulnerable to subtherapeutic concentrations with an intermittent dosing regimen [39, 52]. Some studies have explored whether continuous

antibiotic infusion provides consistently appropriate blood concentrations. Benko, in a cross-over design among 12 critically ill patients, was able to demonstrate that, at steady state, ceftazidime infusions achieved five times the MIC for 100% of the treatment time, whereas intermittent therapy achieved the same concentrations for 92% of the time [13]. Other studies have led to similar findings and indeed have demonstrated in an animal model that for the same daily dose continuous infusion of ceftazidime is more effective than intermittent doses [57, 58]. It has also been suggested, in a study among patients with nosocomial pneumonia, that smaller doses of ceftazidime by infusion might be equally effective and provide a cost saving [59]. However, thus far, there have been no definitive human studies that demonstrate a better outcome with continuous infusion regimens, although some studies are suggestive [60, 61].

A further concern is that sub-therapeutic time-dependent antibiotic concentrations might favour the emergence of resistant organisms. Fantin showed in a rabbit model of endocarditis that the growth of mutants was prevented if antibiotic concentrations remained above MIC for at least 61% of the time [56]. Other studies have suggested that emergence of resistance can only be prevented if concentrations are maintained above MIC for 100% of the time [39].

It has been proposed that vancomycin, a time-dependent antibiotic with a PAE, should be infused in order to achieve constant blood vancomycin concentrations. Two early studies demonstrated that clinical efficacy can be reached when vancomycin is given by infusion. In the first, Brinquin reported cure of post-neurosurgical methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis in eight patients with intravenous vancomycin infusion rates of 37–55 mg/kg/24 h, which achieved CSF penetration (4–7 mg/l) [62]. In the second, Conil demonstrated in burn patients that vancomycin infusions, after an initial loading dose, achieved adequate blood concentrations whereas intermittent doses had failed [63]. Since these early studies, others have demonstrated at least similar clinical outcomes when vancomycin infusion was compared to intermittent dosing with no increase in toxicity, with the advantages of less variability in blood concentration and need for sampling, resulting in cost savings. Loading doses of 15 mg/kg followed by infusions starting at 15–40 mg/kg/day, aimed at achieving plateau concentrations between 15 and 25 mg/l, are generally accepted [64–68].

Among the newer antibiotics, such as linezolid, there is preliminary evidence that administration by continuous infusion is not only more effective than intermittent doses but that in the case of linezolid, normally a bacteriostatic agent, it acquires bactericidal properties [69].

Notwithstanding the theoretical advantages of time-dependent antibiotic infusions, not all β-lactams are best infused. MacGowan suggested that the carbapenems, unlike other β-lactams, also have a concentration effect with variable PAE, particularly against gram negative organisms, and that they might not be more effective by continuous infusion [43].

Concentration-dependent antibiotics

Aminoglycosides, fluoroquinolones, and metronidazole have concentration-dependent activity. In addition, aminoglycosides combine concentration-dependent activity with a consistent PAE against gram-positive and gram-negative bacteria in vivo. This group of antibiotics is water-soluble, mainly distributed to the extracellular space, minimally protein bound, and almost entirely excreted by the kidney. Pennington reported that simply inducing fever in healthy patients resulted in a fall in gentamicin concentrations [70]. These changes were later supported by Triginer, who showed that during septic episodes gentamicin concentrations were lower than expected [71]. He also demonstrated that initiation of intermittent positive pressure ventilation could result in a fall in gentamicin concentrations [72], which was suggested to be due to the increase in Vd associated with critical illness; therefore larger initial doses were recommended.

The idea that gentamicin should be given in doses sufficient to reach high plasma concentrations was alluded to by Moore, in a logistical regression analysis of four studies with a total of 236 patients. A ratio of gentamicin peak plasma concentration (C_{max}) to MIC of 10:1 or more was predictive of a good outcome [73]. Others have shown that to eradicate more serious infections and prevent the emergence of resistance the goal should be a peak concentration at least eight times MIC [74–76]. Kashuba, in a study of patients with gram-negative nosocomial pneumonia, was able to show that it was possible to predict a 90% probability of temperature and leucocyte resolution by the 7th day of treatment if the C_{max}/MIC was equal to or greater than 10 within the first 48 h of starting aminoglycosides [77]. It was also suggested that, by achieving early appropriate peak concentration, the duration of therapy can be shorter and aminoglycoside exposure and toxicity minimised. In a number of meta-analyses, the overall finding has been marginally better clinical responses when large loading doses at extended intervals are compared to multiple dosing regimens [78–81]. Although those studies showed little difference in the incidence of toxicity, a recent, prospective, randomised controlled double-blind study not included in these meta-analyses showed a significant decrease in nephrotoxicity with extended interval dosing [82]. However, there is some evidence that excessive peaks and daily area under the plasma concentration–time curve (AUC) may result in proximal renal tubular damage, while high-pitch deafness has been associated with the duration of therapy [82–84].

Among the many methods suggested for prescribing aminoglycosides, it has become common practice to adopt the nomogram prepared by Nicolau and colleagues at Hartford Hospital, Connecticut, as a guide to interval dosing of gentamicin [85]. This methodology attempts to maximise clinical efficacy and reduce aminoglycoside toxicity. Gentamicin dosing has been aimed at achieving peak concentrations of 20 mg/l to ensure ten times MIC for more difficult infections, such as *P. aeruginosa*. The dosage that consistently achieved this was 7 mg/kg actual body weight and excluding patients 20% over ideal body weight. The nomogram suggests dosing intervals of 24, 36 or 48 h depending on blood gentamicin concentration obtained at any time between 6 and 14 h after the dose. The authors

suggested that patients with reduced renal function should receive normal doses to achieve peak concentrations but repeated doses should be given at extended intervals when concentrations fall to 1 mg/l. Nicolau et al. reported that use of the nomogram on more than 2000 patients reduced the nephrotoxicity rate from a historical 3–5% to 1.2%, and in spite of high peaks only two patient had ototoxicity. Although the Hartford nomogram assumes that peak gentamicin concentrations of 20 mg/l are achieved, after administration of 7 mg/kg many critically ill patients have an increased Vd that might diminish such peaks. It would therefore be prudent in the event of poor therapeutic response to measure peak concentrations before changing therapy.

Other concentration-dependent antibiotics are the 4-quinolones, of which ciprofloxacin is the best example. Some time after its introduction in 1985, the dosage was questioned [34, 86]. Based on AUC, the bio-equivalence of the clinically effective oral dose 750 mg was found to be closer to 600 mg i.v. than the 200 mg i.v. it was licensed for. Since 600 mg produced a C_{max} that was considered toxic, the suggested dose was modified to 400 mg i.v. every 8 h in order to receive FDA approval. In the UK, the recommendation for ciprofloxacin is 400 mg i.v., 12-hourly. Notwithstanding these recommendations, ciprofloxacin continued to be administered at 200 mg i.v. for some time and was frequently associated with the emergence of resistance, sometimes within the treatment period. This was particularly true with *P. aeruginosa* and *S. aureus*, whose MIC were some ten-fold those for *Moraxella sp*. or *Haemophilus sp*. Ciprofloxacin uniquely inhibits bacterial replication by interacting with the active subunit of DNA gyrase, a process which is pH- and concentration-dependent, and it is likely that the emergence of resistance was related to inadequate peak concentrations. The PAE of 4-quinolones has been well-documented [87–89].

It is interesting to note that inadequate concentrations of ciprofloxacin have not only been shown to increase the emergence of strains resistant to ciprofloxacin but also to promote the emergence of strains resistant to antibiotics that have a different mode of action [90].

Studies have confirmed that 400 mg ciprofloxacin i.v., 8-hourly, is required to obtain bacteriological and clinical cure [35, 36]. It has been suggested that the AUIC is a good indicator of antimicrobial activity and is closely associated with the likelihood of clinical or bacteriological cure. AUIC is measured in serum inhibitory units over time (SIT-1) and breakpoints for clinical cure have been identified at 72 SIT-1. However, best results were obtained at values between 250 and 500 SIT-1 [35, 37, 47]. It is notable that Forrest was concerned that, for an organism with MIC above 0.25 mg/l, daily ciprofloxacin doses of 1200 mg might still be inadequate to achieve target AUIC between 250 and 500 SIT-1. He suggested that there was no reason to limit the daily dose to 1200 mg but conceded that a preferred approach might be to seek synergy by introducing another antimicrobial.

Table 2. Tissue penetration of some antibiotics[a]. *R%* Ratio (%) tissue/serum antibiotic concentration after a single dose

	Cells (PMN)		Skeletal muscle		Ascites		Lung		Sputum		Bile		Pleural fluid		CSF	
	I	R%	I	R%	I	R%	I	R%	I	R%	I	R%	I	R%	I	R%
Gentamicin [91–94]	-	21	N	111	Y	90	I	NA	Y	<8	-	64	N	57	Y	2.5
Amoxicillin clavulanic acid [95, 96]	-	-	-	-	N	83	N	32	N	13	-	-	-	-	-	-
Imipenem [97–101]	-	33	N	5	N	85	N	60	N	20	-	48	-	-	Y	8.5
Cefotaxime [102,–106]	110	N	5	Y	120	N	382	y	2	Y	252	N	26	Y	51	
Cefuroxime [107, 108]	-	-	-	-	N	89	-	-	Y	14	-	23	N	30	Y	108
Ceftazidime [109–111, 104]	-	56	N	26	N	45	-	-	Y	18	-	88	N	21	Y	23
Teicoplanin [112]	-	6000	-	-	-	-	-	-	-	-	-	-	-	21	-	-
Vancomycin [91]	-	122	-	-	N	52	-	-	-	-	-	41	N	41	N	0
Amikacin [93, 113–116]	-	-	N	15	N	58	N	40	N	21	N	54	N	40	Y	35
Piperacillin [109, 117–119]	-	<10	Y	32	N	55	N	92	Y	4	-	468	-	-	-	-
Ciprofloxacin [109, 120–123]	-	349	N	79	-	-	N	624	Y	26	-	-	N	26	Y	25

[a]Note that many of these studies had small numbers of patients. Concentrations were measured from multiple sources; e.g. bile was measured from the T tube, gall bladder, or common bile duct. Dosing also varied, e.g. single or multiple, oral IM or IV
For many antibiotics, no data on tissue penetration are available. *I*, tissue infected at the time of measurements; *PMNs*, polymorphonuclear leucocytes; *Y*, yes; *N*, no; *NA*, not available

Conclusions

Specific therapy with antibiotics is one of the influences on outcome which is not always optimised. The evidence would suggest that concentration-dependent agents, such as aminoglycosides, are effective and have fewer side effects when given in large infrequent doses. Equally, there is evidence that time-dependent antibiotics often fail to reach adequate concentrations throughout the treatment period. Adequate therapy can be achieved by an initial loading dose followed by constant infusion. However, to date, there are no randomised controlled prospective trials demonstrating improvement in clinical outcome following infusion rather than intermittent boluses of time-dependent antibiotics. There is a theoretical risk that inadequate antibiotic dosing may not only lead to therapeutic failure, but will also encourage the emergence of resistant strains and inappropriate changing of antibiotics.

Critically ill patients with hepatic dysfunction do not normally need dosage adjustments for most antibiotics, while patients with poor renal function or who are intermittently dialysis-dependent should receive normal antibiotic doses given

less frequently. Patients on continuous RRT with urea clearances above 35 ml/min may need little adjustment to most antibiotic doses. Patient receiving aminoglycosides should be monitored with post-dialysis troughs and post-administration peaks to avoid non-renal antimicrobial toxicity.

Critical illness can grossly alter antibiotic pharmacokinetics, principally through increases in Vd and periods with unsupported renal function. Unfortunately, other than glycopeptides and aminoglycosides, blood concentrations of antibiotics are rarely monitored and therefore adequate concentrations can only be inferred from clinical response. Failure to respond within the first few days of empirical treatment might be due to emergence of antibiotic resistance, emergence of a new organism, or inadequate antibiotic doses for a sensitive organism. The same rigour should be applied to achieving adequate antibiotic concentrations as is applied, for example, to inotropes, which are titrated to achieve predetermined physiological targets.

References

1. McCabe WR, Jackson GG (1962) Gram negative bacteremia. Clinical, laboratory, and therapeutic observations. Arch Intern Med 110:92–100
2. Kreger BE, Craven DE, McCabe WR (1980) Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 68:344–355
3. Rello J, Gallego M, Mariscal D et al (1997) The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 156:196–200
4. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
5. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ (2003) Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. Clin Infect Dis 36:1418–1423
6. MacGowan AP, Wise R (2001) Establishing MIC breakpoints and the interpretation of in vitro susceptibility tests. J Antimicrob Chemother 48(Suppl 1):17–28
7. Bryan CS, Reynolds KL, Brenner ER (1983) Analysis of 1186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. Rev Infect Dis 5:629–638
8. Lorian V, Burns L (1990) Predictive value of susceptibility tests for the outcome of antibacterial therapy. J Antimicrob Chemother 25:175–181
9. Eagle H, Fleischman R, Musselman A (1950) Effect of schedule of adminstration on the therapeutic efficacy of penicillin. Am J Med 9:280–299
10. Vogelman B, Craig WA (1986) Kinetics of antimicrobial activity. J Pediatr 108:835–840
11. Gerber AU, Feller Segessenmann C (1985) In-vivo assessment of in-vitro killing patterns of Pseudomonas aeruginosa. J Antimicrob Chemother 15(Suppl A):201–206
12. Drusano GL, Forrest A, Snyder MJ et al (1988) An evaluation of optimal sampling strategy and adaptive study design. Clin Pharmacol Ther 44:232–238
13. Benko AS, Cappelletty DM, Kruse JA, Rybak MJ (1996) Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. Antimicrob Agents Chemother 40:691–695

14. Mouton JW, den Hollander JG (1994) Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 38:931–936
15. Manduru M, Mihm LB, White RL et al (1997) In vitro pharmacodynamics of ceftazidime against Pseudomonas aeruginosa isolates from cystic fibrosis patients. Antimicrob Agents Chemother 41:2053–2056
16. Craig WA, Ebert SC (1990) Killing and regrowth of bacteria in vitro: a review. Scand J Infect Dis Suppl 74:63–70
17. Thomas JK, Forrest A, Bhavnani SM et al (1998) Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. Antimicrob Agents Chemother 42:521–527
18. Vogelman B, Gudmundsson S, Turnidge J et al (1988) In vivo postantibiotic effect in a thigh infection in neutropenic mice. J Infect Dis 157:287–298
19. Gudmundsson S, Vogelman B, Craig WA (1986) The in-vivo postantibiotic effect of imipenem and other new antimicrobials. J Antimicrob Chemother 18(Suppl E):67–73
20. Hostacka A, Karelova E (1997) Outer membrane proteins profiles of Pseudomonas aeruginosa after the post-antibiotic effect of imipenem. Microbios 90:45–50
21. Fuentes F, Martin MM, Izquierdo J et al (1995) In vivo and in vitro study of several pharmacodynamic effects of meropenem. Scand J Infect Dis 27:469–474
22. Hanberger H, Svensson E, Nilsson LE, Nilsson M (1995) Pharmacodynamic effects of meropenem on gram-negative bacteria. Eur J Clin Microbiol Infect Dis 14:383–390
23. Turnidge JD, Gudmundsson S, Vogelman B, Craig WA (1994) The postantibiotic effect of antifungal agents against common pathogenic yeasts. J Antimicrob Chemother 34:83–92
24. Andes D, van Ogtrop M (1999) Characterization and quantitation of the pharmacodynamics of fluconazole in a neutropenic murine disseminated candidiasis infection model. Antimicrob Agents Chemother 43:2116–2120
25. Barza M (1994) Challenges to antibiotic activity in tissue. Clin Infect Dis 19:910–915
26. Gerding DN, Van Etta LL, Peterson LR (1982) Role of serum protein binding and multiple antibiotic doses in the extravascular distribution of ceftizoxime and cefotaxime. Antimicrob Agents Chemother 22:844–847
27. Wise R, Gillett AP, Cadge B et al (1980) The influence of protein binding upon tissue fluid levels of six beta-lactam antibiotics. J Infect Dis 142:77–82
28. Merrikin DJ, Briant J, Rolinson GN (1983) Effect of protein binding on antibiotic activity in vivo. J Antimicrob Chemother 11:233–238
29. Chambers HF, Mills J, Drake TA, Sande MA (1984) Failure of a once-daily regimen of cefonicid for treatment of endocarditis due to Staphylococcus aureus. Rev Infect Dis 6(Suppl 4):S870–S874
30. Van Etta LL, Peterson LR, Fasching CE, Gerding DN (1982) Effect of the ratio of surface area to volume on the penetration of antibiotics in to extravascular spaces in an in vitro model. J Infect Dis 146:423–428
31. Lambert HP (1978) Clinical significance of tissue penetration of antibiotics in the respiratory tract. Scand J Infect Dis Suppl 14:262–266
32. Pennington JE (1981) Penetration of antibiotics into respiratory secretions. Rev Infect Dis 3:67–73
33. Cruciani M, Gatti G, Lazzarini L et al (1996) Penetration of vancomycin into human lung tissue. J Antimicrob Chemother 38:865–869
34. Echols RM (1993) The selection of appropriate dosages for intravenous ciprofloxacin. J Antimicrob Chemother 31:783–787

35. Forrest A, Nix DE, Ballow CH et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37:1073–1081
36. Lipman J, Scribante J, Gous AG et al (1998) Pharmacokinetic profiles of high-dose intravenous ciprofloxacin in severe sepsis. The Baragwanath Ciprofloxacin Study Group. Antimicrob Agents Chemother 42:2235–2239
37. Highet VS, Forrest A, Ballow CH, Schentag JJ (1999) Antibiotic dosing issues in lower respiratory tract infection: population-derived area under inhibitory curve is predictive of efficacy. J Antimicrob Chemother 43(Suppl A):55–63
38. Rotschafer JC, Zabinski RA, Walker KJ (1992) Pharmacodynamic factors of antibiotic efficacy. Pharmacotherapy 12:64S-70S
39. Young RJ, Lipman J, Gin T et al (1997) Intermittent bolus dosing of ceftazidime in critically ill patients. J Antimicrob Chemother 40:269–273
40. Ronchera-Oms CL, Gregorio S, Sanllehi N (1997) Should continuous infusion of beta-lactam antibiotics be the first-line approach? J Clin Pharm Ther 22:159–161
41. Thalhammer F, Traunmuller F, El Menyawi I et al (1999) Continuous infusion versus intermittent administration of meropenem in critically ill patients. J Antimicrob Chemother 43:523–527
42. Lipman J, Gomersall C, Gin T et al (1999) Continuous infusion ceftazidime in intensive care: a randomised controlled trial. J Antimicrob Chemother 43:309–311
43. MacGowan AP, Bowker KE (1998) Continuous infusion of beta-lactam antibiotics. Clin Pharmacokinet 35:391–402
44. Peterson LR, Gerding DN, Fasching CE (1981) Effects of method of antibiotic administration on extravascular penetration: cross-over study of cefazolin given by intermittent injection or constant infusion. J Antimicrob Chemother 7:71–79
45. Roosendaal R, Bakker Woudenberg IA (1990) Impact of the antibiotic dosage schedule on efficacy in experimental lung infections. Scand J Infect Dis Suppl 74:155–162
46. Mouton JW, Horrevorts AM, Mulder PG et al (1990) Pharmacokinetics of ceftazidime in serum and suction blister fluid during continuous and intermittent infusions in healthy volunteers. Antimicrob Agents Chemother 34:2307–2311
47. Hyatt JM, McKinnon PS, Zimmer GS, Schentag JJ (1995) The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. Clin Pharmacokinet 28:143–160
48. Jawetz E (1946) Dynamics of the action of penicillin in experimental animals. Arch Intern Med 77:1–16
49. Ljungberg B, Nilsson Ehle I (1989) Advancing age and acute infection influence the kinetics of ceftazidime. Scand J Infect Dis 21:327–332
50. Shikuma LR, Ackerman BH, Weaver RH et al (1990) Effects of treatment and the metabolic response to injury on drug clearance: a prospective study with piperacillin. Crit Care Med 18:37–41
51. Gomez CM, Cordingly JJ, Palazzo MG (1999) Altered pharmacokinetics of ceftazidime in critically ill patients. Antimicrob Agents Chemother 43:1798–1802
52. Lipman J, Wallis SC, Rickard C (1999) Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. Antimicrob Agents Chemother 43:2559–2561
53. Friedrich LV, White RL, Kays MB et al (1991) Aztreonam pharmacokinetics in burn patients. Antimicrob Agents Chemother 35:57–61
54. Boucher BA, Kuhl DA, Hickerson WL (1992) Pharmacokinetics of systemically administered antibiotics in patients with thermal injury. Clin Infect Dis 14:458–463
55. Bourget P, Lesne Hulin A, Le Reveille R et al (1996) Clinical pharmacokinetics of

piperacillin-tazobactam combination in patients with major burns and signs of infection. Antimicrob Agents Chemother 40:139–145
56. Fantin B, Farinotti R, Thabaut A, Carbon C (1994) Conditions for the emergence of resistance to cefpirome and ceftazidime in experimental endocarditis due to Pseudomonas aeruginosa. J Antimicrob Chemother 33:563–569
57. Nicolau DP, Nightingale CH, Banevicius MA et al (1996) Serum bactericidal activity of ceftazidime: continuous infusion versus intermittent injections. Antimicrob Agents Chemother 40:61–64
58. Robaux MA, Dube L, Caillon J et al (2001) In vivo efficacy of continuous infusion versus intermittent dosing of ceftazidime alone or in combination with amikacin relative to human kinetic profiles in a Pseudomonas aeruginosa rabbit endocarditis model. J Antimicrob Chemother 47:617–622
59. Nicolau DP, McNabb J, Lacy MK et al (2001) Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 17:497–504
60. Bodey GP, Ketchel SJ, Rodriguez V (1979) A randomized study of carbenicillin plus cefamandole or tobramycin in the treatment of febrile episodes in cancer patients. Am J Med 67:608–616
61. Harding I, MacGowan AP, White LO et al (2000) Teicoplanin therapy for Staphylococcus aureus septicaemia: relationship between pre-dose serum concentrations and outcome. J Antimicrob Chemother 45:835–841
62. Brinquin L, Rousseau JM, Boulesteix G et al (1993) Continuous infusion of vancomycin in post-neurosurgical staphylococcal meningitis in adults. Presse Med 22:1815–1817
63. Conil JM, Favarel H, Laguerre J et al (1994) Continuous administration of vancomycin in patients with severe burns. Presse Med 23:1554–1558
64. Di Filippo A, De Gaudio AR, Novelli A et al (1998) Continuous infusion of vancomycin in methicillin-resistant staphylococcus infection. Chemotherapy 44:63–68
65. Albanese J, Leone M, Bruguerolle B et al (2000) Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. Antimicrob Agents Chemother 44:1356–1358
66. Gauzit R (2002) The use of glycopeptides in intensive care and anaesthesia (French). Ann Fr Anesth Reanim 21:414–417
67. Wysocki M, Delatour F, Faurisson F et al (2001) Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 45:2460–2467
68. Byl B, Jacobs F, Wallemacq P et al (2003) Vancomycin penetration of uninfected pleural fluid exudate after continuous or intermittent infusion. Antimicrob Agents Chemother 47:2015–2017
69. Jacqueline C, Batard E, Perez L et al (2002) In vivo efficacy of continuous infusion versus intermittent dosing of linezolid compared to vancomycin in a methicillin-resistant Staphylococcus aureus rabbit endocarditis model. Antimicrob Agents Chemother 46:3706–3711
70. Pennington JE, Dale DC, Reynolds HY, MacLowry JD (1975) Gentamicin sulfate pharmacokinetics: lower levels of gentamicin in blood during fever. J Infect Dis 132:270–275
71. Triginer C, Izquierdo I, Fernandez R et al (1990) Gentamicin volume of distribution in critically ill septic patients. Intensive Care Med 16:303–306
72. Triginer C, Izquierdo I, Fernandez R et al (1991) Changes in gentamicin pharmacokinetic profiles induced by mechanical ventilation. Eur J Clin Pharmacol 40:297–302
73. Moore RD, Lietman PS, Smith CR (1987) Clinical response to aminoglycoside therapy:

importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 155:93–99
74. Deziel Evans LM, Murphy JE, Job ML (1986) Correlation of pharmacokinetic indices with therapeutic outcome in patients receiving aminoglycosides. Clin Pharm 5:319–324
75. Jackson GG, Lolans VT, Daikos GL (1990) The inductive role of ionic binding in the bactericidal and postexposure effects of aminoglycoside antibiotics with implications for dosing. J Infect Dis 162:408–413
76. Karlowsky JA, Zhanel GG, Davidson RJ, Hoban DJ (1994) Postantibiotic effect in Pseudomonas aeruginosa following single and multiple aminoglycoside exposures in vitro. J Antimicrob Chemother 33:937–947
77. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr (1999) Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 43:623–629
78. Ali MZ, Goetz MB (1997) A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 24:796–809
79. Bailey TC, Little JR, Littenberg B et al (1997) A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 24:786–795
80. Barza M, Ioannidis JP, Cappelleri JC, Lau J (1996) Single or multiple daily doses of aminoglycosides: a meta-analysis. Br Med J 312:338–345
81. Munckhof WJ, Grayson ML, Turnidge JD (1996) A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother 37:645–663
82. Rybak MJ, Abate BJ, Kang SL et al (1999) Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother 43:1549–1555
83. Moore RD, Smith CR, Lietman PS (1984) Risk factors for the development of auditory toxicity in patients receiving aminoglycosides. J Infect Dis 149:23–30
84. Moore RD, Smith CR, Lipsky JJ et al (1984) Risk factors for nephrotoxicity in patients treated with aminoglycosides. Ann Intern Med 100:352–357
85. Nicolau DP, Freeman CD, Belliveau PP et al (1995) Experience with a once-daily aminoglycoside program administered to 2184 adult patients. Antimicrob Agents Chemother 39:650–655
86. Bauernfeind A (1993) Questioning dosing regimens of ciprofloxacin. J Antimicrob Chemother 31:789–798
87. Neu HC, Kumada T, Chin NX, Mandell W (1987) The post-antimicrobial suppressive effect of quinolone agents. Drugs Exp Clin Res 13:63–67
88. Alados JC, Gutierrez J, Garcia F et al (1990) Post-antibiotic effect of three quinolones against gram negative isolates from urine. Med Lab Sci 47:272–277
89. Fuentes F, Martin MM, Izquierdo J et al (1996) Pharmacodynamic effects of ciprofloxacin, fleroxacin and lomefloxacin in vivo and in vitro. Chemotherapy 42:354–362
90. Fung Tomc J, Kolek B, Bonner DP (1993) Ciprofloxacin-induced, low-level resistance to structurally unrelated antibiotics in Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 37:1289–1296
91. Van der Auwera P, Matsumoto T, Husson M (1988) Intraphagocytic penetration of antibiotics. J Antimicrob Chemother 22:185–192
92. Gerding DN, Hall WH, Schierl EA (1977) Antibiotic concentrations in ascitic fluid of patients with ascites and bacterial peritonitis. Ann Intern Med 86:708–713
93. Thys JP, Vanderhoeft P, Herchuelz A et al (1988) Penetration of aminoglycosides in uninfected pleural exudates and in pleural empyemas. Chest 93:530–532

94. Vacek V, Hejzlar M, Skalova M (1969) Penetration of antibiotics into the cerebro-spinal fluid in inflammatory conditions. 3. Gentamicin Int Z Klin Pharmakol Ther Toxikol 2:277–279
95. Grange JD, Gouyette A, Gutmann L et al (1989) Pharmacokinetics of amoxycillin/clavulanic acid in serum and ascitic fluid in cirrhotic patients. J Antimicrob Chemother 23:605–611
96. Cook PJ, Andrews JM, Woodcock J et al (1994) Concentration of amoxycillin and clavulanate in lung compartments in adults without pulmonary infection. Thorax 49:1134–1138
97. Jacobs RF, Thompson JW, Kiel DP, Johnson D (1986) Cellular uptake and cell-associated activity of third generation cephalosporins. Pediatr Res 20:909–912
98. Kummel A, Schlosser V, Petersen E, Daschner FD (1985) Pharmacokinetics of imipenem-cilastatin in serum and tissue. Eur J Clin Microbiol 4:609–610
99. Rolando N, Wade JJ, Philpott Howard JN et al (1994) The penetration of imipenem/cilastatin into ascitic fluid in patients with chronic liver disease. J Antimicrob Chemother 33:163–167
100. Muller Serieys C, Bergogne Berezin E, Rowan C, Dombret MC (1987) Imipenem penetration into bronchial secretions. J Antimicrob Chemother 20:618–619
101. Mayer M, Tophof C, Opferkuch W (1988) Bile levels of imipenem in patients with T-drain following the administration of imipenem/cilastatin. Infection 16:225–228
102. Hand WL, King Thompson NL (1989) The entry of antibiotics into human monocytes. J Antimicrob Chemother 23:681–689
103. Runyon BA, Akriviadis EA, Sattler FR, Cohen J (1991) Ascitic fluid and serum cefotaxime and desacetyl cefotaxime levels in patients treated for bacterial peritonitis. Dig Dis Sci 36:1782–1786
104. Soussy CJ, Deforges LP, Le Van Thoi J et al (1980) Cefotaxime concentration in the bile and wall of the gallbladder. J Antimicrob Chemother 6:A125–130
105. Lode H, Kemmerich B, Gruhlke G et al (1980) Cefotaxime in bronchopulmonary infections—a clinical and pharmacological study. J Antimicrob Chemother 6:A193–198
106. Belohradsky BH, Bruch K, Geiss D et al (1980) Intravenous cefotaxime in children with bacterial meningitis. Lancet 1:61–63
107. Lechi A, Arosio E, Xerri L et al (1982) The kinetics of cefuroxime in ascitic and pleural fluid. Int J Clin Pharmacol Ther 20:493–496
108. Swedish Study Group (1982) Cefuroxime versus ampicillin and chloramphenicol for the treatment of bacterial meningitis. Report from a Swedish Study Group. Lancet 1:295–299
109. Koga H (1987) High-performance liquid chromatography measurement of antimicrobial concentrations in polymorphonuclear leukocytes. Antimicrob Agents Chemother 31:1904–1908
110. Adam D, Reichart B, Williams KJ (1983) Penetration of ceftazidime into human tissue in patients undergoing cardiac surgery. J Antimicrob Chemother 12:A269–273
111. Benoni G, Arosio E, Raimondi MG et al (1985) Pharmacokinetics of ceftazidime and ceftriaxone and their penetration into the ascitic fluid. J Antimicrob Chemother 16:267–273
112. Maderazo EG, Breaux SP, Woronick CL et al (1988) High teicoplanin uptake by human neutrophils. Chemotherapy 34:248–255
113. Lanao JM, Dominguez Gil A, Macias JG et al (1980) The influence of ascites on the pharmacokinetics of amikacin. Int J Clin Pharmacol 18:57–61
114. Dull WL, Alexander MR, Kasik JE (1979) Bronchial secretion levels of amikacin. Antimicrob Agents Chemother 16:767–771

115. Bermudez RH, Lugo A, Ramirez Ronda CH et al (1981) Amikacin sulfate levels in human serum and bile. Antimicrob Agents Chemother 19:352–354
116. Yogev R, Kolling WM (1981) Intraventricular levels of amikacin after intravenous administration. Antimicrob Agents Chemother 20:583–586
117. Hary L, Smail A, Ducroix JP et al (1991) Pharmacokinetics and ascitic fluid penetration of piperacillin in cirrhosis. Fundam Clin Pharmacol 5:789–795
118. Mouton Y, Caillaux M, Deboscker Y et al (1985) Etude de la diffusion bronchique de la piperacilline chez dix-huit patients de reanimation. Pathol Biol (Paris) 33:359–362
119. Brogard JM, Jehl F, Blickle JF et al (1990) Biliary pharmacokinetic profile of piperacillin: experimental data and evaluation in man. Int J Clin Pharmacol 28:462–470
120. Gerding DN, Hitt JA (1989) Tissue penetration of the new quinolones in humans. Rev Infect Dis 11:5s1046–1057
121. Fong IW, Ledbetter WH, Vandenbroucke AC et al (1986) Ciprofloxacin concentrations in bone and muscle after oral dosing. Antimicrob Agents Chemother 29:405–408
122. Reid TM, Gould IM, Golder D et al (1989) Respiratory tract penetration of ciprofloxacin. Am J Med 87:60s-61s
123. Joseph J, Vaughan LM, Basran GS (1994) Penetration of intravenous and oral ciprofloxacin into sterile and empyemic human pleural fluid. Ann Pharmacother 28:313–315

Chapter 13

Evidence for immediate adequate parenteral antibiotics

V. Emmi

Over half of all patients admitted to intensive care units (ICUs) receive one or more antimicrobial agents, and most of these are for the treatment of community-acquired and/or nosocomial infections [1]. In a surveillance study, antibiotic use and related costs were prospectively analysed in a general ICU ward over a 1-year period. Antibiotics were prescribed in 61% of admissions. Categorised by indication, 59% of all antibiotic prescriptions were for bacteriologically proven infections, 28% for non-bacteriologically proven infections and 13% for prophylaxis [2]. In the absence of a precise diagnosis of infection, the modern practice of critical care medicine dictates that empirical antibiotic therapy be given [3]. Providing early antimicrobial therapy, which is effective against the microorganisms responsible for infections in hospitalised patients, is recognised as a crucial step for the treatment of acquired infections, along with drainage of infected fluid collections and the debridement or removal of infected tissues or prostheses [4]. Promptly initiating (at the first sign of an infection) appropriate empirical antimicrobial therapy in patients with life-threatening illnesses seems to be the most effective treatment approach [5]. Traditionally empiric treatment has been to start with an inexpensive narrow-spectrum agent, broadening therapy only if a multi-resistant pathogen is identified or the patient deteriorates. This approach may have served to select continuously from a heterogeneous bacterial population, strains that are first-step resistant mutants and, thus, start us on the slippery slope to resistance crises [3]. One strategy that may be adopted was first suggested almost a century ago by Paul Erlich when he advocated to 'frapper fort et frapper vite', which translates to 'hit them hard, hit them fast' [6]. The goal is to facilitate the eradication of infecting microorganisms in a timely and safe manner while minimising the emergence and spread of resistance [7]. Empirical therapy is about getting it right from the start, to optimise outcome, minimise therapeutic failure, minimise potential resistance, and avoid serious side-effects in a cost-effective manner [8].

The high level of use of antimicrobial agents in ICUs favours the appearance of multi-resistant pathogens, the presence of which is associated both with an increased probability of inappropriate initial empiric antimicrobial treatment of infections in a given patient and selection of a multi-resistant endogenous flora that will influence antibacterial policy of that ICU in the future [9].

For clinical research purposes inadequate antimicrobial treatment of infection was defined recently as a microbiological documentation of an infection (i.e. a positive culture result) that was not being effectively treated at the time of its

identification because of absence of antimicrobial agents directed against a specific class of microorganisms, administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant, or the complete absence of antimicrobial treatment [10]. However, appropriateness of antimicrobial treatment needs to be defined more broadly, if we consider its influence on clinical outcomes. An incomplete understanding of antimicrobial drug therapy principles (e.g. appropriate dosages, dosing intervals, and duration of therapy) also contributes to the inappropriate use of antimicrobial agents. Therapy should take into account antimicrobial pharmacodynamics (PD) and pharmacokinetics (PK). PK/PD profiling describes antimicrobial activity as a function of drug concentration and duration of exposure of the host to the drug. PK/PD knowledge can be used to optimise dosing regimens in relation to mechanisms of killing and penetration to sites of infection [4]. Lack of adherence to these requirements can result in suboptimal antibiotic concentrations, which increase the likelihood that antibiotic resistance will occur and the chance that inadequate antimicrobial treatment will be administered.

Failure to treat infections with antimicrobial agents, delays in the administration of adequate antimicrobial treatment, or the initial use of antimicrobial agents to which the identified pathogens are resistant (i.e. inadequate antimicrobial therapy) all appear to increase the risk for hospital mortality.

In order to understand the positive impact that choosing appropriate therapy early on in treatment can have, it is useful to compare what happens when appropriate versus inappropriate therapy is used.

Twenty-five years ago, the intuitive belief that early use of appropriate antibiotic therapy improved outcome from serious infections with Gram-negative bacteria was confirmed. Kreger et al. [11] found that in patients with Gram-negative bacteraemia, mortality was reduced by 50% in patients who received appropriate therapy compared with those who received inappropriate therapy (19.5% vs 37.2%, respectively). In addition, appropriate antimicrobial therapy was associated with a reduction in the frequency of shock.

Recent clinical investigations have demonstrated that the absence of adequate antimicrobial therapy in patients with pneumonia, peritonitis, bacteraemia or meningitis is associated with adverse patient outcomes, including increasing rates of hospital mortality [12–20].

Kollef was the first to evaluate systematically in the ICU setting the relationship between inadequate antimicrobial treatment and hospital mortality in 2 000 consecutive patients admitted to the medical or surgical ICU of a large urban teaching hospital [12]. A total of 169 (25.8%) of the 655 patients assessed to have a clinically recognised infection present while in the ICU initially received inadequate treatment. The occurrence of inadequate antimicrobial treatment of infection was most common among patients with nosocomial infections that developed after treatment of a community-acquired infection (45.2%), followed by patients with nosocomial infections alone (34.3%) and patients with community-acquired infections alone (17.1%) ($p < 0.001$). Prior antimicrobial administration, which leads to the emergence of and colonisation with resistant organisms, was independently asso-

ciated with the administration of inadequate antimicrobial treatment [odds ratio (OR) 3.39; 95% CI 2.88–4.23; $p < 0.001$] .The hospital mortality rate for patients receiving inadequate antibiotic treatment compared with those receiving adequate treatment was 52.1% and 12.2%, respectively ($p < 0.001$). Similarly, the infection-related mortality of infected patients receiving inadequate antimicrobial treatment (42.0%) was significantly greater than that of infected patients receiving adequate antimicrobial treatment (17.7%) [relative risk (RR) 2.37; 95% CI 1.83–3.08; $p< 0.001$]. The main reason for the administration of inadequate antimicrobial therapy was the presence of antibiotic resistance in clinically important pathogens [12].

Appropriateness of empiric therapy and systemic inflammatory response

Since antibiotic therapy is the cornerstone in the treatment of infections, intuitively one can assume that a correct empirical antibiotic therapy may decrease mortality rate in critically ill patients admitted to the ICU with sepsis; however, the influence of adequate antimicrobial therapy on the prognosis of severe sepsis and septic shock had not been clearly proven.

Three recent investigations have been carried out, which tried to highlight this issue. The study conducted by Garnacho-Montero et al. [21] in Sevilla, Spain, has addressed the impact of empirical antibiotic therapy on the outcome of patients who are admitted to the ICU having sepsis, excluding those episodes of sepsis acquired in the ICU. Four-hundred and six patients of 6 950 (5.84%) meeting criteria for sepsis on admission to the ICU were enrolled during a 4-year study period. Nosocomial origin was found in 166 patients (40.9%). A clinical picture of sepsis was present in 105 patients (25.9%), severe sepsis in 116 (28.6%), and septic shock in 185 (45.6%). Forty-six patients who were admitted with sepsis developed severe sepsis or septic shock and 45 patients with severe sepsis developed septic shock. The risk of impairment in the inflammatory condition was significantly higher in patients with inadequate empirical antibiotic therapy than in patients with adequate empirical antibiotic therapy (RR 1.74; 95% CI 1.04–2.95). Inappropriate empirical antimicrobial therapy was also associated with a significant increase in risk of death over the whole population (RR 1.41; 95% CI 1.1–1.8) and with respect to the patients with adequate therapy (RR 1.55; 95% CI 1.2–2.02). Death rate did not differ between patients with hospital-acquired and community-acquired sepsis. Overall mortality rate for sepsis was estimated to be 11.4%. In contrast, progression to severe sepsis and septic shock was associated with mortality rates of 50% and 68.1%, respectively. Adequate antibiotic use reduced mortality rate by 43.4% in patients with septic shock, by 23.1% in those with severe sepsis, and even by 19.8% in those with sepsis. By multivariate analysis, the presence of fungal infection (OR 47.32; 95% CI 5.56–200.97) and previous antibiotic therapy within the last month (OR 2.23; 95% CI 1.1–5.45) were the independent variables related to the administration of inadequate antibiotic therapy. However, choosing an adequate antibiotic therapy did not influence early (< 3-day) mortality rate, which depends on previous comorbidities and the clinical situation at admission, especially the

presence of respiratory and renal failures. Prompt initiation of adequate antimicrobial therapy seems to be essential for achieving the best possible outcomes. In addition to saving lives and stopping the progression of disease, an initial adequate antimicrobial therapy was found to reduce the length of stay by 15 days for surviving patients [21].

Data from the Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial—a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of afelimomab, an antitumour necrosis factor (TNF) $F(ab')_2$ antibody fragment—provided the opportunity to determine the relationship between mortality and the adequacy of early empiric antibiotic treatment in a large group of septic patients. A total of 2 634 patients were enrolled in 157 centres in North America. Ninety-one per cent of enrolled patients received adequate antibiotic support, and the overall mortality rate was 34%, with rates of 33% and 43% for patients receiving adequate and inadequate antibiotic treatment, respectively. Thus, a 10% decrease in the overall crude mortality rate was associated with adequate early empiric antibiotic treatment. Reductions in mortality rates were apparent even among patients with septic shock and positive blood culture results, clinical features associated with the highest in-hospital mortality rates. Several factors were associated with a greater likelihood of inadequate antibiotic treatment, including multiple infecting organisms per patient, fungal infection, and *Pseudomonas aeruginosa* infection [22].

A prospective observational study was conducted in a medical–surgical (16-bed) ICU in an urban teaching hospital in France during a 3-year period to assess the adequacy of empirical antimicrobial therapy prescribed in septic shock patients and to evaluate the relationship between inadequate antimicrobial therapy and 30-day mortality. One hundred and seven patients (3.87% of all admitted patients) requiring ICU admission presented an episode of septic shock. A source of infection with associated microbiological documentation was identified in 78 of 107 patients (72%). Sixty-nine of the 78 patients (89%) received an adequate therapy and nine (11%) received an inadequate regimen. The overall 30-day mortality rate of septic shock patients was 59%. The crude mortality rate (7/9, 78%) was higher in patients receiving inadequate antimicrobial treatment compared to patients receiving an adequate antibiotic treatment (39/69, 56%, $p = 0.2$). Although a significant difference between the mortality of patients receiving inadequate antimicrobial treatment and those receiving adequate antimicrobial treatment was not found (mainly because of the small size of the inadequate therapy group), inadequate antimicrobial therapy led to a 39% excess of hospital mortality (a figure highly clinically relevant) [23].

The influence of the empirical antimicrobial therapy on the prognosis is best documented for infections such as ventilator-associated pneumonia (VAP), or nosocomial bacteraemia.

Inadequate antimicrobial therapy and ventilator-associated pneumonia

Ventilator-associated pneumonia is the most frequent ICU-acquired infection among patients receiving mechanical ventilation. The mortality rate for VAP ranges from 20% to 50% and can reach 70% in some specific settings or when lung infection is caused by high-risk pathogens [24–26]. Patient survival may improve if pneumonia is correctly diagnosed and treated [27]. Treatment failures in patients with VAP represent a complex issue and form a major challenge for clinicians, and are usually associated with adverse outcomes in terms of morbidity. They are expected to occur in about 30–40% of patients developing pneumonia during mechanical ventilation [14]. The lack of response of VAP to antimicrobial treatment can have various potential causes: inadequate antibiotic treatment, concomitant foci of infection, non-infectious conditions, and factors related to the host response [28]. Inadequate empiric initial antimicrobial treatment is the most frequent reason for treatment failure. It may be caused by resistant strains or by an unusual pathogen not covered by the regular antimicrobial treatment approach.

Inappropriate therapy was strongly associated with fatality with a relative OR of 5.81 when multiple logistic regression analysis was used to study risk factors for death in ventilated patients in whom pneumonia developed [29]. Similarly, inappropriate antibiotic treatment was among six independent risk factors for death, selected by the multivariate analysis, as the factor having the most impact on prognosis [30]. In a study that included 113 ventilated patients judged to have a VAP, a statistically significant increase in related mortality as a result of inappropriate early antibiotic therapy was observed, despite a microbially guided change. In 27 patients (23.6%), therapy was replaced because the antimicrobial agents prescribed were ineffective against the microorganisms involved, and this group showed a significantly greater increase in related mortality than did the adequate initial therapy group (37.0 vs 15.6%, $p < 0.05$). Crude mortality for both groups of patients was 63.0 and 41.5% ($p = 0.06$), respectively. The excess mortality caused by inappropriate initial therapy was estimated to be greater than 20% [15].

The influence of the adequacy of initial empiric antibiotic therapy on the outcome of patients with VAP was examined in a prospective multicentre Spanish study designed to assess the frequency of and the reasons for changing empiric antibiotics during the treatment of ICU-acquired pneumonia. Although crude mortality rates of patients receiving adequate and inadequate antibiotic therapy were 32.5 and 34.9% (NS), respectively, attributable mortality was 16.2% in the former group and 24.7% in the latter one ($p = 0.034$). The empiric antibiotic treatment was modified in 214/565 (43.7%) episodes of pneumonia, in 133 (62.1%) cases because of isolation of a microorganism not covered by treatment [14].

In a series of 130 mechanically ventilated patients for suspected VAP in a medical ICU, prior antibiotic administration or its absence remained unchanged in 51 (39.2%) patients based on the mini-BAL culture results, while in another 51 (39.2%) patients, antibiotic therapy was either begun ($n = 7$) or the existing antibiotic regimen was changed ($n = 44$), and in the remaining 28 (21.6%) patients, antibiotic therapy was discontinued altogether. The hospital mortality rates of

these three groups were statistically different: 33.3, 60.8 and 14.3%, respectively ($p < 0.001$) [12]. Luna et al. [13] conducted a prospective observational study in a 15-bed medical and surgical ICU to define how BAL data affected the selection of antibiotics and outcomes of patients with VAP. A total of 132 intubated and mechanically ventilated patients who developed an infiltrate after being hospitalised for > 72 hours were evaluated. All patients underwent a BAL within 24 hours of establishing a clinical diagnosis of VAP, and most received antibiotic therapy before bronchoscopy. Among the 50 BAL-positive patients, therapy was adequate in 16 of 50 (32%) patients, and the mortality rate among these patients was 38% (6/16). Among the 34 remaining BAL-positive patients receiving inadequate therapy, the mortality rate was significantly greater (31/34, 91%, $p < 0.001$). Furthermore, when patients receiving inadequate therapy were switched to adequate therapy based on BAL data, the mortality rate was comparable with that in patients who continued receiving inadequate therapy. A reduced mortality rate among patients receiving adequate therapy was only observed when this therapy was initiated immediately (i.e. before bronchoscopy). These results show that inadequate empirical treatment of infections in critically ill patients is an important determinant of hospital mortality [13].

The predicted factors of mortality due to postoperative pneumonia (POP) and the impact of initial antibiotic therapy on outcome were analysed by Dupont et al. in a study including 200 centres. Polymicrobial pneumonia or non-fermenting Gram-negative bacteria appeared to be a risk factor for inappropriate antibiotic therapy. Five independent predictors for mortality of POP were identified. Despite a trend toward decreased mortality with appropriate initial antimicrobial treatment, no difference was observed between the groups [31].

Recently, a study including 142 patients with bacteriologically confirmed VAP was conducted in six ICUs to test the hypothesis that inappropriateness of antibiotic therapy might play a differential role according to the severity of the illness. Inadequate empiric treatment was associated with a poor outcome only in patients with intermediate or low baseline severity (logistic organ dysfunction score ≤ 4). In this population, the hospital mortality rate was 44 vs 15% in patients receiving adequate treatment ($p = 0.01$). For the more severe patients at the first suspicion of VAP, on the contrary, the adequacy of initial treatment did not influence the prognosis [32]. Previously, only one other study had tried to evaluate the severity indices at the time of VAP diagnosis [33]. The authors showed that when pneumonia is diagnosed, the severity of illness was the most important predictor of survival, and that the presence of *P. aeruginosa* contributed to an excess of mortality, suggesting the importance of the pathogen in prognosis as well.

Survival in patients with hospital-acquired pneumonia depends above all on the degree of severity at the moment of pneumonia diagnosis. Indeed, the impact of hospital-acquired pneumonia on outcome may be greater in some subsets of patients than in others (and consequently, a similar therapeutic intervention may have different effects). This also may be the case at lower extremes of severity: nosocomial infections do not account for significant excess mortality in patients who present high severity of illness [34]. In contrast, the subgroup of patients with

'intermediate' degrees of severity are likely to suffer the largest 'attributable' mortality [35].

The importance of prognostic role played by the adequacy of the initial empiric antimicrobial therapy appears still to be rather controversial. Some studies [36–40] failed to find statistical significance, whereas others [13, 41] showed a significantly higher mortality in patients with inadequate treatment. Additional studies are needed to determine which patient populations are at greatest risk for harm from the initial administration of inadequate antimicrobial therapy. There is a general agreement, however, that inadequate treatment is related to the emergence of resistant pathogens [42, 43] and to a prolonged ICU stay [44].

Inadequate antimicrobial treatment and bloodstream infections

Bloodstream infections (BSI) are among the most serious infections acquired by hospitalised patients who require intensive care. The coexistence of a pathogen population that has an ever-increasing resistance to many antibiotics and a patient population characterised by increasingly complex clinical problems has contributed to increase BSI, particularly those caused by antibiotic-resistant bacteria. Antibiotic resistance may be associated with administration of inadequate antimicrobial therapy for BSI, particularly hospital-acquired BSI (which are associated with higher hospital mortality rates) [45].

The importance of appropriate antimicrobial therapy on the outcome of BSI has been recognised for more than 20 years. It is intuitively obvious that the empirical treatment of bacteraemia should be started as soon as possible. After Kreger's report [11] in 1980, different studies have demonstrated that the mortality rate of bacteraemia can be reduced with adequate use of antibiotics [46–49]. A more recent study was carried out in a university hospital in Israel during the period 1988–1994 to test whether empirical antibiotic treatment that matches in vitro susceptibility of the pathogen (i.e., appropriate treatment) improves survival in patients (n = 3 413) with BSI. Inappropriate antimicrobial therapy was administered to 1 255 patients (36.8%). The mortality rate in patients with bacteraemia given appropriate antimicrobial therapy was 20% compared with 34% in patients given inappropriate treatment ($p < 0.0001$). On a multivariate logistic regression analysis, the contribution of inappropriate empirical treatment to fatality was independent of other risk factors [adjusted odds ratio (AOR) 1.6; 95% CI 1.3–1.9] [50]. Nevertheless, various studies carried out in critically ill patients with bacteraemia could not prove this effectiveness. Rello found that adequate antibiotic therapy did not reduce mortality rate in 111 episodes of bacteraemia [51]. Among 166 ICU patients with bacteraemia, 39 (23.5%) received inadequate antimicrobial treatment. The global mortality rate was 56.4% in this group vs 50.3% in the group given an appropriate antimicrobial treatment (NS) and the related mortality was 30.8 and 22.8%, respectively [52]. In a Spanish multicentre study that enrolled 590 patients with bacteraemia, inadequate antibiotic therapy was not an independent predictor of fatality [53]. In another study in critically ill patients (n = 492), however,

hospital mortality rates in patients (n = 345; 61.9%) who received appropriate antimicrobial treatment were lower than in those (n = 147; 29.9%) who received inappropriate antimicrobial therapy (28.4% vs 61.9%, respectively; $p < 0.001$). Multivariate analysis showed that the administration of inappropriate antimicrobial treatment was the most important risk for hospital mortality (AOR 6.86; 95% CI 5.09–9.24; $p < 0.001$) [54].

The influence of inappropriate empiric antibiotic treatment and systemic response on the outcome was analysed in a population of 339 critically ill patients with community-acquired BSI. Antibiotic treatment was found to be inappropriate in 14.5% of episodes. Crude mortality was 41.5%. Septic shock was present in 184 patients (55%). Patients in septic shock with inappropriate treatment had a survival rate below 20%. The survival benefit for patients receiving adequate initial antibiotic therapy was estimated to be 10.7% in those with an APACHE II score < 15 points at admission, 35% in those with an APACHE II score between 15 and 24 points, and 58.2% for those with a score > 24 points. From these data it appears that patients with BSI at higher risk of death will derive great benefit from therapeutic interventions focusing on survival [55].

Intra-abdominal infections

While there is a clear association between inappropriate initial empiric therapy and poor clinical outcome in patients with community-acquired pneumonia and hospital-acquired pneumonia or bloodstream infections, few studies have been conducted in patients with intra-abdominal infections.

A previous retrospective chart review of patients with bacterial peritonitis underlined the importance of covering all likely pathogens [56]. A more recent retrospective study of intra-abdominal infection found that initial appropriate antibiotic therapy improved clinical success rates and reduced the length of stay and overall cost of hospitalisation [57].

Based on the high mortality rates associated with community-acquired intra-abdominal infection and the need for empiric antibiotic therapy, 425 patients hospitalised in 20 clinics across Germany were followed for a total of 6 521 patient-days. Fifty-four (13%) patients received inappropriate initial parenteral therapy not covering all bacteria isolated. Crude and adjusted analyses showed that appropriateness of initial antibiotic therapy was significantly associated with clinical success, which in turn was associated with reduced length of stay. Patients were more likely to have clinical success if initial antibiotic therapy was appropriate (78.6%; 95% CI 73.6–83.9) rather than inappropriate (53.4%; 95% CI 41.1–69.3). Inappropriate initial therapy was associated with the need for second-line antibiotic therapy, or repeated operation, whereas no association was observed between appropriateness of initial therapy and total mortality [58].

The impact of empirical antibiotics on the outcome of hospital-acquired peritonitis was evaluated in a study including 100 consecutive patients with postoperative peritonitis. The adequacy of empirical treatment was determined by means

of culture and susceptibility data obtained at the time of re-operation, and the effect of such treatment on outcome was evaluated. One hundred resistant pathogens were isolated from the peritoneal fluid or blood of 70 patients (47 multiple resistant pathogens were cultured from samples from 37/70 patients).

Forty-five per cent of those patients died; by comparison, mortality among those from whom susceptible organisms were isolated was 16% ($p < 0.05$). Inadequate empirical treatment was administered to 54 patients and was associated with poorer outcome (mortality 50% vs 26% in the group of patients given appropriate treatment; $p < 0.05$). The outcome of postoperative peritonitis was affected by the choice and adequacy of the initial empirical antibiotic therapy. Late changes in antibiotic therapy based on culture results did not affect outcome when the initial regimen was inadequate [16].

Timing of antibacterial treatment

Appropriateness of initial empiric antimicrobial treatment includes early administrations of agents. The importance of a timely administration of antibiotic treatment was first suggested for community-acquired severe infections such as bacterial meningitis or pneumonia.

Bacterial meningitis

Despite advances in antibiotic therapy, bacterial meningitis continues to cause significant morbidity and mortality [59]. Whether clinical outcomes are influenced more by disease severity or delay in initiation of antibiotic therapy remains a problematic issue [60–62]. Clinical experiences suggest that patient outcome in bacterial meningitis is a result of multiple factors, since some patients treated within a few hours of symptoms develop an adverse outcome, whereas others who are symptomatic for days prior to presentation suffer no adverse sequelae [63]. Standard reference sources have recommended that patients with bacterial meningitis be given antibiotics within 30 minutes of arrival in the emergency department to prevent many of the long-term sequelae associated with this disorder [64, 65]. However, delay in initiation of antibiotic therapy has not been identified as an independent risk factor after adjustment for other variables that affect clinical outcome [66–69]. In a large retrospective cohort study including 269 persons who, between 1970 and 1995, had community-acquired bacterial meningitis microbiologically proven, Aronin et al. [70] stratified patients into three stages of prognostic severity: low- (I), intermediate- (II) and high-risk (III) subgroups, respectively. The effect of antibiotic timing on clinical outcome was analysed: for those who remained in a given prognostic stage, from arrival in the emergency department until their first dose of antibiotics, the median delay in initiation of antibiotic therapy was 4.0 hours and did not differ significantly between patients with and those without an adverse outcome (4.5 hours compared with 3.9 hours; $p > 0.2$). For this entire group of patients ($n = 227$), as well as within each prognostic stage, antibiotic

delay was not statistically significantly associated with adverse clinical outcome. Patients who advanced from stage I to stage III before initiation of antibiotic therapy had a greater proportion of adverse outcomes (3 of 4, 75%) than those who remained in stage I at the initiation of antibiotic therapy (3 of 35, 9%, $p = 0.008$). Similarly, patients who advanced from stage II to stage III before initiation of antibiotic therapy had a significantly greater proportion of adverse outcomes (20 of 32, 63%) than those who remained in stage II at the initiation of antibiotic therapy (56 of 163, 34%, $p = 0.003$). In these subgroups of patients a clear association between antibiotic timing and clinical outcome emerged.

Timing of appropriate antimicrobial therapy, as defined by consciousness level but not by symptom duration, was found to be a major determinant of survival and neurological patient outcomes in a study including 109 adult patients with culture-proven community-acquired bacterial meningitis [71]. Similarly, in a cohort of 30 patients with *Klebsiella pneumoniae* meningitis, a Glasgow coma scale (GCS) score of 7 points or less at the start of appropriate antimicrobial therapy was found to be a valid predictor of death or permanent vegetative state (sensitivity 82%, specificity 93%, $p = 0.005$), even after adjusting for the effect of confounding variables by logistic regression [72]. According to the authors of the last two studies, the first dose of an appropriate antibiotic should be administered before a patient's consciousness deteriorates to a GCS score of 10 or 7 points, respectively, or less. Short and Tunkel [63] reviewed the literature to determine if there is a standard of care for timing of administration of antimicrobial therapy in patients with a diagnosis of acute bacterial meningitis. Although the clinical data are inconclusive, they state that it makes intuitive sense to initiate antimicrobial therapy as soon as possible in any patient with suspected or proven bacterial meningitis, before the patient's illness advances to a high level of clinical severity, beyond which antimicrobial therapy is less likely to be of benefit.

In a recent retrospective case record study, Proulx et al. [73] reviewed 123 cases of adult acute bacterial meningitis. Using multivariate regression analysis to assess the association between meningitis mortality and the time elapsed between emergency room presentation and antibiotic administration (door-to-antibiotic time), the authors found that there was an independent incremental association between delays in administrating antibiotics and mortality from adult acute bacterial meningitis [OR for mortality 8.4 (95% CI 1.7–40.9) for door-to-antibiotic time > 6 h].

The effect of antibiotic timing on clinical outcome is complex, and varies with different levels of disease severity. For patients with confirmed bacterial meningitis, disease severity is the most important predictor of adverse outcome. For those who arrive in the emergency department with the highest level of clinical severity (that is, stage III according to Aronin, or GCS < 7), the risk for adverse outcome is influenced more by the severity of illness than the timing of initial antibiotic therapy. However, treatment of bacterial meningitis before it advances to a high level of clinical severity may improve clinical outcome.

Community-acquired pneumonia

The importance of prompt initiation of empirical therapy was demonstrated by Meehan in a multicentre retrospective cohort study with medical record review including 14 069 patients at least 65 years old hospitalised with pneumonia. The aim of the study was to determine the relationships between processes of care for pneumonia and outcomes: lower 30-day mortality was associated with antibiotic administration within 8 hours of hospital arrival (OR 0.85; 95% CI 0.75–0.96) and blood culture collection within 24 hours of arrival (OR 0.90; 95% CI 0.81–1.00). For every hour sooner that patients received antibiotic therapy, a further reduction in mortality rate was observed [74].

The relative contribution to variation in length of hospital stay (LOS) of quality-of-care variables relevant to the treatment of community-acquired pneumonia was determined in a study examining 100 cases of pneumonia requiring hospitalisation from each of seven institutions, selected among 700 cases. In this population, the process of administering the initial dose of antibiotics in the emergency department was protective (OR 0.42; 95% CI 0.28–0.61). The LOS for patients treated initially in the emergency department was 6.3 ± 3.5 days, while the LOS for patients receiving antibiotic therapy that was started when they reached the inpatient floor was 8.4 ± 4.7 days ($p < 0.001$). On average, patients who received their initial antibiotic treatment in the emergency department had a door-to-needle time of 3.5 ± 1.4 hours, while patients who had their initial antibiotic treatment on the inpatient floor had a door-to-needle time of 9.5 ± 3 hours ($p < 0.001$). Longer door-to-needle time was strongly associated with prolonged LOS (OR 1.75 per 8 hours; 95% CI 1.34–2.29; $p < 0.001$) [75].

More recently, a retrospective study using medical records from a US national random sample of 18 209 Medicare patients older than 65 years who were hospitalised with community-acquired pneumonia was performed. Data from 13 771 (75.6%) patients who had not received outpatient antibiotic agents provide significant associations between antibiotic administration within 4 hours and reduced in-hospital mortality (6.8 vs 7.4%; AOR 0.85; 95% CI 0.74–0.98), mortality within 30 days of admission (11.6 vs 12.7%; AOR 0.85; 95% CI 0.76–0.95) and LOS exceeding 5-day median (42.1 vs 45.1%; AOR 0.90; 95% CI 0.83–0.96) [76].

A number of investigators have found that delays in the administration of appropriate antibacterial treatment are associated with excess hospital mortality in patients with VAP as well.

The study performed by Luna [13] demonstrated that inadequate empirical treatment of infections in critically ill patients is an important determinant of hospital mortality. This underscored the importance for clinicians to select an effective regimen early in the course of infection potentially to minimise mortality and to ensure that therapy is initiated as soon as the clinical diagnosis is established, since a reduced mortality rate among patients receiving adequate therapy was only observed when this therapy was initiated immediately. Alvarez-Lerma showed that among 490 episodes of pneumonia acquired in the ICU setting, attributable mortality from VAP was significantly lower among patients receiving initial, appro-

priate antibacterial treatment than among those receiving inappropriate treatment requiring a treatment change (16.2 vs 24.7%; $p = 0.034$) [14].

Iregui and colleagues especially examined the influence of initially delayed appropriate antibacterial treatment on the outcomes of 107 patients with VAP who eventually received all treatment with an antibacterial regimen active in vitro against the bacterial pathogens isolated from their respiratory secretions. In 33 (30.8%) patients treatment was delayed for ≥ 24 hours after patients initially met diagnostic criteria for VAP. Patients who received delayed antibacterial treatment have a statistically greater hospital mortality rate than those without the delay (69.7 vs 28.4%; p 0.001) [77].

Delays in the administration of appropriate antibacterial treatment have most recently also been associated with greater mortality for patients with severe sepsis [21, 23].

It has become evident that initial antibiotic therapy can influence the outcomes of patients with serious infections. However, it is equally apparent that excessive antibiotic use promotes the emergence and spread of antibiotic-resistant bacterial pathogens frequently isolated from patients in ICUs. There is clearly a need to eliminate overly broad therapy once culture results become available. Therefore, the dilemma of current antibiotic management in ICUs is the balance between providing enough coverage to ensure adequate treatment against likely pathogens and at the same time minimising selection of antibiotic-resistant organisms [78].

References

1. Vincent JL, Bihari DJ, Suter PM et al (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. JAMA 274:639–644
2. Bergmans DC, Bonten MJ, Gaillard CA et al (1997) Indications for antibiotic use in ICU patients: a one-year prospective surveillance. J Antimicrob Chemother 39:527–535
3. Masterton R, Drusano G, Paterson DL (2003) Appropriate antimicrobial treatment in nosocomial infections—the clinical challenges. J Hosp Infect 55:1–12
4. Livingston DH, Deitch EA (1995) Multiple organ failure: a common problem in surgical intensive care unit patients. Ann Med 27:13–20
5. Niederman MS (2003) Appropriate use of antimicrobial agents: challenges and strategies for improvement. Crit Care Med 31:608–616
6. Erlich P (1913) Chemotherapeutics: scientific principles, methods, and results. Lancet 445–451
7. Wenzel RP, Sahm DF, Thornsberry C et al (2003) In vitro susceptibilities of Gram-negative bacteria isolated from hospitalized patients in four European countries, Canada, and the United States in 2000-2001 to expanded-spectrum cephalosporins and comparator antimicrobials: implications for therapy. Antimicrob Agents Chemother 47:3089–3098
8. Cunha BA (2003) Empiric antimicrobial therapy for bacteremia: get it right from the start or get a call from infectious disease. Clin Infect Dis 39:1170–1173
9. Alvarez-Lerma F, Palomar M, Grau S (2001) Management of antimicrobial use in the intensive care unit. Drugs 61:763–775

10. Kollef MH (2000) Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 31(Suppl.4):S131–138
11. Kreger BE, Craven DE, McCabe WR (1980) Gram-negative bacteremia IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 68:344–355
12. Kollef MH, Ward S (1998) The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 113:412–420
13. Luna CM, Vujacich P, Niederman MS et al (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 111:676–685
14. Alvarez-Lerma F (1996) Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-acquired Study Group. Intensive Care Med 22:387–394
15. Rello J, Gallego M, Mariscal D et al (1997) The value of routine microbial investigation in ventilator-associated pneumonia. Am J Resp Crit Care Med 156:196–200
16. Montravers P, Gauzit R, Muller C et al (1996) Emergence of antibiotic-resistant bacteria in cases of peritonitis after intra-abdominal surgery affects the efficacy of empirical antimicrobial therapy. Clin Infect Dis 23:486–494
17. Chow JW, Fine DM, Shlaes DM et al (1991) Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 115:585–590
18. Romero-Vivas J, Rubio M, Fernandez C et al (1995) Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 21:1417–1423
19. Chang VC, Huang CC, Wang ST et al (1997) Risk factor of complications requiring neurosurgical intervention in infants with bacterial meningitis. Pediatr Neurology 17:144–149
20. Heath CH, Grove DI, Looke DF (1996) Delay in appropriate therapy of Legionella pneumonia associated with increased mortality. Eur J Clin Microbiol Infect Dis 15:286–290
21. Garnacho-Montero OJ, Garcia-GArmendia JL, Barrero-Almodovar A et al (2003) Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 31:2742–2751
22. MacArthur RD, Miller M, Albertson T et al (2003) Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 38:284–288
23. Leone M, Bourgoin A, Cambon S et al (2003) Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med 31:462–467
24. American Thoracic Society; Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
25. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
26. National Nosocomial Infections Surveillance (NNIS) (1999) System report, data summary from January 1990–May 1999, issued June 1999. Am J Infect Control 27:520–532
27. Kollef MH (2003) Appropriate empirical antibacterial therapy for nosocomial infections Getting it right for the first time. Drugs 63:2157–2168
28. Jonas M, Ferrer M, Cavalcanti M et al (2003) Treatment failures in patients with ventilator acquired pneumonia. Infect Dis Clin N Am 17:753–771
29. Torres A, Aznar R, Gatell JP et al (1990) Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 142:523–528

30. Celis R, Torres A, Gateli JM et al (1988) Nosocomial pneumonia: a multivariate analysis of risk and prognosis. Chest 93:318–324
31. Dupont H, Montravers P, Gauzit R et al (2003) Outcome of postoperative pneumonia in the Eole Study. Intensive Care Med 29:179–188
32. Clec'h C, Timsit JF, De Lassence A et al (2004) Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity. Intensive Care Med 30:1327–1333
33. Rello J, Rué M, Jubert P et al (1997) Survival in patients with nosocomial pneumonia; impact of the severity of illness and the etiologic agent. Crit Care Med 25:91–97
34. Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A et al (1994) Influence of nosocomial infection on mortality rate in an intensive care unit. Crit Care Med 22:55–60
35. Rello J, Valles J (1998) Mortality as an outcome in hospital-acquired pneumonia. Infect Control Hosp Epidemiol 19:795–797
36. Kollef MH, Silver P, Murphy DM et al (1995) The effect of late-onset ventilator associated pneumonia in determining patient mortality. Chest 108:1655–1662
37. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F et al (1998) Impact of invasive and non-invasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am J Respir Crit Care Med 157:371–376
38. Dupont H, Mentec H, Sollet JP et al (2001) Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. Intensive Care Med 27:355–362
39. Leroy O, Meybeck A, d'Escrivan T et al (2003) Impact of adequacy of initial antimicrobial therapy on the prognosis of patients with ventilator-associated pneumonia. Intensive Care Med 29:2170–2173
40. Ruiz M, Torres A, Ewig S et al (2000) Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am J Respir Crit Care Med 162:119–125
41. Kollef MH, Sherman G, Ward S et al (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115: 462–474
42. Gruson D, Hilbert G, Vargas F et al (2000) Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am J Respir Crit Care Med 162:837–843
43. Kollef MH, Ward S, Sherman G et al (2000) Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. Crit Care Med 28:3456–3464
44. Dennesen PJ, van der Ven AJ, Kessels AG et al (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375
45. Linden PK (1998) Clinical implications of nosocomial gram-positive bacteremia and surperimposed antimicrobial resistance. Am J Med 104(Suppl 5A):24S–33S
46. Gatell JM, Trilla A, Latorre X et al (1988) Nosocomial bacteremia in a large Spanish teaching hospital: analysis of factors influencing prognosis. Rev Infect Dis 10:203–210
47. Uzun O, Akalin HE, Hayran M et al (1992) Factors influencing prognosis in bacteremia due to Gram-negative organisms: evaluation of 448 episodes in a Turkish university hospital. Clin Infect Dis 15:866–873
48. Cisneros JM, Reyes MJ, Pachon J et al (1996) Bacteremia due to *Acinetobacter baumanii:* epidemiology, clinical findings and prognostic features. Clin Infect Dis 22:1026–1032

49. Pedersen G, Schtnheyder HC, Strensen HT (1997) Antibiotic therapy and outcome of monomicrobial Gram-negative bacteremia: a 3-year population-based study. Scand J Infect Dis 29:601–606
50. Leibovici L, Shraga I, Drucker M et al (1998) The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infections. J Intern Med 244:379–386
51. Rello J, Ricart M, Mirelis B et al (1994) Nosocomial bacteremia in a medical-surgical intensive care unit: epidemiologic characteristics and factors influencing mortality in 111 episodes. Intensive Care Med 20:94–98
52. Zaragoza R, Artero A, Camarena JJ et al (2003) The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. Clin Microbiol Infect 9:412–418
53. Vallés J, Leon C, Alvarez-Lerma F (1997) Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Clin Infect Dis 24:387–395
54. Ibrahim EH, Sherman G, Ward S et al (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155
55. Vallés J, Rello J, Ochagavia A et al (2003) Community-acquired bloodstream infection in critically ill adult patients. Impact of shock and inappropriate antibiotic therapy on survival. Chest 123:1615–1624
56. Mosdell DM, Morris DM, Voltura A et al (1991) Antibiotic treatment for surgical peritonitis. Ann Surg 214:543–549
57. Davey P, Libby G, Hunter K et al (2001) How important is appropriate empirical antibiotic treatment for intra-abdominal infections? Value Health 4:126–127
58. Krobot K, Yin D, Zhang Q et al (2004) Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis 23:682–687
59. Durand ML, Calderwood SB, Weber DJ et al (1993) Acute bacterial meningitis in adults. N Engl J Med 328:21–28
60. Talan DA, Zibulewsky J (1993) Relationship of clinical presentation to time to antibiotics for the emergency department management of suspected bacterial meningitis. Ann Emerg Med 22:1733–1738
61. Meadow WL, Lantos J, Tanz RR (1993) Ought 'standard care' be the 'standard of care'? A study of the time to administration of antibiotics in children with meningitis. Am J Dis Child 147:40–44
62. Bryan CS, Reynolds KL, Crout L (1986) Promptness of antibiotic therapy in acute bacterial meningitis. Ann Emerg Med 15:544–547
63. Short WR, Tunkel AR (2001) Timing of administration of antimicrobial therapy in bacterial meningitis. Curr Infect Dis Rep 3:360–364
64. Scheld WM (1994) Bacterial meningitis and brain abscess. In: Isselbacher KJ, Braunwald E, Wilson JD et al (eds.) Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, pp.2296–2309
65. Tunkel AR, Scheld WM (1995) Acute meningitis. In: Mandell GL, Bennett JE, Dolin R (eds.) Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 4th ed. New York, Churchill Livingstone, pp. 831–865
66. Lebel MH, McCracken GH Jr (1989) Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 83:161–167
67. Kallio MJ, Kilpi T, Anttila M et al (1994) The effect of a recent previous visit to a physician on outcome after childhood bacterial meningitis. JAMA 272:787–791
68. Kilpi T, Anttila M, Kallio MJ et al (1993) Length of prediagnostic history related to the

course and sequelae of childhood bacterial meningitis. Pediatr Infec Dis J 12:184–188
69. Quagliarello VJ, Scheld WM (1997) Treatment of bacterial meningitis. N Engl J Med 336:708–716
70. Aronin SI, Peduzzi P, Quagliarello VJ (1998) Community-acquired bacterial meningitis risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 129:862–869
71. Lu CH, Huang CR, Chang WN (2002) Community-acquired bacterial meningitis in adults: the epidemiology, timing of appropriate antimicrobial therapy, and prognostic factors. Clin Neurol Neurosurg 104:352–358
72. Fang CT, Chen YC, Chang SC et al (2000) Klebsiella pneumoniae meningitis: timing of antimicrobial therapy and prognosis. QJM 93:45–53
73. Proulx N, Frechette D, Toye B (2005) Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 98:291–298
74. Meehan TP, Fine MJ, Krumholz, HM et al (1997) Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA 278:2080–2084
75. Battleman DS, Callahan M, Thaler HT (2002) Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia. Arch Intern Med 162:682–688
76. Houck PM, Braztler DW, Nsa W et al (2004) Timing of antibiotic administration and outcomes for Medicare patients hospitalised with community-acquired pneumonia. Arch Intern Med 164:637–644
77. Iregui M, Ward S, Sherman G et al (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262–268
78. Paterson DL, Rice LB (2003) Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? Clin Infect Dis 36:1006–1012

Chapter 14

Focus on antibiotics: use and misuse in the intensive care unit, and antibiotics monitoring

F. Pea, F. Pavan, M. Furlanut

Patients admitted to the intensive care unit (ICU) are frequently treated with antibiotics because of suspected or documented infections. During the last few years, several authors have documented that the probability of survival in patients with ICU-related infections may be significantly decreased in case of inadequate empiric therapy [1, 2]. Interestingly, most of these studies have usually considered fixed-dose regimens and have not correlated efficacy with antibiotic concentrations at the infection sites. Therefore, considering that critically ill patients often present with unique pathophysiological conditions that may significantly alter the pharmacokinetic behaviour of antibiotics, failure in clinical response could be at least partially related to inappropriate pharmacodynamic exposure to the antibiotic. Accordingly, therapeutic drug monitoring (TDM) may be considered a useful tool to optimise antibiotic exposure in individual patients, while taking into account that drug levels of antibiotics after administration of standard fixed dosages may be unpredictable in the critically ill [3].

Pharmacokinetics/pharmacodynamics of antibiotics and dosing regimens

The question, how often should the dosing regimen of an antibiotic be refracted is dependent on whether the drug exhibits time or concentration-dependent antibacterial activity (Table 1). Beta-lactams, glycopeptides, and oxazolidinones are time-dependent agents, in that the time during which concentrations are above the MIC of the pathogen ($t >$ MIC) is considered the major pharmacodynamic determinant of their efficacy. A $t >$ MIC of 50–60% of the dosing interval should be considered the minimum target for efficacy of time-dependent agents [4]. Conversely, aminoglycosides and fluoroquinolones are concentration-dependent agents, since peak to MIC ratio (C_{max}/MIC) and area under the concentration–time curve to MIC ratio (AUC/MIC) are considered the most important parameters for their efficacy [5]. Several authors have shown that a C_{max}/MIC of 10–12 and an AUC/MIC ratio of 100–125 should be considered as valid thresholds for clinical efficacy with these agents [5–7]. Additionally, beta-lactams exhibit a poor post-antibiotic effect (PAE), especially against gram-negative pathogens, in contrast to either aminoglycosides or fluoroquinolones, which exhibit valid PAE against both gram-negative and gram-positive pathogens [8]. This means that during infections sustained by

gram-negative pathogens, whenever the concentrations of beta-lactams fall below the MIC, the bacteria are able to rapidly resume growth. Therefore, maintaining trough levels above the MIC (C_{min} > MIC) will maximise the efficacy of beta-lactams, and in general with all time-dependent antimicrobial agents. Due to the efficacious PAE of aminoglycosides and fluoroquinolones, sub-MIC concentrations at the end of the dosing interval may be allowed for some hours.

Table 1. Pharmacokinetic/pharmacodynamic characteristics of antibiotics

Time-dependent agents	Concentration-dependent agents
Beta-lactams	Aminoglycosides
Glycopeptides	Fluoroquinolones
Macrolides	
↓	↓
Maximise t > MIC	Maximise C_{max}/MIC
Through a multi-refracted regimen	Through application of a once daily dose
Until continuous infusion	Whenever possible

Based on this information, different schedule regimens of antibiotics must be chosen according to the time- or concentration-dependency of the particular drug. The best approach for time-dependent antimicrobials in order to maintain C_{min} > MIC is the choice of a multi-refracted regimen, with the number of the daily doses depending on the length of the elimination half-life ($t_{1/2}$). For example, q4h administration should be chosen for most penicillins (oxacillin, ampicillin, penicillin G) due to a $t_{1/2}$ < 1 h; q6h administration may be suitable for carbapenems, vancomycin, and most cephalosporins, whose $t_{1/2}$ is longer; q12h may be appropriate for linezolid, teicoplanin, and ceftriaxone. Interestingly, in the ICU setting the use of intravenous continuous infusion may be a helpful tool with the intent of maximising pharmacodynamic exposure with time-dependent agents [9], since under the same total daily dose, this approach may enable the highest C_{min} > MIC. Obviously, the suitability of continuous infusion depends on the chemical stability of the administered agent in aqueous solution. Although there are convincing data for administering continuous infusion of ampicillin, oxacillin, piperacillin, ceftazidime, cefepime, and vancomycin [10, 11], this might not be the case for amoxicillin and carbapenems (imipenem and meropenem), which seem to deteriorate quite rapidly in solution [11, 12] and for which conflicting opinions about this modality of administration still exist in the literature [13, 14].

Conversely, patients may benefit from concentration-dependent antimicrobials administered by once daily dosing, as it ensures, under the same total daily dose, the highest C_{max}/MIC. Although this approach was successfully applied with aminoglycosides, with interesting results coupling efficacy and safety [15] thanks to the hydrophilic nature of those antibiotics, by contrast, when administering high daily dosages of fluoroquinolones, a twice (levofloxacin) to three times (ciprofloxacin) daily dosing regimen should be chosen owing to potential CNS toxicity due to the free diffusion of these drugs across the blood–brain barrier [8].

Physicochemical characteristics of antibiotics and therapeutic drug monitoring

It may be clinically useful to split antimicrobial agents into two major groups according to their hydrophilicity or lipophilicity (Table 2) [16]. Hydrophilic agents, namely beta-lactams, aminoglycosides, and glycopeptides, are characterised by a low volume of distribution due to their inability to freely diffuse through the eukaryotic cell membrane; thus, these drugs are mainly eliminated unchanged by the renal route. In contrast, lipophilic agents, namely macrolides, fluoroquinolones, tetracyclines, rifampin, and linezolid, present a high volume of distribution due to their free penetration into eukaryotic cells, and they often undergo liver metabolism prior to being eliminated. Notable exceptions to this rule are, among the hydrophilic agents, oxacillin and ceftriaxone which are biliary eliminated, and among the lipophilic drugs, levofloxacin and ciprofloxacin, which are totally (levofloxacin) or partially (ciprofloxacin) renally eliminated as unchanged drugs.

Table 2. Physicochemical properties of antibiotics

Hydrophilic agents:	Beta-lactams, aminoglycosides, glycopeptides
Lipophilic agents:	Macrolides, fluoroquinolones, tetracyclines, linezolid

The TDM of antimicrobial agents may be especially helpful in ICU patients, considering that several pathophysiological conditions can affect the pharmacokinetic behaviour of antibiotics (Table 3). However, a wide range of different, day-by-day pharmacokinetic changes of antimicrobials, according to their physicochemical properties, is encountered in the critically ill [16]. Hydrophilic and renally eliminated lipophilic antimicrobials are at the highest risk of significant alterations of their disposition, considering that continuously changing renal function may consistently modify renal drug clearance. An additional factor possibly affecting the pharmacokinetics of hydrophilic agents is an increased extracellular fluid content, causing antibiotic dilution and therefore potential underexposure. Although it is well-known that renal impairment due to reduced elimination of antibiotics may cause drug overexposure, it is less well-perceived that several other pathophysiological and iatrogenic conditions frequently occur in critically ill patients that can alter their pharmacokinetic behaviour and may cause underexposure. Peritonitis, ascites, pleuritis, pericarditis, fluid therapy, oedema, presence of thoraco-abdominal drainages, and hypoalbuminaemia are conditions that may increase extracellular fluid content, therefore causing dilution or loss of antibiotic [16]. Additionally, intravenous drug abuse, extensive burns, hyperdynamic sepsis, use of haemodynamically active drugs (furosemide, dopapimine, and dobutamine), acute leukaemia and hypoalbuminaemia were shown to increase renal elimination of several hydrophilic and moderately lipophilic agents, thus potentially causing underexposure [16]. These conditions, especially when co-existing in the same patient, should lead ICU physicians to require TDM of antimicrobials with the intent of ensuring appropriate exposure for each single patient.

Table 3. Pathophysiological situations potentially affecting drug pharmacokinetics in critically ill patients

Situations increasing extracellular fluid contents:	Effusions in serous cavities, fluid therapy, hypoalbuminaemia, thoraco-abdominal drainages, oedema
Situations decreasing renal function:	Renal failure
Situations increasing renal function:	Extensive burns, intravenous drug abuse, leukaemia, haemodynamically active drugs, hyperdynamic sepsis, hypoalbuminaemia

Antibiotic drug monitoring

In the past, the TDM of antibiotics has been proposed, mainly for safety reasons, for both aminoglycosides and vancomycin. However, over the last few years, several authors have demonstrated that this tool may be helpful in maximising pharmacodynamic exposure to antibiotics in critically ill patients [17–23]. The utility of the TDM-based approach may be maximised by the so-called active TDM, in which a TDM is performed by a clinical pharmacologist who then takes on the responsibility of adjusting, in real time, the dosing regimen in each single patient according to the TDM results and Bayesian forecasting [24, 25]. Our group carried out several observational studies based on the application of a TDM of antibiotics in the ICU setting. We showed a relevant role for active TDM in ensuring appropriate drug exposure in patients with several different patterns of critical illness, including unstable renal function [26–28], as well as for those patients undergoing renal replacement therapies [29, 30], those with acute leukaemia [31–33], and those co-treated with haemodynamically active drugs [27]. Additionally, it should not be overlooked that active TDM may have an educational role, by helping clinicians, through feedback on drug exposure, in decision-making and by deepening their knowledge of pharmacokinetics. For example, in a retrospective study carried out over a 7-year period in critically ill patients, we demonstrated that appropriate loading doses of teicoplanin at the commencement of treatment is important in ensuring the achievement of therapeutically relevant concentrations of drug early in the treatment period [28].

In conclusion, antibiotic monitoring may be helpful in optimising drug exposure in ICU patients, and in avoiding either inefficacy due to undertreatment or toxicity due to overtreatment. The use of TDM in the ICU setting should be more frequent in those patients presenting with unstable renal function or with several different coexisting pathophysiological conditions that may affect the pharmacokinetic behaviour of drugs.

References

1. Hanes SD, Demirkan K, Tolley E et al (2002) Risk factors for late-onset nosocomial pneumonia caused by Stenotrophomonas maltophilia in critically ill trauma patients. Clin Infect Dis 35:228–235
2. Mueller EW, Hanes SD, Croce MA et al (2005) Effect from multiple episodes of inadequate empiric antibiotic therapy for ventilator-associated pneumonia on morbidity and mortality among critically ill trauma patients. J Trauma 58:94–101
3. Belzberg H, Zhu J, Cornwell EE 3rd et al (2004) Imipenem levels are not predictable in the critically ill patient. J Trauma 56:111–117
4. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10
5. Preston SL, Drusano GL, Berman AL et al (1998) Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 279:125–129
6. Forrest A, Nix DE, Ballow CH et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37:1073–1081
7. Schentag JJ (2000) Clinical pharmacology of the fluoroquinolones: studies in human dynamic/kinetic models. Clin Infect Dis 31:S40-S44
8. Burgess DS (1999) Pharmacodynamic principles of antimicrobial therapy in the prevention of resistance. Chest 115:19S-23S
9. MacGowan AP, Bowker KE (1998) Continuous infusion of beta-lactam antibiotics. Clin Pharmacokinet 35:391–402
10. Servais H, Tulkens PM (2001) Stability and compatibility of ceftazidime administered by continuous infusion to intensive care patients. Antimicrob Agents Chemother 45:2643–2647
11. Viaene E, Chanteux H, Servais H et al (2002) Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother 46:2327–2332
12. Jaruratanasirikul S, Sriwiriyajan S (2003) Stability of meropenem in normal saline solution after storage at room temperature. Southeast Asian J Trop Med Public Health 34:627–629
13. Kuti JL, Nightingale CH, Knauft RF et al (2004) Pharmacokinetic properties and stability of continuous-infusion meropenem in adults with cystic fibrosis. Clin Ther 26:493–501
14. Krueger WA, Bulitta J, Kinzig-Schippers M et al (2005) Evaluation by monte carlo simulation of the pharmacokinetics of two doses of meropenem administered intermittently or as a continuous infusion in healthy volunteers. Antimicrob Agents Chemother 49:1881–1889
15. Olsen KM, Rudis MI, Rebuck JA et al (2004) Effect of once-daily dosing vs multiple daily dosing of tobramycin on enzyme markers of nephrotoxicity. Crit Care Med 32:1678–1682
16. Pea F, Viale P, Furlanut M (2005) Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and huge pharmacokinetic variability. Clin Pharmacokinet 44:1009–1034
17. MacGowan AP (1998) Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. Ther Drug Monit 20:473–477
18. Thomson AH, Whiting B (1992) Bayesian parameter estimation and population pharmacokinetics. Clin Pharmacokinet 22:447–467

19. van Lent-Evers NA, Mathot RA, Geus WP et al (1999) Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit 21:63–73
20. Welty TE, Copa AK (1994) Impact of vancomycin therapeutic drug monitoring on patient care. Ann Pharmacother 28:1335–1339
21. Balram C, Lim BL, Lee EJ et al (1996) Validity of Bayesian forecasting programme in therapeutic drug monitoring of vancomycin in a surgical intensive care unit: a prospective evaluation. Ann Acad Med Singapore 25:492–495
22. Fernandez de Gatta MM, Fruns I, Dominguez-Gil A (1994) Individualizing vancomycin dosing regimens: an evaluation of two pharmacokinetic dosing programs in critically ill patients. Pharmacotherapy 14:196–201
23. Wrishko RE, Levine M, Khoo D et al (2000) Vancomycin pharmacokinetics and Bayesian estimation in pediatric patients. Ther Drug Monit 22:522–531
24. Hansen M, Christrup LL, Jarlov JO et al (2001) Gentamicin dosing in critically ill patients. Acta Anaesthesiol Scand 45:734–740
25. Pea F, Bertolissi M, Di Silvestre A et al (2002) TDM coupled with Bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients. Int J Antimicrob Agents 20:326–332
26. Pea F, Furlanut M, Bianchi L (2000) Systemic vancomycin overexposure in a patient with spinal cord injury who had Staphylococcal sepsis and Clostridium difficile colitis. Ther Drug Monit 22:233–234
27. Pea F, Porreca L, Baraldo M et al (2000) High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. J Antimicrob Chemother 45:329–335
28. Pea F, Brollo L, Viale P et al (2003) Teicoplanin therapeutic drug monitoring in the critically ill patients: a retrospective study emphasizing the importance of a loading-dose. J Antimicrob Chemother 51:971–975
29. Pea F, Brollo L, Lugano M et al (2001) Therapeutic drug monitoring-guided high teicoplanin dosage regimen required to treat a hypoalbuminemic renal transplant patient undergoing continuous venovenous hemofiltration. Ther Drug Monit 23:587–588
30. Pea F, Viale P, Lugano M et al (2004) Linezolid disposition after standard dosages in critically ill patients undergoing continuous venovenous hemofiltration: a report of 2 cases. Am J Kidney Dis 44:1097–1102
31. Pea F, Poz D, Baraldo M et al (2000) Optimisation of vancomycin regimen in neutropenic haematological patients with normal renal function: multiple daily soses may be preferable. Clin Drug Invest 19:213–218
32. Pea F, Viale P, Candoni A et al (2004) Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet 43:405–415
33. Pea F, Viale P, Damiani D et al (2005) Ceftazidime in patients with febrile neutropenia during acute myeloid leukemia: helpfulness of intravenous continuous infusion in maximizing pharmacodynamic exposure. Antimicrob Agents Chemother 49:3550–3553

CENTRAL NERVOUS SYSTEM

Chapter 15

Clinical significance of monitoring the central nervous system in the operation room and the intensive care unit

E. Freye

Electrophysiological monitoring of the central nervous system (CNS) has become a valuable adjunct, and in selected circumstances, a standard of care for surgical procedures where there is a possibility of neuronal injury. Electrophysiological monitoring is made possible by the inborn electrical properties of the human nervous system, thus assessing both structural and functional aspects of the neural pathways tested. These methods can be used when the patient is unable to cooperate (e.g. traumatic coma) or is rendered unconscious (e.g. anaesthesia, intensive care unit, ICU). Although limited to specific neural pathways of the central and the peripheral nervous system, these techniques have become an essential component of some surgical procedures, where their use provides a matchless contribution to intraoperative decision making.

Awake testing – is it still necessary?

Since electrophysiological methods are limited to specific neuronal pathways, they cannot assess the wide variety of functions tested by awake examination. A good example is awake monitoring during cerebral surgery for the resection of a seizure focus, where the exact areas of cortical function can be defined prior to resection of seizure focus. Another good example is carotid endarterectomy conducted under regional block. Here, awake testing is more sensitive to blood flow reductions (25 cc/min per 100 g) than the electroencephalogram (EEG) and the somatosensory evoked potential (SSEP), which are affected only at a lower blood flow (15–20 cc/min per 100 g). Furthermore, awake testing can assess areas of the brain (e.g. speech) that cannot be judged by electrophysiological methods. Another example of awake testing is the wake-up test during Harrington rod placement for scoliosis [1]. Unfortunately, advances in surgical methods (especially hardware techniques) have increased the possibilities of neural risk in these procedures from one identifiable event (distraction) to multiple, potentially deleterious events (sublaminar wires, multiple hooks, pedicle screws, etc.). Because of such possibilities, a more continuous method of neural assessment is mandatory. Thus, controversy has evolved whether a wake-up test alone is sufficient for such surgical procedures [2].

The electroencephalogram

For CNS monitoring, different techniques nowadays present a high resolution. And although computer tomography (CT), magnetic resonance imaging (MRI), magnet resonance tomography (MRT), electromagnetic tomography (EMT) from the EEG, magnetencephalography (MEG), or positron emission tomography (PET) are available for the clinician to gain further insight into cerebral function and metabolism, these methods cannot be used routinely to monitor the CNS and replace the EEG. Basically, the EEG is the measurement of spontaneous electrical activity of the brain, which is produced by inhibitory and excitatory post-synaptic potentials in the pyramidal layer of the cortex [3]. The EEG is measured from electrode pairs on the scalp and represents comparative activity in the two cerebral regions immediately below the electrodes. A variety of methods have been used for monitoring, including raw and processed EEG. In general, a reduction in amplitude and frequency (delta-dominance) or abnormal distribution of activity of the EEG is consistent with ischaemia, as well as a variety of other causes including the deepening of anaesthesia.

EEG monitoring is particularly useful for the detection of electrical seizure activity and for the detection of cortical ischaemia. The EEG has therefore become essential for intraoperative mapping of seizure foci that are not associated with any structural abnormality such as a tumour. Because EEG changes during ischaemia precede cell death, use of the EEG has been advocated during procedures interfering with the vascular supply of the brain (e.g. intracranial aneurysm, arterio-venous malformation and the need for shunting during carotid endarterectomy). In these procedures the EEG can be used to detect ischaemia from a variety of causes (see below) and help to guide the anaesthesia and surgical management to reduce the risk of intraoperative stroke. Several relevant studies have indicated the value of the EEG in reducing cortical morbidity in carotid endarterectomy. And since vascular shunting has associated risks, stroke risk can be reduced tenfold when selective shunting in carotid endarterectomy is based on EEG monitoring [4]. However, its value in reducing overall morbidity remains controversial because some studies demonstrated a lack of efficacy. Such latter failing may be related to the fact that many strokes are due to postoperative occlusion by clot formation in the bare carotid or are a result of emboli of air or atherosclerotic material during the case, which might be better detected by transcranial Doppler sonography. Furthermore, the development of stroke is dependent on the interaction of the degree of reduced cerebral blood flow and the duration of reduction. Thus, patients with short cross-clamp times (10–15 minutes) have low ischaemic stroke risk. Advocates of monitoring in carotid endarterectomy suggest that EEG monitoring may be able to assist the detection of major ischaemia related to cross-clamping and:

1. Prompt the selective use of a shunt
2. Detect an occluded shunt after it has been placed
3. Assess cerebral tolerance to ischaemia (i.e. judge the adequacy of collateral blood flow)

4. Detect unexpected ischaemia in other cerebral regions as a consequence of vertebral-basilar insufficiency from positioning or inadequacies in collateral flow through the Circle of Willis.

Although changes in the EEG have long been recognised as a consequence of deepening anaesthesia, the raw EEG patterns associated with anaesthesia vary between drugs. Increased interest in EEG monitoring for the adequacy of anaesthesia has been sparked by newer techniques for EEG measurement (e.g. bispectral index, patient state index). Current studies of the processed EEG, or the EEG combined with facial muscle activity (e.g. response and state entropy) show promise for the assessment of anaesthesia depth and the detection of intraoperative awareness. These techniques utilise mathematical measures to focus the analysis on EEG parameters, which appear to correlate not only with sedation scores and the depth of anaesthesia, but in addition can be used to determine the level of sedation in the ICU [5]. Application of these methods appears to reduce the cost of anaesthetic drugs, improve awakening times, and reduce recovery costs. Also, evidence is accumulating suggesting that its use may also reduce intraoperative awareness, which, according to the 'Awareness Incidence Multi Trial' in the USA, is on average around 0.13%. It should be noted, however, that the EEG in no way is able to determine the level of analgesia.

Sensory evoked potentials

Evoked potentials are a measurement of electrical potentials evoked by a stimulus and allow assessment of a specific neuronal tract by observing its reaction to the stimulus. There is an abundance of literature on their usefulness for diagnostic testing [6, 7] and intraoperative monitoring [8–12]. Since these evoked electrical potentials are very small signals, averaging is used to resolve them from the much larger underlining EEG and electrocardiogram (ECG) activity. This method involves repetitive stimulation of the nervous system and measuring the response over the corresponding cortex for a set window of time, evoked neural activity being resolved from other electrical activity. Thus, evoked response becomes apparent because the unwanted background activity is unrelated to the stimulus and averaged out. The peaks (and valleys) of the evoked response arise from specific neural generators, often comprising more than one neuronal structure per peak. This method therefore can be used to follow the response at various points along the stimulated tract.

The selective application of evoked potentials to surgical procedures has been successful where they assist in operative decision making so as to reduce, but not totally eliminate, the risk of neural complications. The most commonly utilised evoked potentials are those produced by stimulation of the sensory system: sensory evoked potentials (SEP). Many surgeons have found the SEP indispensable for procedures where they can demarcate neural structures such as a neuroma-in-situ or for the identification of the sensory area on the exposed cerebral cortex. Standards of care have defined monitoring as an essential part of some procedures (e.g.

spine monitoring in scoliosis and facial nerve monitoring in vestibular schwannoma or acoustic neuroma). The notion is that the reduction in neural risk associated with monitoring offsets the added cost. This has been underlined by several studies, which have confirmed the efficacy and cost-effectiveness of intraoperative monitoring. The American Academy of Neurology has published a review of intraoperative monitoring, concluding that there is considerable evidence favouring the use of monitoring as a safe and efficacious tool in clinical situations where there is significant nervous system risk, provided that its limitations are appreciated [13].

Somatosensory evoked potentials

The electrophysiological technique with the widest possible application is the SSEP. In this technique a peripheral nerve (typically the posterior tibial, the common peroneal, the ulnar or the median nerve) is stimulated and the neural response measured over the corresponding sensory area of the cortex. It is currently thought that the incoming volley of neural activity from the upper extremity represents primarily the activity in the spinal pathway of proprioception and vibration (posterior columns). The response from the lower extremity more likely includes a contribution from the antero-lateral spinal cord (spinocerebellar pathways), in addition to the posterior column activity.

The most common application of the SSEP is for monitoring during spinal corrective surgery such as during scoliosis or spinal trauma. Several studies in spine surgery have shown that monitoring is predictive of neural outcome and can reduce neural morbidity in patients undergoing operation for spinal instability due to trauma [15] or other pathology [16]. The Scoliosis Research Society and the European Spinal Deformities Society reviewed the effectiveness of monitoring in over 51 000 scoliosis cases [17, 18]. In this review, the occurrence of a neurological deficit without SSEP warning (false negative) was 0.63%. SSEP changes were seen in the remainder of the patients experiencing a deficit. This report also points out that the surgical teams with the most experience in monitoring had a neurological complication rate less than half of the rate of less experienced teams. The author concluded that these results confirm the clinical efficacy of experienced SSEP spinal cord monitoring. The Scoliosis Research Society developed a position statement concluding that neurophysiological monitoring can assist in the early detection of complications and possibly prevent postoperative morbidity in patients undergoing operations on the spine. Therefore electrophysiological monitoring during scoliosis correction has become a fundamental standard of care.

The SSEP can also be used for monitoring the viability of pathways as they travel through the brainstem (e.g. posterior fossa surgery) and cerebral cortex [19]. A good example of SSEP use is the detection of cerebral ischaemia in subarachnoid haemorrhage associated with intracranial aneurysm rupture. It has also been used during intraoperative vascular procedures, where it can assist in the detection of:

1. Adequacy of collateral blood flow during temporary vessel clipping (i.e. assess the tolerance to temporary occlusion)

2. Inadvertent vessel occlusion (i.e. improper clip application)
3. Safety of vessel sacrifice in arterio-venous malformations
4. Tolerance to deliberate hypotension
5. Vasospasm.

Of particular interest is the detection of tolerance to multiple factors (e.g. retractor pressure and hypotension, retractor pressure and temporary clipping, deliberate hypotension and hyperventilation) to identify ischaemia that otherwise may be overlooked. And lastly, evoked responses have been used successfully during neuroradiological procedures such as occlusion of vessels (e.g. arterio-venous malformations), or during streptokinase dissolution of occluding blood clots.

Some individuals believe that the SSEP may be less useful than the EEG for the detection of cerebral ischaemia because the SSEP can only assess the specific neural tract being stimulated. However, as opposed to the EEG, the SSEP can detect ischaemia in subcortical regions of the neural tracts being monitored. Evoked potentials have also been termed indispensable during craniotomy for localisation of the sensory-motor area of the brain [20]. Here, the gyrus separating the motor and sensory strip (rolandic fissure) is identified by a phase reversal of the evoked response.

Recordings from deep structures can be utilised to identify the location of depth probes in preparation for lesioning. For example, recordings from the tip of the lesion probe can assist placement of lesions in the thalamus or the globus pallidus for Parkinson's disease and other movement disorders. Similarly, depth recordings have been used during lesioning for pain syndromes and lesions of dorsal root entry.

One important limitation of the SSEP is the sensitivity of the cortical responses to anaesthesia. As such, techniques have been developed for stimulation or recording from the spinal cord that are less susceptible to anaesthetic effects. There, recording electrodes are placed in the spine bony elements, the intraspinous ligament or the subdural and the epidural space. Epidural electrodes have become quite popular, particularly in Japan, the UK and in our institution for thoraco-abdominal aneurysm repair, where they can be used for stimulation as well as recording of neuronal activity within the spinal pathways.

Monitoring of the peripheral nervous system

Several innovative monitoring techniques similar to the SSEP have been developed to monitor the peripheral nervous system. In all of these techniques the nervous system is electrically or mechanically stimulated and a sensory or motor response recorded. One major area of application has been the monitoring of spinal roots during spinal disc surgery or vertebral pedicle screw placement. Initially, evoked responses from dermatome stimulation were used. More recently, monitoring of muscle activity from intentional or inadvertent mechanical stimulation of the nerve root has been advocated [21]. This latter technique has also allowed monitoring of bladder and rectal sphincter innervation during cauda equina procedures. Finally, assessment of the peripheral nerve and spinal cord can be done using reflex testing. In these cases the H and F reflex is assessed by peripheral nerve stimulation [22].

Similar techniques can also be used for selective dorsal rhizotomy conducted to relieve leg spasticity and thereby improve gait in cerebral palsy where bothersome dorsal rootlets are sectioned [23]. The advantages of muscle recording have made continuous electromyography (EMG) commonplace during spinal surgery [24].

The SEP technique is also indispensable for intraoperative evaluation and monitoring during surgical procedures of the peripheral nerves and plexus regions [14]. For example, stimulation and recording across neuronal structures allows identification of the functional integrity of nerves or nerve trunks in injury areas when peripheral function has been lost. Identification of residual function in damaged nerves (continuity) and identification of a pre-ganglionic or a post-ganglionic injury of a plexus allows selective and focused repair. In addition, evoked response has been used to detect sciatic nerve injury with hip procedures and positioning-related nerve compromise.

Motor evoked potentials for motor tract monitoring

Monitoring techniques that include monitoring of spinal motor tracts as well as sensory tracts have become popular since occasional unpredicted motor deficits occur with SSEP spine monitoring. These include epidural stimulated techniques and so-called neurogenic motor evoked potentials. Recording of responses from peripheral nerves is done following stimulation of the spinal cord by electrodes placed near or in the vertebral bodies rostral to the region of spinal surgery [23]. Unfortunately, responses recorded following spinal stimulation contain variable amounts of responses mediated by sensory and motor tracts. Pure motor tract monitoring is best accomplished by means of motor cortex stimulation using transcranial electrical [25–28] or magnetic [29–32] stimulation. These responses can be recorded in the spinal cord or as compound muscle action potentials (CMAP). When CMAPs are being recorded intraoperatively, a continuous and controlled level, and at the same time limited muscle relaxation is mandatory in order not to blunt the response signal.

Several approved transcranial electrical stimulation devices for producing potentials in motor evoked potential monitoring have shown this to be quite safe [33]. However, because they are very sensitive to anaesthetic, resulting in a depression of the response, newer multi-pulse stimulation techniques are evolving that appear to be less susceptible to the commonly used anaesthetic agents [34]. Therefore, transcranial multipulse electrical motor evoked potential monitoring is gaining more importance in clinical monitoring.

Cranial nerve monitoring

The most common monitoring application for posterior fossa surgery is monitoring of facial nerve function and hearing, since many of the procedures in the posterior fossa are for benign tumours, which may grow to a large size (4 cm), which

obscure or interweave with the cranial nerves. Although the most commonly involved nerves are VIII (hearing) and VII (facial), several other cranial nerves can also be monitored when appropriate. Because of the importance of facial nerve function, extensive experience is available with facial nerve monitoring [35]. This technique is usually accomplished by placing bipolar recording electrodes in the orbicularis oris and orbicularis oculi. The muscle recordings (EMG) are presented on an oscilloscope screen as well as played through a loudspeaker system, which is being suppressed during cautery. Two basic types of neural activity have been identified. First are brief phasic bursts of activity usually caused by mechanical stimulation of the nerve. This serves to indicate to the surgeon that the nerve is in the immediate vicinity of the surgical field. More injurious stimuli can cause tonic or train-activity, which is due to continuous, synchronous motor unit discharges in trains of tonic activity, lasting up to several minutes.

The latter is associated with nerve compression, traction or ischaemia of the nerve, and is an indication of nerve injury. The surgeon can also utilise facial nerve monitoring by intentional electrical stimulation using a handheld stimulating probe in the operative field to locate the facial nerve or to identify the area of nerve injury. Data suggest that if the anatomic integrity of the nerve can be maintained by monitoring, neural function is highly likely. Several studies utilising facial nerve monitoring have demonstrated an improvement in facial nerve and hearing outcome in posterior fossa surgery [36–37]. There is sufficiently strong evidence for maintenance of facial nerve integrity, that the benefits of routine intraoperative monitoring of the facial nerve have been clearly established by a consensus meeting. This technique should be included in all surgical interventions, where this nerve is at risk, suggesting that routine monitoring of other cranial nerves should also be considered [38]. Thus, facial nerve monitoring is an established standard of care during vestibular schwanoma (acoustic neuroma) surgery in cases where monitoring can be accomplished.

Brainstem auditory evoked potentials

A second widely used sensory evoked response is the brainstem auditory evoked response (BAER). The BAER is produced when sound activates the cochlea following transmission through the external and the middle ear. The sensory evoked response is measured as a series of peaks (I–V) produced by the neural pathway of hearing. Cortical responses to auditory stimulation recorded over the auditory cortex (mid-latency cortical auditory evoked potential) appear to correlate with the depth of anaesthesia. The BAER can be used for monitoring of brainstem viability such as during procedures for microvascular decompression for relief of hemifacial spasm, trigeminal neuralgia or glossopharyngeal neuralgia and for monitoring to reduce the risk of surgically induced hearing impairment. It is also used in conjunction with procedures to relieve tinnitus and disabling positional vertigo, during decompression of space-occupying defects in the cerebellum, and for the removal of cerebellar vascular malformations. Because the cochlear nerve is responsible for hearing, it can be termed one of the most fragile cranial nerves being

frequently involved in tumours of the posterior fossa. Many studies have shown an improvement in hearing outcome using BAEPs in vestibular schwanoma [39–41]. However, with large tumours, or some other tumour types or locations, the involvement of the cochlear nerve in the tumour makes hearing preservation more difficult. Several variations of the BAEPs have been developed to monitor the auditory system more specifically. Cochlear microphonics and cochlear nerve action potentials and monitoring of the exposed intracranial portion of the eighth cranial nerve (cochlear nerve action potentials) have also been used, as well as monitoring of the nerve in the lateral recess of the fourth ventricle.

Other cranial nerves

Monitoring of the motor component of other cranial nerves has been used extensively in surgery on the base of the skull, and cavernous sinus, as well as with surgery in the posterior fossa [8, 35]. Many other cranial nerves can be monitored by recording the muscle activity of innervated muscle in response to mechanical or intentional stimulation of the nerves (Table 1). Methods have been described for monitoring cranial nerves III–VII and IX–XIII, usually by techniques similar to those for the facial nerve, as discussed above.

Monitoring of the lower cranial nerves (cranial nerves IX, X, XI and XII) is important during resection of large low brainstem lesions because injury may cause airway collapse and inadequate protection from aspiration of gastric contents. Of particular interest is the monitoring of vagal innervation of the larynx. This can be done using electrodes placed in the false vocal chords via direct laryngoscopy, surface electrodes placed in the larynx or by a specially designed endotracheal tube with electrode contacts on each lateral surface. This monitoring has been advocated in resection of tumours of the lower brainstem, thyroidectomy, parathyroidectomy and anterior cervical spine surgery.

Table 1. Cranial nerve monitoring

Type of cranial nerve	Technique for monitoring
II	Visual evoked potentials (VEPs)
III	Oculomotor inferior rectus (motor)
IV	Trochlear superior oblique (motor)
V	Trigeminal masseter, temporalis (motor)
VI	Abducens lateral rectus (motor)
VII	Facial nerve monitoring; orbicularis oculi, orbicularis oris (motor)
VIII	Auditory evoked potentials, BAEPs
IX	Glossopharyngeal posterior soft palate (stylopharyngeus) (motor)
X	Vagus-> vocal folds, cricothyroid muscle (motor)
XI	Spinal accessory sternocleidomastoid, trapezius (motor)
XII	Hypoglossal tongue, genioglossus (motor)

Visual evoked potentials

Visual evoked potentials (VEPs) are produced by light stimulation of the eyes and recorded by electrodes over the corresponding occipital cortex. This classical monitoring application is in procedures near the anterior visual pathways, such as transphenoidal pituitary tumour removal or other procedures in which monitoring allows the identification of surgical infraction on the optic pathways (e.g. lesioning of the globus pallidus for Parkinson's disease). Monitoring of typical flash VEPs appears to have limited application in the operating room. Technical problems have limited the application of large, bulky light-emitting diodes (goggles). Because VEP monitoring consistently could not be correlated with visual outcome, this lack of consistency has made the VEPs a less effective monitor than the other modalities [42]. However, other research teams have had better success rates using smaller stimulators made with contact lenses or scleral caps.

Conclusions

Electrophysiological monitoring has become a valuable adjunct to the clinical neurological examination, especially in circumstances in which the clinical examination is hampered by injury or by medications, which do not allow patient participation such as during surgery, or in an ICU environment. Due to newer innovative techniques, better operative decision making is possible during certain procedures where the neuronal system is at risk.

References

1. Vauzelle C, Stagnara P, Jouvinroux P (1973) Is a desflurane-remifentanil based anesthetic really the best for the wake-up test? Clin Orthop 93:173–178
2. Sloan TB (1997) Scoliosis surgery. Anesth Clin North Am 15:573–591
3. Cooper R, Osselton JW, Shaw JC (1980) EEG Technology. Butterworths, Boston
4. Nuwer MR (1993) Intraoperative electroencephalography. J Clin Neurophys 10:437–444
5. Rampil IJ (1998) A primer for EEG signal processing in anesthesia. Anesthesiology 89:980–1002
6. Chiappa KH (1990) Evoked potentials in clinical medicine. Raven Press, New York
7. Luders H (1989) Advanced evoked potentials. Kluwer Academia Publishers, Boston
8. Moller AR (1988) Evoked potentials in intraoperative monitoring. Williams & Wilkins, Baltimore
9. Nuwer MR (1986) Evoked potential monitoring in the operating room. Raven Press, New York
10. Jacobson GP, Tew JM Jr (1987) Intraoperative evoked potential monitoring. J Clin Neurophysiol 4:145–176
11. Sloan T (1996) Evoked potentials. In: Albin MS (ed) A textbook of neuroanesthesia with neurosurgical and neuroscience perspectives. McGraw-Hill, New York, pp 221–276

12. Erwin CW, Erwin AC (1993) The use of brainstem auditory evoked potentials in intraoperative monitoring. J Clin Neurophysiol 10:425
13. Anonymous (1990) Assessment: intraoperative neurophysiology. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 40:1644–1646
14. Friedman WA, Grundy BL (1987) Monitoring of sensory evoked potentials is highly reliable and helpful in the operating room. J Clin Monit 3:38–44
15. Meyer PR, Cotler HB, Gireesan GT (1988) Operative complications resulting from thoracic and lumbar spine internal fixation. J Clin Orthop 237:125–131
16. Epstein NE, Danto J, Nardi D (1993) Evaluation of intraoperative somatosensory-evoked potential monitoring during 100 cervical operations. Spine 18:737–747
17. Dawson EG, Sherman JE, Kanim LE et al (1991) Results of the Scoliosis Research Society and the European Spinal Deformity Society survey. Spine 16:S361–S364
18. Nuwer MR, Dawson EG, Carlson LG et al (1995) Somatosensory evoked potential spinal cord monitoring reduces neurologic deficits after scoliosis surgery: results of a large multicenter survey. Electroencephalogr Clin Neurophysiol 96:6–11
19. Sloan TB (1997) Evoked potential monitoring of the central nervous system intraoperatively. Anesth Clin North Am 15:593–611
20. Friedman WA (1988) Somatosensory evoked potentials in neurosurgery. Neurosurgery 22:140–142
21. Owen JH, Kostuik JP, Gornet M et al (1994) The use of mechanically elicited electromyograms to protect nerve roots during surgery for spinal degeneration. Spine 19:1704–1710
22. Leppanen R, Maguire J, Wallace S et al (1995) Intraoperative lower extremity reflex muscle as an adjunct to conventional somatosensory-evoked potentials and descending neurogenic monitoring in idiopathic scoliosis. Spine 20:1872–1877
23. Staudt LA, Nuwer MR, Peacock WJ (1995) Intraoperative monitoring during selective posterior rhizotomy: technique and patient outcome. Electroencephalogr Clin Neurophysiol 97:296–309
24. Holland NR (2002) Intraoperative electromyography. J Clin Neurophysiol 19:444–453
25. Owen JH, Laschinger J, Bridwell K et al (1988) Sensitivity and specificity of somatosensory and spinal evoked potentials. Spine13:1111–1118
26. Levy WJ, York DH, McCaffrey M, Tanzer F (1984) Motor evoked potentials from transcranial stimulation of the motor cortex in cats. Neurosurgery 15:214–227
27. Levy WJ (1987) Clinical experience with motor and cerebellar evoked potential monitoring. Neurosurgery 20:169–182
28. Day BL, Dressler D, Maertens de Noordhout A et al (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J Physiol 412:449–473
29. Day BL, Thompson PD, Dick JP et al (1987) Different sites of action of electrical and magnetic stimulation of the human brain. Neurosci Lett 75:101–106
30. Rothwell JC, Thompson PD, Day BL et al (1987) Motor cortex stimulation in intact man. 2. Multiple descending volleys. Brain 110:1173–1180
31. Edmonds H Jr, Paloheimo MPJ, Backman MH et al (1989) Motor evoked potential monitoring during upper cervical spine surgery. Spine 14:683[AQ1]
32. Shields CB, Paloheimo MPJ, Backman MH et al (1990) Intraoperative use of transcranial magnetic motor evoked potentials. In: Chokroverty S (ed) Magnetic stimulation in clinical neurophysiology. Butterworths, London, pp173–184
33. MacDonald DB (2002) Safety of intraoperative transcranial electric stimulation motor evoked potentials. J Clin Neurophysiol 19:416–429

34. Cheek JC (1993) Posterior fossa intraoperative monitoring. J Clin Neurophysiol 10:412–424
35. Taniguchi M, Cedzich C, Schramm J (1993) Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. Neurosurgery 32:219–226
36. Yingling CD (1994) Intraoperative monitoring of cranial nerves in skull base surgery. In: Jackler RK, Brackmann DE (eds) Neurology. Mosby, St. Louis, pp 967–1002
37. Apel DM, Marrero G, King J et al (1991) Avoiding paraplegia during anterior spinal surgery. The role of somatosensory evoked potential monitoring with temporary occlusion of segmental spinal arteries. Spine 16 (8 Suppl): S365–S370
38. Anonymous (1991) National Institutes of Health (NIH) Consensus Development Conference (December 11-13, 1991). Consensus Statement 9
39. Harper CM, Harner SG, Slavit DH et al (1992) Effect of BAEP monitoring on hearing preservation during acoustic neuroma resection. Neurology 42:1551–1553
40. Nadol JB Jr, Chiong CM, Ojemann RG et al (1992) Preservation of hearing and facial nerve function in resection of acoustic neuroma. Laryngoscope 102:1153–1158
41. Fischer G, Fischer C, Remond J (1992) Hearing preservation in acoustic neurinoma surgery. J Neurosurg 76:910–917
42. Cedzich C, Schramm J (1990) Monitoring of flash visual evoked potentials during neurosurgical operations. Int Anesthesiol Clin 28:165–169

Chapter 16

Global hypothermia for neuroprotection after cardiac arrest

W. Behringer, M. Holzer, F. Sterz

Sudden cardiac arrest remains a major unresolved public health problem. It is still the single leading cause of death and very few cardiopulmonary–cerebral resuscitation (CPCR) attempts on cardiac arrest victims lead to neurologically intact long-term survivors [1, 2].

The pathogenesis of cerebral ischaemia and post-ischaemic encephalopathy are multifactorial and only partially understood [2–5]. Brain ischaemia results in rapid loss of high-energy phosphate compounds [6] and generalised membrane depolarisation, leading to increased intracellular calcium and release of large amounts of glutamate [4]. These mechanisms initiate multiple independent chemical cascades and fatal pathways during reperfusion, resulting in neuronal death due to necrosis and apoptosis [5]. Due to the multifactorial pathogenesis of post-arrest neuronal death, multifaceted treatment strategies or a combination of single-molecule targeted drugs is required to achieve survival without brain damage [7, 8]. Mild hypothermia seems to be the perfect therapy for multifaceted treatment in the postresuscitation period of cardiac arrest.

Resuscitative hypothermia

Hypothermia is 'a state of body temperature which is below normal in a homoeothermic organism' [9]. Accidental (uncontrolled) hypothermia is non-therapeutically altered body temperature in a homoeothermic organism, which results in the activation of defence mechanisms such as hypermetabolism, increased oxygen consumption, and shivering, and which is associated with particular complications and requires specific treatments. In contrast, therapeutic hypothermia, as for cardiac surgery and neurosurgery, or resuscitation from cardiac arrest, necessitates controlled conditions to induce poikilothermia by insult or anaesthesia and paralysis. In therapeutic hypothermia, different degrees of cooling are defined: mild (36–33°C), moderate (32–28°C), deep (27–11°C), profound (10–6°C), and ultra-profound (5–0°C) hypothermia [2].

The benefit of protective-preservative cerebral hypothermia on outcome was already shown in the 1950s [10–12]. Experimental and clinical trials were complicated by the injurious systemic effects of total body cooling, such as shivering, vasospasm, increased plasma viscosity, increased haematocrit, hypocoagulation,

arrhythmias, ventricular fibrillation when temperatures dropped below 30°C, and lowered resistance to infection during prolonged moderate hypothermia [9, 12–14]. The discovery in the late 1980s that even mild hypothermia is neuroprotective [8, 15, 16], led to renewed interest in this field. Resuscitative and preservative hypothermia for cardiac arrest was documented in a series of clinically reliable dog-outcome studies with evaluation of brain histology at 3–4 days after the insult. Moderate hypothermia provided some benefit for the brain, but had side-effects on the heart [17]; mild hypothermia, which is safer and simpler than moderate hypothermia, improved function and brain histology after normothermic ventricular fibrillation cardiac arrest of 10–12 min of no-flow [18–22]; deep hypothermia via cardiopulmonary bypass (CPB) after prolonged normothermic cardiac arrest did not improve function but worsened brain histology [20]; mild resuscitative hypothermia essentially normalised cerebral outcome after 11 min of cardiac arrest no-flow when prolonged (12 h) and combined with measures promoting cerebral blood flow [22]; a 15-min delay in the initiation of brief (1–2 h) mild hypothermia after normothermic reperfusion did not improve functional outcome but did improve histological damage [21]. Prolonged hypothermia, even if delayed, was effective in rats [23, 24].

While the benefit of intra-ischaemic hypothermia on neuronal death is regarded as long-lasting [25], results on the long-term benefit of post-ischaemic hypothermia have been more controversial. Brief (4 h) post-arrest mild hypothermia after normothermic incomplete forebrain ischaemia in rats postponed but did not permanently salvage hippocampal neurons, while moderate intra-ischaemic hypothermia, resulted in lasting salvage of neurons at 2 months [26]. Minimal delay and long duration of mild hypothermia seem to be of critical importance. In gerbils, a 24-h duration of moderate hypothermia (32°C), even when initiated 1 h after insult, was highly protective in terms of neurological recovery and histological damage at 30 days [27], while neuroprotection was less when hypothermia was initiated 4 h after insult [28]; however, increasing the duration of hypothermia to 48 h resulted in long-lasting protection of neurons at 1 month, even when hypothermia was delayed for 6 h [29]. The long-lasting effect of delayed (6 h), prolonged (48 h) hypothermia (32–34°C) on functional and histological outcome at 1 month was confirmed in rats [30].

Clinical trials with hypothermia after cardiac arrest

Therapeutic hypothermia after cardiac arrest in patients was dormant until the late 1990s, when Bernard et al. [31] showed that induced moderate hypothermia increased the number of patients with good outcome (Glasgow Outcome Coma Scale category 1 or 2) compared to a historic control group (11 of 22 vs 3 of 22; $P < 0.05$), and reduced mortality rate (10 of 22 vs 17 of 22; $P < 0.05$). This was a non-randomised study with a matched historic control group. Cooling was by surface cooling with ice packs over 12 h.

In the study of Yanagawa et al. [32], cardiac arrest survivors were cooled to a core temperature between 33 and 34°C over 48 h using water-filled cooling blankets

in combination with alcohol. Three of 13 patients in the hypothermia group survived without disabilities as compared to 1 of 15 patients in the historical control group. A higher rate of pulmonary infection was observed in the hypothermia group, although pneumonia was not lethal in these patients.

In the pilot study of the European multicentre trial [33], 27 comatose patients after successful resuscitation of ventricular fibrillation cardiac arrest were enrolled. Surface cooling was initiated within 62 ± 33 min after cardiac arrest with a water-filled blanket. The target temperature (33 ± 1°C) was reached after 287 ± 145 min and was maintained for additional 24 h. Thereafter, patients were allowed to re-warm passively. The aim of this study was to investigate possible harmful side-effects of mild therapeutic hypothermia, and no major complications related to treatment with mild hypothermia were detected. As a secondary outcome parameter, neurological outcome was evaluated using the cerebral performance category (CPC) score, which was subdivided into good outcome (CPC 1 or 2), poor outcome (CPC 3 or 4), or death at 6 months. Good neurological recovery was achieved in 14 (52%) patients, poor neurological recovery in two (7%) patients, and 11 (41%) patients died before discharge. This was a two-fold improvement in neurological outcome compared to historic controls.

Encouraged by the positive results of the feasibility studies described above, prospective randomised clinical trials were conducted, and the results of these studies were published recently.

The first randomised trial took place in one of the centres also participating in the European multicentre study [34]. In contrast to the multicentre trial, only patients with asystole and pulseless electrical activity were included, and therefore none of the patients were included in more than one trial. A helmet device (Frigicap) containing a solution of aqueous glycerol was placed around the head and neck and used to induce mild hypothermia in 30 patients. Once a bladder temperature of 34°C was reached, or if cooling took longer than 4 h, the patient was allowed to rewarm spontaneously over the next 8 h. Two of 16 patients in the hypothermia group and none of the 14 patients in the normothermia group had a favourable neurological recovery ($P = 0.49$). Three patients in the hypothermia group survived vs one patient in the normothermia group ($p = 0.60$). Oliguria occurred in four hypothermic and in five normothermic patients. There were no further complications reported.

In the Australian trial [35], 77 patients with return of spontaneous circulation after cardiac arrest of cardiac origin (ventricular fibrillation or pulseless ventricular tachycardia) were randomly assigned to treatment with hypothermia (33°C core temperature over 12 h, cooled with ice packs) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurological function to be discharged to home or to a rehabilitation facility. Good neurological outcome was achieved in 21 of 43 patients (49%) treated with hypothermia compared to nine of 34 patients (26%) treated with normothermia ($P = 0.046$). After adjustment for baseline differences, the odds ratio for a good neurological outcome was 5.25 (95% confidence interval, 1.47–18.76; $P = 0.011$) for patients treated with hypothermia compared to patients treated with normothermia. There

was no difference in the frequency of adverse events but hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycaemia.

In the European multicentre trial [36], 273 patients with restoration of spontaneous circulation after cardiac arrest of cardiac origin (ventricular fibrillation or pulseless ventricular tachycardia) were randomly assigned to therapeutic hypothermia (32–34°C bladder temperature, cooled with cold air) over a period of 24 h, or to standard treatment with normothermia. All patients received standard intensive care according to a detailed protocol, including the use of sedation and muscle relaxation for 32 h. The primary end point was a favourable neurological outcome within 6 months after cardiac arrest, defined as CPC 1 or CPC 2; secondary end points were mortality within 6 months and the rate of complications within 7 days. Favourable neurological outcome was achieved in 75 of 136 patients (55%) in the hypothermia group compared to 54 of 137 patients (39%) in the normothermia group (risk ratio, 1.40; 95% confidence interval 1.08–1.81). Mortality at 6 months was 41% in the hypothermia group (56 of 137 patients died) compared to 55% in the normothermia group (76 of 138 patients died; risk ratio, 0.74; 95% confidence interval 0.58–0.95). No difference in the rate of complications was observed between the two groups.

In a meta-analysis [37] that included individual patient data of all three randomised trials of therapeutic hypothermia after cardiac arrest, it was shown that more patients in the hypothermia group were discharged with favourable neurological recovery (risk ratio, 1.68; 95% confidence interval 1.29–2.07). Furthermore, the 95% confidence interval of the number-needed-to-treat to allow one additional patient to leave the hospital with favourable neurological recovery was 4–13. Additionally, patients were more likely to be alive at 6 months with favourable functional neurological recovery if they were treated with hypothermia (risk ratio, 1.44; 95% confidence interval 1.11–1.76).

Future perspectives

Cooling methods

Delay in cooling can negate the beneficial effects of preservative and resuscitative hypothermia [21]. Therefore, a technique to induce hypothermia, already feasible in the pre-hospital setting, is required. Surface cooling, as used in the two prospective randomised clinical trials described above [35, 36], was very slow, and up to 8 h were needed to reach target temperature. However, whether faster cooling results in even better outcome remains to be determined.

Infusion of a large volume (40 ml/kg) of ice-cold intravenous fluid in healthy humans changed core temperature only by 0.6°C (SD 0.1) [38], or by 2.5°C (SD 0.4) [39]. Recently, 30 ml ice-cooled saline/kg, administered intravenously over 30 min, decreased core temperature about 1.6°C in cardiac arrest survivors [40]. More invasive blood-cooling techniques might be more powerful in inducing hypother-

mia, but are limited to use by advanced emergency medical personnel, resulting in delay of initiation. Virkkunen et al. [41] cooled patients already in the pre-hospital setting. They used ice-cold Ringer's solution in 13 adult patients after successful resuscitation from non-traumatic cardiac arrest. After haemodynamic stabilisation, 30 ml of Ringer's solution/kg was infused at a rate of 100 ml/min into the antecubital vein. Of these 13 patients, four (31%) survived to hospital discharge with favourable neurological recovery.

Veno-venous extra-corporeal pump cooling was shown to be quite efficient in rapidly inducing hypothermia [42–44], but this cooling technique requires a double-lumen venous catheter with portable miniaturised pump, heat-exchanger, and a cold source, a device not available yet. Other novel endovascular cooling devices, using cold fluid pumped through a balloon at the tip of the catheter (inserted into the superior or inferior vena cava), are already in use in the clinic [45–47]. This approach seems to be safe, with the advantage of no fluid entering the circulation, although the cooling rate averaged only 0.8 ± 0.3°C/h (range 0.22–1.12°C/h) [47].

Suspended animation

About one half of out-of-hospital resuscitation attempts for sudden cardiac death fail to restore heartbeat, and these patients are given little chance in the field [1]. It is suspected that many of these deaths occur in patients with potential for complete cardiac and cerebral recovery, provided prolonged cardiopulmonary bypass is induced before loss of cerebral viability, to support the heart until recovery by stunning, repair, or replacement [48, 49]. Cardiopulmonary bypass is not available in the field. Therefore preservation of the organism is needed until it can be initiated in the emergency department. In 1984, Bellamy and Safar introduced the concept of 'suspended animation for delayed resuscitation,' in rapidly exsanguinating trauma patients. Suspended animation was defined as 'preservation of the organism during transport and surgical haemostasis, under prolonged controlled clinical death, followed by delayed resuscitation to survival without brain damage' [50].

Preservative hypothermia, induced and reversed with cardiopulmonary bypass before cardiac arrest, has been shown to preserve the organism for up to 15 min by mild hypothermia (34–36°C) [8], for up to 20 min by moderate hypothermia (28–32°C) [10], for up to 30 min by deep hypothermia (11–27°C) [51, 52], and for up to 60 min by profound hypothermia (6–10°C) [53]. To rapidly preserve the brain with mild to moderate hypothermia until more prolonged preservation with profound hypothermic circulatory arrest is induced and reversed by cardiopulmonary bypass [49, 53, 54], the use of an aortic cold saline flush, via a balloon catheter, was introduced [55–57]. In a clinically realistic, exsanguination cardiac arrest dog-outcome model, the induction of suspended animation using cold (4°C) aortic flush within the first 5 min of cardiac arrest has shown to preserve brain viability for a cardiac arrest time of 15 min [55], 20 min [56], 30 min [57], and 90 min, perhaps 120 min [58].

This approach of preserving the organism with rapidly induced mild to mode-

rate cerebral hypothermia to buy time for transport to the hospital needs to be also explored for normovolaemic cardiac arrest patients who are temporarily resistant to conventional resuscitation attempts [48, 50]. The clinical scenario would be (modified after [48]): After cardiac arrest, a bystander will initiate basic life support and already induce cooling by exposure; ambulance personnel arrives at the scene and begins conventional advanced life support with hypothermic i.v. infusion with a vasoconstrictor and defibrillation attempts; if restoration of spontaneous circulation cannot be achieved within 10 min, the emergency physician will further attempt cooling to achieve systemic temperatures as low as possible to preserve the brain and heart, leaving the patient in cardiac arrest for transport to the emergency department, where cardiopulmonary bypass will be initiated.

In preliminary normovolaemic cardiac arrest studies in swine (unpublished data), suspended animation was shown to be feasible. After 15 min of normothermic ventricular fibrillation, the aortic flush decreased brain temperature to approximately 20°C. Aortic flush was followed by a period of 20 min of hypothermic no-flow, and then the animals were resuscitated with cardiopulmonary bypass. Five out of six animals could be resuscitated and all survived to 9 days, with two animals showing good neurological recovery. In the control group with 20 min resuscitation attempts before cardiopulmonary bypass, four out of seven animals could be resuscitated, and only one animal survived, with poor neurological recovery (survival $P = 0.03$).

References

1. Eisenberg MS, Horwood BT, Cummins RO et al (1990) Cardiac arrest and resuscitation: a tale of 29 cities. Ann Emerg Med 19:179–186
2. Safar P, Behringer W (2003) Brain resuscitation after cardiac arrest. In: Layon AJ, Gabrielli A, Friedman WA (eds) Textbook of neurointensive care. Saunders, Philadelphia, pp 457–498
3. Safar P (1997) Resuscitation of the ischemic brain. In: Albin MS (ed) Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives. McGraw-Hill, New York, pp 557–593
4. Siesjo BK (1988) Mechanisms of ischemic brain damage. Crit Care Med 16:954–963
5. White BC, Sullivan JM, DeGracia DJ et al (2000) Brain ischemia and reperfusion: molecular mechanisms of neuronal injury. J Neurol Sci 179:1–33
6. Michenfelder JD, Theye RA (1970) The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. Anesthesiology 33:430–439
7. Safar P (1986) Cerebral resuscitation after cardiac arrest: a review. Circulation 74:IV138-IV153
8. Safar P (1988) Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. Crit Care Med 16:923–941
9. Reuler JB (1978) Hypothermia: pathophysiology, clinical settings, and management. Ann Intern Med 89:519–527
10. Bigelow WG, Linsay WK, Greenwood WF (1950) Hypothermia: Its possible role in cardiac surgery. Ann Surg 132:849–866

11. Rosomoff HL, Holaday A (1954) Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 179:85–88
12. Friedman EW, Davidoff D, Fine J (1956) Effect of hypothermia on tolerance to hemorrhagic shock. In: Dripps RD (ed) The physiology of induced hypothermia Washington, DC: National Academy of Science Publication, pp 369–380
13. Steen PA, Soule EH, Michenfelder JD (1979) Detrimental effect of prolonged hypothermia in cats and monkeys with and without regional cerebral ischemia. Stroke 10:522–529
14. Steen PA, Milde JH, Michenfelder JD (1980) The detrimental effects of prolonged hypothermia and rewarming in the dog. Anesthesiology 52:224–230
15. Busto R, Dietrich WD, Globus MY et al (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729–738
16. Hossmann KA (1988) Resuscitation potentials after prolonged global cerebral ischemia in cats. Crit Care Med 16:964–971
17. Leonov Y, Sterz F, Safar P et al (1990) Moderate hypothermia after cardiac arrest of 17 minutes in dogs. Effect on cerebral and cardiac outcome. Stroke 21:1600–1606
18. Leonov Y, Sterz F, Safar P et al (1990) Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 10:57–70
19. Sterz F, Safar P, Tisherman S et al (1991) Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 19:379–389
20. Weinrauch V, Safar P, Tisherman S et al (1992) Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. Stroke 23:1454–1462
21. Kuboyama K, Safar P, Radovsky A et al (1993) Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 21:1348–1358
22. Safar P, Xiao F, Radovsky A et al (1996) Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke 27:105–113
23. Coimbra C, Wieloch T (1994) Moderate hypothermia mitigates neuronal damage in the rat brain when initiated several hours following transient cerebral ischemia. Acta Neuropathologica 87:325–331
24. Hickey RW, Ferimer H, Alexander HL et al (2000) Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. Crit Care Med 28:3511–3516
25. Green EJ, Dietrich WD, van Dijk F et al (1992) Protective effects of brain hypothermia on behavior and histopathology following global cerebral ischemia in rats. Brain Res 580:197–204
26. Dietrich WD, Busto R, Alonso O et al (1993) Intraischemic but not postischemic brain hypothermia protects chronically following global forebrain ischemia in rats. J Cereb Blood Flow Metab 13:541–549
27. Colbourne F, Corbett D (1994) Delayed and prolonged post-ischemic hypothermia is neuroprotective in the gerbil. Brain Res 654:265–272
28. Colbourne F, Corbett D (1995) Delayed postischemic hypothermia: a six month survival study using behavioral and histological assessments of neuroprotection. J Neurosci 15:7250–7260
29. Colbourne F, Auer RN, Sutherland GR (1998) Behavioral testing does not exacerbate ischemic CA1 damage in gerbils. Stroke 29:1967–1970
30. Colbourne F, Li H, Buchan AM (1999) Indefatigable CA1 sector neuroprotection with

mild hypothermia induced 6 hours after severe forebrain ischemia in rats. J Cereb Blood Flow Metab 19:742–749
31. Bernard SA, Jones BM, Horne MK (1997) Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 30:146–153
32. Yanagawa Y, Ishihara S, Norio H et al (1998) Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation 39:61–66
33. Zeiner A, Holzer M, Sterz F et al (2000) Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke 31:86–94
34. Hachimi-Idrissi S, Corne L, Ebinger G et al (2001) Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 51:275–281
35. Bernard SA, Gray TW, Buist MD et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346:557–563
36. Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549–556
37. Holzer M, Bernard SA, Hachimi-Idrissi S et al (2005) Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med 33:414–418
38. Baumgardner JE, Baranov D, Smith DS et al (1999) The effectiveness of rapidly infused intravenous fluids for inducing moderate hypothermia in neurosurgical patients. Anesth Analg 89:163–169
39. Rajek A, Greif R, Sessler DI et al (2000) Core cooling by central venous infusion of ice-cold (4 degrees C and 20 degrees C) fluid: isolation of core and peripheral thermal compartments. Anesthesiology 93:629–637
40. Bernard S, Buist M, Monteiro O et al (2003) Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 56:9–13
41. Virkkunen I, Yli-Hankala A, Silfvast T (2004) Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 62:299–302
42. Behringer W, Safar P, Wu X et al (2002) Veno-venous extracorporeal blood shunt cooling to induce mild hypothermia in dog experiments and review of cooling methods. Resuscitation 54:89–98
43. Piepgras A, Roth H, Schurer L et al (1998) Rapid active internal core cooling for induction of moderate hypothermia in head injury by use of an extracorporeal heat exchanger. Neurosurgery 42:311–317
44. Holzer M, Behringer W, Janata A et al (2005) Extracorporeal venovenous cooling for induction of mild hypothermia in human-sized swine. Crit Care Med 33:1346–1350
45. Keller E, Imhof HG, Gasser S et al (2003) Endovascular cooling with heat exchange catheters: a new method to induce and maintain hypothermia. Intensive Care Med 29:939–943
46. Dixon SR, Whitbourn RJ, Dae MW et al (2002) Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. J Am Coll Cardiol 40:1928–1934
47. Al Senani FM, Graffagnino C, Grotta JC et al (2004) A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. Resuscitation 62:143–150
48. Safar P, Tisherman SA, Behringer W et al (2000) Suspended animation for delayed

resuscitation from prolonged cardiac arrest that is unresuscitable by standard cardiopulmonary-cerebral resuscitation. Crit Care Med 28:N214-N218
49. Safar P, Abramson NS, Angelos M et al (1990) Emergency cardiopulmonary bypass for resuscitation from prolonged cardiac arrest. Am J Emerg Med 8:55–67
50. Bellamy R, Safar P, Tisherman SA et al (1996) Suspended animation for delayed resuscitation. Crit Care Med 24:S24-S47
51. Hickey PR (1985) Deep hypothermic circulatory arrest: current status and future directions. Mt Sinai J Med 52:541–547
52. Livesay JJ, Cooley DA, Reul GJ et al (1983) Resection of aortic arch aneurysms: a comparison of hypothermic techniques in 60 patients. Ann Thorac Surg 36:19–28
53. Capone A, Safar P, Radovsky A et al (1996) Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. J Trauma 40:388–395
54. Tisherman SA, Safar P, Radovsky A et al (1991) Profound hypothermia (less than 10 degrees C) compared with deep hypothermia (15 degrees C) improves neurologic outcome in dogs after two hours' circulatory arrest induced to enable resuscitative surgery. J Trauma 31:1051–1061
55. Woods RJ, Prueckner S, Safar P et al (1999) Hypothermic aortic arch flush for preservation during exsanguination cardiac arrest of 15 minutes in dogs. J Trauma 47:1028–1036
56. Behringer W, Prueckner S, Safar P et al (2000) Rapid induction of mild cerebral hypothermia by cold aortic flush achieves normal recovery in a dog outcome model with 20-minute exsanguination cardiac arrest. Acad Emerg Med 7:1341–1348
57. Behringer W, Prueckner S, Kentner R et al (2000) Rapid hypothermic aortic flush can achieve survival without brain damage after 30 minutes cardiac arrest in dogs. Anesthesiology 93:1491–1499
58. Behringer W, Safar P, Wu X et al (2003) Survival without brain damage after clinical death of 60–120 mins in dogs using suspended animation by profound hypothermia. Crit Care Med 31:1523–1531

Chapter 17

Vegetative state

N. Latronico

Consciousness

Historically speaking, the term 'consciousness' appeared in relatively recent times, around the 17th century. Its etymology has Latin roots (*cum*/with and *scio*/know) that indicate the necessity to share consciousness with someone or oneself. Interestingly, the foremost philosophers of the past from Plato to Aristotle up to Saint Thomas had never felt the need for such a term, and likely attributed its characteristics to divinity [1, 2].

Today, consciousness is part of everyday language, even if it can have a wide variety of meanings [3, 4]. According to Zeman [3], consciousness may indicate 'to be awake', or the fundamental condition in order to interact with the surrounding environment. In this context, consciousness is the behavioural expression of a normal state of wakefulness [3]. At the other extreme, consciousness can be considered as experience, or as the knowledge of awareness, meaning the sum of events that permit an individual to feel himself, and not another. Consciousness can thus refer not only to the knowledge of oneself and one's surroundings, which can be considered as a causal experience of behaviour, but can also be a subjective quality of experience that is not directly accessible to observation. Consciousness can be identified as the mind; any mental state with a constructive content is a mental act (I am conscious of the fact that I may be boring the reader). Finally, from an electro-encephalographic standpoint, three states of consciousness can be identified [5]: a state of wakefulness, sleep with rapid eye movements (REM), and slow wave sleep (SWS). To each of these states, a particular activity can be attributed, such as the oneiric behaviour of REM sleep or the loss of muscle tone during SWS.

Self-consciousness and unconscious perception

Self-consciousness and unconscious perception [5] further complicate the definition of consciousness. Self-consciousness can be interpreted as the appreciation of one's limits or as the physical identification of one's own body, or the self-consciousness that starts at around 18 months after birth, as for chimpanzees or orangutans (but not apes), which are able to recognise their own reflection in a mirror [5]. Self-consciousness can also be interpreted as the consciousness of having consciousness; the lack of this dimension appears to be particularly rele-

vant, for example, in understanding the causes of autism [5]. Lastly, self-consciousness may be seen as self-awareness, or the consciousness not only of oneself as body and mind, but also as part of a social group with particular linguistic and socio-economic characteristics.

Unconscious, implicit or subliminal perception refers to the perception that arises in the absence of any other conscious perception about perceived information: the subject receives new information that is elaborated and assessed. Such information and the fact that it is new can be demonstrated, although the subject is not conscious of this fact [6]. The classic example of such a phenomenon is that of blindsight, or the ability to 'see' objects in the absence of vision [7, 8]. Patients with unilateral lesions of the optical radiation or visual cortex are able to point to or localise visual stimuli with their eyes when present in the blind half-field. They can also discriminate the orientation, direction of movement, and colour if forced to choose or asked to guess. The same is true of monkeys that move freely about objects placed in a test area, in spite of the fact that they have had bilateral ablation of the striate cortex years before [7]; they do not touch the objects, indicating that, even if blind, they nonetheless use some visual information in order to navigate about. Monkeys subjected to removal of the primary visual cortex of the left hemisphere and callosotomy can be taught to push two different buttons according to whether presented with a luminous or non-luminous stimulus in the visual field [8]. When a luminous visual stimulus is present in the blindfield (right side), the monkey pushes a button corresponding to a non-luminous stimulus; they are thus able to recognise the stimulus, but in a different, unconscious manner.

Coma

The above discussion helps to clarify the limits of the following equation: coma = opposite of consciousness, for which the former can be defined as the absence of the latter. The question then arises, 'The absence of what?' Is coma the absence of consciousness defined as the state of awareness? Furthermore, is awareness a purely subjective dimension, internal, and therefore one that cannot be demonstrated? This latter question is particularly difficult to answer in patients in a vegetative state (VS). With these limits in mind, and leaping into a clinical context, the absence of awareness can be defined as the absence of any form of cognitive activity, even elementary, in patients who have had documented cerebral damage. The awareness requires a state of wakefulness in order to be fully functional. In contrast, the state of wakefulness, identified as the opening of the eyes, can be present in the absence of awareness. Coma is the only condition in human pathology for which both components of consciousness are lost. The patient never opens his eyes, not even under intense stimulation; moreover, there is no state of even rudimental awareness and thus no comprehensible sounds are emitted. Even simple orders cannot be followed and the patient has no intentional movements.

Anatomical and physiological basis of consciousness: brainstem, thalamus and basal forebrain

The traditional concept that the ascending reticular activating system (ARAS) is essential in maintenance of consciousness can be traced to the beginning of the 20th century in studies by Bremer [9], Von Economo [10], Morison and Dempsey [11], Jasper and Droogelever–Fortuyn [12] and Moruzzi and Magoun [13]. The latter report, published in 1949, demonstrated that stimulation of the ARAS causes the appearance of an electro-encephalographic (EEG) tracing characterised by a high frequency and low amplitude ('desynchronised') that is typical of wakefulness, while lesion of the same areas causes coma and the EEG is characterised by a low frequency and elevated amplitude ('synchronised') [13]. The concept of synchronisation and desynchronisation remains valid, even though it is more complex than initially believed and only partly understood. For example, the pathological synchronisation induced by generalised epileptic discharge explains why the pathology leads to alterations in consciousness. Moruzzi and Magoun supposed that the ARAS present in the most cranial part of the brainstem needed to activate the cerebral cortex and that it was essential for maintaining consciousness. Successive studies demonstrated how the ARAS extends dorsally in the pons and mesencephalon [14]. The nucleus pontis oralis, the locus ceruleus, the raphe complex, the latero-dorsal tegmental nucleus and the parabrachial nucleus are the structures of the brainstem that are most critical for maintaining consciousness. Lesion of these structures, especially if bilateral, invariably causes coma [14].

The thalamus [15], through the intralaminar nucleus, and the basal forebrain [5, 16] are the other two structures necessary for the process of diffuse activation of the cerebral cortex that is believed to be fundamental for consciousness. The high-frequency oscillatory activity of the thalamic-cortical circuit [17, 18] is considered strategic in the maintenance of consciousness under physiological conditions, in the sleep–wake transition, as well as in pathological conditions as documented in some cases of VS, for which the return of function of the circuit is accompanied by the return of consciousness [19]. At present, the thalamus is believed to play a role not only in storing sensorial information originating from external stimuli; it is rather a 'compact' version of the cerebral cortex with critical vascularisation. Bilateral thalamic lesions, in general secondary acute cerebrovascular lesions [20, 21], invariably lead to prolonged coma or even a persistent VS, as in the famous case of Karen Ann Quinlan, a young woman who went into cardiac arrest in 1975 and died 10 years later without ever regaining consciousness [22].

Vegetative state

Coma does not last longer than 6–8 weeks [23]. After this period the patient recovers the capacity for wakefulness (the patient opens his eyes), thus passing into a VS. The VS is characterised by the complete absence of behavioural evidence for self or environmental awareness, accompanied by the persistence of sleep–wake

rhythms and complete or partial maintenance of autonomic functions [24, 25]. In their pivotal publication [1], Jennett and Plum described the clinical characteristics of vegetative patients: 'Their eyes are open or they open after an intensely painful stimulation, possess erratic ocular movements and are incapable of following objects, have limb movements that are never intentional, sometimes emit sounds but not words. Grasp reflexes are present as well as grimacing, mastication, and deglutition'.

Diagnosis of VS is clinical and requires careful and repeated neurological examination, and especially adequate observation over a lengthy period of time. The sensory modality assessment and rehabilitation technique (SMART) [26] has been proposed recently for more accurate and specific assessment of patients in VS (http://www.rhn.org.uk/institute/cat.asp?catid=1278). Recently, neuroimaging and activation studies (positron-emission tomography [PET], functional magnetic resonance imaging [MRI], magnetoencephalography, EEG, event-related potentials) have demonstrated that patients in VS lose connectivity between cerebral areas that are normally interconnected, allowing an important step in the understanding of damage mechanisms [27, 28]; this demonstration also permitted comprehension of how evoked potentials (e.g. somatosensory) can be maintained in these patients [6]. These represent the activation of primary cortical areas without the transfer of information to higher-order associative cortices, this latter event being essential for conscious elaboration of the message. At the same time, the demonstration that the connectivity between cerebral areas is maintained in patients that are clinically defined as VS has opened new areas of discussion [27–33]. In fact, cases that remain in a vegetative state for years, but that are at least 'minimally conscious' are not uncommon [34, 35].

Persistent and permanent vegetative state

The term 'persistent' refers to a 'past condition and a continuous disability with an uncertain future' and does not imply that the condition is 'irreversible' [24]; the term 'persistent' is used when the condition lasts at least one month [24]. This definition, proposed in 1994 by a North-American Multi-Society Task Force on PVS [24], was not agreed upon by everyone. In fact, the American Congress of Rehabilitation Medicine observed how temporal specification is superfluous and suggests that the term 'persistent' be used followed by the actual duration of this condition [36].

To define a VS as permanent is not a diagnosis, but rather, provides prognostic information. At present, permanent VS is defined as that lasting longer than 3–6 months [25, 37] after anoxia or more than 12 months following brain trauma [25]. An important limitation of this definition is that it refers to the lack of the possibility to recover not necessarily awareness, but also function, defined as the 'capacity to communicate, comprehend, and have adaptive behaviour, including movement, autonomy and participation in recreation and professional activities' [25]. In other words, after the above-described time interval, a patient should be defined as being in a permanent VS if unable to carry out a functionally autonomous life, even if

awareness has been recovered. One inconsistency should be evident, namely that the fundamental condition of the vegetative patient is that there is no awareness. This problem was studied by an Italian working group in 2000 [38] and was recently reconsidered in the updated guidelines of the Royal College of Physicians of London [39]. In this latter document, it was stressed that the permanent loss of awareness is crucial to the diagnosis of permanent VS [39].

A further limitation of the definition of 'permanent' is that it should indicate the outcome with 100% certainty. The available data, however, do not consent such certainty [36, 38, 40]. According to the analysis of the Italian working group, 6–7% of patients with severe brain trauma recover consciousness even after 1 year following the trauma [38]. The case reported by Childs et al. in an 18-year-old girl is emblematic [40]. Fifteen months after trauma, for the first time the rehabilitation staff noted that the patient followed simple orders. At 17 months, the girl, even though paralysed and mute, was conscious. She communicated with her mother by blinking her eyes and had her write 'Mom, I love you'. Five years later, she can carry out a conversation and communicate with words and short sentences.

Differential diagnosis: the locked-in syndrome and minimally conscious state

A long list of clinical conditions must be excluded before a diagnosis of VS is made. An equally long list exists for meaningless, which should not be used (e.g. apallic state). The reader is referred to other publications for more details [1, 23, 41–43]; in the present report only the two most important syndromes in the differential diagnosis will be discussed.

Locked-in syndrome (LIS) is a condition in which the patient is conscious, but is tetraplegic and anarthric (and therefore mute). The characterisation of the syndrome was reported by Plum and Posner during the 1960s [23], even though several descriptions can be found in common literature, such as the splendid description of Monsieur Noirtier de Villefort in the 'The Count of Montecristo' by Alexandre Dumas [41, 44]. The cause is often a ventral pons infarction that interrupts the cortical-descending motor pathways, but traumatic, infective, and neoplastic causes have also been described [45–47]. In some cases, paralysis is secondary to involvement of the peripheral nervous system by acute inflammatory processes [48]. I have observed on several occasions patients with transitory LIS secondary to a 'critical illness myopathy and neuropathy' that affects nerves and muscles of the limbs, of the respiratory system, and in parts of the head. Such patients were functionally mute due to the tracheal intubation necessary for mechanical ventilation. In patients with a favourable evolution, LIS is resolved with the resolution of critical illness myopathy and neuropathy, which is in reality rather frequent [49–51].

In patients with LIS, generally the only movements possible are raising the eyelids and vertical eye movements; patients communicate by nictitation (e.g. one blink is 'yes', two blinks mean 'no'), although the medical literature has described

various ingenious methods for patient communication (e.g. Morse code). The advent of computers has obviously revolutionised communicative capacity to the point that patients have been able to describe their condition and the way in which they live. One example is the stunning book *The Diving Bell and the Butterfly* by Jean-Dominique Bauby. Jean-Dominique, reporter and editor-in-chief of *Elle*, founder of an association of patients affected by LIS (http://www.club-internet.fr/alis), will continue to fly, a butterfly from the diving bell, in the two years since the onset of his disease until his death, describing that his new world is not always as horrible as observed from healthy eyes: 'Do you have something to say to people that move? Go ahead. But be careful to not be devoured by your agitation. Even immobility is a source of joy' (from an interview of Bauby by Erik Orsenna in *Elle*). Massi is a young patient with LIS, by now a friend, whom I have followed for over 10 years. By using a sophisticated computerised system, he is able to communicate with the outside world, write phrases and letters, and can even send e-mail.

The *minimally conscious state* (MCS) is a condition of severely altered consciousness in which minimal but definite behavioural evidence of self or environmental awareness is demonstrated [52]. MCS is distinguished from the vegetative state by the partial preservation of awareness. Akinetic mutism is a rare state that has been described as a subcategory of MCS [36], although other authors suggest that this term should be avoided [43]. This subject has been described in detail elsewhere [42]. In order to diagnose MCS, the Aspen Neurobehavioral Conference Workgroup proposed that limited but clearly discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis by one or more of the following criteria [52]: (a) following simple commands; (b) gestures or verbal yes/no responses (regardless of accuracy); (c) intelligible verbalisation; (d) purposeful behaviour, including movements or affective behaviours that occur in relation to relevant environmental stimuli and are not due to reflexive activity (i.e. appropriate smiling or crying, appropriate vocalisations or gestures, reaching for objects, pursuit eye movement or sustained fixation, etc.).

The advent of diagnostic techniques such as PET, providing the possibility to measure variations in cerebral blood flow and cerebral metabolism in response to various stimuli, has revealed that vegetative patients can have fragments of cerebral cortex that remain functional [31]. In a patient who has been in VS for 20 years, and who occasionally emits words that are uncorrelated with events or external stimuli, PET demonstrated a reduction in cerebral metabolism of over 50% in the majority of cerebral areas, with the exception of a small area of the left hemisphere where the metabolism was found to be higher [30]. Magnetoencephalographic responses to bilateral auditory stimulation were confined to the left hemisphere and localised to primary auditory areas. These data suggest that the left-sided thalamocortical–basal ganglia loops that support language are partially preserved. In patients with brain trauma, in which diffuse axonal injury is prevalent, the possibility to describe cortical islands, each of which maintains its activity although disconnected from the others, is theoretically more frequent than in other pathological conditions such as the post-anoxic state. Various studies on small patient populations in VS secondary to diverse pathological conditions have confirmed such a

possibility [27–33]. The actual significance of this, and in particular whether it can be considered as mental activity, remains in doubt. Using PET and functional MRI, respectively, Boly et al. [53] and Schiff et al. [54] demonstrated that patients with MCS can have activation of hearing mechanisms that are quire similar to those present in normal subjects, including the activation of areas dedicated to understanding of language. As proposed by Laureys et al. [55], the preservation of large-scale networks in patients with MCS may underlie rare instances of their late recoveries of verbal fluency [56]. These patients have thus the potential for a series of cognitive functions in spite of their incapacity to follow simple instruction or communicate in an efficacious manner. Kotchoubey et al., in an important paper on event-related brain responses [57], demonstrated the presence of cortical responsiveness in all patients in VS having an EEG frequency > 4 Hz. This cortical responsiveness was limited in some cases to the primary cortical areas, without evidence of diffusion to higher-order integrative cortices. However, more complex cortical responses were also present. The mismatch negativity was found in about one half of these patients, an oddball-P3 in about one third, and cortical evidence for semantic differentiation in about one quarter of cases. The probability of recording indicators of complex cortical functions such as mismatch negativity, oddball-P3, and brain responses to semantic stimuli, was not correlated to the clinical diagnosis of VS or MCS, but rather with a background EEG activity > 4 Hz. This highlights the importance of the activity of thalamocortical gating systems in maintenance or in recovery of consciousness [19, 42]. On the other hand, it gives room for doubts that have already been raised [27–33] on the accuracy of differential diagnosis of VS and MCS based on clinical examination alone. This differential diagnosis is extremely important due to its medical and ethical implications.

Conclusions

Vegetative state is an important medical and ethical problem and provides an extraordinary possibility to study mechanisms at the basis of consciousness. Activation studies using PET, functional MRI, magnetoencephalography, EEG and event-related potentials appear to be able to evaluate the functional state of areas of the cerebral cortex that are distinct in terms of analysis and comprehension of information. These studies have demonstrated that, in patients in VS, residual cortical processes are present, but lack proper connections among various cortical areas. This particularly concerns the primary areas and the higher-order multimodal association cortices, thus impeding integrative processes that are necessary for awareness. This is the basis for better differentiating patients who are truly vegetative from those who maintain variable grades of awareness, although they are unable to provide direct evidence for this.

References

1. Jennett B, Plum F (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet 1:734–737
2. Oro JJ (2004) Evolution of the brain: from behavior to consciousness in 3.4 billion years. Neurosurgery 54:1287–1296; discussion 1296–1287
3. Zeman AZ, Grayling AC, Cowey A (1997) Contemporary theories of consciousness. J Neurol Neurosurg Psychiatry 62:549–552
4. Crick F, Koch C, Kreiman G, Fried I (2004) Consciousness and neurosurgery. Neurosurgery 55:273–281; discussion 281–272
5. Zeman A (2001) Consciousness. Brain 124:1263–1289
6. Latronico N, Alongi S, Guarneri B et al (2000) Approccio al paziente in stato vegetativo. Parte I: diagnosi. Minerva Anestesiol 66:225–231
7. Stoerig P, Cowey A (1997) Blindsight in man and monkey. Brain 120(Pt 3):535–559
8. Cowey A, Stoerig P (1995) Blindsight in monkeys. Nature 373:247–249
9. Bremer F (1929) Cerveau isolé et physiologie du sommeil. C R Seanc Soc Biol 102:1235–1241
10. Von Economo C (1931) Encephalitis lethargica: its sequelae and treatment. London, Oxford University Press.
11. Morison RS, Dempsey EW (1942) A study of thalamo-cortical relationships. Am J Physiol 135:281–292
12. Jasper HH, Droogelever-Fortuyn J (1947) Experimental studies on the functional anatomy of petit mal epilepsy. Res Pub Assist Nerv Ment Disord 26:272–298
13. Moruzzi G, Magoun HW (1949) Brain stem reticular formation and the activation of the EEG. Electroencephalogr Clin Neurophysiol 1:455–473
14. Parvizi J, Damasio AR (2003) Neuroanatomical correlates of brainstem coma. Brain 126:1524–1536
15. Llinas R, Ribary U (2001) Consciousness and the brain. The thalamocortical dialogue in health and disease. Ann NY Acad Sci 929:166–175
16. Sinton CM, McCarley RW (2000) Neuroanatomical and neurophysiological aspects of sleep: basic science and clinical relevance. Semin Clin Neuropsychiatry 5:6–19
17. Kahn D, Pace-Schott EF, Hobson JA (1997) Consciousness in waking and dreaming: the roles of neuronal oscillation and neuromodulation in determining similarities and differences. Neuroscience 78:13–38
18. Ward LM (2003) Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 7:553–559
19. Laureys S, Faymonville ME, Luxen A et al (2000) Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet 355:1790–1791
20. Adams JH, Graham DI, Jennett B (2000) The neuropathology of the vegetative state after an acute brain insult. Brain 123 (Pt 7):1327–1338
21. Adams JH, Jennett B, McLellan DR et al (1999) The neuropathology of the vegetative state after head injury. J Clin Pathol 52:804–806
22. Kinney HC, Korein J, Panigrahy A et al (1994) Neuropathological findings in the brain of Karen Ann Quinlan. The role of the thalamus in the persistent vegetative state. N Engl J Med 330:1469–1475
23. Plum F, Posner JB (1966) The diagnosis of stupor and coma. Philadelphia, F. A. Davis Co.
24. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (1). N Engl J Med 330:1499–1508

25. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (2). N Engl J Med 330:1572–1579
26. Gill-Thwaites H, Munday R (2004) The Sensory Modality Assessment and Rehabilitation Technique (SMART): a valid and reliable assessment for vegetative state and minimally conscious state patients. Brain Inj 18:1255–1269
27. Menon DK, Owen AM, Williams EJ et al (1998) Cortical processing in persistent vegetative state. Wolfson Brain Imaging Centre Team. Lancet 352:200
28. Laureys S, Faymonville ME, Degueldre C et al (2000) Auditory processing in the vegetative state. Brain 123(Pt 8):1589–1601
29. de Jong BM, Willemsen AT, Paans AM (1997) Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. Clin Neurol Neurosurg 99:213–216
30. Schiff N, Ribary U, Plum F, Llinas R (1999) Words without mind. J Cogn Neurosci 11:650–656
31. Schiff ND, Ribary U, Moreno DR et al (2002) Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain 125:1210–1234
32. Owen AM, Menon DK, Johnsrude IS et al (2002) Detecting residual cognitive function in persistent vegetative state. Neurocase 8:394–403
33. Kassubek J, Juengling FD, Els T et al (2003) Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a 15O-H2O PET study. J Neurol Sci 212:85–91
34. Childs NL, Mercer WN, Childs HW (1993) Accuracy of diagnosis of persistent vegetative state. Neurology 43:1465–1467
35. Andrews K, Murphy L, Munday R, Littlewood C (1996) Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ 313:13–16
36. American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. Arch Phys Med Rehabil 76:205–209
37. Anoymous (1996) The permanent vegetative state. Review by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their faculties of the United Kingdom. J R Coll Physicians Lond 30:119–121
38. Latronico N, Alongi S, Facchi E et al (2000) Approccio al paziente in stato vegetativo. Parte III: prognosi. Minerva Anestesiol 66:241–248
39. Dyer C (2003) Permanent loss of awareness is crucial to diagnosis of PVS. BMJ 327:67
40. Childs NL, Mercer WN (1996) Brief report: late improvement in consciousness after post-traumatic vegetative state. N Engl J Med 334:24–25
41. Latronico N, Antonini L, Taricco M et al (2000) Approccio al paziente in stato vegetativo. Parte II: diagnosi differenziale. Minerva Anestesiol 66:233–240
42. Schiff ND, Plum F (2000) The role of arousal and 'gating' systems in the neurology of impaired consciousness. J Clin Neurophysiol 17:438–452
43. American Neurological Association Committee on Ethical Affairs (1993) Persistent vegetative state: report of the American Neurological Association Committee on Ethical Affairs. Ann Neurol 33:386–390
44. Dumas A (1979) Il signor Noirtier Villefort. In: Dumas A (ed) Il Conte di Montecristo. Mondadori, Milano, pp 478–484
45. Latronico N, Candiani A (1987) Brainstem herpes virus encephalitis. Lancet 2:690–691
46. Latronico N, Tansini A, Gualandi GF et al (1993) Ischaemic pontomedullary transection with incomplete locked-in syndrome. A case report with MRI. Neuroradiology 35:332–334
47. Smith E, Delargy M (2005) Locked-in syndrome. BMJ 330:406–409

48. O'Donnell PP (1979) 'Locked-in syndrome' in postinfective polyneuropathy. Arch Neurol 36:860
49. Latronico N, Fenzi F, Recupero D et al (1996) Critical illness myopathy and neuropathy. Lancet 347:1579–1582
50. Latronico N, Peli E, Botteri M (2005) Critical illness myopathy and neuropathy. Curr Opin Crit Care 11:126–132
51. Latronico N, Shehu I, Seghelini E (2005) Neuromuscular sequelae of critical illness. Curr Opin Crit Care 11:381–390
52. Giacino JT, Ashwal S, Childs N et al (2002) The minimally conscious state: definition and diagnostic criteria. Neurology 58:349–353
53. Boly M, Faymonville ME, Peigneux P et al (2004) Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol 61:233–238
54. Schiff ND, Rodriguez-Moreno D, Kamal A et al (2005) fMRI reveals large–scale network activation in minimally conscious patients. Neurology 64:514–523
55. Laureys S, Owen AM, Schiff ND (2004) Brain function in coma, vegetative state, and related disorders. Lancet Neurol 3:537–546
56. Bekinschtein T, Leiguarda R, Armony J et al (2004) Emotion processing in the minimally conscious state. J Neurol Neurosurg Psychiatry 75:788
57. Kotchoubey B, Lang S, Mezger G et al (2005) Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. Clin Neurophysiol 116:2441–2453

CARDIOVASCULAR

Chapter 18

A personal account from four decades of cardiac care: is there a case for mechanical heart rhythm management?

J.L. Atlee

This chapter offers a personal account based on my nearly 40 years of providing cardiac care in emergency and critical care medicine, and anaesthesiology. First, I must tell you some of my background, since I was supposed to be a surgeon. Seven generations of my family have been in medicine, and the previous three generations were all very prominent surgeons in America. Forty years ago, I was a junior student at Temple University Medical School in Philadelphia, and had just begun my clinical clerkships. Strongly urged by my father to pursue a career in surgery, I decided on training in general and cardiac surgery at the Mayo Clinic. However, all that changed when my then wife informed me in late 1966 that she would enter Temple Medical School in the fall of 1967, the year I would began my internship. Also, Vietnam loomed on the horizon. I was in the Naval Reserves during Medical School, but was unable to obtain deferment to complete my training in General and Cardiac Surgery. Also, I feared service in Vietnam as a General Medical Officer just after my internship, especially in support of a marine combat unit. However, both the Navy and Marines needed trained anaesthesiologists, so I was able to get the necessary deferment to complete my Residency in Anaesthesiology and Fellowship in Pharmacology at Temple. Unfortunately, my first wife was killed in an automobile accident on her way to work at Merck, Sharpe and Dohme in April 1967. However, by then, I was committed to Anaesthesiology and the Navy deferment. In those days, we honoured such commitments. There was no turning back.

I am not a cardiologist, much less a certified clinical cardiac electrophysiologist (i.e. heart-rhythm specialist). However, I have long had a very keen interest in cardiovascular medicine and management. Also, as many of you know, in addition to clinical anaesthesiology and teaching, I devoted nearly 30 years to basic research in cardiac electrophysiology (EP) in animal models, beginning as a graduate student in the Department of Pharmacology at Temple University (1970–1971) [1]. This led to the development of a canine model for awake-anaesthetised cardiac EP testing at the University of Wisconsin, in Madison [2]. This work continued after my move to the Medical College of Wisconsin (MCW) in 1988, but was expanded to include in vitro and in vivo methods for canine cardiac EP testing [3, 4]. The in vivo model was refined at MCW to include excision of the sinoatrial (SA) node or SA node and subsidiary atrial pacemakers. This was in order to determine the effects of anaesthetics and other drugs on the stability of subsidiary atrial and AV junctional pacemakers, and EP mechanisms for escape rhythms (especially, wandering atrial pacema-

ker or AV junctional rhythm). These were common with the potent inhalation anaesthetics in use at the time (e.g. halothane, enflurane, isoflurane).

Also, to gain a more complete perspective on perioperative heart rhythm management, I undertook comprehensive work on this topic in 1984. This dealt with mechanisms, recognition and clinical management for perioperative dysrhythmias [5]. The results of this work were published in textbook form and were based on then-available basic and clinical research heart rhythm management. This work was revised for a second edition in 1990, and later condensed to a more practical version in 1996 [6]. I also published several review articles pertaining to perioperative heart rhythm management between 1990 and 2001 [7–10]. Thus, I became recognised as knowledgeable in the perioperative management of patients with cardiac arrhythmias or implanted cardiac rhythm management devices.

However, there is no longer a need for a book solely devoted to this topic for anaesthesia and critical care physicians. It is addressed in chapters in more comprehensive works in anaesthesia and critical care, including my own work on complications in anaesthesia and critical care [11]. This now has an Italian version [12], thanks largely to Professor Gullo and his colleagues in Rome. The second English edition will appear in late 2006.

So, what have I learned from nearly 40 years of clinical heart rhythm management, and is there a case for mechanical heart rhythm management? This is addressed in the following under three headings: (1) arrhythmia tolerance and clinical priorities, (2) antiarrhythmic drugs and proarrhythmia, and (3) selection of antiarrhythmic therapy: drugs vs devices.

Arrhythmia tolerance and clinical priorities

Factors that influence arrhythmia tolerance include: (1) its duration, (2) the status of atrial transport function, (3) the presence or absence of AV dissociation, (4) the rate of tachycardia, (5) the presence of structural heart disease (often serves as the 'substrate'), and (6) cardiac functional status. If not treated immediately, ventricular fibrillation (VF) or pulseless electrical activity (PEA) are incompatible with life.

All tachycardias, regardless of mechanism, increase myocardial O_2 demand and decrease diastolic time. Tachycardia tolerance depends on its mechanism, but even sinus tachycardia may be poorly tolerated in patients with structural heart disease and reduced left ventricular (LV) function (i.e. ejection fraction ≤ 0.40). However, most tachycardia under 150 beats/min does not cause rate-related signs or symptoms [13]. Finally, seemingly benign sinus bradycardia or AV junctional rhythm may not be tolerated by patients with severely impaired right (RV) or LV diastolic dysfunction (i.e. impaired RV and/or LV active and/or passive relaxation).

For tachycardias, the clinician should first determine whether the signs or symptoms are due to tachycardia. If so, the 2000 Guidelines (likely, now being updated) advise immediate cardioversion rather than a trial of antiarrhythmic drugs [13]. Since today we are even more aware of the potential dangers of drugs as primary antiarrhythmic therapy, an update of the existing guidelines will likely

strongly re-emphasise the foregoing. If cardioversion is not indicated (e.g. ectopic atrial tachycardia), then the Guidelines emphasise making a specific rhythm diagnosis and identifying patients with impaired cardiac function (ejection fraction < 40%). Furthermore, they discourage the use of adenosine for determining the origin of wide QRS tachycardias (i.e. ventricular aberration vs ectopy). Not only does this unnecessarily expose patients to the unpleasant side effects of adenosine, but also it may provoke worse arrhythmias, as well as destabilise heart rate and blood pressure. Instead, more attention should be devoted to explicit diagnoses within the scope of the clinician's available resources.

Antiarrhythmic drugs and proarrhythmia

Proarrhythmia

Proarrhythmia is the provocation of new or worse arrhythmias by antiarrhythmic drugs. All antiarrhythmics pose some proarrhythmia risk. This ranges from 1–2% with amiodarone to 10% or higher with class IC antiarrhythmics (e.g. encainide, flecainide—withdrawn from the market in the USA). Proarrhythmia may present as torsades de pointes (TdP) (polymorphic ventricular tachycardia in association with QT interval prolongation) or incessant monomorphic ventricular tachycardia without QT prolongation. The latter is more commonly the mechanism for proarrhythmia in patients with structural heart disease and severe functional impairment. Also, proarrhythmia is more likely in these patients.

Antiarrhythmics alter the EP properties of both normal and diseased myocardium, usually favourably, to modify the triggers and/or substrates for tachyarrhythmias. Use of two or more antiarrhythmic drugs exponentially compounds the proarrhythmia potential. Therefore, the ACLS Guidelines advise one and only one antiarrhythmic drug per patient [13, 14].

Causes and management of the acquired long QT syndrome

As discussed above, QT prolongation predisposes to proarrhythmia as possibly fatal TdP [15–17]. While long QT syndrome (LQTS) is often considered as congenital (C-LQTS) or acquired (A-LQTS), it likely involves a gene–environment interaction [15]. 'Pure' C-LQTS is rare, but carries a high risk of sudden death. Several forms are known (LQT1, LQT2, LQT3), each with different clinical manifestations and outcomes, including factors that trigger arrhythmias to cause sudden death or syncope [15, 16]. Physical activity triggers events in LQT1, auditory stimuli in LQT2, and rest or sleep in LQT3. Each form involves mutations of genes encoding cardiac ion channels involved in depolarisation (LQT3) or repolarisation (LQT1 and LQT2). While the risk for cardiac events is significantly higher with LQT1 or LQT2, that for lethal events is higher with LQT3. Finally, there can be incomplete penetrance of gene defects in C-LQTS [17]. Thus, family members of persons with C-LQTS may have gene

mutations, but near normal QT intervals and no predisposition to lethal arrhythmias.

Drugs that prolong the QT interval and pose proven risk for TdP are listed in Table 1. A more extensive listing, including drugs with lower risk, can be found at

Table 1. Drugs with potential to cause QT interval prolongation and torsades de pointes (TdP)

Drug	Trade name(s) (USA)	Clinical indication(s)	Comments
Amiodarone	Cordarone	Antiarrhythmic Pacerone	TDP risk low (<1–2%)
Arsenic trioxide	Trisenox	Anti-neoplastic, leukemia	Unlikely
Bepridil	Vasocor	Anti-anginal	Females > males
Chloroquine	Arelan	Anti-malarial	Unlikely
Clorpromazine	Thorazine	Anti-psychotic, schizophrenia, nausea, anti-emetic	Unlikely
Cisapride	Propulsid	Prokinetic and reduces gastric secretions	Females > males; cisapride use is restricted in the USA
Clarithromycin	Biaxin	Antibiotic	TDP risk is high (≤ 10%)[a]
Disopyramide	Norpace	Antiarrhythmic (class I)	Unlikely
Dofetilide	Tikosyn	Antiarrhythmic (class III)	Unlikely
Dromperidone	Motilium	Antiemetic-antinauseant	Unlikely
Droperidol	Inapsine	Unlikely	Unlikely
Erythromycin	Erythrosin, E.E.S.	Antibiotic, prokinetc	Unlikely
Halofantrine	Halfan	Antimalarial	Females > males
Haloperidol	Haldol	Antipsychotic, agitation or schizophrenia	Unlikely
Ibutilide	Covert	Antiarrhythmic (class III)	Females > males; TdP risk high (≤ 10%[a])
Levomethadyl	Orlaam	Opiate agonist, pain control, narcotic dependence	Unlikely
Mesoridazine	Serentil	Antipsychotic, schizophrenia	Unlikely
Methadone	Dolophine	Opiate agonist, pain control, narcotic dependence	Females > males
Pentamidine	NebuPent	Antimicrobial, pneumocystis pneumonia	Females > males
Pimozide	Orap	Antipsychotic/Tourette's	Females > males
Procainamide	Pronestyl	Antiarrhythmic (class IA)	Unlikely
Sotolol	Betapace	Antiarrhythmic (class III)[b]	Females > males
Sparfloxacin	Zagam	Antibiotic	Unlikely
Thioridazine	Mellaril	Antipsychotic	Unlikely

[a]Highest in patients with structural heart disease. Source: http://www.torsades.org. (accessed 5/7/04).
[b]Also has class II activity.

http://www.torsades.org. With baseline QTc prolongation (men > 450 ms; women > 460 ms), but no interventricular conduction defects, one should avoid any QT-prolonging medications (Table 1) [15]. Regarding QT-prolonging antiarrhythmic drugs, TdP risk is highest for patients with structural heart disease within the first few days of beginning therapy. For this reason, it is advised that such patients be hospitalised to monitor for warning signs of TdP (QTc > 500–520 ms[1]) [15].

When exposed to QT-prolonging drugs or imbalance (e.g. hypokalaemia), individuals without life-threatening QT prolongation may develop it with or without TdP, or not develop it at all [15, 17]. Current evidence suggests that 5–10% of persons in whom TdP develops on exposure to QT-prolonging drugs have gene mutations associated with LQTS, and are viewed as having a subclinical form of the congenital syndrome [17]. Another explanation is that common gene polymorphisms cause subtle variations in ion-channels generating cardiac action potentials. These defects become apparent only when the person is exposed to drugs that block K-channels (sotalol, ibutilide, dofetilide, amiodarone) or other stresses (e.g. hypokalaemia or heart failure) [17]. Such variants may be frequent (~15% in some populations) and vary among ethnic groups [17].

Predisposing factors for acquired QT prolongation (A-LQTS) and TdP are older age, female sex, reduced LV ejection fraction, especially when the associated remodelling provides a substrate for TdP[2]. TdP management requires urgent suppressive measures. Magnesium may suppress it, but it does not shorten the QT interval [16]. Increasing heart rate with atropine or isoproterenol, or preferably in a more controlled fashion with temporary atrial or ventricular pacing, often suppresses TdP. Fast pacing shortens action potential duration and the QT interval, thereby suppressing early afterdepolarisations. Also, one must correct any electrolyte abnormalities and remove QT-interval-prolonging drugs. Finally, K-channel openers (pinacidil, cromakalim) may be useful in both C-LQTS and A-LQTS [18].

Selection of antiarrhythmic therapy: drugs vs devices

The case against drugs

Even IV antiarrhythmic drugs (AD) take some time to act. Also, they may have the following potent effects on cardiovascular function: (1) depress systolic ventricular function, 2) dilate the venous capacitance bed to reduce preload, (3) alter ventricular diastolic function, and (4) cause AV heart block or bradycardia. All AD block

1 There is no clear consensus on the degree of drug-induced QT prolongation that should require discontinuation of a drug that prolongs the QT interval, although respondents to a survey [15] were more likely to stop a QT-prolonging medication for a QT of 520 ms vs one of 500 ms.

2 TdP are likely initiated by early afterdepolarisations (EAD). EAD generate 'triggered' action potentials (AP) [17]. Certain cells (e.g. Purkinje fibers, M cells) appear more likely to develop EAD on exposure to drugs (Table 1). EAD in tissue vulnerable to reentry (i.e. heterogeneity in AP excitation and duration) likely triggers reentry, the proximate cause for TdP.

ion channels found in cardiac and vascular smooth muscle, and the central nervous system. Chronic use may have other untoward effects (e.g. pulmonary fibrosis with amiodarone, systemic lupus-erythematosus-like syndrome with procainamide). Also, AD may interact with drugs that affect autonomic or neural function. Importantly, once an AD is given, there is no turning back. Finally, AD interactions with abnormal myocardium can be complex, leading to inadequate arrhythmia control or proarrhythmia [19]. However, having said this, there still is and always will be a place for AD and other adjunct drug therapy in arrhythmia management (see below).

The case for devices: pacing, cardioversion, and defibrillation

In contrast to drugs, pacing, cardioversion or defibrillation can be turned on or off at will. Also, the needed energy can easily be titrated to effect, and the effects are immediate. Given the widely recognised deficiencies of ADs, it is not surprising that 'electricity' has assumed a more prominent place in the overall management and prevention of arrhythmias [20, 21].

Concerning drugs or electricity for arrhythmia management, some generalisations can be made [6, 8–10, 19–22]. First, *acute* disadvantageous bradycardia, regardless of origin or cause, is best treated with temporary pacing vs drugs to accelerate the rate of sinus or lower pacemakers. Positive chronotropes may provoke untoward tachycardia or arrhythmias or precipitate an acute coronary syndrome. Also, chronic, symptomatic, disadvantageous bradycardia and lower escape rhythms are indications for a permanent pacemaker [23]. Second, automatic tachyarrhythmias are not amenable to cardioversion. Also, cardioversion will not affect arrhythmia, accelerate it, or provoke far worse arrhythmias, even VF. Third, if destabilising tachycardia is amenable to cardioversion, use it! However, consider the use of drugs to prevent recurrences. Fourth, not all wide QRS tachycardia is ventricular in origin. If destabilising, the origin does not much matter! Early cardioversion or defibrillation is required [13, 14]. For example, pre-excited atrial fibrillation (AFB) will probably cause severe impairment due to extremely fast ventricular rates (250–300 beats/min). Both the haemodynamic effects and appearance will be similar to those of polymorphic ventricular tachycardia (PMVT) or VF. For preexcited AFB, PMVT and VF, treatment is the same: cardioversion (with clearly defined R or S waves) or defibrillation (without clearly defined R or S waves). Again, drugs are used to prevent recurrences. Fifth, drugs should not be used to suppress isolated extrasystoles (whether of atrial, atrial with ventricular aberration, or ventricular origin), unless they trigger recurrences of disadvantageous tachycardia. Finally, often overlooked is the effect of physiologic imbalance to cause or promote arrhythmias. It is necessary to identify and correct any such imbalance. Not only may this be sufficient therapy alone, but also it will go a long way to prevent recurrences and will facilitate more specific therapy.

Amiodarone as adjunct drug therapy

Amiodarone has all four Vaughan-Williams class actions [14], but far lower proarrhythmia potential (2–4%) vs other antiarrhythmics (5 ≤ 10%). IV amiodarone is useful: (1) for ventricular rate control of rapid atrial arrhythmias with severely impaired ventricular function when digitalis has proved ineffective, (2) for control of haemodynamically stable wide-QRS complex tachycardia of uncertain origin, (3) for control of potentially extremely rapid ventricular rates (250–300 beats/min) with preexcited atrial tachyarrhythmias, and (4) as adjunct therapy to electrical cardioversion of drug-refractory paroxysmal supraventricular tachycardia (SVT) or reentrant atrial tachycardia, and for drug conversion of AFB or atrial flutter [2]. Concerning the latter, in 665 patients with persistent AFB and receiving anticoagulants, amiodarone and sotalol were equally effective for converting AFB to sinus rhythm [24]. However, amiodarone was superior for maintaining sinus rhythm. The median times to recurrence of AFB were 487, 74 and 6 days for amiodarone, sotalol, and placebo, respectively, based on intention to treat, and 808, 209, and 13 days, respectively, based on treatment received. Both drugs were superior to placebo for converting AFB to sinus rhythm. For patients with ischaemic heart disease (96 of 665), the median time to a recurrence of AFB was 569 (amiodarone) vs 428 days (sotalol). Thus, both drugs had similar efficacy. Also, in patients with persistent AFB (likely after failed electrical conversion), it appears that amiodarone and sotalol are equally efficacious for converting AFB to sinus rhythm, although amiodarone appears superior for maintaining sinus rhythm in patients without ischaemic heart disease.

With severely impaired myocardial function, IV amiodarone is preferred to other IV drugs for atrial and ventricular tachyarrhythmias due to greater efficacy and less proarrhythmia [2]. Amiodarone is indicated after defibrillation, and epinephrine or vasopressin for ventricular tachycardia or VF that persists [2, 25–30]. Also, amiodarone may suppress AV junctional tachycardia, especially in children after open-heart surgery. However, removal of all inciting factors (e.g. digitalis, catecholamines, or theophylline [14]) is also required. AV junctional tachycardia (AVJT) is not terminated by electrical cardioversion. However, AVJT can be overdriven with temporary atrial pacing (either direct or indirect transoesophageal atrial[3]), with subsequent gradual weaning from pacing.

Other adjunct therapy

Most life-threatening arrhythmias occur in patients with severe heart disease that has progressed to NYHA Class III or IV (AHA/ACC Stage C or D)[4]. Despite

3 Author: unpublished observations in patients after cardiopulmonary bypass or with myocardial ischaemia.

4 NYHA (New York Heart Association) *functional classification* of heart failure (HF): Class I: asymptomatic on ordinary physical activity, Class II: symptoms with usual exertion, Class III: symptoms

convincing evidence that combined diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists (i.e. optimal drug therapy) can reduce hospitalisations and mortality in patients with heart failure, such life-prolonging therapy continues to be underutilised [31].

Concluding remarks

When I began practicing medicine nearly 40 years ago, lidocaine followed by cardioversion or defibrillation was conventional management for malignant ventricular arrhythmias. Also, in patients with acute myocardial infarction, lidocaine or procainamide were used as prophylaxis for recurrences of malignant ventricular arrhythmias, and lidocaine for suppression of ventricular extrasystoles or non-sustained VT (NSVT). The latter was due to the widely held belief (1960s and 1970s) that ventricular extrasystoles (VES) were the harbingers for more dangerous arrhythmias. This idea carried over into the 1980s, and was extended to use of Class IC oral antiarrhythmic drugs (e.g. encainide, flecainide, moricizine) for chronic suppression of frequent VES or NSVT in patients after acute myocardial infarction. However, the unanticipated results of both CAST I [32] and CAST II [33][5], of actually increased mortality from ventricular arrhythmias, cast a new light on the use of antiarrhythmic drugs for secondary or primary arrhythmia prevention due to increased risk for fatal proarrhythmic events. Extension of this practice to anaesthesiology and critical care settings has never been tested in a properly controlled, large prospective trial. However, given that the myocardial substrate (often, ischaemic, dilated or hypertrophic cardiomyopathy) that is conducive to VES or NSVT is affected by other drugs the patient may be receiving (including anaesthetics) or co-existing physiologic imbalance, presumably the risk for proarrhythmia is increased in these settings as well. Thus, it is my firm belief that electricity (mechanical) heart rhythm management is preferred to drugs, at least as initial therapy. Then, after correction of any obvious imbalance, and when indicated, drugs may be used cautiously to prevent recurrences.

with < ordinary exertion, and Class IV: symptoms at rest. The ACC/AHA (American College of Cardiology/American Heart Association) emphasises the *evolution and progression* of HF: Stage A: high risk for HF, but without evident structural heart disease (SHD); Stage B: with SHD, but without HF symptoms; Stage C: with SHD and past or current symptoms of HF; Stage D: with end-stage SHD and need for advanced therapy (i.e. positive inotropes, mechanical circulatory support, cardiac transplantation, or hospice care).

5 CAST I and II: Cardiac Arrhythmia Suppression Trial

References

1. Atlee JL, Rusy BF (1972) Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 36:112–118
2. Atlee JL, Dayer AM, Houge JC (1984) Chronic recording from the His bundle of the awake dog. Basic Res Cardiol 79:627–632
3. Laszlo A, Polic S, Atlee JL et al (1991) Anesthetics and automaticity in latent pacemaker fibers. I. Effects of halothane, enflurane and isoflurane on automaticity and recovery of automaticity from overdrive suppression in Purkinje fibers derived from canine hearts. Anesthesiology 75:98–105
4. Woehlck HJ, Vicenzi MJ, Bosnjak ZJ et al (1993) Anesthetics and automaticity of dominant and latent pacemakers in chronically instrumented dogs. I. Methodology, conscious state and halothane anesthesia: Comparison with and without muscarinic blockade during exposure to epinephrine. Anesthesiology 79:1304–1315
5. Atlee JL (1985) Perioperative cardiac dysrhythmias: Mechanisms, recognition, management. Yearbook Medical Publishers, Chicago
6. Atlee JL (1996) Arrhythmias and pacemakers. Practical management for anesthesia and critical care practitioners. W.B. Saunders, Philadelphia
7. Atlee JL, Bosnjak ZJ (1990) Mechanisms for cardiac dysrhythmias during anesthesia. Anesthesiology 72:347–374
8. Atlee JL (1997) Management of perioperative dysrhythmias. Anesthesiology 86:1397–1424
9. Atlee JL, Bernstein AD (2001) Cardiac rhythm management devices. Part 1. Indications, device selection and function. Anesthesiology 95:1265–1280
10. Atlee JL, Bernstein AD (2001) Cardiac rhythm management devices. Part 2. Perioperative management. Anesthesiology 95:1492–1506
11. Atlee JL (ed) (1999) Complications in Anesthesia. W.B. Saunders, Philadelphia
12. Atlee JL (ed) (2001) Complicanze in Anestesia. Verduci Editore, Roma
13. Anonymous (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: section 7D: the tachycardia algorithms. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:I158-I165
14. Anonymous (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: section 5: Pharmacology II: Agents for arrhythmias. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102:I112-I128
15. Al-Khatib SM, LaPointe NM, Kramer JM et al (2003) What clinicians should know about the QT interval. J Am Med Assoc 289:2120–2127
16. El-Sherif N, Turitto G (1999). The long QT syndrome and Torsades de Pointes. PACE 22:91–110
17. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350:1013–1322
18. Olgin JE, Zipes DP (2001). Specific arrhythmias: Diagnosis and treatment. In: Braunwald E, Zipes DP, Libby P (eds) Heart Disease. 6th edition. Saunders, Philadelphia, pp 815–889
19. Zipes DP, Wellens HJJ (2000) What have we learned about cardiac arrhythmias? Circulation 102:IV52-IV57
20. Crystal E, Connolly SJ, Dorian P (2003) Prevention and treatment of life-threatening ventricular arrhythmia and sudden death. In: Yusef S, Cairns JA, Camm AJ, Fallen EL,

Gersch BJ (eds) Evidence-Based Cardiology. 2nd edition. BMJ Books, London, pp 577–586
21. Toff WD, Camm AJ (2003) Impact of pacemakers: when and what kind? In: Yusef S, Cairns JA, Camm AJ, Fallen EL, Gersch BJ (eds) Evidence-Based Cardiology. 2nd edition. BMJ Books, London, pp 587–618
22. Crijns H JGM, Van Gelder IC, Savelieva I et al (2003) Atrial fibrillation: antiarrhythmic therapy. In: Yusef S, Cairns JA, Camm AJ, Fallen EL, Gersch BJ (eds) Evidence-Based Cardiology. 2nd edition. BMJ Books, London, pp 519–547
23. Gregoratos G, Abrams J, Epstein AE et al (2002) ACC/AHA/NASPE 2002 Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. Circulation 106:2145–2161
24. Singh BN, Singh SN, Reda D J et al (2005) Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 352:1861–1872
25. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350:1013–1022
26. Levine JH, Massumi A, Scheinman M et al (1996) Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. J Am Coll Cardiol 27:67–75
27. Scheimann MM, Levine JH, Cannom DS et al (1995) Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. Circulation 92:3264–3272
28. Kowey PR, Levine JH, Herre JM et al (1995) Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation 92:3255–3263
29. Kudenchuk PJ, Cobb LA, Copass MK et al (1999) Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 341:871–878
30. Dorian P, Cass D, Schwartz B et al (2002) Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 346:884–890
31. Fonarow GC (2005) Strategies to improve the use of evidence-based heart failure therapies. Rev Cardiovasc Med 6:S32–42
32. Anonymous (1989) Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med 321:406–412
33. Anonymous (1992). Preliminary Report: Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. N Engl J Med 333:227–232

Chapter 19

Oesophageal pacing and cardioversion–defibrillation

J.L. Atlee

Overview of the evolution of pacing, cardioversion, and defibrillation technology

Indirect oesophageal cardiac pacing evolved from indirect (transcutaneous pacing) and direct (thoracotomy epicardial; transvenous endocardial) approaches to cardiac pacing [1]. Similarly, indirect oesophageal cardioversion and defibrillation (CV and DF) were developed for definitive or 'rescue' CV and DF, with the latter for failed transcutaneous CV or DF.

CV and DF differ. With CV, shocks are synchronised to electrocardiographic (ECG) R or S waves, depending on the lead selected and whichever has a higher amplitude. Generally, lower energies are required for CV. CV is effective against reentry tachyarrhythmias with organised ventricular activity, while DF is used for those without (Table 1). Ventricular activity may be considered organised if there are distinct ventricular (QRS) complexes. If so, an ECG isoelectric interval will separate the QRS complexes.

Table 1. Reentry tachyarrhythmias with organised or disorganised ventricular activity. *SVT* Supraventricular tachycardia, *SAN* sinoatrial or sinus node, *AVN* atrioventricular (AV) node, *AP* accessory AVN bypass pathway, *ECG* electrocardiogram, *AFT* or *AFB* atrial flutter or atrial fibrillation, *VT* ventricular tachycardia, *WPW* Wolff-Parkinson-White syndrome

Organised ventricular activity (terminated by cardioversion[a])	Disorganised ventricular activity (terminated by defibrillation[b])
• Paroxysmal SVT (SAN, atrial, AVN, or AP with AVN reentry)	• AFT or AFB[c,d]
• AFT (type 1 or 2)[c,d]	• Polymorphic VT (indistinct R or S waves)
• AFB (except with WPW[d])	• Ventricular flutter
• Monomorphic and polymorphic VT (with distinct R or S waves)	• Ventricular fibrillation

[a]Lower energy shocks that are synchronised with the R or S waves on the ECG

[b]Higher energy shocks that are not synchronised to R or S waves, since these are indistinct

[c]With type 1 AFT, the atrial rate is ≤ 340 beats/min. With type 2 AFT, it is > 40 beats/min

[d]With WPW, there may be 1:1 AV conduction with AFT or AFB, and ventricular rates may exceed 250 beats/min (even > 300 beats/min). If so, R or S waves may be indistinct. If so, lower energy, defibrillation shocks are used for termination

Epicardial direct CV or DF, was pioneered in the 1950s. Epicardial electrodes were used for pacing during and after cardiac surgery, and then in patients with complete atrioventricular (AV) heart block. By the early 1960s, transcutaneous indirect DF or CV had become available for the management of cardiac arrest in hospitals, and shortly thereafter for elective conversion of atrial or ventricular tachyarrhythmias with distinct ECG R or S waves. By the early 1970s, paramedics used DF or CV in the out-of-hospital setting to terminate ventricular fibrillation (VF) in cardiac arrest or ventricular tachycardia (VT) with cardiovascular collapse. The pioneering work of Mirowski's group at John Hopkins in 1980 [2] led to clinical implantation of the first internal cardioverter-defibrillators in the early 1980s [3, 4].

The first lead systems used with implantable (internal) cardioverter-defibrillators (ICD) were epicardial. These required formal thoracotomy for implantation. Next, transvenous endocardial leads were developed for CV or DF with ICD. Today, except in infants and very small children, ICD lead systems are transvenous, and deployed under radiographic guidance. By the late 1980s and early 1990s, transvenous (direct) and oesophageal (indirect) electrodes began to be used with cutaneous patch (indirect) electrodes as rescue therapy for failed transcutaneous CV or DF.

Access, lead and electrode configuration, and pulse waveform polarity

The distinction between direct (epicardial or transvenous endocardial) and indirect access (transcutaneous or oesophageal) for pacing or CV and DF is clinically relevant. Direct pacing CV and DF are more efficient and reliable for pacing or tachyarrhythmia termination. Furthermore, less energy is required due to lower impedances with direct pacing. Yet, indirect oesophageal pacing CV and DF are still more efficient than transcutaneous indirect pacing CV or DF. Because the oesophagus is quite proximate to the left atrium and base of the left ventricle (Fig. 1), tissue impedance is lower than with transcutaneous pacing CV or DF. This proximity also has implications for oesophageal echocardiography. Reputedly, Cremer (1906) was the first to record an oesophageal ECG—in a human sword-swallower. However, the first definitive work on the subject was that of WH Brown in 1936. Brown was the first to describe the application of oesophageal ECG leads for observing atrial T waves (Ta), bundle-branch block, and disorders of atrial rhythm [5, 6]. The technique was further refined, especially bipolar oesophageal ECG, by Brody and Copeland's group in the 1950s [7, 8]. Highly amplified bipolar oesophageal ECG P waves (Fig. 2) are invaluable for determining the origin of wide QRS tachycardias, especially when distinguishing supraventricular tachycardia (SVT) with ventricular aberration from ventricular tachycardia.

Electrodes vary by type (e.g. discreet bands or rings, coils, spring- or J-wires), and leads by configuration. With unipolar configurations, the ICD and/or pacing pulse generator serve as the anode, and electrodes as the cathode. With bipolar configurations, electrodes are located within (endocardial) or on (epicardial) the heart. When used for sensing, bipolar lead configurations are far less subject to

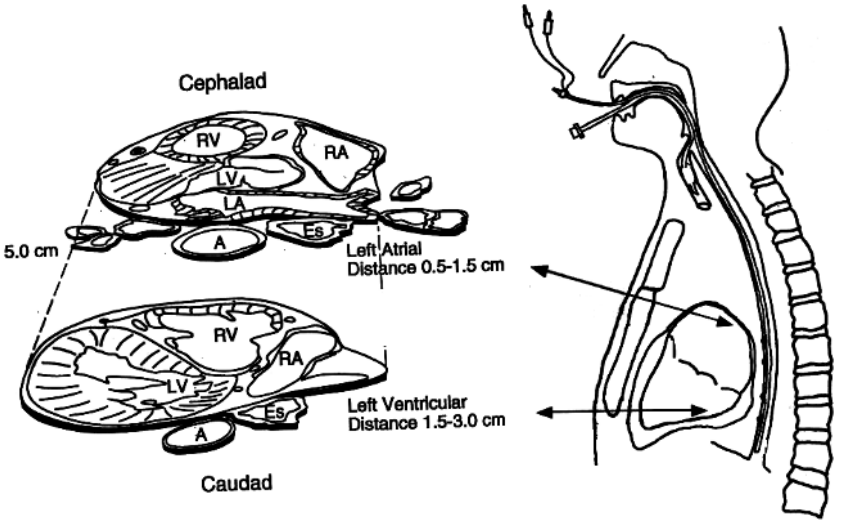

Fig. 1. *Left.* Mediastinal sections from a frozen human cadaver at the closest approximation of esophagus (*Es*) to the left atrium (LA, *top*) and left ventricular base (LV, *bottom*). *A* aorta, *RA/RV* right atrium/ventricle. *Right.* Saggital section of head and thorax depicting a quadripolar oesophageal electrode catheter positioned for simultaneous atrial ECG or pacing and ventricular ECG. Ventricular pacing is not feasible with electrodes configured as shown. The LA and LV base are 0.5–1.0 cm and 1.5–3.0 cm from the oesophagus, respectively, when the atrial electrodes (proximal electrode pair) are positioned at P_{max} (see Fig. 2)

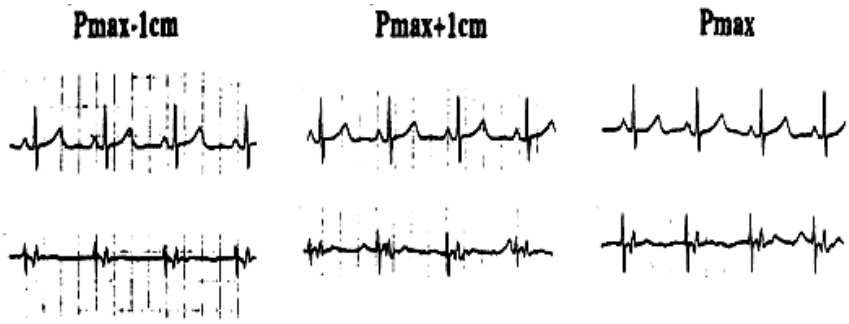

Fig. 2. Surface ECG lead II (*top*) and bipolar oesophageal ECG (*bottom*) recorded at the position of maximal amplitude P waves (P_{max}), and 1 cm proximal and distal. Note that P waves at P_{max} have a higher amplitude than the QRS complexes. Such amplified P waves aid in the diagnosis of wide QRS tachycardias, especially if P waves are nonapparent on surface ECG

detecting biologic or electromechanical interference (EMI). Also, less energy is needed for pacing capture and/or shocks.

Finally, distinction is made between monophasic and biphasic shock waveforms for CV or DF. First- and second-generation ICDs, and most external cardioverter–defibrillators (ECDs) until the 1990s provided monophasic shock waveforms. The transition from monophasic to biphasic shocks occurred with the third and subsequent generation ICDs. Furthermore, today, automatic ECDs provide biphasic shock waveforms.

Evolution of oesophageal indirect pacing, cardioversion, and defibrillation

Indirect oesophageal pacing and CV or DF have not enjoyed anywhere near the technological evolution that has affected direct (invasive) endocardial or epicardial pacing and CV-DF or ECDs. As noted above, the pioneering work in this field was that of Brown in relation to oesophageal ECG in the 1930s [5, 6], and later that of Body and Copeland in the late 1950s [7]. Burack and Furman first showed the feasibility of oesophageal indirect atrial pacing in 1969 [8]. Andersen and Pless extended on this work, including the development of electrodes for dual-chamber pacing in 1983 [9, 10]. In the early 1990s, Atlee's group developed and used an atrial (indirect) pacing oesophageal stethoscope to treat bradycardia and overdrive escape rhythms in anaesthetised patients [11–13]. Atlee and Bilof subsequently modified the pacing oesophageal stethoscope for indirect ventricular pacing [14, 15]. Cohen first tested oesophageal DF in dogs [16], and then used it as rescue therapy in patients in 1993 [17]. Oesophageal indirect atrial and ventricular pacing require further technological refinements to make the technique an acceptable alternative to transcutaneous or transvenous endocardial pacing. At first, high-energy monophasic shock waveforms were used for oesophageal indirect CV or DF. Today, in parallel with refinements to ICD and automatic ECD technology, low-energy monophasic shock waveforms are used for oesophageal CV or DF.

Transoesophageal indirect atrial pacing for bradyarrhythmias

Sinus bradycardia and AV junctional or idioventricular escape rhythms were not uncommon in anaesthetised patients prior to the early 1990s, when potent volatile anaesthetic agents (i.e. halothane, enflurane, isoflurane, or methoxyflurane) or high-dose, narcotic-based anaesthetic techniques (e.g. fentanyl and sufentanil ± N_2O and/or a volatile agent) were more commonly used. Often, sinus bradycardia and escape rhythms were treated with positive chronotropic drugs (e.g. atropine, glycopyrrolate, ephedrine, isoproterenol, or dopamine) to increase the sinus rate, especially outside of cardiovascular surgery. However, chronotropes were notoriously unreliable for increasing sinus rate to (effectively) 'overdrive' escape rhythms. Indeed, chronotropes often only increased the rate of escape

rhythms; for example, converting AV junctional rhythm to accelerated AV junctional rhythm, or idioventricular rhythm to accelerated idioventricular rhythm. Worse, chronotropic drugs occasionally provoked even more dangerous supraventricular or ventricular tachyarrhythmias.

However, bradycardia and escape rhythms were anticipated prior to cardiopulmonary bypass in cardiac surgical patients, or when patients had cardiac pathology that required maintenance of a high cardiac rate (e.g. valvular insufficiency, heart failure). In these patients, an A/V-pacing pulmonary artery catheter or transvenous pacing electrodes were inserted prior to surgery. For prophylaxis of escape rhythms or other arrhythmias after cardiopulmonary bypass, epicardial atrial and ventricular pacing wires were placed by the surgeons.

The author became aware of the developments in transoesophageal pacing in the mid-1980s [5–10]. This led to interest in the development of the pacing oesophageal stethoscope as a preferred therapy for intraoperative bradycardia and escape rhythms, especially outside of cardiac surgery [11–13]. At first, a quadripolar electrode catheter (Tapcath, CardioCommand, Tampa, FL, USA) that was designed for oesophageal ECG and stress transoesophageal atrial pacing (TAP) was attached to a standard oesophageal stethoscope [11]. Then, a stethoscope with bipolar ring electrodes (Tapscope, CardioCommand) was tested in patients [12]. Subsequently, this device was used to treat sinus bradycardia and escape rhythms [13]. This work confirmed our expectation that the haemodynamic benefit of TAP would be greatest in patients with lower escape rhythms, due to the restoration of atrial transport function. In none of our experience with TAP, were new arrhythmias provoked by TAP. However, some other interesting observations were made:

1. Apparent failure to capture: Especially in patients receiving high-dose narcotics, or high concentrations of enflurane or halothane (but less so with isoflurane and sevoflurane or desflurane), it was not uncommon to see non-capture beats with TAP rates set above 80 paced pulses/min (ppm). This was also a problem in some patients receiving verapamil, diltiazem, or β-blockers. It was soon obvious that this was not due to capture failure, but rather to Wenckebach (type 1, 2) AV heart block. In fact, the stimulus or atrial QRS interval gradually lengthened prior to dropped beats. In all probability, AV nodal refractoriness was increased by drugs the patient was receiving prior to surgery, and/or this was compounded or caused by opiates or potent volatile anaesthetics.
2. Diaphragmatic pacing: In some patients, especially when TAP current was increased to ³ 15 mA (2-ms pulse widths), phrenic nerve stimulation can lead to diaphragmatic pacing at the selected pacing rate. However, since TAP capture thresholds were much lower than this with Tapscope 'I' [7.3 ±0.3 mA (SEM) and 8.5 ± 0.4 mA in males and females, respectively] [12], this was rarely seen with the version of Tapscope that we developed and tested. However, since occasionally the ring electrodes of Tapscope 'I' slipped along the stethoscope barrel assembly, exposing the lead wire (with potential damage to the oesophageal mucosa), a new design for Tapscope 'II', with fixed electrodes, was introduced and is the version available today. However, the current for reliable TAP

capture is higher with Tapscope 'II' (13–17 mA in our experience); thus, the risk for phrenic nerve stimulation is also higher.

3. Overdrive pacing for escape rhythms: It soon became apparent that TAP was useful for overdriving AV junctional escape rhythms [13], and also occasionally for idioventricular rhythm in some patients before cardiopulmonary bypass and/or the placement of epicardial pacing wires (unpublished observations).

In the author's opinion, TAP is a preferred therapy for haemodynamically disadvantageous bradycardia or escape rhythms in perioperative settings, as compared to chronotropic drugs. With topical anaesthesia and light sedation, it is tolerated by non-anaesthetised patients. However, except in surgeries likely to be associated with disadvantageous bradycardia (e.g. carotid endarterectomy, ophthalmologic surgery, intracranial surgery, and radical neck dissection), there is less impetus for its use today due to a lower incidence of disadvantageous intraoperative bradycardia and escape rhythms with contemporary anaesthetics and techniques.

Transoesophageal indirect ventricular pacing for bradyarrhythmias or asystole

Other than the work of Andersen and Pless [9, 10], and preliminary observations by Atlee and Bilof [14, 15], there are no clinical reports of transoesophageal ventricular pacing (TVP). TVP is more problematic due to the increased oesophago–left ventricular (LV) distance (estimated to be 1.5–2.0 cm) vs the oesophago–left atrial distance (estimated to be 0.5–1.0 cm). Due to this, TVP with Tapscope 'I' was feasible in only one-third of subjects, and the only with a custom stimulator that supplied up to 10-ms pulse widths and 100 mA of current [14]. One approach to reduce the oesophago–LV distance has been to use inflatable balloon electrodes that more nearly approximate the LV base [9, 10]. We tried yet another approach, in which 'point' electrodes directed toward the LV base were projected using an inflatable balloon [15]. TVP capture was observed in all 11 patients tested. However, TVP thresholds were unacceptably high (22–77 mA) for 2-ms pulse widths. Whether the difficulties with TVP can be resolved remains to be seen. But, for the time-being, for transoesophageal pacing to be an acceptable alternative to more invasive routes for pacing, or transcutaneous (ventricular) pacing, the capability for low-energy TVP ($\leq$ 15-mA, 2-ms pulse widths) and dual-chamber pacing must be developed.

Transoesophageal atrial pacing stethoscope and transoesophageal echocardiography

Hesselvik and Otega determined the effect of transoesophageal echocardiography (TEE) probe insertion on TAP thresholds in 20 patients with an indwelling TAP stethoscope [18]. They also examined whether the latter would affect the feasibility

and image quality of TEE. After TEE placement, there was a average 5-mA increase in TAP thresholds (from 19 to 24 mA). Loss of TAP capture during TEE manipulation occurred in 15 patients, was transient in ten patients, but permanent in five. Due to the TAP stethoscope, there were problems with manipulating the TEE probe in ten patients. Also, there was poor TEE image quality in two patients while the TAP stethoscope was present. After removal of the TAP stethoscope, image quality improved.

Oesophageal indirect pacing, cardioversion, or defibrillation for tachyarrhythmias

Electrophysiological considerations fundamental to the selection of therapy

Even with organised tachyarrhythmias (Table 1), QRS complexes may be narrow ($\leq$ 120 ms) or widened ($\geq$ 120 ms). Also, the QRS complexes may appear uniform (monophasic) or multiform (polyphasic). Furthermore, wide QRS tachycardias may be supraventricular or ventricular in origin. If of supraventricular origin, the tachycardia originates within or above the common (His) bundle. If of ventricular origin, the QRS complexes will invariably be widened, unless the tachycardia originates above the His bundle bifurcation or trifurcation[1].

Thus, not all wide QRS beats with ectopic beats or tachycardias are of ventricular origin. They may be due to ventricular aberration, which can be anatomic or functional. If anatomic, it may be due to fixed right or left bundle-branch, or intraventricular conduction block. However, if functional, the rate of SVT (cycle length in ms) must exceed the functional refractory period (ms) of some portion of the ventricular conduction system below the His bundle bifurcation or trifurcation.

SVT has many possible sites of origin, including the sinoatrial (SA) node, the atria, the atrial approaches, i.e. functionally distinct conduction pathways to the AV node (AVN), and the AVN itself. Also, SVT (or VT) can have different cellular electrophysiologic (EP) mechanisms (Table 2). Reentry is macroreentry if it involves a large anatomic circuit, such as the leading circle reentry around vena cava orifices in type I atrial flutter, or the AVN with or without an accessory AV bypass pathway (AP) in paroxysmal SVT. If microreentry is present, many small reentry circuits (wavefronts) co-exist (i.e. atrial or ventricular fibrillation).

All of the above considerations affect the choice between CV and DF, and their efficacy [19, 20]. Also, overdrive atrial or ventricular pacing is effective against some tachyarrhythmias. For example, CV is not an effective therapy for automatic tachycardias, such as ectopic atrial tachycardia (EAT), especially when digitalis

[1] The left and right bundle branches (LBB, RBB) commonly arise directly from the His bundle (i.e. bifurcation), or there may be no distinct left bundle branch (LBB). Rather, the LBB anterior and posterior fascicles arise from the His bundle along with the RBB (trifurcation). Or, the His bundle may trifurcate into septal branch, LBB and RBB.

Table 2. Likely electrophysiological mechanisms for common clinical supraventricular and ventricular brady- or tachyarrhythmias that impact on the efficacy of cardioversion, defibrillation and antibradycardia or antitachycardia pacing therapies[a]. *AV* Atrioventricular, *VT* ventricular tachycardia, *SVT* supraventricular tachycardia, *AVN* AV node, *AP* accessory AV conduction pathway, *EAD* early afterdepolarisations, *DAD* delayed afterdepolarisations.

Automatic (normal or abnormal automaticity)[b]
• AV junctional rhythm (= 70 beats/min) and tachycardia
• Idioventricular rhythm (= 60 beats/min) and tachycardia
• Ectopic atrial tachycardia (uniform or multiform), especially in association with chronic pulmonary disease, pulmonary hypertension, and chronic ethanol abuse
• Some focal ventricular tachycardia (e.g. right ventricular outflow tract tachycardia)
Triggered from early or delayed afterdepolarisations (EAD, DAD)
• EAD: Polymorphic VT with congenital or acquired QT-interval prolongation (i.e. Torsades de Pointes)
• DAD: Ectopic atrial or AV junctional tachycardia with digitalis toxicity
Macroreentry (involves a fixed anatomical circuit)
• Paroxysmal SVT due to AVN reentry, or reentry involving the AVN and an AP
• VT (monomorphic or polymorphic) in patients with coronary heart disease and: (1) acute coronary syndromes, or (2) healed myocardial infarction
• Atrial flutter (reentry circuit around the vena cava orifices)
• Bundle-branch reentry VT
Microreentry (depends on functional electrophysiological differences at the myocardial cellular or tissue level)
• Atrial fibrillation—likely, the sustaining mechanism; however, often triggered from ectopic foci located at the pulmonary vein orifices
• Ventricular fibrillation—again, the most plausible sustaining mechanism. It could be triggered by ectopic beats be consequent to sustained VT → 'micro'-electrophysiological changes

[a] Listed are only the best known examples. Other brady- or tachyarrhythmias may be due to the listed mechanisms

[b] Automaticity arising from partially depolarised (even working) myocardial fibres, and brought about by loss of cellular transmembrane potential

toxicity is the cause. Further, CV or DF will not terminate AV junctional tachycardia (AVJT) or idioventricular tachycardia (IVT). AVJT and IVT are rapid AV junctional or ventricular escape rhythms, and believed to be due to abnormal automaticity[2]. Their rate is often 70–110 beats/min, and rarely above 120–130 beats/min. Either AVJT or IVT can be overdriven by atrial pacing, provided AV conduction is intact, which it usually is. Similarly, EAT can be overdriven by rapid atrial pacing while the proximate cause is corrected, and provided the required high rate of atrial pacing is haemodynamically tolerated. After treatment of the cause for EAT, pacing is gradually slowed and then stopped. Often, sinus rhythm resumes with the termination of pacing. Finally, programmed trains of rapid atrial or ventricular pacing stimulation (antitachycardia pacing, ATP) are used in most contemporary

[2] Automaticity arising in cells with a reduced transmembrane potential. This type of automaticity usually occurs in the setting of myocardial ischaemia or reperfusion injury.

ICDs as initial therapy for SVT or VT and to reduce the need for painful shocks. ATP sequences are programmed at the time of ICD implantation during EP studies. ATP effectively terminates most reentrant SVT and 90% or more of VT [20].

Oesophageal antitachycardia pacing

Volkmann et al. [21] used rapid TAP or TVP to terminate various tachyarrhythmias in 233 patients. Atrial flutter (mostly type I AFT; flutter rate ≤ 340 beats/min) was terminated in 136 of 162 patients. In 75 patients, AFT converted to sinus rhythm. In another 61 patients, atrial fibrillation (AFB) was induced. In the remaining 26, AFT persisted. However, conversion to AFB is not necessarily a bad early result, because rate control is easier with AFB than with AFT [19]. However, due to the increased risk for stroke caused by cerebral thromboembolism, persistent AFB is often electively cardioverted, especially when of recent onset. TAP appeared less effective against type II AFT (flutter rate > 340 beats/min). Volkmann's group also interrupted ectopic atrial tachycardias in 17 of 31 patients, converting 11 to sinus rhythm, and another six to AFT. Finally, rapid TAP was also used against SVT due to AVN reentry or AV reciprocation (the reentry circuit includes both the AVN and an AP). SVT was converted to sinus rhythm in 58 patients and to AFB in four. One patient failed to convert with TAP. With TVP, Volkmann et al. were also able to terminate VT in 10 of 15 patients. They concluded that the success of transoesophageal pacing for terminating SVT or VT was influenced both by the pacing cycle length (rate) and type of tachyarrhythmia (e.g. type I vs II AFT).

Long-duration pulse widths (e.g. 10 ms) and high current (> 15–20 mA) had been used to pace terminate AFT. However, such high current and long stimulus durations can cause severe chest pain (similar to 'pulsating' heart burn[3]). Therefore, Ajisaki et al. investigated the effect of low-output (≤ 15 mA), short-duration (10 pulses over ≤ 4 s) TAP burst pacing at paced cycle lengths 20 ms shorter than that of AFT wavelength in 31 patients with AFT [22]. Sixteen patients (52%) converted to sinus rhythm, and 12 (38%) to AFB. TAP was ineffective in three patients. Patients who converted to sinus rhythm had significantly longer AFT cycle lengths than those who did not (248 vs 221 ms). No patients had complications related to TAP burst pacing or complained of chest pain.

Several groups have investigated the efficacy of oral or IV propafenone to facilitate elective TAP conversion of type I or II AFT. In contrast to type I AFT (leading circle reentry around the caval orifices with an excitable gap), type II AFT usually cannot be interrupted by rapid atrial pacing. The mechanism for type II AFT is believed to be leading circle atrial macroreentry (vs microreentry with AFB), but without an excitable gap. In one small observational trial, 15 patients were randomised to oral propafenone (600 mg) prior to TAP CV, while another 15 patients received no drug [23]. TAP was significantly more effective for interrupting type I AFT after propafenone (13/15) than without the drug (8/15). A significant lengthening

[3] Based on the author's experience as a participant in a volunteer study of TAP pain thresholds.

of the AFT cycle length was observed in patients receiving propafenone prior to termination of AFT. The investigators concluded that the slowing effect of propafenone on intraatrial conduction and its possible stabilising effect on the AFT reentry circuit were outweighed by a positive effect (lengthening) on the excitable gap of the reentry circuit, thereby facilitating atrial capture with TAP during AFT. In another small observational trial, out of 50 patients with type I AFT in whom termination of AFT with TAP was unsuccessful, 25 were randomised to undergo repeat TAP after receiving IV propafenone, while the other 25 received placebo [24]. After propafenone or placebo, TAP converted 36% or 4% of AFT ($P = 0.005$), suggesting that propafenone increases the success of failed TAP for conversion of type I AFT.

As earlier noted, type II AFT, cannot usually be interrupted by atrial pacing because there is no excitable gap. In another observational trial, Doni et al. investigated whether oral propafenone (600 mg) had a beneficial effect on TAP conversion of type II AFT in 12 patients [25]. Propafenone primarily increases atrial conduction velocity. Half of the patients were randomised to propafenone, and the others to placebo. Sinus rhythm was restored with TAP in 4 of 6 patients after propafenone, but in none without ($P \leq 0.05$). Propafenone lengthened the mean cycle length of type II AFT by about 45 ms. The authors speculated that propafenone facilitated conversion of type II AFT by converting it to type I AFT, thereby providing an excitable gap.

Oesophageal atrial stress pacing and electrophysiological testing

Atrial stress pacing

Atar's group investigated the feasibility and accuracy of bedside transoesophageal pacing stress echocardiography (PASE) in patients with new-onset chest pain or unstable angina, after acute myocardial infarction had been excluded [26, 27]. In the first study, PASE was correlated with myocardial stress scintigraphy in 70 patients within 24 h of bedside PASE [26]. In the second study, PASE was validated in 54 consecutive patients by coronary angiography within 24 h of bedside PASE [27]. In the first study [26], PASE and myocardial perfusion stress scintigraphy correlated well for identification or exclusion of myocardial ischaemia in 90% of patients. Also, the extent of inducible ischaemia by vascular territories correlated with stress scintigraphy in 74% of patients. Both findings were highly significant. In the second study [27], the sensitivity of PASE for identifying patients with significant coronary artery disease (CAD) vs coronary angiography was 95%, specificity was 87%, and accuracy was 92%. Moreover, the extent of significant CAD (single- or multivessel was highly concordant with coronary angiography (kappa = 0.73, $P < 0.001$). Finally, bedside PASE testing was well tolerated, with the average test (including echocardiographic image interpretation) lasting 38 ± 6 min. Thus, PASE appears to be accurate and sensitive for identifying inducible myocardial ischaemia or significant CAD in patients with new-onset chest pain or unstable angina.

EP testing

Kesek et al. used TAP and oesophageal atrial and surface ECG recording for cardiac EP testing as a screening procedure for evaluation of suspected SVT in 128 patients (group 1) [28]. Group 2 consisted of 77 routine follow-up investigations performed 3–5 months after radiofrequency catheter ablation of SVT. Clinical inductions for the study were, palpitations ($n = 49$), paroxysmal narrow QRS tachycardia ($n = 38$), AFT or AFB ($n = 15$), wide QRS tachycardia ($n = 5$), evaluation of preexcitation on resting ECG ($n = 20$), or presyncope ($n = 1$). The investigations were carried out as outpatient procedures with patients in a fasting, non-sedated state with a secured IV line. All antiarrhythmic drugs were discontinued five half-times before oesophageal EP testing. Induced tachycardias were analysed for QRS width, and the R–R and V–A and intervals, and were terminated by overdrive TAP. A bipolar electrode catheter (Medtronic 6992) with an Arzco 7A stimulator attached to a Medtronic 5328 stimulator was used for TAP. The catheter was positioned to obtain a maximal amplitude, bipolar atrial deflection (i.e. 'P_{max},' Fig. 2). TAP thresholds were determined with 10-ms pulse widths. Drug provocation (IV isoproterenol + atropine) was used in group 1 patients with symptomatic arrhythmias, but not in asymptomatic patients of group 2. The endpoint for a successful procedure was either an induced tachycardia consistent with the reported symptoms or completion of the protocol. An interrupted procedure in which some diagnostic information could be obtained for at least one pacing moment was defined as partially successful. A procedure interrupted before completion of the first pacing moment was classified as unsuccessful. Of the 205 procedures analysed, 193 (94%) were successful and seven (3%) were partially successful. The limiting factor was patient discomfort in four investigations, induction of AFB in two, and TAP threshold elevation in one. Five procedures were unsuccessful due to uncontrolled vomiting (3 patients) and to failure to obtain capture (2 patients). The mean TAP threshold was 12.6 ± 3.1 mA. The sensitivity and specificity of the TAP EP protocol for group 1 and 2 patients was 74 and 90%, respectively. This compares favourably to other non-invasive methods used in cardiology, such as myocardial stress imaging methods for ischaemic heart disease prior to coronary angiography.

TAP was also used to document arrhythmias in 67 infants and children age 2 months to 16 years who had palpitations or symptoms suggesting tachyarrhythmias, but no documented cardiac arrhythmias [29]. TAP induced various tachyarrhythmias in 47 of 67 (70%) patients with suspected tachyarrhythmias. In ten patients, tachycardia was induced during infusion of isoproterenol. Tachycardia was induced in 14 of 15 patients $\leq$ 6-years-old, and in 33 of 52 patients $\geq$ 6-years-old. Of the induced tachycardias, 25 of 47 were AV reciprocating tachycardia (i.e. reentry involving the AVN and an AP), 16 were AVN reentry, and six were idiopathic LV tachycardia. Both TAP and invasive EP studies were performed in ten patients. Except for one patient, mechanisms for induced tachycardia were identical with both methods.

Transoesophageal cardioversion

Monophasic shocks

McKeown's group tested transoesophageal cardioversion (TOECV) as therapy for SVT, AFT, AFB, or VT. For TOECV, a quadripolar oesophageal electrode was coupled to a cutaneous electrode at the cardiac apex [30]. TOECV was performed 131 times in 105 patients. Of the tachyarrhythmia episodes, 109 were AFB, 16 were AFT, two were SVT, and four were VT. The mean predicted TOECV impedance (± SEM) of 52.6 ± 1.1 Ω was significantly lower than the mean predicted transthoracic impedance (63.1 ± 1.6 Ω). Of the 88 patients presenting with AFB as the initial rhythm disturbance, TOECV was successful in 70 (79.5%). Maximal delivered transoesophageal energy (monophasic shocks) was 100 J in 84 patients and 200 J in four patients. TOECV required a mean delivered energy of 63.1 ± 4.2 J and a mean peak current of 20.3 ± 0.6A. Transthoracic countershock (maximal delivered energy of 360 J) was used in 17 of 18 patients when the TOECV was unsuccessful. This was successful in ten of 17 patients. While TOECV did not convert all episodes of AFB, all episodes of AFT, SVT, and VT were successfully terminated with TOECV.

Subsequently, McKeown's group used the previously described TOECV electrode system for countershock of atrial and ventricular tachyarrhythmias, with special regard to the measurement of transoesophageal and transthoracic impedances, and their association with anthropometric variables [31]. TOECV was attempted for 131 episodes of tachyarrhythmias in 105 patients, including 109 episodes of AFB. The TOECV system was also used in cardiac electrophysiologic (EP) testing for 29 patients with ventricular tachyarrhythmias. Both transoesophageal and transthoracic impedances were estimated during passage of a high-frequency, low-amplitude current between the cutaneous and oesophageal electrodes. These estimates were associated with anthropomorphic measurements using linear regression. In the patients with attempted TOECV, the estimated mean transoesophageal impedance (52.6 ± 1.7 Ω) was significantly lower than the estimated mean transthoracic impedance (63.1 ± 16.4 Ω). For all patients, transoesophageal and transthoracic impedances were significantly associated with patient weight, body-mass index, and chest-wall circumference. Thus, the TOECV electrode system results in lower impedance values for monophasic CV waveforms vs conventional transthoracic placement. However, since oesophageal electrodes are referenced to a cutaneous electrode for TOECV, it is not surprising that both transcutaneous CV and TOECV impedances depend on anthropomorphic factors.

Low-energy internal (intracardiac) CV (ICV) is considered the elective alternative method for acute restoration of sinus rhythm when transcutaneous CV (TCCV) fails or is contraindicated. TOECV is yet a another alternative method for CV and obviates the potential complications of low-energy ICV that requires transvenous insertion of intracardiac electrodes. Zardo et al. prospectively evaluated the acute efficacy, and patient acceptance and preference among ICV, TOECV, and TCCV in 30 patients with persistent AFB [32]. Apparently, biphasic shocks were used for all types of CV. Sinus rhythm was acutely restored in 29 patients, but persisted in only

12 of these after 1 month, despite drug prophylaxis. Discomfort induced by electrical shocks was minimal or mild in 40 patients. TOECV was usually preferred by patients who had previously been submitted to TCCV or ICV. No complications were reported with any of the above methods for CV.

Biphasic shocks

The feasibility of combined TEE and TOECV was examined in 26 patients by Scholten et al. [33]. A custom TEE-TOECV probe and biphasic shocks were used. TOECV for AFB employed a step-up protocol (20J → 30–50 J). The presence of spontaneous echo contrast was scored, and the cumulative energy to restore sinus rhythm was calculated. Patient discomfort was scaled. Sinus rhythm was restored in 24/26 (92%) of patients with a mean cumulative energy of 42.3 J. Sixteen of 26 patients converted with 20-J shocks. However, six of these had early recurrence of AFB. Left atrial (LA) appendage velocity was significantly reduced after TOECV. Thus, the use of a combined TEE/TOECV probe allows effective CV with low energy levels, is well-tolerated, and allows assessment of haemodynamics before and after CV. The authors concluded that early CV, after exclusion of LA thrombus, was time-saving and cost-effective. More recently, Kronzon et al. published on the technical aspects of combined TEE-TOECV probe construction, its use, and the prospects for future practice [34].

Oesophageal defibrillation

Ventricular fibrillation that fails to respond to transthoracic (transcutaneous–TC) DF leaves the clinician with few alternatives. Cohen et al. developed a transoesophageal technique for rescue DF (TOEDF) and tested it in anaesthetised dogs weighing 20–30 kg [16]. Two electrodes (surface area 300 mm^2) were mounted 8 cm apart on an oesophageal probe and positioned 40 cm from the mouth. Alternating current was used to induce VF. TOEDF was between the distal oesophageal (anode) and anterior cutaneous electrodes (cathode). After 15 s of VF, TOEDF and TC DF thresholds (DFT—monophasic shocks) were determined in random order. TOEDF DFT (90 ± 15 J) were lower than TC DFT (115 ± 30 J), although this was not statistically significant. One dog was not defibrillated by TC DF, but responded to TOEDF.

This same group tested several innovative techniques as 'rescue' DF for VF refractory to conventional TC DF in 15 patients in a variety of hospital settings between 1986 and 1992 [17]. The selected patients had failed ≥ two, TC high-energy, monophasic shocks. The rescue techniques included intracardiac DF (RV catheter electrode to posterior cutaneous patch electrode) in nine patients during EP testing. Emergency simultaneous transthoracic and epicardial DF was performed with standard paddles placed over the thorax and in contact with epicardial patch or pacing lead connectors in two patients in the operating room who underwent ICD placement and had failed standard rescue DF. All 'rescue' DF was with monophasic shocks, and was successful in all patients. TOEDF–monophasic shocks was perfor-

med in four patients in the emergency room after 50 min of cardiac arrest due to refractory VF in-the-field. TOEDF successfully terminated VF in each patient.

Conclusions

The oesophagus provides alternative non-invasive access for pacing, CV and DF, compared to the more conventional transcutaneous (TC) pacing, CV or DF. Also, it is less invasive than direct epicardial or transvenous endocardial pacing, CV or DF. There were no reports of oesophageal DF with biphasic shock waveforms at the time of this writing (July 2005). But, energy requirements for TOEDF should be lower than with monophasic-shock waveforms, as has been reported with TOECV. Over the next two to three decades, the oesophagus will most likely become the preferred non-invasive site for most initial in- and out-of-hospital, critical patient monitoring and pacing, CV and DF. Why? Because the oesophagus is easily accessed by non-physician first responders and healthcare providers. Also, therapeutic efficacy and quality of patient informatics will likely exceed that of the more traditional approaches.

References

1. Ellenbogen KA, Kay GN, Wilkoff BL (eds) (2000) Clinical cardiac pacing and defibrillation, 2nd ed. WB Saunders, Philadelphia
2. Mirowski M, Reid PR, Mower MM et al (1980). Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 303:322–324
3. Mirowski M (1985) The automatic implantable cardioverter-defibrillator: An overview. J Am Coll Cardiol 6:461–466
4. Mirowski M, Mower MM, Veltri EP et al (1985) Recent clinical experience with the automatic implantable cardioverter-defibrillator. Cardiol Clin 3:623–630
5. Brown WH (1936) A study of the esophageal lead in clinical electrocardiography. Part 1. Am Heart J 12:1–45
6. Brown WH (1936) A study of the esophageal lead in clinical electrocardiography. Part 2. Am Heart J 12:307–338
7. Brody DA, Copeland GD (1959) The principles of esophageal electrocardiography. Am Heart J 57:3–18
8. Burack B, Furman S (1969) Transesophageal cardiac pacing. Am J Cardiol 23:469–472
9. Andersen H, Pless P (1983) Transesophageal pacing. PACE 6:674–679
10. Andersen H, Pless P (1984) Transesophageal dual-chamber pacing. Int J Cardiol 5:745–748
11. Pattison CZ, Atlee JL, Mathews EL et al (1991) Transesophageal atrial pacing thresholds with esophageal stethoscope modified for pacing in anesthetized adults. Anesthesiology 74:854–859
12. Atlee JL, Pattison CZ, Mathews EL et al (1992) Evaluation of transesophageal atrial pacing stethoscope in adult surgical patients under general anesthesia. PACE 15:1515–1525

13. Atlee JL, Pattison CZ, Mathews EL et al (1993) Transesophageal atrial pacing for intraoperative sinus bradycardia or AV junctional rhythm: Feasibility as prophylaxis in 200 anesthetized adults and hemodynamic effects of treatment. J Cardiothor Vasc Anes 7:436–441
14. Atlee JL, Bilof RM (1992) Feasibility of transesophageal indirect ventricular pacing with a pacing esophageal stethoscope. Anesthesiology 77:A77
15. Atlee JL, Bilof RM (1993) Transesophageal ventricular pacing in anesthetized adults. Anesthesiology 79:A75
16. Cohen TJ, Chin MC, Oliver DG et al (1993) Transesophageal defibrillation: animal studies and preliminary clinical studies. PACE 16:1285–1292
17. Cohen TJ (1993) Innovative emergency defibrillation methods for refractory ventricular fibrillation in a variety of hospital settings. Am Heart J 126:962–968
18. Hesselvik JF, Ortega RA (1998) Simultaneous transesophageal atrial pacing and transesophageal echocardiography in cardiac surgical patients. J Cardiothor Vasc Anes 12:281–283
19. Atlee JL (1997) Management of perioperative dysrhythmias. Anesthesiology 86:1397–1424
20. Atlee JL, Bernstein AD (2001) Cardiac rhythm management devices. Part 1. Indications, device selection and function. Anesthesiology 95:1265–1280
21. Volkmann H, Dannberg G, Heinke M et al (1992) Termination of tachycardias by transesophageal electrical pacing. PACE 15:1962–1966
22. Ajisaka H, Hiraki T, Ikeda H et al (1997). Direct conversion of atrial flutter to sinus rhythm with low-output, short-duration transesophageal atrial pacing. Clin Cardiol 20:762–766
23. Doni F, Della Bella P, Manfredi M et al (1995) Atrial flutter termination by overdrive transesophageal pacing and the facilitating effect of oral propafenone. Am J Cardiol 76:1243–1246
24. D'Este D, Bertaglia E, Mantovan R et al (1997) Effect of intravenous propafenone in termination of atrial flutter by overdrive transesophageal pacing previously ineffective. Am J Cardiol 79:500–502
25. Doni F, Staffiere E, Manfredi M et al (1996) Type II atrial flutter interruption with transesophageal pacing: Use of propafenone and possible change of the substrate. PACE 19:1958–1961
26. Atar S, Cercek B, Nagai T et al (2000) Transthoracic stress echocardiography with transesophageal atrial pacing for bedside evaluation of inducible myocardial ischaemia in patients with new-onset chest pain. Am J Cardiol 86:12–16
27. Atar S, Nagai T, Cercek B et al (2000) Pacing stress echocardiography: An alternative to pharmacologic stress testing. J Am Coll Cardiol 36:1935–1941
28. Kesek M, Sheikh H, Bastani H et al (2000) The sensitivity of transesophageal pacing for screening atrial tachycardias. Int J Cardiol 72:239–242
29. Ko JK, Ryu SJ, Ban JE et al (2004) Use of transesophageal atrial pacing for documentation of arrhythmias suspected in infants and children. Jap Heart J 45:63–72
30. McKeown PP, Croal S, Allen JD et al (1993) Transesophageal cardioversion. Am Heart J 125:396–404
31. McKeown PP, Croal S, Allen JD et al (1995) Esophageal countershock: Anthropomorphic determinants of impedance. Acad Emer Med 2:63–68
32. Zardo F, Brieda M, Hrovatin E et al (2002) Transesophageal electrical cardioversion of persistent atrial fibrillation: A new approach for an old technology. Ital Heart J 3:354–359
33. Scholten MF, Thornton AS, Jordaens LJ et al (2004) Usefulness of transesophageal

echocardiography using a combined probe when converting atrial fibrillation to sinus rhythm. Am J Cardiol 94:470–473

34. Kronzon I, Tuncick PA, Scholten MF et al (2005) Combined transesophageal echocardiography and transesophageal cardioversion probe: technical aspects. J Am Soc Echocardiography 18:213–215

Chapter 20

Thrombolysis during cardiopulmonary resuscitation

F. Spöhr, B.W. Böttiger

Cardiac arrest has been associated with a very poor prognosis. Only 15–37% of patients suffering in-hospital cardiac arrest are expected to leave the hospital alive, and only 5–14% of patients can be discharged from hospital after an out-of-hospital cardiac arrest [1–3]. Due to the lack of specific therapeutic strategies shown to improve the outcome of patients requiring cardiopulmonary resuscitation (CPR) after sudden cardiac arrest [4, 5], the prognosis of these patients has hardly improved during the last 20 years [6].

In more than 70% of patients, cardiac arrest is caused by acute myocardial infarction (AMI) or massive pulmonary embolism (PE) [7, 8]. Systemic thrombolysis is widely used in the treatment of patients suffering from AMI or PE occurring with haemodynamic instability [9]. However, the danger of causing life-threatening bleeding complications has been a major drawback for using thrombolytic drugs during CPR. Prolonged or traumatic CPR has been regarded as a relative contraindication for thrombolytic treatment [10, 11]. Although this recommendation was never based sufficiently on clinical data [12], a high incidence of fatal bleeding complications may theoretically outweigh the potential therapeutic benefit of thrombolysis during CPR.

This article will briefly review the theoretical and experimental background and then focus on clinical data and studies on thrombolytic therapy during CPR. In the light of the currently available data, the safety of this treatment will be discussed.

Mechanisms of action

There are at least two mechanisms that contribute to the effect of thrombolytics during CPR. The most intuitive mechanism of thrombolytic agents administered during CPR is direct thrombolysis at the site of coronary or pulmonary occlusion. Therefore, these agents treat the *cause* of cardiac arrest, specifically very early after AMI or PE has caused cardiac arrest. In addition, thrombolysis is suggested to improve microcirculatory reperfusion after cardiac arrest. This second mechanism of action may be of particular importance for cerebral reperfusion. Microcirculatory reperfusion failure, also referred to as the 'no-reflow' phenomenon, is common after cardiac arrest and represents one of the most important causes for cerebral dysfunction. Cerebral no-reflow is a regional phenomenon that can occur despite sufficient systemic reperfusion conditions. It may be caused by leu-

cocyte–endothelial interactions and coagulation activation following cardiac arrest [13, 14]. Thrombolytics have been shown to reduce the cerebral no-reflow effect—significantly in the brain of cats after cardiac arrest of 15 min [14]. In patients after cardiac arrest, an imbalance of the blood coagulation system may be responsible for the failure of cerebral microcirculation during reperfusion. A marked activation of blood coagulation was found 8–48 h after return of spontaneous circulation (ROSC) in patients after out-of-hospital resuscitation. In contrast, in most patients, the plasma levels of d-dimer, an indicator of endogenous fibrinolytic activity, were not markedly increased during CPR [15]. Massive fibrin generation with consecutive impairment of fibrinolysis during and after CPR in patients who suffered out-of-hospital cardiac arrest was reported in another study [16]. Therefore, it has been concluded that, in patients after cardiac arrest, a marked activation of blood coagulation was not counterbalanced by an appropriate activation of endogenous fibrinolysis [15]. The exceptionally good neurological outcomes of patients receiving thrombolytic treatment even during prolonged CPR [17] are most likely the result of both the direct actions of thrombolytics on coronary thrombosis or pulmonary emboli and the effect of thrombolytics on microcirculatory reperfusion. Although the attenuation of microcirculatory failure after cardiac arrest by thrombolytics is clinically most evident for the brain, it is probably not limited to cerebral perfusion and is likely to occur also in other organs (kidneys, intestine, etc.).

In-hospital studies

More than 30 years ago, a German anaesthesiologist reported the first case of thrombolysis during CPR in a patient with fulminant postoperative PE [18]. Since then, many other case reports have been published, most of them demonstrating an exceptionally high rate of ROSC after unsuccessful conventional treatment. Interestingly, the case reports included a surprising number of neurologically intact survivors even after prolonged CPR. Although the exceptional outcome results of these reports may, in part, be attributed to a selection bias in publication (i.e. the bias to publish positive rather than negative results), the success of thrombolysis during CPR as a therapy option of last resort was exceptionally high. These case reports have been reviewed in detail before [19, 20].

The results of the studies on in-hospital thrombolysis during CPR are shown in Table 1. A small prospective study comprising 20 patients requiring CPR after massive PE was presented by Köhle et al. in 1984 [21]. In these patients, PE was diagnosed by pulmonary angiography, and streptokinase was administered locally by pulmonary angiography catheter. ROSC was achieved in 11 patients (55%). In another prospective study, 28 patients suffering from AMI were administered thrombolytic drugs during resuscitation. Nine patients were stabilised primarily, three of them were long-term survivors [22]. Kürkciyan and coworkers presented a retrospective study with 21 patients suffering cardiac arrest after massive PE who were given a bolus dose of recombinant tissue plasminogen activator (alteplase, rt-PA) during CPR. They compared this group to 21 patients receiving conventio-

nal resuscitation [23]. Nine conventionally treated patients showed ROSC, whereas 17 patients of the thrombolysis group could be stabilised primarily ($P < 0.05$). However, the number of survivors was generally low and not significantly different in both groups. In an uncontrolled prospective multicentre observational trial, tenecteplase was administered to patients who had been unresponsive to conventional resuscitation efforts. Thirty patients with pre-hospital (83%) and in-hospital (17%) cardiac arrest were included. Of these patients, 30% had ROSC, 17% were admitted to the intensive care unit, 10% survived 24 h, and 7% were discharged from hospital. Again, all survivors had a good neurological outcomes [24].

Table 1. Thrombolysis during cardiopulmonary resuscitation (CPR): in-hospital studies. *AMI* Acute myocardial infarction, *n.r.* not reported, *PE* pulmonary embolism, *rt-PA* recombinant tissue plasminogen activator (alteplase), *SK* streptokinase, *TNK* tenecteplase, *UK* urokinase

Reference	Study type	Underlying disease	Number of patients	Thrombolytic agent	CPR-related bleeding	Number of survivors
Köhle 1984 [21]	Prospective	PE	20	SK	-	11
Scholz 1990 [37]	Retrospective	PE	9	SK/UK/rt-PA	Pectoral/sternal haemorrhage, liver laceration	5
Gramann 1991 [22]	Prospective	AMI	28	SK/rt-PA	Pericardial/sternal haemorrhage (4)	3
Scholz 1992 [38]	Retrospective	AMI	6	SK/UK/rt-PA	-	3
Kürkciyan 2000 [23]	Retrospective	PE	21	rt-PA	Two liver ruptures, mediastinal bleeding	2
Kleiner 2003 [24]	Prospective	n.r.	30	TNK	-	2
Fatovich 2004 [25]	Randomised, placebo-controlled	n.r.	19	TNK	-	1
Total			133		9 (6.7%)	27 (20.3%)

The most recent clinical study on thrombolysis during CPR in an in-hospital setting was a small, prospective, randomised, double-blind, placebo-controlled pilot study [25]. Patients were enrolled after they had had a prolonged resuscitation following an out-of-hospital cardiac arrest. No drugs were given outside the hospital, and the first drug patients received in the emergency department (about 40 min after cardiac arrest) was tenecteplase or placebo. Patients treated with tenecteplase more often achieved ROSC compared to the control group (42% vs 6%). However, there were no differences in survival between the tenecteplase and placebo group at hospital discharge. Unfortunately, the study had to be stopped after 35 patients due to funding difficulties and therefore, was not powered to show a significant difference in outcome.

In conclusion, current in-hospital clinical studies show an improved rate of

ROSC in patients receiving thrombolysis during cardiac arrest after AMI or massive PE. In addition, they suggest an improved long-term survival (20.3%, see Table 1) compared to patients receiving standard in-hospital treatment (approximately 15% survivors [1, 26]).

Out-of-hospital studies

A large number of patients suffer cardiac arrests outside the hospital; unfortunately, the outcome of these patients is even more unfavourable than in the in-hospital setting [2]. Table 2 summarises the out-of-hospital studies on thrombolysis during CPR. The first study of out-of-hospital cardiac arrest patients was performed in 1995 by Klefisch and coworkers, who administered streptokinase during CPR as 'rescue thrombolysis' to 34 patients with suspected AMI or massive PE. Five patients, all presenting with ventricular fibrillation refractory to conventional resuscitation, survived, three of them without neurological deficit [27]. The first controlled, prospective study on thrombolysis during CPR was performed in our department [28]. Ninety patients were enrolled, 50 of whom received standard advanced cardiac life support, and 40 who were administered alteplase during CPR after resuscitation had been unsuccessful for more than 15 min. In the thrombolysis group, ROSC was achieved significantly more often (68% vs 44%) and more patients were admitted to hospital (58% vs 30%) than in the control group. At hospital discharge, there was a trend towards better survival in the thrombolysis group (15% vs 8%) that was not statistically significant due to the relatively small number of patients. Almost at the same time, these results were confirmed by a retrospective study with 108 out-of-hospital patients that were administered alteplase during CPR. Compared to 216 conventionally resuscitated patients using a

Table 2. Thrombolysis during CPR. Out-of-hospital studies. *CPR* Cardiopulmonary resuscitation, *rt-PA* recombinant tissue plasminogen activator (alteplase), *SK* streptokinase

Reference	Study type	Number of patients	Thrombolytic agent	CPR-related bleeding	Number of survivors
Klefisch 1995 [27]	Prospective	34	SK	Haemothorax	5
Böttiger 2001 [28]	Prospective, controlled	40	rt-PA	-	6
Lederer 2001 [29]	Retrospective, controlled	108	rt-PA	Two pericardial tamponades, one haemothorax	27
Abu-Laban 2002 [30]	Prospective, randomised, controlled	117	rt-PA	One pulmonary haemorrhage, one major haemorrhage (not clearly specified)	1
Total		299		6 (2.0%)	39 (13.0%)

'matched-pairs' analysis, both short- and long-term survival were improved in the thrombolysis group. ROSC occurred in 70.4% treated with alteplase (vs 51.0% in the control group), and 25.0% of patients who were administered thrombolytic treatment survived to discharge (vs 15.3% in the control group) [29]. In contrast to these studies, the first randomised, double-blind, placebo-controlled trial on out-of-hospital thrombolysis during cardiac arrest did not show a benefit of thrombolytic treatment on survival [30]. This study, however, focused on patients with pulseless electrical activity of the heart, and in more than one third of patients, collapse was not witnessed. Since no patient in the control group survived, the study was underpowered to detect a difference in outcome of patients with an extraordinary poor prognosis. Therefore, the data are difficult to interpret. The study has been criticised for its substantial methodological problems [31].

In conclusion, data from out-of-hospital studies suggest a beneficial effect of thrombolysis on outcome and potentially also on neurological performance of survivors.

The TROICA study

As outlined above, despite a number of positive clinical trials on thrombolysis during cardiac arrest in an in-hospital and out-of-hospital setting, no study has been powered to answer the question whether thrombolytic therapy can generally improve the poor prognosis of patients suffering sudden cardiac arrest. Therefore, a large international multicentre study on thrombolysis during CPR after pre-hospital cardiac arrest was designed. The Thrombolysis in Cardiac Arrest (TROICA) study is a randomised, double-blind, placebo-controlled trial comprising approximately 1300 patients suffering pre-hospital cardiac arrest of presumed cardiac origin. Patients either receive tenecteplase or placebo during resuscitation after the first vasopressor. Patients can be enrolled if either basic life support had started within 10 min of onset of cardiac arrest and had been performed up to 10 min, or if advanced life support is started within 10 min of onset of cardiac arrest. Patients must be at least 18-years-old and presenting with ventricular fibrillation, pulseless ventricular tachycardia, or pulseless electrical activity. Primary endpoints are the survival rate after 30 days and at hospital admission. Important secondary endpoints are ROSC, survival after 24 h, and neurological outcome. Bleeding complications will be monitored closely and evaluated as safety endpoints [32]. The results of the TROICA study are expected in 2006.

Risks of thrombolytic therapy during CPR

Thrombolytic therapy is associated with several risks, most importantly intracranial haemorrhage and systemic haemorrhage. Immunologic complications, hypotension, and reperfusion injury have also been described [33] but play a less important role in the setting of cardiac arrest. As recent international recommen-

dations still regard 'prolonged' or 'traumatic' CPR as a contraindication for thrombolysis [10, 11], severe haemorrhages represent the major safety concern in thrombolysis during CPR. However, this recommendation was never supported by sufficient clinical data [12].

The use of thrombolytic drugs is clearly associated with an increased risk of haemorrhagic complications. A meta-analysis of nine large randomised trials on thrombolysis for the treatment of AMI showed an incidence of 1.1% of major bleedings compared to an incidence of 0.4% in the control group. The risk of intracranial bleeding after thrombolysis for AMI was 0.8% compared to 0.1% in the control group without thrombolysis [34]. If thrombolysis is used for the treatment of PE, the incidence of intracranial bleeding may be up to 1.9%, one third of the cases being fatal [35]. Therefore, the risk for severe bleeding events in patients with AMI or PE who were administered thrombolytics without CPR can be estimated to be between 1.9% and 3.0% as compared to 0.5% in patients not receiving thrombolytics [12]. In addition, autopsy studies in patients after unsuccessful CPR show that significant haemorrhagic complications may occur in more than 15% of all patients after CPR [12]. Haemorrhages of the heart and the great vessels were found in more than 10% of these patients, followed by abdominal bleedings, haemothorax, and lung contusions [36].

As shown in Table 1, the incidence of severe bleeding complications in in-hospital studies on thrombolysis during CPR was 6.7%. Although this incidence is higher than in thrombolysis without CPR, it does not appear excessively high compared to the incidence of haemorrhagic complications of about 15% in autopsy studies, as described above. In addition, most of the severe bleeding complications can be treated by transfusion or surgery. Of all bleeding events reported from the in-hospital studies, there was only one pericardial haemorrhage that had a fatal outcome [22].

Pre-hospital studies on thrombolysis during CPR revealed an incidence of severe bleeding of 2.0% (Table 2). In the study by Klefisch, one patient who had undergone a prolonged resuscitation (75 min) had a haemothorax [27]. The most relevant data on bleeding complications in out-of-hospital patients were provided by Lederer et al. [29]. In their retrospective study of 108 patients, six severe bleeding incidents were discovered during autopsy in a subgroup of 45 non-surviving patients. Three of these were directly related to CPR. Interestingly, in the corresponding control group (patients without thrombolysis), there were seven severe bleeding events, i.e. the incidence of bleeding complications was not significantly different between the treatment and control groups. The study of Abu-Laban et al. reported pulmonary haemorrhage in the only surviving patient, and one more major haemorrhage that was not clearly specified [30].

In conclusion, currently available data from out-of-hospital studies show an incidence for CPR-related bleeding complications of 2.0% and therefore, suggest that thrombolysis is not likely to cause an increased bleeding risk. The endpoints of the TROICA study include a safety endpoint to assess the safety of thrombolysis during pre-hospital CPR.

References

1. Bedell SE, Delbanco TL, Cook EF et al (1983) Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569–576
2. Böttiger BW, Grabner C, Bauer H et al (1999) Long term outcome after out-of-hospital cardiac arrest with physician staffed emergency medical services: the Utstein style applied to a midsized urban/suburban area. Heart 82:674–679
3. Newman DH, Greenwald I Callaway CW (2000) Cardiac arrest and the role of thrombolytic agents. Ann Emerg Med 35:472–480
4. Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549–556
5. Kudenchuk PJ, Cobb LA, Copass MK et al (1999) Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 341:871–878
6. Herlitz J, Bang A, Gunnarsson J et al (2003) Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Goteborg, Sweden. Heart 89:25–30
7. Silfvast T (1991) Cause of death in unsuccessful prehospital resuscitation. J Intern Med 229:331–335
8. Spaulding CM, Joly LM, Rosenberg A et al (1997) Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 336:1629–1633
9. Arcasoy SM, Kreit JW (1999) Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 115:1695–1707
10. Antman EM, Anbe DT, Armstrong PW et al (2004) ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 110:588–636
11. Van de Werf F, Ardissino D, Betriu A et al (2003) Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 24:28–66
12. Spöhr F, Böttiger BW (2003) Safety of thrombolysis during cardiopulmonary resuscitation. Drug Saf 26:367–379
13. Böttiger B (1997) Thrombolysis during cardiopulmonary resuscitation. Fibrinolysis 11:93–100
14. Fischer M, Böttiger BW, Popov-Cenic S et al (1996) Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. Intensive Care Med 22:1214–1223
15. Böttiger BW, Motsch J, Böhrer H et al (1995) Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. Circulation 92:2572–2578
16. Gando S, Kameue T, Nanzaki S et al (1997) Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. Thromb Haemost 77:278–282
17. Böttiger BW, Böhrer H, Bach A et al (1994) Bolus injection of thrombolytic agents during cardiopulmonary resuscitation for massive pulmonary embolism. Resuscitation 28:45–54
18. Renkes-Hegendörfer U, Herrmann K (1974) Successful treatment of a case of fulminant massive pulmonary embolism with streptokinase. Anaesthesist 23:500–501

19. Böttiger BW, Martin E (2001) Thrombolytic therapy during cardiopulmonary resuscitation and the role of coagulation activation after cardiac arrest. Curr Opin Crit Care 7:176–183
20. Padosch SA, Motsch J, Böttiger BW (2002) Thrombolysis during cardiopulmonary resuscitation. Anaesthesist 51:516–532
21. Köhle W, Pindur G, Stauch M et al (1984) Hochdosierte Streptokinasetherapie bei fulminanter Lungenarterienembolie. Anaesthesist 33:469
22. Gramann J, Lange-Braun P, Bodemann T et al (1991) Der Einsatz von Thrombolytika in der Reanimation als Ultima ratio zur Überwindung des Herztodes. Intensiv- und Notfallbehandlung 16:134–137
23. Kürkciyan I, Meron G, Sterz F et al (2000) Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med 160:1529–1535
24. Kleiner DM, Ferguson KL, King K et al (2003) Empiric tenecteplase use in cardiac arrest refractory to standard advanced cardiac life support interventions. Circulation 108:318–319
25. Fatovich DM, Dobb GJ Clugston RA (2004) A pilot randomised trial of thrombolysis in cardiac arrest (The TICA trial). Resuscitation 61:309–313
26. Ballew KA, Philbrick JT, Caven DE et al (1994) Predictors of survival following in-hospital cardiopulmonary resuscitation. A moving target. Arch Intern Med 154:2426–2432
27. Klefisch F, Gareis R, Störk T et al (1995) Präklinische ultima-ratio Thrombolyse bei therapierefraktärer kardiopulmonaler Reanimation. Intensivmedizin 32:155–162
28. Böttiger BW, Bode C, Kern S et al (2001) Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. Lancet 357:1583–1585
29. Lederer W, Lichtenberger C, Pechlaner C et al (2001) Recombinant tissue plasminogen activator during cardiopulmonary resuscitation in 108 patients with out-of-hospital cardiac arrest. Resuscitation 50:71–76
30. Abu-Laban RB, Christenson JM, Innes GD et al (2002) Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 346:1522–1528
31. Böttiger BW, Padosch SA, Wenzel V et al (2002) Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 17:1281–1282
32. Spöhr F, Arntz HR, Bluhmki E et al (2005) International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. Eur J Clin Invest 35:315–323
33. Califf RM, Fortin DF, Tenaglia AN et al (1992) Clinical risks of thrombolytic therapy. Am J Cardiol 69:12A-20A
34. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (1994) Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 343:311–322
35. Kanter DS, Mikkola KM, Patel SR et al (1997) Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. Chest 111:1241–1245
36. Krischer JP, Fine EG, Davis JH et al (1987) Complications of cardiac resuscitation. Chest 92:287–291
37. Scholz KH, Hilmer T, Schuster S et al (1990) Thrombolysis in resuscitated patients with pulmonary embolism. Dtsch Med Wochenschr 115:930–935
38. Scholz KH, Tebbe U, Herrmann C et al (1992) Frequency of complications of cardio-

pulmonary resuscitation after thrombolysis during acute myocardial infarction. Am J Cardiol 69:724–728

Chapter 21

Cardiac resynchronisation therapy: do we know everything?

C. Fantoni, A. Auricchio

Despite striking advances in medical therapy of heart failure (HF) over the last decades [1, 2], morbidity and mortality of HF patients remain high [3]. Heart transplantation and ventricular assist devices offer an important, but limited alternative therapy. Cardiac transplantation can be an extremely effective therapy, but its provision is severely limited by lack of available organs. Mechanical devices to augment cardiac output are currently only suitable for short-term use and the financial cost of these devices is likely to limit their widespread application. On this background, cardiac resynchronisation therapy (CRT) has emerged as an effective option in selected HF patients who present with electro-mechanical dyssynchrony. Its safety and clinical efficacy have been demonstrated in several prospective, randomised controlled trials [4–7]. Furthermore, CRT has been proven able to reduce morbidity and mortality of HF patients [8–10], especially when combined with a defibrillator back-up [7].

Mechanical consequences of electrical delays

'… Obviously the shorter the distance that must be transversed in order to reach the Purkinje conducting system, the smaller the fractionate contraction element derived from fiber to fiber excitation and the greater the number of fractions excited over the natural pathways, with the result that more vigorous beats occur…' [11].

Wiggers [11] first recognised the acute effects of a non-physiological activation sequence on left ventricular function. The strict relationship between conduction delays and abnormal mechanical function has since been confirmed in many other animal models [12] and in humans [13]. Given the tight relation between excitation and contraction in the myocardium, it is not surprising that asynchronous electrical activation also leads to asynchronous contraction.

Patients with HF often present with conduction delays located at various levels of the conduction system, which may depress cardiac performance. Spontaneous or pharmacologically induced sinus node incompetence may contribute to further reduce the already impaired functional capacity of HF patients [14].

About 50% of HF patients show different degrees of atrio-ventricular block, a prolonged atrio-ventricular conduction time being the most frequent. Prolongation of atrio-ventricular time delays ventricular contraction (and consequently

relaxation of the ventricle), so that early passive filling overlaps the active filling, with consequent shorter total filling time and reduced atrial booster contribution to ventricular filling. Finally, loss of atrio-ventricular synchrony may determine a ventriculo-atrial tele-diastolic gradient with early re-opening of the mitral valve leading to significant 'pre-systolic or diastolic' mitral regurgitation [15]. All together these phenomena lead to impaired ventricular pre-load.

A significant prolongation of QRS complex of more than 120 ms may be found in approximately 30% of HF patients. The negative prognostic value related to QRS widening, independently of QRS morphology, has been proven in several studies [16, 17]. At our best understanding, prolongation of QRS duration is the result of electrical asynchrony at the inter-ventricular, intra-ventricular and intramural level [18]. Inter-ventricular mechanical delay is defined as the time difference between the onset of pulmonary artery flow and the onset of aortic flow with respect to the beginning of the QRS complex. A delay longer than 40 ms is usually considered indicative of significant inter-ventricular dyssynchrony. Nevertheless, many studies have questioned the real importance of such delay in impairing systolic function compared to the intra-ventricular electrical delay [19].

Left bundle branch block is the most common intra-ventricular conduction disturbance occurring in patients with depressed ventricular function. Recent electrophysiological findings have demonstrated that left bundle branch block is a rather complex and heterogeneous electrical disease [20–22]. There is increasing evidence that disarray of myocardial layers may partly account for this heterogeneity [21]. During left bundle branch block local contraction patterns differ not only in the onset of contraction, but also, and more importantly, in the pattern of contraction. These contraction patterns imply that opposing regions of the ventricular walls are out of phase and that energy generated by one region is dissipated in opposite regions.

In patients with left bundle branch block, the region of earliest ventricular activation (usually the inter-ventricular septum) contracts while the remaining ventricular myocardium is still in a non-activated phase. Thus, a consistent part of contraction energy is wasted as no effective intra-ventricular pressure can develop. At the same time, the latest activated regions of the left ventricle (usually the lateral and postero-lateral walls) are passively stretched with increasing wall tension at this site and further waste of energy. By the time that the latest depolarised ventricular regions contract, the septum starts to relax and is no more able to withstand the increasing pressure development, and is pushed toward the right ventricle (paradoxical septal motion). In this way, pressure is generated asynchronously by different regions of the left ventricle without effective ejection and with higher waste of energy.

Furthermore, the delayed depolarisation of the lateral wall causes a delayed and slow contraction of the postero-lateral papillary muscle. This event, in the presence of a dilated chamber and abnormal ventricular geometry, contributes to significant worsening of mitral regurgitation. Finally, the heterogeneous electrical and mechanical ventricular activation may further impair systolic ventricular function by delaying relaxation phase and reducing ventricular filling time.

Structural changes related to electro-mechanical dyssynchrony

In different heart models [23–25], it has been demonstrated that the abnormal loading and work distribution caused by electro-mechanical dyssynchrony may induce regional alterations of myocardial metabolism, gene expression and protein synthesis [24]. These changes could lead to rearrangement of both contractile and non-contractile cells, fibrosis and apoptosis. Experimentally induced left bundle branch block causes eccentric hypertrophy [26] with an apico-basal and septo-lateral oriented gradient and determines altered synthesis of stress kinases and calcium-handling proteins in the high stress areas [24]. Furthermore, it has been demonstrated that mechanical dyssynchrony causes a redistribution of regional flows [27] with consequent chronic hypoperfusion of unloaded regions. The meaning of such complex interactions between changes in regional loading conditions, myocardial metabolism, gene expression, protein synthesis and blood flow distribution induced by an abnormal activation sequence is not fully understood. All together it appears that mechanical dyssynchrony arising from conduction disturbances favours a maladaptive structural remodeling process. Thus, it is conceivable that dyssynchrony represents a newly appreciated pathophysiological process that directly depresses ventricular function and ultimately leads to further ventricular dilatation and progression of HF.

Cardiac resynchronisation therapy: how does it work?

With the introduction of CRT, cardiac pacemakers have seen their use transformed from just artificially maintaining the heart rhythm, to the restoration of pump function. Indeed, the restoration of ventricular mechanical synchrony by pacing the left ventricle alone or in combination with the right ventricle also has as its objective the restoration and/or maintenance of the proper timing of the atrial and ventricular contractions by modulating the atrio-ventricular delay.

During left bundle branch block, the most common conduction delay in patients with HF, the activation spreads from the right bundle branch to the right ventricular wall and, after trans-septal conduction, within the left ventricle—from the septum to the left ventricular lateral wall. Thus, pacing at the left ventricular lateral wall is used to create an activation wavefront, which starts from the opposite direction of a spontaneously occurring activation wavefront [28]. Consequently, during biventricular pacing, two activation wavefronts are generated in the right and left ventricle, merging approximately in the middle. A similar effect is obtained by single-site left ventricular pacing, using an atrio-ventricular interval that allows merging of the intrinsic activation originating from the right bundle branch with the wavefront derived from the left ventricular pacing lead. This merging of wavefronts leads to a reduction of electrical asynchrony compared to left bundle branch block. Due to the tight excitation–contraction coupling in the heart, CRT also improves coordination of contraction between the cardiac chambers and within the left ventricular walls, as shown using different imaging techniques [29,

30]. The improved mechanical synchrony leads to improvement of cardiac pump function, as determined by LVdP/dt, pulse pressure, cardiac output and ejection fraction [31, 32]. Such improved systolic pump function is achieved at unchanged or even decreased filling pressures, denoting a true improvement of ventricular contractility through improved coordination of contraction. Moreover, Nelson et al. [33] have shown that the better coordination of contraction improves mechanical pump function while slightly decreasing myocardial energy consumption, thus suggesting that CRT increases heart efficiency. Further improvement in pump function is possibly mediated by reduction of mitral regurgitation [30] and prolongation of diastolic filling time. These beneficial effects occur almost immediately after starting resynchronisation.

A variety of cardiac and extracardiac processes are triggered by CRT, which are responsible for its long-term beneficial effect. First of all, the improved pump function reduces neurohumoral imbalance, which is evidenced by a reduction in plasma norepinephrine and B-type natriuretic peptide levels and an increase in heart rate variability [34]. Furthermore, the improved contractility and pump efficiency at a smaller end-diastolic volume reduces mechanical ventricular stretch. This latter reduction and the probably associated reduction in neurohumoral activation may well explain the beneficial reverse remodeling effect of CRT [30, 35]. Interestingly, CRT is also able to reverse the eccentric hypertrophy of the left ventricle related to mechanical dyssynchrony, reducing the thickness of the latest activated regions [36]. These structural changes are important because hypertrophy is associated with various molecular changes, resulting in increased risk for contractile failure and arrhythmias.

Clinical effects of cardiac resynchronisation therapy

Several prospective, randomised controlled trials [4–6, 10, 37], conducted in patients with functional New York Heart Association (NYHA) class III–IV, due to dilated cardiomyopathy of any aetiology, presenting with electro-mechanical dyssynchrony, have proven the safety and clinical effectiveness of CRT. All these studies demonstrated a significant improvement of quality of life, NYHA functional class, exercise tolerance, and a significant reduction in hospitalisations for HF. Furthermore, there was a consistent report of significant improvement of left ventricular ejection fraction and partial reversal of maladaptive remodelling process [6, 30]. CRT also showed a favourable effect on sympathetic–parasympathetic activity with a reduction of plasma norepinephrine levels and increase of heart rate variability [34]. Finally, the recently concluded CARE-HF study (Cardiac Resynchronisation in Heart Failure) [10] demonstrated a clear survival benefit given by CRT in addition to optimal medical therapy compared to optimal medical therapy alone.

Based on these evidences, CRT is currently indicated (Table 1) for patients with symptomatic HF (NYHA III–IV) despite optimal medical therapy, due to dilated cardiomyopathy of any aetiology (left ventricular ejection fraction $\leq$ 35%), who

present with ventricular conduction delays (QRS ≥ 120 ms) for the improvement of symptoms, functional status and exercise capacity [38].

Table 1. Current indications for cardiac resynchronisation therapy (American Heart Association Science Advisory [38])

· Sinus rhythm
· Functional New York Heart Association class III or IV
· Ischaemic or non-ischaemic cardiomyopathy
· QRS Duration ≥ 120 ms
· Left ventricular ejection fraction ≤ 35%
· Maximal pharmacological therapy for heart failure

It has been reported that a small proportion of patients treated with CRT remain symptomatic. These individuals are usually considered as non-responder patients to CRT. All randomised clinical CRT trials have used statistical techniques to define the response of groups of patients to CRT. No standardised criteria are available to predict reliably the clinical response of a given individual. The large clinical improvement that is observed in some individuals after CRT has created the perception that patients who do not exhibit such improvement are not responding positively to CRT. However, many patients who do not show overt improvement may nevertheless benefit from a slowing of disease progression by living longer and not undergoing hospitalisations. Although major efforts have been made for identifying such patients, there are still several unresolved issues in the definition of non-responders and in how best to identify and then treat these patients.

Effects on morbidity and mortality

The COMPANION trial (Comparison of Medical therapy, Pacing, and Defibrillation in chronic heart failure) [7] has shown marked reduction in combined measures of morbidity and mortality both with CRT alone and with CRT plus defibrillator back-up (CRT-D) with a similar 1-year event-free survival rate. Nevertheless, in contrast to CRT alone, which demonstrated a relative risk reduction in all-cause mortality of about 24% ($p = 0.060$), CRT-D provided a larger (36%) and significant relative risk reduction in all-cause mortality compared to optimal drug therapy ($p = 0.003$). These results are consistent with data of a recent meta-analysis showing that CRT alone may be able to reduce all-cause mortality by about 21% [8]. Based on these data, the number of patients who need to be treated to save one life is about 25 for CRT alone and 14 when CRT is combined with an implantable cardioverter defibrillator (ICD). These numbers are comparable with many pharmacological trials, which enrolled similarly sick HF patients.

The recently concluded CARE-HF trial [10] that randomised 813 advanced HF patients to optimal medical therapy alone or in combination with a CRT device showed a 36% reduction in the relative risk of all-cause mortality with CRT compared with medical therapy alone. Nevertheless, 32 and 35% of the deaths that

occurred among patients randomised to medical therapy and to CRT respectively were sudden deaths, which could have been avoided by associating a defibrillator back-up.

Finally, results of the CARE-HF and COMPANION trials and those from another important meta-analysis [9] were consistent in showing a similar risk reduction for the combined end-point—hospitalisations and death—in patients treated with CRT. This finding may suggest a substantial reduction of medical resources with CRT.

Implantation issues

The implantation technique is similar to a standard dual chamber sequential pacemaker or cardioverter defibrillator. The most challenging aspect for achieving resynchronisation therapy is placing a permanent left ventricular lead. A transvenous or thoracotomic approach can be used. The transvenous approach requires the retrograde cannulation of the coronary sinus, a selective angiography of the coronary sinus and its tributaries, which delineates the venous anatomy, and the final placement of a specifically designed pacing lead into a coronary vein lying over the surface of the left ventricle. Several reports have demonstrated the importance of targeting the latest activated wall, which requires implantation of a pacing lead into a lateral or postero-lateral vein [39]. The transvenous approach may be a difficult and time-consuming technique. The major limitation is that options for lead placement are governed largely by the patient's venous anatomy, which shows considerable inter-individual variability. In about 10–15% of cases, it is not possible to achieve a satisfactory left ventricular pacing position or left phrenic nerve stimulation may occur, so that a thoracotomic approach becomes necessary.

Selection of patients

Duration of QRS complex has so far been used as the most practical and readily available criterion to select patients who are candidates for CRT. Indeed, QRS duration is one of the simplest ways to measure electrical delays that may have a mechanical correlate. Baseline QRS duration has been shown to be associated with degree of mechanical dyssynchrony and with short-term clinical improvement obtained from CRT. Nevertheless there are increasing data [40] suggesting that a considerable proportion of HF patients presenting with narrow QRS complex (< 120 ms) may present echocardiographically assessed mechanical dyssynchrony of similar magnitude as patients with prolonged QRS duration (> 120 ms).

Recently introduced tissue Doppler imaging (TDI) techniques permit precise evaluation of regional systolic and diastolic synchrony by comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. TDI appears to offer a comprehensive assessment of cardiac mechanical synchrony. A number of parameters based on TDI have been proposed to evaluate intra-ventri-

cular dyssynchrony but the validity of TDI and other echocardiographic parameters in selecting patients with both narrow and wide QRS who can benefit from CRT needs to be confirmed in prospective, randomised long-term studies.

Open questions

Cardiac resynchronisation therapy is not currently indicated in patients with NYHA class II, even though some data suggest that application of CRT in mildly symptomatic HF patients could prevent or slow HF progression. Furthermore, the increasing indications for ICD implantation, based on results of recent big trials (MADIT, MADIT II, SCD-HeFT) raise the problem of considering implementation of the ICD devices with a CRT back-up in less symptomatic (NYHA II) patients with ventricular conduction delays.

Not enough data are so far available about CRT in patients with atrial fibrillation, although preliminary results support its efficacy in this clinical setting [41]. Furthermore, there is increasing evidence that the implantation of a CRT device instead of a standard single- or dual-chamber pacemaker may be appropriate for HF patients who undergo His-bundle ablation.

The question of whether HF patients with a standard pacemaker indication for bradycardia benefit from CRT is still unanswered. Nevertheless, data from the DAVID trial [42] encourage implantation of a CRT device in patients with impaired ventricular systolic function who are candidates for chronic pacing.

Recent data suggest that patients with narrow QRS (< 120 ms), but with echocardiographic evidence of mechanical dyssynchrony, may also benefit from CRT. Nevertheless, CRT should not be extended to this group of patients before results of prospective randomised trials are available.

The important issue raised by the COMPANION study [7] is whether all HF patients who are candidates for CRT should be treated with an ICD back-up. The recently concluded SCD-HeFT trial (Sudden Cardiac Death–Heart Failure trial) [43] has provided further evidence that implantation of a defibrillator in addition to best pharmacological therapy is the most effective long-term (5-year) treatment to prolong life in HF patients compared to optimal medical therapy alone with or without amiodarone. Therefore, despite the fact that CRT-D devices have larger initial costs, and may require more extensive follow-up than CRT alone, this strategy may be more cost-effective, particularly when measured in terms of gain in quality-adjusted life-years.

Conclusions

Cardiac resynchronisation therapy is an effective, adjunctive treatment to pharmacological therapy for a selected group of HF patients who remain symptomatic despite optimal medical therapy, and who present with electro-mechanical dyssynchrony. Safety and effectiveness of CRT have been demonstrated by many clinical

controlled trials, with patients achieving significant improvement in symptoms, functional status and exercise capacity. Furthermore, CRT promotes reverse remodelling and reduces morbidity and mortality of HF patients. Importantly, CRT should not be considered an alternative to medical therapy but a synergistic therapy. Indeed, in those patients in whom optimal dosage of ACE inhibitors or beta-blockers cannot be achieved because of haemodynamic intolerance or severe bradycardia, CRT may be considered in order to support ventricular systolic function, allowing optimisation of beta-blocking and ACE-inhibitor treatment. Whether CRT should be delivered in NYHA class II, in HF patients with QRS < 120 ms and in HF candidates to chronic pacing needs to be confirmed by randomised controlled trials.

References

1. Anonymous (1983) A placebo-controlled trial of captopril in refractory chronic congestive heart failure. Captopril Multicenter Research Group. J Am Coll Cardiol 2(4):755–763
2. Anonymous (1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353:2001–2007
3. Rodeheffer RJ, Naftel DC, Stevenson LW et al (1990) Secular trends in cardiac transplant recipient and donor management in the United States, to 1994. Circulation 94:2883–2889
4. Auricchio A, Stellbrink C, Sack S et al (2002) Long-term clinical effect of hemodynamically optimised cardiac resynchronisation therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol 39:2026–2033
5. Cazeau S, Leclercq C, Lavergne T et al (2001) Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 344:873–880
6. Abraham WT, Fisher WG, Smith AL et al (2002) Cardiac resynchronisation in chronic heart failure. N Engl J Med 346:1902–1905
7. Bristow MR, Saxon LA, Boehmer J et al (2004) Cardiac-resynchronisation therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
8. McAlister FA, Ezekowitz JA, Wiebe N et al (2004) Systematic review: cardiac resynchronisation in patients with symptomatic heart failure. Ann Intern Med 141:381–390
9. Bradley DJ, Bradley EA, Baughman KL et al (2003) Cardiac resynchronisation and death from progressive heart failure. A meta-analysis of randomised controlled trials. JAMA 289:730–740
10. Cleland JGF, Daubert JC, Erdmann E et al (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
11. Wiggers CJ (1925) The muscular reactions of the mammalian ventricles to artificial surface stimuli. Am J Physiol 73:346–378
12. Liu L, Tockman B, Girouard S et al (2002) Left ventricular resynchronization therapy in a canine model of left bundle branch block. Am J Physiol Heart Circ Physiol 282:H2238–2244
13. Grines CL, Bashore TM, Boudoulas H et al (1989) Functional abnormalities in isolated

left bundle branch block. The effect of interventricular asynchrony. Circulation 79:845–853
14. Kass DA (2003) Ventricular resynchronization: pathophysiology and identification of responders. Rev Cardiovasc Med 4:S3–S13
15. Meisner JS, McQueen DM, Shida Y et al (1985) Effects of timing of atrial systole on LV filling and mitral valve closure: computer and dog studies. Am J Physiol 249:H604–H619
16. Baldasseroni S, Opasich C, Gorini M et al (2002) Left bundle branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian Network on Congestive Heart Failure Investigators. Am Heart J 143:398–405
17. Hesse B, Diaz LA, Snader CE et al (2001) Complete bundle branch block as an independent predictor of all-cause mortality: report of 7,073 patients referred for nuclear exercise testing. Am J Med 110:253–259
18. Auricchio A, Abraham WT (2004) Cardiac resynchronisation therapy: current state of the art. Cost versus benefit. Circulation 109:300–307
19. Fauchier L, Marie O, Casset-Senon D et al (2002) Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy. A prognostic study with Fourier phase analysis of radionuclide angioscintigraphy. J Am Coll Cardiol 40:2022–2030
20. Rodriguez L-M, Timmermans C, Nabar A et al (2003) Variable patterns of septal activation in patients with left bundle branch block and heart failure. J Cardiovasc Electrophysiol 14:135–141
21. Auricchio A, Fantoni C, Regoli F et al (2004) Characterization of left ventricular activation in patients with heart failure and left bundle branch block. Circulation 109:1133–1139
22. Fung JWH, Yu CM, Yip G et al (2004) Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. Heart 90:17–19
23. Prinzen FW, Hunter WC, Wyman BT et al (1999) Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 33:1735–1742
24. Spragg D, Leclercq C, Loghmani M et al (2003) Regional alterations in protein expression in the dyssynchronous failing heart. Circulation 108:929–932
25. Ukkonen H, Beanlands RS, Burwash IG et al (2003) Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation 107:28–31
26. Van Oosterhout FM, Prinzen FW, Arts T et al (1998) Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 98:588–595
27. Prinzen FW, Van Oosterhout FM, Arts T et al (2000) Mismatch of local myocardial growth and blood flow during chronic ventricular pacing. Circulation 102:196
28. Lister JW, Klotz DH, Jomain SL et al (1964) Effect of pacemaker site on cardiac output and ventricular activation in dogs with complete heart block. Am J Cardiol 14:494–503
29. Sogaard P, Egeblad H, Kim WY et al (2002) Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 40:723–730
30. Yu CM, Chau E, Sanderson JE et al (2002) Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 105:438–445
31. Dekker AL, Phelps B, Dijkam et al (2004) Epicardial left ventricular lead placement for cardiac resynchronization therapy: optimal pace site selection with pressure-volume loops. J Thorac Cardiovasc Surg 127:1642–1647
32. Leclercq C, Cazeau S, Le Breton H et al (1998) Acute hemodynamic effects of biventri-

cular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 32:1825–1831
33. Nelson G, Berger RD, Fetics BJ et al (2000) Left or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle branch block. Circulation 102:3053–3059
34. Adamson PB, Smith AL, Abraham WT et al (2004) Continuous autonomic assessment in patients with symptomatic heart failure. Prognostic value of heart rate variability measured by an implanted cardiac resynchronisation device. Circulation 110:2389–2394
35. St John Sutton MG, Plappert T, Abraham WT et al (2003) Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 107:1985–1990
36. Vernooy K, Verbeek XA, Peschar M et al (2005) Left bundle branch block induces ventricular remodeling and functional septal hypoperfusion. Eur Heart J 26:91–98
37. Saxon LA, Boehmer JP, Hummel J et al (1999) Biventricular pacing in patients with congestive heart failure: two prospective randomised trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol 83:120D–123D
38. Strickberger SA, Conti J, Daoud EG et al (2005) Patient selection for cardiac resynchronization therapy. AHA Science Advisory. Circulation 111:2146–2150
39. Butter C, Auricchio A, Stellbrink C et al (2000) Should stimulation site be tailored in the individual heart failure patient. Am J Cardiol 86:K144–K151
40. Yu CM, Lin H, Zhang Q et al (2003) High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 89:54–60
41. Leon AR, Greenberg JM, Kanuru N et al (2002) Cardiac resynchronisation in patients with congestive heart failure and chronic atrial fibrillation: effects of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 39:1258–1263
42. Wilkoff BL, Cook JR, Epstein AE et al (2002) Dual-chamber pacing or ventricular back-up pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) trial. JAMA 288:3115–3123
43. Bardy GH, Lee KL, Mark DB et al (2005) Amiodarone or an implantable-defibrillator for congestive heart failure. N Engl J Med 352:225–237

Chapter 22

Minimising reperfusion injury in settings of myocardial ischaemia[1]

R.J. Gazmuri

The myocardium is a prime target for injury caused by ischaemia and reperfusion during cardiac arrest and resuscitation, leading to functional abnormalities that may adversely affect ultimate outcome. These functional abnormalities are described below and include the development of ischaemic contracture during cardiac resuscitation, the development of reperfusion arrhythmias upon return of spontaneous circulation, and the development of largely reversible global post-resuscitation myocardial dysfunction. Ischaemic contracture is a term used for describing progressive left ventricular wall thickening with reductions in cavity size as a result of ischaemia. Ischaemic contracture occurs during cardiac resuscitation and compromises preload-dependent forward blood flow generation, partly explaining time-dependent reductions in the haemodynamic efficacy of closed-chest resuscitation [1, 2]. We have documented in rat and pig models of ventricular fibrillation (VF) that ischaemic contracture begins shortly after starting the resuscitation efforts, suggesting that reperfusion plays a pivotal role [2–4]. In the absence of reperfusion, the time to onset of ischaemic contracture is substantially delayed [5, 6]. These observations indicate that a more proper term for ischaemic contracture developing during resuscitation might be 'reperfusion contracture.' In humans, ischaemic (reperfusion) contracture has been described as myocardial 'firmness' and was also found to compromise resuscitability [7]. Reperfusion arrhythmias commonly occur after return of spontaneous circulation, with VF being the most serious manifestation and occurring in up to 79% of successfully resuscitated victims [8–10]. The underlying mechanism of reperfusion arrhythmias (including VF) is likely to involve cytosolic Ca^{2+} overload, predisposing to delayed afterdepolarisations, and electrical alternans, leading to triggered activity along with shortening of the action potential duration (possibly related to opening of potassium channels), which favours excitable gaps and reentry. These abnormalities are typically short-lived, occurring predominantly during the early minutes after return of spontaneous circulation. Post-resuscitation myocardial dysfunction characteristically develops after resuscitation from cardiac arrest and represents

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the functional manifestation of global myocardial ischaemia and reperfusion injury compounded by adverse effects of interventions, such as repetitive electrical shocks [11] and the administration of adrenergic vasopressor agent [12]. In addition, post-resuscitation myocardial dysfunction encompasses systolic and diastolic dysfunction. Systolic dysfunction is characterised by decreases in contractility and reductions in ejection fraction, while diastolic dysfunction is characterised by left ventricular wall thickening with reductions in end-diastolic volume [11], and probably represents resolving ischemic contracture. Diastolic dysfunction can preclude ventricular dilation compromising compensatory responses to decreased contractility [2]. Post-resuscitation myocardial dysfunction commonly reverses within hours or days [13]; however, if severe enough it may preclude restoration of stable circulation. The combination of reperfusion arrhythmias and post-resuscitation myocardial dysfunction is likely to account for the nearly 40% death rate of initially resuscitated victims of out-of-hospital sudden cardiac arrest before admission to a hospital [14].

At the core of the functional myocardial abnormalities described above is the severe injury that cells suffer consequent to ischaemia and reperfusion. However, an improved understanding of ischaemia and reperfusion is providing innovative concepts for novel approaches to cardiac resuscitation. Because reperfusion is an obligatory step in the resuscitation process, we hypothesise that a more favourable outcome results from securing that reperfusion occurs under conditions in which the associated injury is minimised and cell survival mechanisms are activated. To this end, we propose to group resuscitation interventions into three main categories: (1) those aimed at enhancing the benefits of reperfusion (type-A intervention), (2) those aimed at blocking specific pathways or mechanisms of reperfusion injury (type-B intervention), and (3) those aimed at activating specific pathways of cell survival (type-C intervention). Within this conceptual framework, our group has examined the effects of blocking the sarcolemmal sodium-hydrogen exchanger isoform-1 (NHE-1), representing a type-B intervention, and the effects of administering erythropoietin, representing a type-C intervention. In the sections below, we provide a succinct overview of these two interventions and their potential role for resuscitation from cardiac arrest.

NHE-1 inhibition

Increased sarcolemmal Na^+ influx causes the accumulation of cytosolic Na^+ due to the inability of the Na^+-K^+ pump to extrude Na^+. This sequence of events represents an important pathogenic mechanism responsible for cell injury during ischaemia and reperfusion [15]. Na^+ can enter the cell during ischaemia through the NHE-1, the Na^+-HCO_3- cotransporter, and/or Na^+ channels; however, NHE-1 seems to be the principal route during ischaemia and reperfusion. NHE-1 is activated by the intense intracellular acidosis that accompanies ischaemia, initiating an electroneutral sarcolemmal Na^+-H^+ exchange. It is believed that, as protons exit the cell and accumulate in the extracellular space, the trans-sarcolemmal proton gradient

declines, hence diminishing but not eliminating Na^+-H^+ exchange. Reperfusion with normo-acidic fluid washes out the acidic extracellular space, re-establishing the proton gradient and intensifying sarcolemmal Na^+-H^+ exchange. When reperfusion occurs with normal flows, this pathogenic mechanism presumably resolves as aerobic metabolism and Na^+-K^+ pump functions are restored. During closed-chest resuscitation, however, the coronary blood flow generated rarely exceeds 20% of normal [16, 17] and typically fails to reverse ischaemia. Yet, this flow is sufficient to supply the coronary circuit with normo-acidic blood, thus creating conditions favourable for NHE-1 to remain active throughout the resuscitation effort.

Cytosolic Na^+ accumulation worsens ischaemia by driving Ca^{2+} entry through the sarcolemmal Na^+-Ca^{2+} exchanger isoform-1 operating in reverse mode [18]. Ca^{2+} overload leads to cell injury, through mechanisms that involve mitochondrial dysfunction, and favours reperfusion arrhythmias through delayed afterdepolarisations causing triggered activity.

In addition to these local mechanisms, cardiac arrest prompts a massive neuroendocrine stress response with release of mediators that can further enhance NHE-1 activity through activation of α_1-adrenergic [19, 20], endothelin-1 [21, 22], and angiotensin II [23] receptors. Activation of these receptors increase the 'H^+ sensor' sensitivity of NHE-1 through phosphorylation of cytoplasmic residues, thus increasing the Na^+-H^+ exchange rate for a given intracellular pH level.

We reported that selective NHE-1 inhibition by cariporide, given after induction of VF (ischaemia) but before or shortly after starting closed-chest resuscitation (reperfusion), can ameliorate the aforementioned functional myocardial abnormalities. Accordingly, administration of cariporide ameliorates ischaemic contracture, enabling haemodynamically more effective chest compression [24–26]. We recently demonstrated in a rat model of VF that cariporide was associated with the generation of systemic and myocardial blood flows with less depth of chest compression than in control rats [17]. The improved capability for forward blood flow generation resulted in a favourable interaction with vasopressor agents, such that higher coronary perfusion pressures could be generated with fewer vasopressor agent doses [26]. Post-resuscitation, cariporide markedly reduced ventricular ectopic activity and essentially eliminated episodes of recurrent VF [24, 25]. Cariporide also ameliorated post-resuscitation left ventricular dysfunction and enabled greater post-resuscitation haemodynamic stability [24, 27]. Moreover, in preliminary studies using a rat model of VF and closed-chest resuscitation, zoniporide, which is another selective NHE-1 inhibitor, mitigated brain injury and improved recovery of neurological function [28].

NHE-1 inhibition during clinical resuscitation may therefore lead to increased resuscitability with more stable haemodynamic function, enabling a greater number of cardiac arrest victims to be resuscitated and restored to productive lives. However, the potential clinical applicability of NHE-1 inhibitors for the moment has been halted. A recent clinical trial in patients undergoing coronary artery bypass graft surgery demonstrated increased incidence of cerebrovascular occlusive events and higher overall mortality despite a significant reduction in non-fatal post-operative myocardial infarction [29]. In this clinical trial, cariporide was given

as an infusion before surgery and continued post-operatively for 48 h. In our studies, no adverse neurological effects related to administration of cariporide were noted. Although information on the mechanism of this adverse effect of cariporide is not currently available, it appears to be unrelated to the mode of action. Development of newer compounds is anticipated.

Erythropoietin

Erythropoietin is a 30.4-kDa glycoprotein best known for its action on erythroid progenitor cells and regulation of circulating red cell mass [30]. However, within the past few years, investigators have reported that erythropoietin also signals survival responses during ischaemia and reperfusion in a broad range of tissues, including the heart [31–40], brain [41–44], spinal cord [45], retina [46], kidney [47, 48], liver [48], and skin [49]. Some of these protective actions are induced immediately upon administration of erythropoietin and result in attenuation of ischaemia and reperfusion injury, even when given after the onset of ischaemia and at the time of reperfusion [37, 39, 50, 51], suggesting the erythropoietin could be beneficial for cardiac resuscitation.

The mechanisms underlying the beneficial effects of erythropoietin involve activation of the erythropoietin receptor, which is a member of the type-I superfamily of single-transmembrane cytokine receptors. The receptor exists as homodimers with distinctive extracellular, transmembrane, and intracellular domains, and is constitutively associated with Janus tyrosine kinase 1 (JAK1) and 2 (JAK2) [30]. Binding of erythropoietin to the extracellular domains of the receptor induces conformational changes of the intracellular domains, prompting cross-phosphorylation and activation of JAK [30, 52]. JAK activation phosphorylates several tyrosine residues in the intracellular domain, thus creating docking sites for recruitment and activation of multiple signalling proteins that have Src-homology-2 (SH2) domains [52]. Through this mechanism, erythropoietin orchestrates a coordinated, multi-targeted, and highly effective cell survival response [51, 53]. Protective pathways/mechanisms in the heart include activation of: signal transducer and activators of transcription (STAT) proteins isoforms 3 and 5A [53]; protein kinase C epsilon (PKCε) [53]; phosphatidylinositol 3-kinase (PI3K) and its main target, protein kinase B (Akt) [50, 54]; extracellular signal-regulated kinase (ERK) 1/2 [54]; and raf/mitogen activated protein kinase (MAPK) p38 and p42/44 [53]. Of these mechanisms, PIK3/Akt and PKCε seem to play leading roles in immediate protection.

The PI3K/Akt pathway

Akt is a serine/threonine kinase that requires phosphorylation of both the serine and threonine residues for full activation. Phosphorylation is partly dependent on binding of Akt to the PI3K products phosphatidylinositol 3,4 biphosphate (PIP2) and phosphatidylinositol 3,4,5 triphosphate (PIP3), and subsequent phosphoryla-

tion of Akt by activated phosphoinositide-dependent kinase 1 (PDK1) [55, 56]. Activated Akt signals physiologically favourable effects by phosphorylating a diverse array of substrates [57, 58]. This includes phosphorylation of apoptotic proteins such as Bcl-2 associated death protein (Bad), Bcl-2–associated X protein (Bax), p53, and procaspase-9. Bad, for example, exerts its apoptotic effects by associating with the anti-apoptotic proteins B cell lymphoma-X_L (Bcl-X_L) and B cell lymphoma-2 (Bcl-2), thereby neutralising their anti-apoptotic effects [59]. Phosphorylated Bad instead associates with 14-3-3 proteins, enabling Bcl-X_L and Bcl-2 to remain active [59]. Akt also phosphorylates glycogen synthase kinase 3 beta (GSK-3β), which has recently been identified as a regulator of the mitochondrial permeability transition pore (MPTP) and as the point of convergence for multiple protective pathways [60]. GSK-3β is constitutively active, and phosphorylation of its serine-9 inactivates the enzyme and increases the threshold for MPTP opening by reactive oxygen species. Inactivation of GSK-3β also signals, downstream, a shift towards an anti-apoptotic state. Akt can promote translocation of the glucose transporter 4 (GLUT4) from the cytosol to the plasma membrane, enhancing glucose entry and glycolytic ATP production [61, 62]. Akt also signals survival responses through phosphorylation of I kappa B kinase alpha (IKK-α) and forkhead proteins [58]. PIK3/Akt can be activated by various upstream ligand-receptor systems besides erythropoietin, such as insulin, insulin-like growth factor-1 (IGF-1), cardiotrophin-1 (CT-1), urocortin, and bradykinin [58].

Protein kinase Cε

Activation of PKCε plays an important role in myocardial protection [54, 63]. The mechanism is thought to involve phosphorylation by PDK1 and translocation from the cytosol to cell membranes, including mitochondria, with opening of putative mitochondrial ATP-sensitive K^+ channels (K_{ATP} channels) expressed in the inner mitochondrial membrane. Increased mitochondrial conductivity to K^+ has been shown to be energetically favourable and to mediate preconditioning and acute protection [64]. In isolated perfused rabbit hearts subjected to ischaemia and reperfusion, inhibition of mitochondrial K_{ATP} channels abrogated the protective effects of erythropoietin [65]. Administration of K_{ATP} channel openers during cardiac resuscitation can minimise post-resuscitation myocardial dysfunction [66]. Protective action after PKCε activation is rapid and demonstrable within 5 min [53]. In addition to K_{ATP} channels, erythropoietin also activates Ca^{2+}-sensitive K^+ channels (K_{Ca} channels), which are expressed in mitochondria and sarcolemma [65]. Inhibition of K_{Ca} channels also abrogates the protective effects of erythropoietin. However, it is not clear whether the mechanism for K_{Ca} activation also involves PKCε.

Evidence that erythropoietin protects the heart during ischaemia and reperfusion was first reported in 2003 [31, 32, 34, 35] and continues to accumulate. Studies have been conducted in isolated rat cardiomyocytes [32]; isolated rat [31, 36, 54], and rabbit heart models of global or regional ischaemia followed by reperfusion; and in intact rat [32, 37, 54], rabbit [34, 38], and dog [50] models of coronary

occlusion and reperfusion. The studies collectively show that erythropoietin given before [36], at the onset of ischaemia [34, 35], or at the time of reperfusion [37, 48, 50, 54] can limit post-ischaemic dysfunction and decrease infarct zone associated with decreased apoptosis. Erythropoietin can also mitigate post-ischaemic dysfunction of viable cells through mechanisms that are not well-established.

We recently completed pilot studies in a rat model of prolonged VF (unpublished) and found that administration of erythropoietin (5000 U/kg) at the start of closed-chest resuscitation enabled haemodynamically more effective chest compression and improved post-resuscitation haemodynamic function.

Concluding remarks

Scientific developments in the area of ischaemia and reperfusion are providing unprecedented levels of understanding and paving the way for novel therapeutic approaches. However, it is unlikely that novel agents will be developed specifically for use in the cardiac arrest setting. A more likely scenario is that drugs developed for other indications, with a greater potential market, but which are also found to exert rapid protection against myocardial ischaemia and reperfusion, may be further developed for use in the cardiac arrest setting. One such scenario involves erythropoietin, which is already approved for use in humans and might have a role for cardiac resuscitation.

References

1. Klouche K, Weil MH, Sun S et al (2002) Evolution of the stone heart after prolonged cardiac arrest. Chest 122:1006–1011
2. Ayoub IM, Kolarova JD, Yi Z et al (2003) Sodium-hydrogen exchange inhibition during ventricular fibrillation: beneficial effects on ischemic contracture, action potential duration, reperfusion arrhythmias, myocardial function, and resuscitability. Circulation 107:1804–1809
3. Gazmuri RJ, Berkowitz M, Cajigas H (1999) Myocardial effects of ventricular fibrillation in the isolated rat heart. Crit Care Med 27:1542–1550
4. Gazmuri RJ, Ayoub IM, Hoffner E, Kolarova JD (2001) Successful ventricular defibrillation by the selective sodium-hydrogen exchanger isoform-1 inhibitor cariporide. Circulation 104:234–239
5. Berg RA, Sorrell VL, Kern KB et al (2005) Magnetic resonance imaging during untreated ventricular fibrillation reveals prompt right ventricular overdistention without left ventricular volume loss. Circulation 111:1136–1140
6. Sorrell VL, Altbach MI, Kern KB et al (2005) Images in cardiovascular medicine. Continuous cardiac magnetic resonance imaging during untreated ventricular fibrillation. Circulation 111:e294
7. Takino M, Okada Y (1996) Firm myocardium in cardiopulmonary resuscitation. Resuscitation 33:101–106
8. Weaver WD, Cobb LA, Copass MK, Hallstrom AP (1982) Ventricular defibrillation –

A comparative trial using 175-J and 320-J shocks. N Engl J Med 307:1101–1106
9. White RD, Russell JK (2002) Refibrillation, resuscitation and survival in out-of-hospital sudden cardiac arrest victims treated with biphasic automated external defibrillators. Resuscitation 55:17–23
10. van Alem AP, Post J, Koster RW (2003) VF recurrence: characteristics and patient outcome in out-of-hospital cardiac arrest. Resuscitation 59:181–188
11. Gazmuri RJ, Deshmukh S, Shah PR (2000) Myocardial effects of repeated electrical defibrillations in the isolated fibrillating rat heart. Crit Care Med 28:2690–2696
12. Cao L, Weil MH, Sun S, Tang W (2003) Vasopressor agents for cardiopulmonary resuscitation. J Cardiovasc Pharmacol Ther 8:115–121
13. Kern KB, Hilwig RW, Rhee KH, Berg RA (1996) Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol 28:232–240
14. Laurent I, Monchi M, Chiche JD et al (2002) Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 40:2110–2116
15. Imahashi K, Kusuoka H, Hashimoto K et al (1999) Intracellular sodium accumulation during ischemia as the substrate for reperfusion injury. Circ Res 84:1401–1406
16. Duggal C, Weil MH, Gazmuri RJ et al (1993) Regional blood flow during closed-chest cardiac resuscitation in rats. J Appl Physiol 74:147–152
17. Kolarova JD, Ayoub IM, Gazmuri RJ (2005) Cariporide enables hemodynamically more effective chest compression by leftward shift of its flow-depth relationship. Am J Physiol Heart Circ Physiol 288:H2904–H2911
18. An J, Varadarajan SG, Camara A et al (2001) Blocking Na(+)/H(+) exchange reduces [Na(+)](i) and [Ca(2+)](i) load after ischemia and improves function in intact hearts. Am J Physiol 281:H2398–H2409
19. Yasutake M, Avkiran M (1995) Exacerbation of reperfusion arrhythmias by alpha 1 adrenergic stimulation: a potential role for receptor mediated activation of sarcolemmal sodium-hydrogen exchange. Cardiovasc Res 29:222–230
20. Yokoyama H, Yasutake M, Avkiran M (1998) Alpha1-adrenergic stimulation of sarcolemmal Na+-H+ exchanger activity in rat ventricular myocytes: evidence for selective mediation by the alpha1A-adrenoceptor subtype. Circ Res 82:1078–1085
21. Wu ML, Tseng YZ (1993) The modulatory effects of endothelin-1, carbachol and isoprenaline upon Na(+)-H+ exchange in dog cardiac Purkinje fibres. J Physiol 471:583–597
22. Ito N, Kagaya Y, Weinberg EO et al (1997) Endothelin and angiotensin II stimulation of Na+-H+ exchange is impaired in cardiac hypertrophy. J Clin Invest 99:125–135
23. Matsui H, Barry WH, Livsey C, Spitzer KW (1995) Angiotensin II stimulates sodium-hydrogen exchange in adult rabbit ventricular myocytes. Cardiovasc Res 29:215–221
24. Gazmuri RJ, Ayoub IM, Hoffner E, Kolarova JD (2001) Successful ventricular defibrillation by the selective sodium-hydrogen exchanger isoform-1 inhibitor cariporide. Circulation 104:234–239
25. Ayoub IM, Kolarova JD, Yi Z et al (2003) Sodium-hydrogen exchange inhibition during ventricular fibrillation: beneficial effects on ischemic contracture, action potential duration, reperfusion arrhythmias, myocardial function, and resuscitability. Circulation 107:1804–1809
26. Kolarova J, Yi Z, Ayoub IM, Gazmuri RJ (2005) Cariporide potentiates the effects of epinephrine and vasopressin by nonvascular mechanisms during closed-chest resuscitation. Chest 127:1327–1334
27. Ayoub IM, Kolarova JD, Kantola RL et al (2005) Cariporide minimizes adverse myo-

cardial effects of epinephrine during resuscitation from ventricular fibrillation. Crit Care Med (In press)
28. Sanders RW, Ayoub IM, Kolarova JD, Gazmuri RJ (2004) Possible neuroprotective effects of zoniporide during resuscitation from cardiac arrest. Crit Care Med 32:A57
29. Mentzer RJ (2003) Effects of Na+/H+ exchange inhibition by cariporide on death and nonfatal myocardial infarction in patients undergoing coronary artery bypass graft surgery: The EXPEDITION study. Circulation 108:3M
30. Fisher JW (2003) Erythropoietin: physiology and pharmacology update. Exp Biol Med (Maywood) 228:1–14
31. Cai Z, Manalo DJ, Wei G et al (2003) Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. Circulation 108:79–85
32. Calvillo L, Latini R, Kajstura J et al (2003) Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. Proc Natl Acad Sci USA 100:4802–4806
33. Moon C, Krawczyk M, Ahn D et al (2003) Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats. Proc Natl Acad Sci USA 100:11612–11617
34. Parsa CJ, Matsumoto A, Kim J et al (2003) A novel protective effect of erythropoietin in the infarcted heart. J Clin Invest 112:999–1007
35. Tramontano AF, Muniyappa R, Black AD et al (2003) Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway. Biochem Biophys Res Commun 308:990–994
36. Cai Z, Semenza GL (2004) Phosphatidylinositol-3-kinase signaling is required for erythropoietin-mediated acute protection against myocardial ischemia/reperfusion injury. Circulation 109:2050–2053
37. Lipsic E, van der MP, Henning RH et al (2004) Timing of erythropoietin treatment for cardioprotection in ischemia/reperfusion. J Cardiovasc Pharmacol 44:473–479
38. Parsa CJ, Kim J, Riel RU et al (2004) Cardioprotective effects of erythropoietin in the reperfused ischemic heart: a potential role for cardiac fibroblasts. J Biol Chem 279:20655–20662
39. Wright GL, Hanlon P, Amin K et al (2004) Erythropoietin receptor expression in adult rat cardiomyocytes is associated with an acute cardioprotective effect for recombinant erythropoietin during ischemia-reperfusion injury. FASEB J 18:1031–1033
40. Namiuchi S, Kagaya Y, Ohta J et al (2005) High serum erythropoietin level is associated with smaller infarct size in patients with acute myocardial infarction who undergo successful primary percutaneous coronary intervention. J Am Coll Cardiol 45:1406–1412
41. Brines ML, Ghezzi P, Keenan S et al (2000) Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. Proc Natl Acad Sci USA 97:10526–10531
42. Siren AL, Fratelli M, Brines M et al (2001) Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. Proc Natl Acad Sci USA 98:4044–4049
43. Ruscher K, Freyer D, Karsch M et al (2002) Erythropoietin is a paracrine mediator of ischemic tolerance in the brain: evidence from an in vitro model. J Neurosci 22:10291–10301
44. Ghezzi P, Brines M (2004) Erythropoietin as an antiapoptotic, tissue-protective cytokine. Cell Death Differ 11:S37–S44
45. Celik M, Gokmen N, Erbayraktar S et al (2002) Erythropoietin prevents motor neuron apoptosis and neurologic disability in experimental spinal cord ischemic injury. Proc Natl Acad Sci USA 99:2258–2263

46. Junk AK, Mammis A, Savitz SI et al (2002) Erythropoietin administration protects retinal neurons from acute ischemia-reperfusion injury. Proc Natl Acad Sci USA 99:10659–10664
47. Vesey DA, Cheung C, Pat B et al (2004) Erythropoietin protects against ischaemic acute renal injury. Nephrol Dial Transplant 19:348–355
48. Abdelrahman M, Sharples EJ, McDonald MC et al (2004) Erythropoietin attenuates the tissue injury associated with hemorrhagic shock and myocardial ischemia. Shock 22:63–69
49. Buemi M, Vaccaro M, Sturiale A et al (2002) Recombinant human erythropoietin influences revascularization and healing in a rat model of random ischaemic flaps. Acta Derm Venereol 82:411–417
50. Hirata A, Minamino T, Asanuma H et al (2005) Erythropoietin just before reperfusion reduces both lethal arrhythmias and infarct size via the phosphatidylinositol-3 kinase-dependent pathway in canine hearts. Cardiovasc Drugs Ther 19:33–40
51. Hanlon PR, Fu P, Wright GL et al (2005) Mechanisms of erythropoietin-mediated cardioprotection during ischemia-reperfusion injury: role of protein kinase C and phosphatidylinositol 3-kinase signaling. FASEB J 19:1323–1325
52. Baker JE (2005) Erythropoietin mimics ischemic preconditioning. Vascul Pharmacol 42:233–241
53. Rafiee P, Shi Y, Su J et al (2005) Erythropoietin protects the infant heart against ischemia-reperfusion injury by triggering multiple signaling pathways. Basic Res Cardiol 100:187–197
54. Bullard AJ, Govewalla P, Yellon DM (2005) Erythropoietin protects the myocardium against reperfusion injury in vitro and in vivo. Basic Res Cardiol 100:397–403
55. Alessi DR, Deak M, Casamayor A et al (1997) 3-Phosphoinositide-dependent protein kinase-1 (PDK1): structural and functional homology with the Drosophila DSTPK61 kinase. Curr Biol 7:776–789
56. Feldman RI, Wu JM, Polokoff MA et al (2005) Novel small molecule inhibitors of 3-phosphoinositide-dependent kinase-1. J Biol Chem 280:19867–19874
57. Cantley LC (2002) The phosphoinositide 3-kinase pathway. Science 296:1655–1657
58. Hausenloy DJ, Yellon DM (2004) New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. Cardiovasc Res 61:448–460
59. Datta SR, Dudek H, Tao X et al (1997) Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery. Cell 91:231–241
60. Juhaszova M, Zorov DB, Kim SH et al (2004) Glycogen synthase kinase-3beta mediates convergence of protection signaling to inhibit the mitochondrial permeability transition pore. J Clin Invest 113:1535–1549
61. Wang Q, Somwar R, Bilan PJ et al (1999) Protein kinase B/Akt participates in GLUT4 translocation by insulin in L6 myoblasts. Mol Cell Biol 19:4008–4018
62. Matsui T, Tao J, del Monte F et al (2001) Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in vivo. Circulation 104:330–335
63. Liu H, Zhang HY, Zhu X et al (2002) Preconditioning blocks cardiocyte apoptosis: role of K(ATP) channels and PKC-epsilon. Am J Physiol Heart Circ Physiol 282:H1380–H1386
64. Holmuhamedov EL, Jovanovic S, Dzeja PP et al (1998) Mitochondrial ATP-sensitive K+ channels modulate cardiac mitochondrial function. Am J Physiol 275:H1567–H1576
65. Shi Y, Rafiee P, Su J et al (2004) Acute cardioprotective effects of erythropoietin in infant rabbits are mediated by activation of protein kinases and potassium channels. Basic Res Cardiol 99:173–182

66. Tang W, Weil MH, Sun S et al (2000) K(ATP) channel activation reduces the severity of postresuscitation myocardial dysfunction. Am J Physiol Heart Circ Physiol 279:H1609–H1615

Chapter 23

Non-invasive haemodynamic monitoring: where we are in 2005

R. Muchada

Non-invasive haemodynamic monitoring tries to obtain information about performances and failures of the cardiovascular system without crossing the cutaneous–mucosal barrier of the organism.

Scientific interest in accessing this information appears to have started with the study of the arterial pulse characteristics. Some historical facts are linked to Egyptian medicine. They are recorded on the EBERT papyrus (museum of the University of Leipzig), and on the walls of the temple of Kom-Ombo, taking into account only two of the most widespread historical sources.

More recently, the Arabic physician Avicena (980–1037 AD) described in his book '*The Canon*' (a scholastic and dogmatic structure) the fundamental characteristics of pulse during the arrhythmic, hyper- or hypokinetic cardiac states.

The notions of pulsed cycles derive from the palpation of the arterial wall. Through the skin, variations of wall movements can be detected and even stopped with an external compression, allowing the subjective evaluation of arterial wall tension.

The first measurement of arterial pressure was carried out by Hales [1], who used an invasive system to measure the intra-carotid pressure in his mare. He could observe the oscillatory movements of the blood column filling the glass pipe used for the experiment. The oscillatory characteristics of the wave, produced by intermittent variations in blood flow, introduced the notion of a maximum pressure (systolic) and a minimum pressure (diastolic). Later, the notions of mean and differential arterial pressure were introduced, allowing conceptualisation of some haemodynamic notions, derivatives from arterial pressure values.

Research into less aggressive and non-invasive methods to measure the arterial pressure has led to the development of the arterial wall compression–decompression sequential and regulated method. The former, coupled with palpation of the pulse and using a manometric system, has allowed measurement of the systolic blood pressure.

The description by Korotkoff [2] of the noises linked to variations in the intra-arterial flow during a progressive decompression has facilitated acquisition of information about modifications in the systolic, diastolic and differential arterial pressure.

Finally, the possibility of detecting movements of the arterial wall using the oscillometric system, associating Gallavardin's double pneumatic cuff and Pa-

chon's oscillometer, opened the perspective of also measuring the mean arterial pressure.

The technical evolution has allowed integration of the ancient methods with new automatic systems, such as the Dynamap (Ramsey–Critickon, USA) for oscillometric measurement, the Doppler arterial cuff, adapted to the Korotkoff noises method (Abbott, USA) and even the ancient Penaz's pressure-measurement technique in the Finapress (Ohmeda, USA). This last system measures continuously and non-invasively at a digital level, the systolic, diastolic and mean and differential arterial pressure, with heart-rate recording and visualisation of the pulsed wave and data trends.

At the beginning of the twentieth century, the cardiac electrical exploration initiated by Eithoven gave access to a new dimension for non-invasive haemodynamic exploration.

Monitoring systems associating arterial pressure, heart rate and electrocardiographic (ECG) signals have become a classic bedside method for 'non-invasive monitoring'. They were generalised with the devices marketed by Hewlett Packard in the 1960s.

This kind of approach is popular even today, despite experimental and clinical studies on cardiovascular physiology and physiopathology and despite concepts repeated insistently by authors such as C. Bernard (France 1813–1878), B. Houssey (Argentina, Nobel Prize for Medicine 1947) and A.C. Guyton (USA 1919–2003). The interpretation of variations in arterial blood pressure (ABP) should take into account the fact that arterial pressure is a dependent parameter derived from two factors, namely blood flow (cardiac output, CO) and vascular resistance (VR).

$$\Delta ABP = \Delta CO \times \Delta VR$$

Without knowing the value of at least one of these two determinant factors, blood pressure measurements provide arbitrary information, conditioned by the clinic valuation and the experience of the practitioner. Even so, blood pressure remains one of the basic parameters to appreciate the haemodynamic state, in clinical practice, even today.

As measurement of vascular resistance is practically impossible, efforts have been concentrated on the development of techniques to measure blood flow, not only to increase interest on data obtained, but also to open new horizons in haemodynamic monitoring.

As long ago as 1896, Fick [3] introduced his method for intermittent measurement of CO, allowing the possibility of obtaining an integrated haemodynamic profile. But technical difficulties for daily utilisation of Fick's method did not allow it to be integrated as a monitoring technique for clinical usage.

In the mid-1960s, Kubicek [4, 5] worked on methods based on trans-thoracic bio-impedance variation. Daigele developed ultrasound techniques applied to the measurement of blood flow and later the 'indirect' Fick's method has caused a renewal in interest for non-invasive bedside monitoring devices.

The most common methods currently used in anaesthesia and intensive care are:

- Bio-impedance

- Ultrasound combining the echo scan and the Doppler effect
- The 'indirect' Fick's method.

Bio-impedance: summary of the method

The basis of this technique is the detection of the variation in intensity of an electrical current (resistance) passing through organic tissues (impedance). This electrical resistance variation is strongly influenced, at any moment in time, by the blood volume crossing the explored field, because the plasma is the body element presenting low electrical resistance (plasmatic resistance = 65 ohms/cm^3; total blood resistance = 130 ohms/cm^3; fat tissues and lung resistance = 300–500 ohms/cm^3). Trans-thoracic impedance therefore partially depends on the quantity of blood, varying with time, contained in the thoracic cavity.

Using a calculation to process rhythmical variations of the trans-thoracic impedance, it is possible to evaluate the stroke volume (SV). Multiplying this volume by the heart rate (HR), the CO value is obtained.

The use of the bio-impedance method supposes that the thorax is a relatively uniform electrical conductor, with a resistance depending essentially on the intra-thoracic blood volume and its cyclic variations. In a steady-state situation, this conductor would therefore have stable average impedance. This impedance will vary with the passage of blood into the thoracic cavity, which itself depends partially on the intra-thoracic aortic pulsed flow. The impedance variation during the left ventricle ejection time would give the SV, which, multiplied by the HR, determines the aortic blood flow (ABF) (Fig. 1).

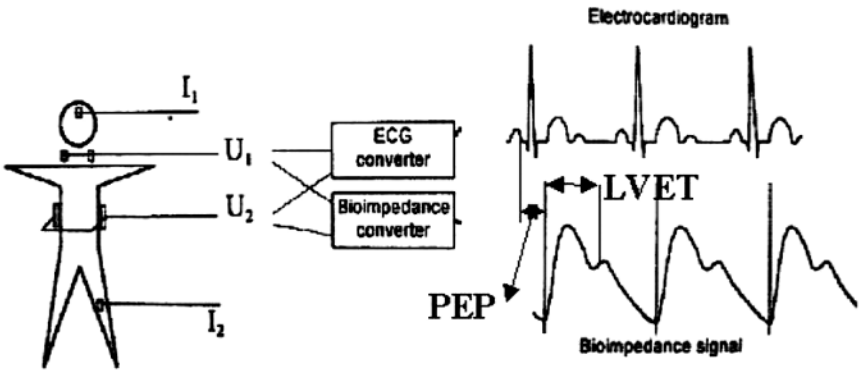

Fig. 1. The bio-impedance is a low-cost technique to monitor haemodynamics non-invasively, allowing a cardiovascular profile to be obtained. The detection of the Q wave on the ECG, coupled with bio-impedance variation signal, where the opening and the closing of the aortic valve are detected, facilitate the measurement of systolic time intervals. This information, integrated with the other data given for the bio-impedance method, permits an evaluation of modification of performance in the left ventricle

Limitations of the technique

This technique, although theoretically interesting because it is non-invasive and measures ABF in a continuous way, comprises a certain number of limits [6]:

- The impedance variation does not correspond only to left ventricle SV. Other factors can be involved (blood volume in the atriums, left ventricle, right ventricle, pulmonary vessels, intra-thoracic veins).
- The orientation of the red cell column can vary the thoracic resistance by up to 50% of the basic value.
- Thoracic cutaneous wounds, variation in hydration (interstitial or pulmonary oedema), cardiac arrhythmias, pacemakers, hyperventilation with high intra-thoracic pressure variations, are some other factors involved in the modification of the thoracic bio-impedance.
- The thoracic morphology and the disposition of explorer electrodes can also influence the impedance variation and the calculation of the SV.
- The correlation studies between bio-impedance, thermodilution or electromagnetic perivascular ring measurements are contradictory [7, 8].

Using the bio-impedance technique seems to be possible for the follow-up of the CO relative evolution and to obtain a haemodynamic profile, without pushing the criticism to the extreme, as done by Weil [9].

Echo Doppler aortic blood flow measurement: summary of the method

Using a Doppler transducer, and the approach of the Austrian physician Christian Johann Döppler (Salzburg 1803–1853), when the ultrasound emission frequency is known, by measuring the reception frequency of an ultrasound beam reflected over a particle moving across the beam, we can calculate the velocity of displacement of the particle. But, used alone, a Doppler system allows only measurement of the velocity of particles. A Doppler system alone does not measure flow. To determine the flow, we need to measure or calculate the section of the pipe or the vessel in which the particles are moving.

By definition, flow (Q) as a function of time (t) is equal to the section (S) multiplied by velocity (V).

$$Q(t) = S(t) \times V(t)$$

Currently, there is a preference among clinicians for using the trans-oesophageal probe for the ultrasound measurement of ABF, as proposed by Daigle [10].

Only one system currently marketed measures simultaneously the aortic diameter and calculates the section, together with blood velocity at the same anatomical region, to obtain flow (Hemosonic 100 Arrow, USA) [11]. If we consider that calculation of the section involves the square power of the diameter, for a determined velocity, an error in measurement can have extremely important repercussions on the calculation of flow. In the same way, an erroneous calculation of the

section of the vessels can introduce a great error in the ABF determination [12].

Advantages of the Hemosonic system include:

- The utilisation of a divergent Doppler beam allows practically the full transverse section of the aorta to be covered up to a diameter of 40 mm.
- An extremely thin echo beam pilots this divergent beam. When we visualise the echoes of the two walls of the aorta, we can be sure that the impact of the Doppler beam is oriented for a maximal exploration of the vessel surface (patent INSERM, US, Europe, Japan) [12].
- The system can be used in paediatrics (children from 3 to 15 kg body weight) [13].
- The flow is measured with objective markers, avoiding subjective appreciations. A modest but real haemodynamic profile can be obtained.

Despite these advantages, some difficulties persist, in particular:

- The necessity to ensure a good depth of introduction of the probe to avoid turbulence where the aorta crosses the angle of ultrasound impact.
- The non-integration of very rapid blood velocities (Fig. 2).

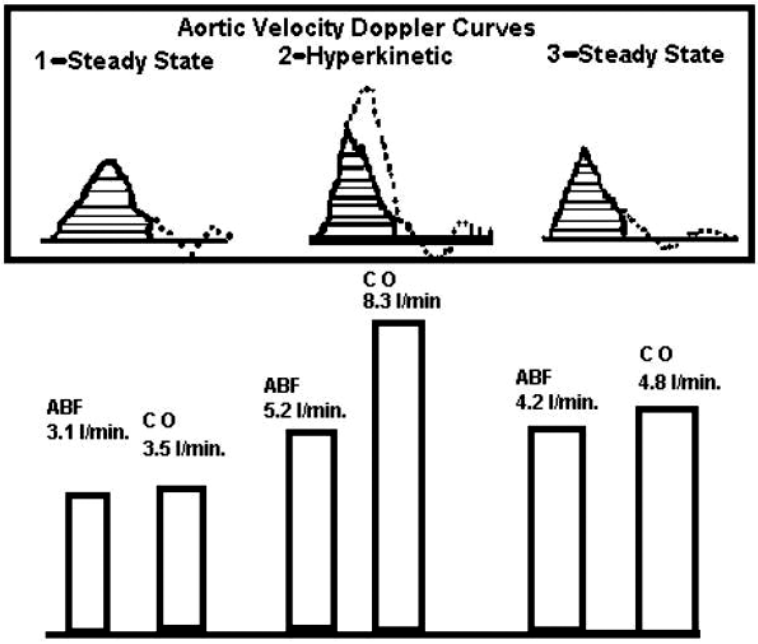

Fig. 2. When the aortic blood flow is measured with an echo Doppler system and when the intra-aortic high velocities exceed the Doppler measurement limits, an under-flow estimation can be made. The differences between echo Doppler (ABF) and thermodilution (CO) increase during a hyperkinetic (2) syndrome under 10 μg/kg/min of dobutamine. The relationship between ABF and CO returns to a 'normal' difference when dopamine perfusion is reduced at 4 μg/kg/min

- The limit imposed by pathological or anatomical problems (cyphoscoliosis, malformation, and coarctation of the thoracic aorta, oesophageal pathology, varices, diverticulum, hiatus hernia, and mega-oesophagus). In some cases, anomalies or oropharyngeal trauma forbid the introduction of a probe.
- It is difficult to use the system in awake patients or in particular conditions (aortic cross-clamping)

'Indirect' Fick method: summary of the method

In his postulate, Adolph Fick said that the quantity of O_2 taken up by the blood during its passage at the pulmonary level was equivalent to the volume of O_2 transferred through the alveolar capillary membrane. CO can then be calculated when O_2 consumption is measured and when CvO_2 and CaO_2 are calculated, requiring central venous and arterial blood samples.

But with a modification of the method, using an 'indirect' Fick principle with partial respiratory re-inhalation, as is currently used in the NICO device (Novametrix, Medical System Inc.), CO can be measured non-invasively [13, 14]. For this calculation, it is necessary that the patient be intubated and under controlled ventilation.

Every 3 min the NICO re-inhalation system (Fig. 3) is activated, for 50 s. Since during this period $PvCO_2$ does not vary, the value of $PetCO_2$ during open ventilation and during the re-inhalation period is assimilated to the value of $PaCO_2$. The variation of $PetCO_2$ between normal ventilation and the re-inhalation period allows calculation of the volume of eliminated CO_2 (VCO_2).

From all these elements, we can calculate the CO:

$$DC = VCO_2/CvCO_2 - CaCO_2$$

To obtain valid information, it is necessary to assume that CO, $CvCO_2$, alveolar ventilation and the gradient P (a–et) CO_2 remain constant during measurements.

Advantages of the technique

This method has the advantage of simplicity, because the connection of a transducer near the intubation probe and the use of a specific ventilatory circuit, allowing measurement of $PetCO_2$, are enough to obtain an absolute value of CO. Comparative measurements obtained with the NICO and other techniques have been made. Results seem acceptable to be used in clinical practice [15].

We can describe it as a non-invasive method because there is no break into the cutaneous–mucosal barrier, but the patient does need to have tracheal intubation and mechanical ventilation.

The simplicity of the system is therefore its principal factor, but, as for all monitoring techniques, there are some disadvantages.

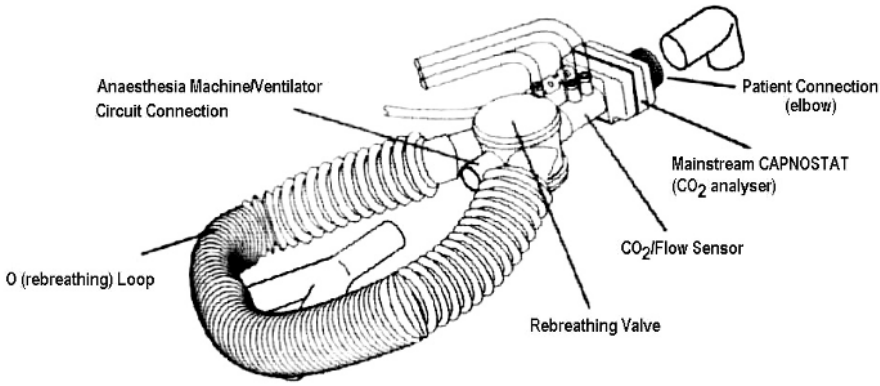

Fig. 3. The mainstream CO_2 analyser measures determine the $PetCO_2$. The CO_2 flow sensor integrates the total CO_2 volume exhaled. Finally, the automatic respiratory circuit allows intermittent re-breathing periods to be introduced, conditioning the measurement of the ΔpCO_2. With these parameters the calculation of CO by an indirect Fick method is possible. Unfortunately the price of the disposable circuit and some other limits (see text) linked to this technique diminish the practical interest of the method

Limitations of the NICO system

- An endotracheal probe is necessary.
- Some restrictive conditions have to be respected during the CO determination:
  – the patient has to be under controlled ventilation at a constant tidal volume, without spontaneous respiratory cycles
  – $PetCO_2$ has to be maintained between 15 and 70 mmHg
  – the respiratory rate has to be superior to 3 c/min
  – VCO_2 has to be between 20 and 500 ml/min
  – tidal volume has to be higher than 200 ml (this technique is not suitable for paediatric monitoring).
- As $PetCO_2$ is taken as the pivotal element, it is assumed that the stability of the gradient between $PaCO_2$ and $PetCO_2$ remains constant during the re-inhalation period. Stability could be modified by many circumstances, one of the most important of which is the sampling point of the gas for the determination of expired CO_2 [16].
- Variation in the intrapulmonary shunt can also alter CO measurement. In reality, the indirect Fick method measures only the pulmonary capillary flow implied in gaseous transfer. To appreciate the total pulmonary blood flow, it is necessary to use a correction factor, based on the shunt curves described by Nunn [17].
- It is therefore necessary also to monitor simultaneously SaO_2.
- Errors of measures can be increased for a $FIO_2 > 0.6$.
- The CO value can equally be erroneous when haemoglobin is < 9 g/100 ml or >16 g/100 ml.

- The administration of any product liberating CO_2 during measuring, such as bicarbonate, completely alters the results.
- Calculation of CO has to be made at least 3 min after the declamping of a large venous or arterial vessel (to avoid the CO_2 tissue wash-out phenomena).

Conclusions

After this analysis it seems that not one of the techniques on the market fulfils, in a precise and clear manner, the clinician's expectation. Three sectors could be rendered responsible for this:

1. The medical sector, through lack of training, information and interest.
2. The system inventors and developers, who have a tendency to increase the complexity, introducing a lot of low-interest functions, without taking into account the real needs of clinicians.
3. Commercial companies marketing the products; in general, when searching for a maximum profit, they do not risk sufficient investment in the development of already existing techniques, which could bring real solutions to some problems that have been known for a long time.

Is it therefore necessary to make a negative statement for the future of non-invasive cardiovascular monitoring? Certainly not.

Increasing our basic knowledge of the physiology and physiopathology will guide us to a clear and necessary understanding of the haemodynamic variations in the pathological contexts. This better understanding could drive us to obtain a correct system imbalance, compensating the alterations, as a result of monitored and oriented therapeutic action, according to the sequence, diagnosis, decision, monitoring, follow-up or rectification. And for this action haemodynamic non-invasive monitoring becomes a fundamental tool, allowing us, with the information obtained, to complete the clinical evaluation.

Even if nowadays an understanding of cellular molecular biology is becoming more and more important in diagnosis and therapeutic actions, we have to remember that cellular metabolism and biological processes need energy to proceed. Metabolic component transport and residual recovery are ensured for the cardiovascular system, when it maintains a correct tissue perfusion with a harmonic flow distribution. And this fact could be another main objective to be attempted in the future, associating cardiovascular monitoring with some other parameters (VO_2, VCO_2, etc.) to appreciate the quality of global or regional perfusion.

New therapeutic perspectives could be developed as a result of better understanding of the cardiac and vascular receiver specificity. Shouldered for an adapted non-invasive haemodynamic monitoring, a new strategy could be developed for the use of new agents or the association of already existing agents, looking for better modulation of the cardiovascular reactivity.

Finally, clinicians' interest in this kind of monitoring could be accelerated, thanks to technological improvements integrated in a simplified device that is easy

to use, with diagnostic and therapeutic soft orientations, helping the clinicians' decisions.

References

1. Hales S (1740) Statistical essays, containing: Haemastatics. The Royal College, London
2. Korotkoff MS (1905) On the subjects of methods of determining blood pressure. Bull Imperial Med Acad 11:367–371
3. Fick A (1870) Ueber tells messung the blutquantums in der herzenventrklen. Sitzung der Phys Med Gezell zu Wirzburg, July 9, p 36
4. Kubicek WG, Karnegis JN, Patterson RP (1966) Development and evaluation of an impedance cardiac output system. Aerosp Med 37:1208–1212
5. Kubicek WG, Kottke J, Ramos MU et al (1974) The Minnesota impedance cardiograph: theory and applications. Biomed Eng 9:410–416
6. Visser KR (1989) Electrical properties of flowing blood and impedance cardiography. Ann Biomed Eng 17:463–473
7. Castor G, Klocke PK, Stoll M et al (1994) Simultaneous measurement of cardiac output by thermodilution, thoracic electrical bioimpedance and Doppler ultrasound. Br J Anaesth 72:133–138
8. Shoemaker WC, Wo CC, Bishop MH et al (1994) Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. Crit Care Med 22:1907–1912
9. Weil MH (1997) Electrical bioimpedance for non invasive measurement of the cardiac output. Crit Care Med 25:1455
10. Daigle RE, Miller CW, Histand MB et al (1973) Non-invasive aortic blood flow sensing using ultrasonic esophageal probe. J Appl Physiol 38:1153–1160
11. Ultrasonic method and apparatus for flow measurement. Brevet USA No. 5.479.928 2/01/1996
12. Muchada R, Cathignol D, Fontaine B, Lavandire B (1990) Les données morphométriques permettent-elles de déterminer le diamètre de l'aorte thoracique pour une mesure précise du débit sanguin chez l'adulte? JEMU 11:76–80
13. Orr JA, Westenskow D, Kofoed S, Turner R (1996) A non-invasive cardiac output system using the partial rebreathing Fick method. J Clin Monitor 12:464–465
14. Gedeon A, Krill P, Kristensen J, Gottlieb I (1992) Noninvasive cardiac output determined with a new method based on gas exchange measurements and carbon dioxide rebreathing: a study in animals/pigs. J Clin Monit 1992;8:267–78
15. Jopling MW (1998) Noninvasive cardiac output determination utilizing the method of partial CO_2 rebreathing. A comparison with continuous and bolus and thermodilution cardiac output. Anesthesiology 89:A554
16. Jomain C, Tournadre JP, Boulétreau P, Chassard D (1997) Espace mort et gradient alvéolo artériel en COZ pendant l'anesthésie en ventilation contrôlée. Ann Fr Anesth Reanim 6:8359
17. Nunn JF (1993) Nunn's applied respiratory physiology, 4th edn. Butterworth Ltd, Oxford, pp 461–475

Chapter 24

Role of shock timing in cardiac vulnerability to electric shocks

B. Rodriguez, N. Trayanova, D. Gavaghan

Induction of ventricular fibrillation by an electric shock applied during the vulnerable window (VW) is rapidly becoming a standard clinical practice during implantation of internal cardioverter/defibrillators or postoperative defibrillation threshold testing. Furthermore, a large body of research has demonstrated that defibrillation failure and cardiac vulnerability to electric shocks are driven by the same mechanisms [1–3]. Therefore, understanding the mechanisms by which a shock applied during the VW results in arrhythmia is pivotal to optimising the clinical practice of defibrillation.

Recently, optical mapping and computer simulation studies have demonstrated that the outcome of the shock depends on the shock-induced virtual electrode polarisation (VEP) [4–6]. Shock-induced areas of negative polarisation represent excitable gaps through which postshock activations, generated at the borders between oppositely polarised areas, could propagate. Conversely, tissue strongly depolarised by the shock remains refractory for a significant period of time after the shock ends, blocking propagation of postshock activations. Only shocks applied during the VW result in re-entry. The goal of this study is to investigate, in the three-dimensional (3D) volume of the ventricles, the mechanisms of shock-induced arrhythmogenesis that underlie the existence of the VW.

Methods

We used the anatomically based rabbit ventricular model described in a previous study [7]. The model was generated from data by Vetter and McCulloch [8], which incorporate realistic geometry and fibre orientation, and included representation of the blood in the ventricular cavities and the perfusing bath. The electrical activity in the myocardium was simulated using the bidomain equations. The augmented Luo–Rudy dynamic model suitable for defibrillation was used to represent the kinetics of the ionic currents [9]. Simulations were performed using a semi-implicit finite element method with a variable time step as previously described [7].

The protocol for determining the vulnerability area has been described in a previous paper [10]. In brief, the rabbit ventricular model was paced at the apex at a basic cycle length of 250 ms. Truncated exponential monophasic shocks of 8-ms duration and 65% tilt were applied via two large planar electrodes located at the

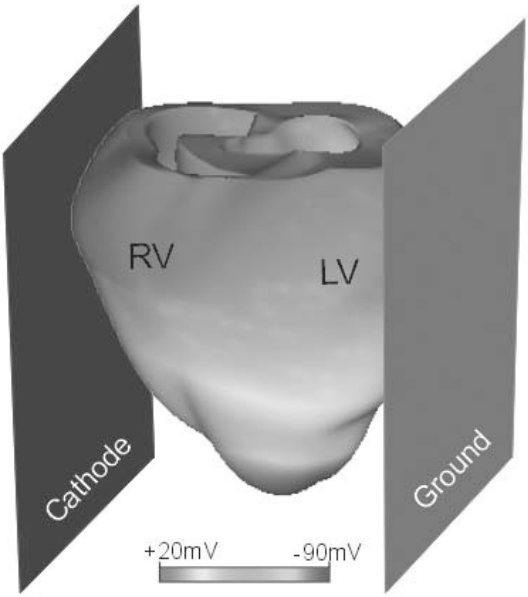

Fig. 1. Anterior view of the rabbit ventricular model with shock electrodes in the bath. Preshock transmembrane potential distribution corresponds to CI = 130 ms

vertical walls of the perfusing chamber (Fig. 1). The electrode near the right ventricle (RV) was the cathode, and the one near the left ventricle (LV) was a grounding electrode. Shock strength referred to the leading-edge value of the electric field between electrodes. The shock timing (coupling interval, CI) was defined as the time interval between the last pacing stimulus and the onset of the shock. Shocks of several strengths were administered at various CIs, in order to determine the lowest and highest CI (CI_{min} and CI_{max}) at which sustained arrhythmia was induced. The VW was estimated to be the interval in time between CI_{min} and CI_{max}. An arrhythmia was considered sustained if more than two beats were induced following the shock.

Results

In this study, the VW extends from CI_{min} = 120 to CI_{max} = 170 ms, and occurs for shock strength of 11.5 V/cm. The VW limits in our simulations are in close agreement with experimental results using a similar protocol and electrode configuration, where the VW extends from 116 ± 8.9 to 184 ± 16.7 ms [6]. In order to understand the mechanisms by which shock timing (i.e. CI) affects cardiac vulnerability to electric shocks, we analysed VEP and postshock electrical activity for shocks applied at CIs shorter than CI_{min}, CIs within the VW, and CIs longer than CI_{max}.

Figure 2 shows the transmembrane potential distribution at the time of shock

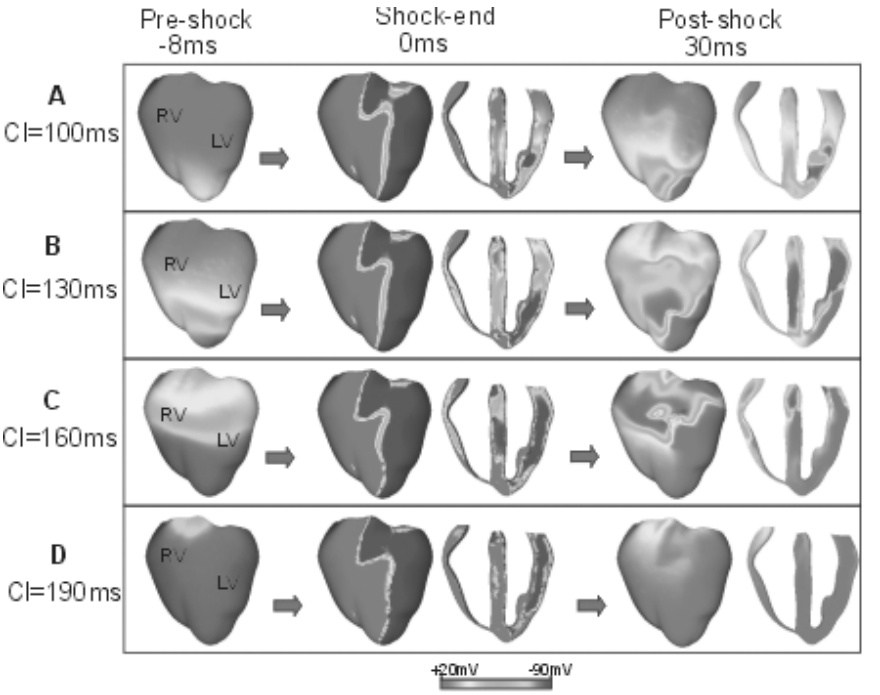

Fig. 2. Transmembrane potential distribution at time of shock delivery (*left*, epicardial view), at shock end (*middle*, epicardial and transmural views), and at 30 ms after the shock (*right*, epicardial and transmural views) for a 11.5 V/cm shock applied at CI = 100, 130, 160 and 190 ms in panels A, B, C and D, respectively. Colour scale is saturated, i.e. transmembrane potentials above 20 mV and below 90 mV appear red and blue, respectively

delivery (left panels, anterior epicardial view), at shock end (middle panel, anterior epicardial and transmural views), and at 30 ms post-shock (right panel, anterior epicardial and transmural views) for 11.5 V/cm shocks applied at CIs of 100, 130, 160 and 190 ms (panels A, B, C and D, respectively). As observed previously by optical recordings [5, 6], VEP on the epicardium is represented by two main areas of opposite polarisation and of nearly the same spatial extent: the RV epicardium, which is near the cathode, is positively polarised, while the LV epicardium is negatively polarised by the shock. In contrast to the surface VEP, transmural views in the 0 ms panels of Fig. 2 present a very complex shock-end distribution of transmembrane potential throughout the mid-myocardium, which strongly depends on the CI at which the shock is applied.

For CI < CI_{min} (e.g. CI = 100 ms, Fig. 2A), the ventricles are mostly depolarised at the time of shock delivery (left panel). At shock end, most of the myocardial tissue in the RV and the septum is positively polarised, and only tissue on the LV epicardium and in a small region close to the apex within the LV free wall is negatively polarised by the shock (middle panel). This finding is quantified in Fig.

3, which presents the amount of myocardial tissue experiencing potentials > +20 mV and < –90mV (calculated as a percentage of all nodes in the ventricular volume), plotted as a function of CI. For CI < CI_{min}, positively polarised tissue represents more than 33% of all myocardial tissue, while the percentage of nodes negatively polarised at shock end is less than 15% of all myocardial nodes. Following the shock end, the large amount of tissue strongly depolarised by the shock leads to blockade of propagation as it surrounds the wavefront, resulting in failure to induce arrhythmia. This is shown in the 30 ms panels of Fig. 2A and in Fig. 4A for the 11.5 V/cm shock applied at CI = 100 ms. After the shock, propagation starts at the apex (Fig. 4A, 12 ms panel) through the small postshock excitable area located within the LV free wall (Fig. 2A, transmural view in 0 ms panel). However, 20 ms postshock, the entire ventricles are refractory and the shock fails to induce arrhythmia (Fig. 4A, 20, 50 and 100 ms panels).

Increasing CI above CI_{min} (e.g. from CI = 100 ms to 130 ms and 160 ms) results in an increase in the amount of repolarised tissue at the time of shock delivery, which leads to two main changes in transmembrane potential distribution at shock end: first, the amount of tissue strongly depolarised decreases, particularly within the septum and the basal part of the LV wall; and second, the regions negatively polarised by the shock extend towards the basal part of the LV free wall (compare transmural images in 0 ms panel in Figs. 2A and 2B). Figure 3 shows that for CIs

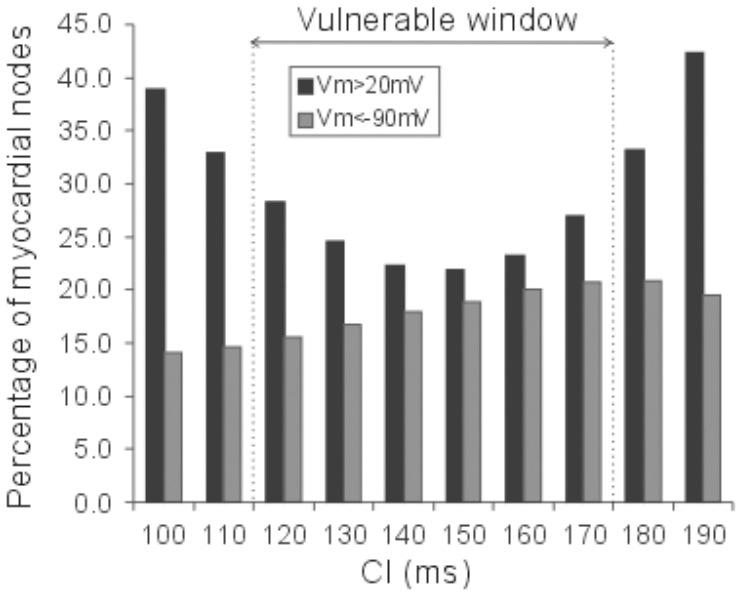

Fig. 3. Percentage of myocardial nodes that are of transmembrane potential above +20 mV (*black bars*) and below –90 mV (*grey bars*) at the end of 11.5 V/cm shocks applied at CIs in the range between 100 and 190 ms

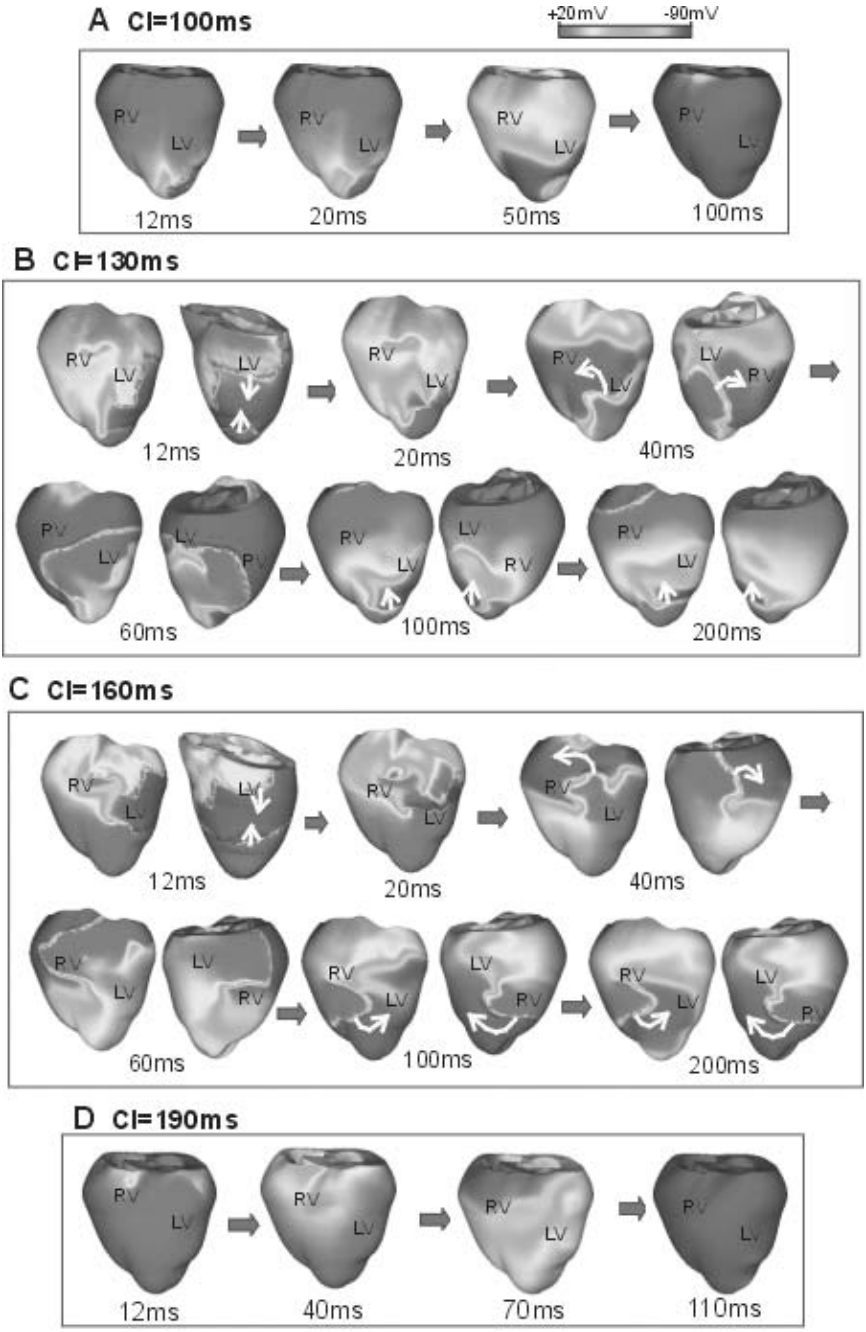

Fig. 4. Evolution of postshock electrical activity following 11.5 V/cm shocks applied at CIs of 100, 130, 160 and 190 ms in panels A, B, C and D, respectively. Colour scale as in Fig. 2

within the VW, the extent of tissue polarised above +20 mV is between 20 and 30% of total myocardial volume, while the regions polarised below –90 mV represent between 15 and 21% of total myocardial volume. As a consequence of these changes, for CIs within the VW (e.g. CI = 130 and 160 ms), large excitable areas within the LV wall are still present at 30 ms postshock (Figs. 2B and 2C, 30 ms panels), allowing propagation and ultimately, re-entry induction. Figures 4B and 4C illustrate postshock electrical activity during the first two cycles of re-entry for the shocks applied at CIs of 130 and 160 ms, respectively. Shortly after the shock, two wavefronts propagate through the LV free wall, while the septal and RV free wall tissue recovers (12 and 20 ms panels). When the two wavefronts collide within the LV wall, propagation continues through the anterior and posterior of the ventricles, first towards the septum and then towards the RV wall (40 ms panels). Two wavefronts engulf the RV, one propagating towards the base and the other towards the apex (60 ms panels). The wavefront that propagates towards the base dies out, surrounded by refractory tissue, while the wavefront propagating towards the RV apex re-enters through the LV free wall, closing the loop of the first cycle of re-entry (100 ms panels), and establishing a self-perpetuating re-entrant activity (200 ms panels). A figure-of-eight re-entry is induced, with two rotors, one counterclockwise and one clockwise, on the anterior and the posterior of the ventricles, respectively.

Figure 3 shows that for CI < 150 ms, while increasing CI leads to a decrease in the extent of the positively polarised areas, this trend changes for CI > 150 ms, where increasing CI results in an increase in the extent of the areas positively polarised by the shock (also, compare transmural views in 0 ms panels of Fig. 2). For CI > CI_{max}, the extent of tissue with V_m > 20 mV at shock end increases above 33% of total myocardial volume, while the percentage of myocardial nodes polarised below –90 mV remains between 19 and 21% (Fig. 3). For these long CIs, at shock end, positively polarised areas are induced in the main part of the RV and the septum, and around the main postshock excitable area located within the LV free wall (0 ms panel in Fig. 2D for CI = 190 ms). When the shock is turned off, propagation quickly proceeds through the postshock excitable regions located mostly in the LV free wall, but soon thereafter it is blocked, surrounded by strongly depolarised tissue (Fig. 4D, 12 and 40 ms panels, and Fig. 2D, 30 ms panel). Thus, for CI > CI_{max}, the shock fails to induce arrhythmia (Fig. 4D, 70 and 110 ms panels).

Discussion

In this study, we have examined, within the framework of the VEP theory, the role of shock timing in cardiac vulnerability to electric shocks, in order to determine the mechanisms underlying the existence of the VW. For this purpose, we conducted computer simulations using an anatomically based rabbit ventricular model with realistic fibre architecture that incorporates the non-linear kinetics of the membrane ionic currents. Bidomain simulations using this model have the ability to predict faithfully the VEP pattern and postshock electrical activity in the depth of the ventricular wall, not achievable by any imaging technique thus far. Therefore,

this model presents a unique opportunity to investigate the mechanisms underlying the existence of the VW by exploring the postshock electrical events that take place in the 3D volume of the ventricles.

Similar to previous studies [6], our results demonstrate that the mid-myocardium exhibits a complex shock-induced VEP, which is not predictable from the epicardial VEP. Furthermore, the effect of varying shock timing on VEP differs significantly in the mid-myocardium and on the epicardium. On the epicardium, the shock induces two large areas of opposite-in-sign polarisation of nearly the same extent for all CIs (Fig. 2, epicardial views in 0 ms panel). In contrast, in the depth of the ventricular wall, varying shock timing results in important changes in the extent and location of VEP (Fig. 2, transmural views in 0 ms panel). These changes ultimately determine the outcome of shocks applied at different CIs, and thus explain the existence of the VW.

Our bidomain simulations reveal that varying CI in the range 100–190 ms results in large changes in the extent of positively polarised areas of up to 93.2% (between 22 and 42.3% of total myocardial volume, see Fig. 3), while the extent of negatively polarised areas changes only by up to 48.6% (between 14 and 21% of total myocardial volume, see Fig. 3). These large changes in the extent of shock-end positively polarised areas are caused by the strong dependence of the septal transmembrane potential distribution on CI. For CIs outside the VW, the septal tissue is strongly depolarised at shock end and the total extent of the positively polarised regions represents more than 33% of total myocardial volume. Thus, a large amount of tissue, mostly in the septum and the RV free wall, remains refractory for tens of milliseconds after shock end, blocking propagation of postshock activations (Figs. 2A and 2D, and Figs. 4A and 4D). In contrast, for CIs within the VW, septal tissue is either negatively polarised by the shock (Fig. 2C), or it is weakly depolarised and thus it recovers shortly after shock end (Fig. 2B). Thus, for CIs inside the VW, following the end of the shock, propagation proceeds through the LV free wall and the septum, while the RV wall recovers, allowing the establishment of a scroll wave on each side of the ventricles with a common apical pathway (Figs. 4B and 4C). Therefore, our 3D simulations demonstrate that the shock-end septal transmembrane potential distribution plays a major role in the mechanisms underlying the existence of the VW.

Acknowledgements

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References

1. Chen PS, Shibata N, Dixon EG et al (1986) Activation during ventricular defibrillation in open-chest dogs. J Clin Invest 77:810–823
2. Chen PS, Feld GK, Mower MM, Peters BB (1991) Effects of pacing rate and timing of defibrillation shock on the relation between the defibrillation threshold and the upper limit of vulnerability in open chest dogs. J Am Coll Cardiol 18(6):1555–1563
3. Malkin RA, Idriss SF, Walker RG, Ideker RE (1995) Effect of rapid pacing and T-wave scanning on the relation between the defibrillation and upper-limit-of-vulnerability dose-response curves. Circulation 92(5):1291–1299
4. Efimov IR, Cheng Y, Van Wagoner DR et al (1998) Virtual electrode-induced phase singularity: a basic mechanism of defibrillation failure. Circ Res 82:918
5. Efimov IR, Aguel F, Cheng Y et al (2000) Virtual electrode polarization in the far field: implications for external defibrillation. Am J Physiol 279:H1055–H1070
6. Rodriguez B, Li L, Eason J et al (2005) Differences between left and right ventricular chamber geometry affect cardiac vulnerability to electric shocks. Circ Res 97:168–175
7. Trayanova NA, Eason JC, Aguel F (2002) Computer simulations of cardiac defibrillation: a look inside the heart. Comput Visual Sci 4:259
8. Vetter FJ, McCulloch AD (1998) Three-dimensional analysis of regional cardiac function: a model of rabbit ventricular anatomy. Prog Biophys Mol Biol 69:157–183
9. Ashihara T, Trayanova N (2004) Asymmetry in membrane responses to electric shocks: insights from bidomain simulations. Biophys J 87:2271–2282
10. Rodríguez B, Tice B, Eason J et al (2004) Cardiac vulnerability to electric shocks during phase 1A of acute global ischemia. Heart Rhythm 1(6):695–703

Chapter 25

Analysis of arterial pulse and ventricular devices

S. Scolletta, S.M. Romano, B. Biagioli

Cardiac transplantation is the ultimate surgical treatment for end-stage heart failure, but the chronic shortage of donor hearts has necessitated other surgical options. Mechanical circulatory support (MCS) systems are being used with increaing frequency to support patients with severe heart failure, and implantable ventricular assist system (VAS) are now available commercially for use as a bridge to transplantation, and as a bridge to recovery of myocardial function [1].

The first generation of VAS produces intermittent, or pulsatile, blood flow at physiologic rates, thus mimicking the normal circulation. Although the implantable VAS devices have been shown to be safe and effective, serious and frequent complications associated with their use persist [2]. New MCS devices are being developed in an attempt to provide more cost-effective systems with fewer complications. New MCS systems range from small intraventricular blood pumps (based on axial flow technology) that provide partial cardiac assistance to total cardiac replacement systems [1, 2]. To date, clinicians who treat the increasing number of heart failure patients can choose from a variety of extracorporeal and implantable circulatory support systems. Therefore, anaesthesiologists are now confronted more frequently with the specialised needs of patients who receive left ventricular assist devices (LVADs) [3–5].

Ventricular assist devices and blood flow

Some of the new VADs designs (HeartMate II, Jarvik 2000, DeBakey pump) are based on axial flow technology and provide continuous nonpulsatile blood flow. In contrast, an implantable pulsatile assist device provides intermittent blood flow at physiologic rates. Another significant difference is that the axial flow VAD provides submaximal blood flow from the left heart only, whereas a pulsatile VAD can provides total circulation to the systemic arterial system. The arterial blood pressure waveform and amount of blood flow provided by the axial flow pumps and the pulsatile VAD differ, as do the physiologic response of heart failure patients to each system. When using an axial flow pump for an LVAD, the flow wave changes with the native heart flow wave because the axial flow pump produces a nonpulsatile flow wave and the native heart produces a pulsatile flow wave. Therefore, if a nonpulsatile pump is used as an LVAD, a peripheral arterial flow probe will detect the flow wave that is generated by both the pulsatile and nonpulsatile flows.

The influence of nonpulsatile pumps on native heart function remains unclear, however, understanding the differences between these two systems (pulsatile and nonpulsatile) is important to ensure proper patient care and management [2].

Pulse wave analysis (PWA) can provide new insights into principles governing the function of VAD and may help optimise coupling between the LVAD and the vascular system. Nakata and colleagues analysed the LVAD's outflow waveform and calculated the pulsatility index (PI) and the pulse power index (PPI) to examine their relationship with LVAD output [6, 7]. The authors used a mock circulation system followed by an animal model, and then applied fast Fourier transform (FFT) to calculate the PI and the PPI. The PI is the sum of the square of its harmonic components divided by the square of the mean flow. PPI quantifies the relative power of a pulsatile waveform with respect to a nonpulsatile equivalent flow [8]. Similar to the first in vitro study, the authors then changed the LVAD rotational speed (and consequently the LVAD flow) and found that PI and PPI decreased exponentially with the increase of the assist ratio during left heart bypass with the LVAD [6, 7]. The pulsatility of the arterial blood pressure waveform during nonpulsatile LVAD implantation was quantified using the PI and PPI, and these seemed to be good indicators of arterial blood pressure waveform changes depending on changes in the pulsatility.

Even if the evaluation of the arterial blood pressure waveform using the FFT technique may be effective in estimating an ideal LVAD condition for clinical use, this method requires accuracy and a noise-free pressure signal. Minimal noise due to a movement or arrhythmia may produce a major distortion [6, 7].

Arterial pressure waveform monitoring and VAD

To manage patients with a VAD, assessment of the perfusion of vital organs (heart, brain, kidneys) is of great importance. Because the driving pressure immediately upstream from an organ determines its perfusion, aortic pressure determines perfusion of vital organs. The pressure waveform undergoes significant variations during LVAD, and it also undergoes significantly amplification toward the periphery. Thus, peripheral systolic pressure may be significantly higher than corresponding central aortic systolic pressure, such that usual monitoring of a peripheral artery (radial or femoral) in clinical practice may not reflect real end-organ perfusion [9]. This becomes particularly important in patients undergoing VAD insertion, who often have low cardiac output (CO) and multiorgan dysfunction as a result of severe ventricular impairment [5]. In those patients, a 'reassuring' measurement in the periphery may correspond to actual low-pressure values in the aorta. Another issue is that only the maximal and minimal values of peripheral pressure waveform usually are taken into account, thereby neglecting the contour of the waveform and losing the important information that it may convey [9]. In fact, when only peak systolic and nadir diastolic values are taken into account, we gain estimations of pressure fluctuations only for the systolic period. However, pressure augmentation during the diastolic period aids perfusion of coronary

arteries and may be particularly beneficial, as has been shown with intra-aortic balloon counterpulsation patients. To better interpret peripheral pressure recordings and to gain insight into central haemodynamics in patients on pulsatile LVAD, Vlachopoulos and colleagues used a valid non-invasive tonometric technique to analyse the arterial pulse wave [9, 10]. They chose an appropriate method to analyse peripheral pressure waveform and to generate the pressure waveform in the central aorta. Systolic and diastolic central aortic pressures were also calculated, along their integrals during the respective phases, which are indexes of perfusion of vital organs [9]. Vlachopoulos found that, after LVAD implantation, the assist device completely overrode native left ventricular function and was the sole source of pump output. Both radial and aortic pulse waveforms were substantially altered, and peak pressures were significantly improved. Most important, the reflected wave (from the peripheral to the central site) was responsible for a second systolic hump of the aortic waveform that corresponded to a more prolonged pump ejection. In contrast, in the radial artery the second peak was only slightly higher than the first, and thus did not alter the peak systolic value of the waveform [9].

Vlachopoulos and colleagues studied only two patients on pulsatile LVAD, and did not examine continuous and nonpulsatile VAD. The cardiovascular response of patients undergoing total implantable nonpulsatile VAD differs from intermittent (pulsatile) MCS in several important aspects. The physiology is unique in that flow is nonpulsatile and continuous. The left ventricle is offloaded and blood flow is provided throughout the cardiac cycle. Ideally, these pumps act as a true LVAD, functioning synergistically with the native pulsatility of the heart. However, if necessary, end-organ perfusion can be completely supported. Since axial-flow VADs provide positive continuous pressure and flow during systole and diastole, end-organ perfusion is further augmented. Moreover, diastolic blood pressure increases, systolic blood pressure remains unchanged, and the mean blood pressure increases. The pulse pressure is normally reduced during support with axial flow pumps, and the amount of blood flow through an axial flow pump depends primarily on the differential pressure across the pump [11]. As a consequence, the PWA in patients on VAD could be of great aid.

Cardiac output monitoring of patients on VAD

To manage patients with a VAD, assessment of the resulting left ventricular (LV) CO is of great importance in order to avoid low output syndrome, which remains one of the leading causes of death after MCS. In addition, although indirectly, LV-CO monitoring can provide an estimation of the remaining right ventricular function in patients on only right ventricular assist devices (RVADs), and it could be useful to determine the timing of weaning from right circulatory support [2].

Although several methods are available for CO estimation, many of them are either unsuitable for continuous measurement or inapplicable in subjects on MCS. Undoubtedly, flowmetry from the graft's outflow is considered as the gold standard method, but it is invasive and its use is limited to the intraoperative period.

Transoesophageal echocardiography (TEE) has emerged as the procedure of choice for evaluation of cardiac performance in patients on MCS. However, this technique depends mainly on an experienced operator and cannot be used continuously. Continuous thermodilution cardiac output (CCO) measurements have advantages over intermittent bolus thermodilution (ThD) technique because they provided continuous data. The CCO technique is used increasingly to monitor cardiac function in patients on LVAD [12]. However, since ThD-CCO incorporates a thermal coil integrated into the PAC, it cannot be used in RVAD patients due to indicator loss via the venous cannula of the pump [13]. Pulse contour methods (PCMs) derive the CO from analysis of the pressure waveform, and theoretically may have advantages over PAC-derived thermodilution measurements. PCMs provide a faster response time (beat-to-beat readout), and abrupt changes in CO resulting from blood loss, tamponade, mechanical device malfunction or inadequate setting may be detected more quickly than with ThD-CCO.

In a recent report, Wiesenack and co-authors described the reliability of a femoral pulse contour method (PiCCO, Pulsion Medical System) in a patient on a centrifugal right ventricular pump (BE Rotaflo, Jostra). The technique consisted of a modified setup with a left atrial catheter to inject an iced solution for calibrating the system [13]. The authors judged that the method was feasible for use in patients on a RVAD.

The PiCCO system requires calibration by reference bolus thermodilution via a central venous line to obtain a reference CO value, so it cannot be used in patients on RVAD due to loss of the injected cold indicator. Furthermore, the modified setup procedure of Wiesenack et al. could raise similar drawbacks in patients on LVAD and, as result, also cannot be used in patients on biventricular assist devices (BIVADs). Finally, since an iced solution must be injected with a left atrial catheter, the potential hazard due to air entrapment into the left heart cavities makes the method unsafe [13].

Recently, a less-invasive pulse contour method was developed [14–16]. This new CO monitoring system, called PRAM (pressure recording analytical method), is based on the analysis of the blood pressure profile changes derived from the radial artery (see Fig. 1 and Appendix). It allows beat-by-beat stroke volume (SV) monitoring and, using a transfer function, allows the peripheral pressure waveform to be analysed in order to generate the pressure waveform in the central aorta. Since PRAM does not require any external ThD calibration, it provides two major advantages: (1) a central venous line can be avoided, and (2) it continues to work in patients on RVAD and LVAD.

Pulse wave analysis by PRAM in a LVAD-implanted patient

We studied PRAM in a patient with severe cardiogenic shock who underwent axial flow LVAD implant. A pulmonary artery catheter (PAC) was placed for the CCO evaluation, and intraoperatively a transoesophageal echocardiography (TEE) probe was used to adjust the pump speed. An ultrasonic flow-probe was placed

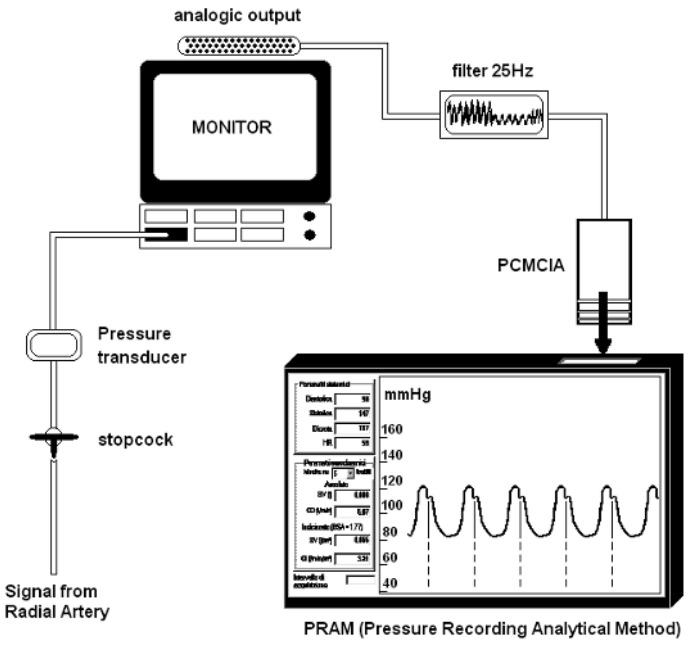

Fig. 1. PRAM (pressure recording analytical method) is connected to the analogic-output of the monitoring system for continuous non-invasive recording of the radial arterial pressure waves. The signals are acquired at 1000 Hz by means of an analogic-digital multifunction card (PCMCIA) and filtered at 25 Hz to avoid resonance effects caused by the catheter-transducer system without degrading the pressure wave amplitude. Beat-by-beat displayed PRAM-CO values (left side) and radial pressure waves (right side) are monitored using a personal computer. *Dotted lines* under the pressure curve represent the exact identification of the dicrotic notches

on the pump's outflow graft to verify flow rates against varying mean arterial pressure. PRAM was connected to the analogue-output of the monitoring system for non-invasive continuous recording and analysis of the radial artery pressure wave and the subsequent CO computation (Fig. 1). The axial flow pump speed was varied by increments or decrements of 1000 rotations per min (rpm) throughout the entire operating range to obtain aortic valve opening and the best flow-to-rate correlation on the basis of haemodynamic parameters. CCO, flowmeter-CO, and CO measures obtained by PRAM in the operating room after the end of cardiopulmonary bypass (CPB) were compared. CO comparisons are shown in Table 1.

PRAM measurements obtained from the radial artery overestimated flowmetry CO values. However, since PRAM analyses the pressure waveform of a peripheral artery (the radial or femoral artery), its CO estimations should represent the total amount of blood flow (blood flow generated by the axial flow plus the SV produced by the left ventricle). In this case, it is possible that PRAM determinations represent

Table 1. Cardiac output measurements by flowmeter, ThD, and PRAM

Axial-flow pump (LVAD)			ThD	PWA	Blood pressure
rpm	Flowmetry		CCO	PRAM-CO	ABP (mmHg)
8 000	2.3	3.4	3.7	76/60	(65)
9 000	2.8	3.5	4.5	76/62	(67)
10 000	2.8	3.6	4.9	74/63	(67)
11 000	3.0	3.7	5.1	71/65	(67)
12 000	3.1	3.6	4.9	70/66	(67)
10 000	2.9	3.5	4.7	72/64	(67)

Cardiac output (*CO*) values are in l/min; *LVAD*, left ventricular assist device; *rpm*, rotations per minute; *ThD*, thermodilution; *PWA*, pulse wave analysis; *CCO*, continuous cardiac output; *PRAM-CO*, pressure recording analytical method cardiac output; *ABP*, arterial blood pressure systolic, diastolic and (mean)

the true blood flow. With respect to flowmetry, a trend toward increased or decreased CO values was observed as the axial flow pump speed was varied. Since this method is based on the analysis of pulsatile flows, it is not expected to work in patients on axial flow pumps, which cause continuous blood flow throughout the cardiac cycle. With axial flow pumps, diastolic and mean blood pressures increase, and systolic blood pressure remains unchanged. This results in a reduction of pulse pressure (Table 1) and in the disappearance of the dicrotic notch due to aortic valve closure [5]. However, since some pulsatility in arterial pressure should always be present to avoid stasis in the aortic root and subsequent decreased coronary flow, the speed of the axial flow pump (in rpm) needs to be adjusted to allow the aortic valve to open [2]. In our patient, the aortic valve opened from 8 000 to 10 000 rpm (intraoperative TEE control). But despite the loss of ventricular ejection through the aortic valve at pump speeds over 10 000 rpm, PRAM continued to detect a peripheral pulsatile flow (Fig. 2). This may account for ventricular ejection through the axial flow pump. Most important, this PWA system is capable of identifying the dicrotic notch of the arterial wave during each cardiac cycle, and consequently is able to detect aortic valve opening. Therefore, PRAM may permit the pump speed to be adjusted when other monitoring systems are not disposable or when they cannot detect the dicrotic notch.

Conclusions

Measurement of CO is of crucial importance in patients on MCS, and continuous monitoring of SV allows physicians to avoid a detrimental low output state. LVAD implantation yields a unique opportunity to evaluate the accuracy of various monitoring systems in vivo because it provides a contemporaneous, independent, intravascular measure of CO. Moreover, in the presence of a LVAD, the flow wave changes with the flow wave of the native heart because the flow pump produces a nonpulsatile (or pulsatile) flow, and the native heart continues to produce a pulsatile flow wave. Understanding the differences between pulsatile and nonpul-

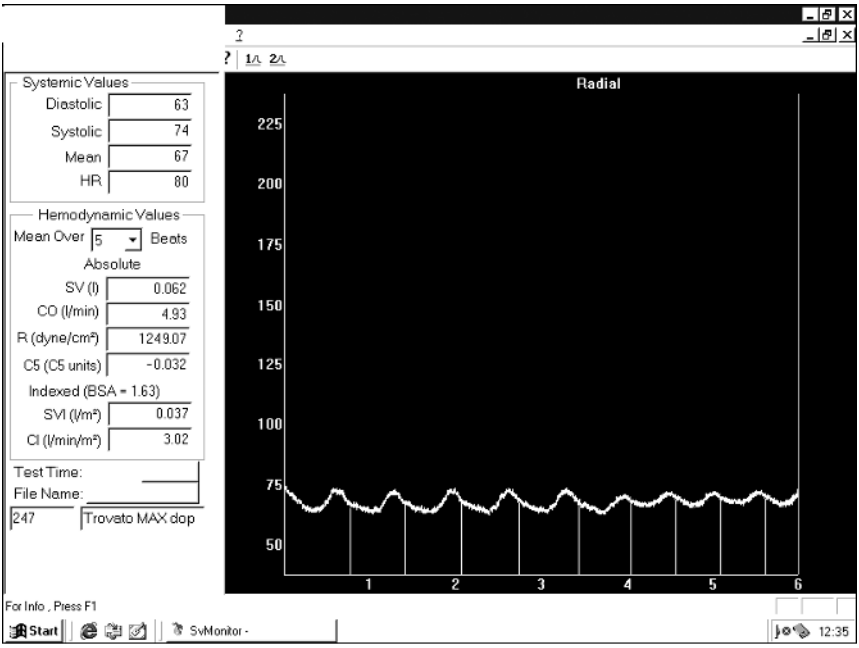

Fig. 2. Image of beat-by-beat online recording of radial artery pressure waveform by PRAM and the subsequent computation of CO. *Left* Haemodynamic parameters, *top* blood pressure values, *bottom* stroke volume, cardiac output and systemic vascular resistances averaged over the first five waves. *Right* Pressure waveforms non-invasively acquired by PRAM from the monitoring system. The first five waves were recorded at an axial pump speed of 10 000 rpm, the last four waves at 11 000 rpm. Although the aortic valve did not open at 11 000 rpm (echo control), PRAM continued to detect a pulsatile flow (see text for details)

satile devices is important to ensure proper patient care and management. Finally, pulse contour methods that allow beat-by-beat analysis of the arterial waveform could be helpful as additional continuous monitoring techniques in patients on circulatory support.

Appendix: basic physical principles of PRAM

The changes in volume that occur in all arterial vessels are mostly due to wall radial expansion in response to blood pressure changes. This depends on various physical factors, such as the force of cardiac contraction, the arterial impedance and compliance, and the peripheral resistance. With PRAM, the area under the pressure curve is measured in each cardiac cycle. At the same time the impedance (Z) is obtained from morphologic analysis of both the pulsatile and the continuous components of the pressure waveform. Briefly, according to PRAM, Z is equal to $(P/t) \times K$, and SV is calculated as follows (cm^3):

$$SV = \frac{A}{P/t \times K}$$ where:

A (mmHg × s) is the area under the systolic portion of the pressure curve; P/t (mmHg × s^{-1}) is a description of the pressure wave profile expressed as the variations in pressure (P) over time (t); K is a factor inversely related to the instantaneous acceleration of the vessel cross-sectional area ($s^2 \times cm^{-1}$) × ($1 \times cm^{-2}$). Cardiac output is computed by heart rate and SV [14, 16].

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References

1. Stevenson LW, Rose EA (2003) Left ventricular assist devices. bridge to transplantation, recovery, and destination for whom? Circulation 108:3059–3063
2. Myers TJ, Robertson K, Pool T et al (2003) Continuous flow pumps and total artificial hearts: management issues. Ann Thorac Surg 75:S79–S85
3. Metz B (2000) Anesthesia for left ventricular assist device placement. J Cardiothorac Vasc Anesth 14:316–326
4. Nicolosi AC, Pagel PS (2003) Perioperative consideration in the patients with a left ventricular assist device. Anesthesiology 98:565–570
5. Nussmeier NA, Probert CB, Hirsch D et al (2003) Anesthetic management for implantation of the Jarvik 2000 left ventricular assist system. Anesth Analg 97:964–971
6. Nakata K, Ohashi Y, Tayama E et al (1998) Estimation of the native cardiac output from a rotary blood pump flow: in vitro study. Artif Organs 22:411–413
7. Kawahito S, Takano T, Nakata K et al (2000) Analysis of the arterial blood pressure waveform during left ventricular nonpulsatile assistance in animal models. Artif Organs 24:816–820
8. Grossi EA, Connolly MW, Krieger KH et al (1985) Quantification of pulsatile flow during cardiopulmonary bypass to permit direct comparison of the effectiveness of various types of pulsatile and nonpulsatile flow. Surgery 98:547–54
9. Vlachopoulos C, McDonald P, Spratt P et al (2001) Pulse wave analysis in the assessment of patients with left ventricular assist device. J Heart Lung Transplant 20:98–102
10. Nichols WW, O'Rourke MF (1998) McDonald's blood flow in arteries, 4th ed. Edwards Arnold, London, pp 170–200, 450–476
11. Frazier OH, Myers TJ, Gregoric ID et al (2002) Initial clinical experience with the Jarvik 2000 implantable axial-flow left ventricular assist system. Circulation 150:2855–60
12. Mets B, Frumento RJ, Bennett-Guerrero E et al (2002) Validation of continuous thermodilution cardiac output in patients implanted with a left ventricular assist device. J Cardiothorac Vasc Anesth 16:727–730
13. Wiesenack C, Prasser C, Liebold A et al (2004) Assessment of left ventricular cardiac output by arterial thermodilution technique via a left atrial catheter in a patient on a right ventricular assist device. Perfusion 19(1):73–75
14. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30:1834–1841

15. Giomarelli P, Biagioli B, Scolletta S (2004) Cardiac output monitoring by pressure recording analytical method in cardiac surgery. Eur J Cardiothorac Surg 26:115–120
16. Scolletta S, Romano SM, Biagioli B et al (2005) Pressure recording analytical method (PRAM) for measurement of cardiac output during various haemodynamic states. Br J Anaesth 95(2):159–165

Chapter 26

Ventilatory-metabolic monitoring and analysis of arterial pulse

P. Giomarelli, E. Casadei, S. Scolletta

The assessment of cardiac output (CO) continues to challenge physiologists who study human endurance, clinical pharmacologists interested in the effects of treatment on cardiac output, and intensivists concerned with the measurement of oxygen consumption/oxygen delivery (VO_2/DO_2) dependency and the prevention of organ dysfunction or failure in haemorrhagic, cardiogenic, or septic shock. In clinical exercise testing, employed for the evaluation cardiac function in patients with chronic heart failure (CHF), the measurement of CO is mainly used to record the stroke volume in patients who have an unexpectedly high heart rate during exercise. A low stroke volume implies impaired cardiac function. If cardiac function is normal and output is high, the tachycardia is presumed to be due to impaired control of the peripheral circulation [1].

Arterial pulse contour analysis is very useful in the management of haemodynamically unstable patients, in whom inappropriate or delayed treatment can increase the risk of mortality and morbidity. This approach allows changes in CO and responses to vasoactive therapies, fluid resuscitation, or inotrope infusion to be recorded. Furthermore, among the various monitoring systems, arterial pulse contour is probably the most frequently used device to calculate CO, as it provides physicians with a wealth of information.

Stroke volume variation

Pulse pressure variation (PPV) and stroke volume variation (SVV) reflect central capacitor tone. Since the ratio of mean arterial blood pressure changes to SVV reflects arterial tone, such ratios could be used to continuously monitor arterial tone, a major determinant of cardiovascular performance. This approach has been criticised due to the fact that, during mechanical ventilation, positive pressure ventilation alters the arterial pressure power spectrum in the time domain, inducing phase-dependent changes in arterial impedance [2].

The pressure recording analytical method (PRAM) is a new system for real-time beat-to-beat quantification of peripheral blood flow. It provides point-to-point reconstruction of the aortic waveform from a peripheral arterial site, thus allowing SV to be calculated with no other prefixed parameter and avoiding inaccuracies derived from patient variability and instant variations of impedance [3, 4].

The capability to reconstruct the central aortic waveform from the radial artery with a proper transfer function facilitates more precise SV measurements and more accurate analysis of the dP/dT ratio. As a consequence, PRAM permits evaluation of both physiologic and drug-induced haemodynamic changes.

Figure 1 shows an example of beat-to-beat haemodynamic changes as monitored by PRAM in a patient with heart failure who underwent a dobutamine-stress test. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and dicrotic blood pressure (DicBP) values are shown at the top, while at the bottom stroke volume (SV) values are given. The patient had a history of heart failure and, before starting the dobutamine-stress test, he had sinus tachycardia (125 bpm), a blood pressure of 95/70, and a stroke volume of 30 ml/beat. After 10 μg/kg/min dobutamine administration, the HR and SBP increased by 20% with respect to baseline values, whereas DBP and DicBP remained unchanged. Of note, the SV did not show any increase, but instead was stable during the first part of the stress test and decreased shortly afterwards. The dotted vertical line indicates the start of dobutamine infusion.

Figure 2 shows the same variables as Fig. 1 (same patient). At the bottom, instead of stroke volume, the beat-to-beat dP/dT ratio, obtained by the pulse wave analysis with PRAM, is shown. The first portion of the arterial wave (anacrotic phase)

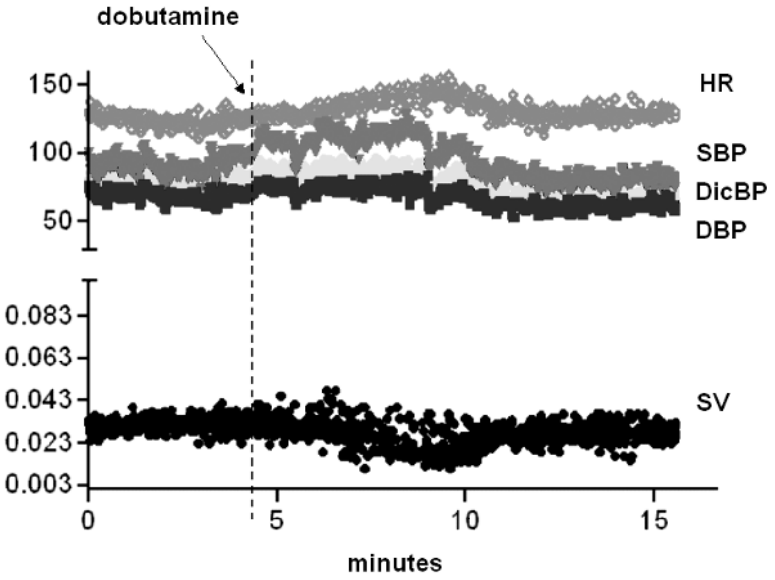

Fig. 1. Monitoring of beat-to-beat haemodynamic changes by pressure recording analytical method (PRAM) in a patient with heart failure who underwent a dobutamine-stress test (see text for further details). *Dotted vertical line* Start of dobutamine infusion. *HR*, heart rate; *SBP*, systolic blood pressure; *DicBP*, dicrotic blood pressure; *DBP*, diastolic blood pressure; *SV*, stroke volume

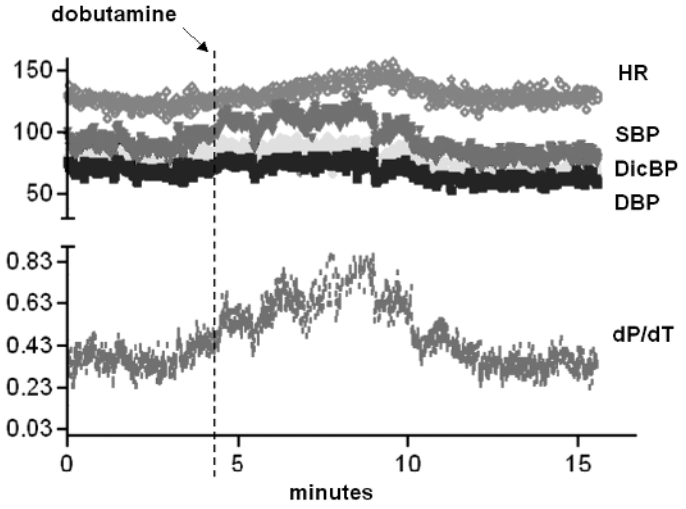

Fig. 2. *Top* Same variables as in Fig. 1 (same patient); *bottom* beat-to-beat dP/dT ratio obtained by pulse wave analysis with PRAM (see text for further details). *Dotted vertical line* Start of dobutamine infusion. *HR*, heart rate; *SBP*, systolic blood pressure; *DicBP*, dicrotic blood pressure; *DBP*, diastolic blood pressure; *SV*, stroke volume

represents the main index of myocardial performance and contractility. For this reason, analysis of the changes of that component of the waveform provides very useful monitoring in clinical practice [5].

Pulsatile phenomena and arterial stiffness, according to recent studies confirming the importance of arterial pressure in cardiac disease, seem to be in the foreground regarding diastolic and mean pressures in human adults. Arterial stiffness is not only a well-known risk factor of cardiovascular disease, but also a predictor of cardiovascular events; in addition, it has important haemodynamic consequences [6].

Ventilatory-metabolic monitoring in chronic heart failure

Despite recent advances in the treatment of patients with CHF, mortality in these patients remains high. Reliable risk stratification is a continuing challenge, as the number of candidates for heart transplantation is increasing and the supply of donor hearts is limited. The identification of patients at highest risk for early death is clearly of special importance. Increasing experience has confirmed the prognostic value of peak oxygen consumption (VO_2): the 24th Bethesda Conference for Cardiac Transplantation listed peak $VO_2 < 10$ ml/kg per min with achievement of anaerobic metabolism as an accepted indication for heart transplantation. Left ventricular ejection fraction (LVEF), NYHA class IV disease, and neurohormonal

markers are considered undisputable features in the diagnosis of CHF. At the same time, they have not been the subject of interest as valid risk predictor factors since they do not represent metabolic indexes [7].

Peak VO_2 might be underestimated due to reduced patient motivation as well as to premature termination of exercise by the examiner in spite of the recognised exercise end point: severe ventricular tachycardia of > 5 beats, high degree of AV block, ST-segment depression > 3 mm, systolic blood pressure > 250 mmHg, or a progressive decrease in blood pressure. The anaerobic threshold (VO_2AT) measures sustainable O_2 uptake and is an objective parameter that can be derived from submaximal exercise testing; it is therefore independent of patient and examiner motivation. During heavy exercise, or under pathologic conditions, an anaerobic component of metabolism causes lactate to increase significantly. This is accompanied by an almost equal reduction in bicarbonate concentration in the blood, resulting in accelerated CO_2 production and an increased respiratory CO_2 output. The threshold at which this begins is termed the anaerobic threshold (AT) and has been used as an effective gauge of physical fitness in patients with cardiopulmonary diseases, as well as in healthy normal subjects. Arterial lactate measurement is one way of detecting, during a period of increasing work or during a pathologic condition, the lactate threshold (LT). It is theoretically possible to detect an increase in blood lactic acid from the evaluation of CO_2 production, since bicarbonate is the major buffer of metabolic acids in body fluid. By visual inspection of a graphical plot of ventilatory equivalents, end tidal gas concentration, and respiratory exchange ratio, or using a computer-implemented method, it is possible to detect the AT. Either method is noninvasive and thus preferable for a wide range of applications and at reduced cost [8]. The ventilatory efficiency, measured as the slope of VE vs VCO_2 below the ventilatory compensation point for exercise metabolic acidosis, was found to be a reliable predictor of prognosis in patients with CHF. A VO_2AT < 11 ml/kg per min, and a slope of VE vs VCO_2 > 34, combined, was better able than peak VO_2 to identify patients at high risk for early death from CHF [7].

In conclusion, in patients with CHF, haemodynamic parameters are useful to detect pathophysiologic mechanisms of cardiac dysfunction and to titrate therapy. Metabolic evaluations, such as AT and VE vs VCO_2 slope, seem to be reliable predictors of mortality.

Ventilatory-metabolic monitoring in critically ill patients

Researchers have worked for many years to identify morbidity and mortality risk factors in intensive care patients and in those suffering from shock. For example, mortality following cardiac surgery is related to low cardiac indexes, while venous oxygen saturation (SvO_2) has been demonstrated to be a good predictor of the critical oxygen delivery (DO_2) point below which the VO_2/DO_2 relationship becomes dependent [9, 10].

CO and SV monitoring may indicate that a patient is probably close to passing the AT, but this can only be confirmed by measuring lactic acid levels. Beat-to-beat

monitoring of SV, as obtained with PRAM together with continuous pulse oximetry allows the DO_2 to be calculated. The detection of tissue hypoxia by measuring the arteriovenous gradient for pCO_2 and pH was validated as an approach many years ago [11]. The $\Delta PCO_2/Da\text{-}vO_2$ ratio seems to be the parameter that best identifies an anaerobic condition [12].

We studied 13 consecutive patients admitted to the intensive care unit (head injury, subarachnoid haemorrhage, major vascular surgery, sepsis). The end point was to validate DO_2 and the $DPCO_2/Da\text{-}vO_2$ ratio with respect to lactic acid values as possible indicators of tissue anaerobic metabolism. Data were collected at T1 (admission at ICU) and T2 (after 24 h). An inverse relationship ($R^2 = 0.61$; $P < 0.05$) between the arterial lactate values at T2 and the DO_2 index at T1 was found. As shown in Fig. 3, 75% of patients with a low DO_2I (< 300 ml/min/m^2) had lactic acid values greater than 1.5. Conversely, only 20% of patients (2 of 9) with a higher DO_2I (> 300 ml/min/m^2) presented high lactate levels. A correlation between DO_2I at T1 and lactic acid values at T1 was not found. This could have been due to the early evaluations of our study, but confirms that even if DO_2 could indicate the risk for anaerobic metabolism, it cannot certainly indicate the individual response to hypoxia. We found a good direct correlation ($R^2 = 0.60$; $P < 0.05$) between lactic acid values and the $DPCO_2/Da\text{-}vO_2$ ratio calculated at T1 (Fig. 3). The cut-off point for this ratio that classifies tissue anaerobic vs aerobic metabolism has been

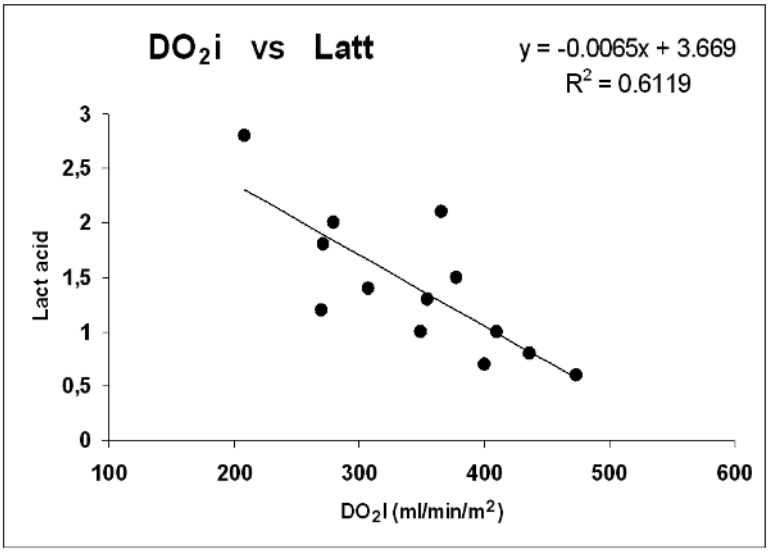

Fig. 3. Relationship between the oxygen delivery index (DO_2I), calculated at ICU admission, and lactic acid values, measured 24 h later. As shown, 75% of patients with a low DO_2I (<300 ml/min/m2) had lactic acid values greater than 1.5 (see text for further details)

demonstrated to be 1.4 [12]. It is firstly related to the increased CO_2 venoarterial gradient due to H^+ release, but is secondarily associated with the degree of the arteriovenous difference of oxygen, and is thus an index of tissue perfusion [12]. Figure 4 shows that seven patients had a DCO_2/avO_2 ratio of 1.4 at T1. Among these subjects, 85% (6 of 7) had lactic acid levels greater than 1.5.

An anaerobic component of metabolism causes lactate to increase significantly. This is accompanied by an almost equal reduction in the bicarbonate concentration in the blood, causing CO_2 production to accelerate, evidenced as an increased venoarterial differences and an increased respiratory CO_2 output. The threshold at which this begins is termed the anaerobic threshold and is evidenced 'in primis' by venoarterial differences in CO_2.

Usually, tissues reach the anaerobic threshold when the capillary PO_2, due to a DO_2 reduction, reaches a critical value at which lactic acid increases. However, that critical point has a wide range of values because of the capability of tissues to gain oxygen. The tissue capability of oxygen consumption can be represented as: $VO_2 = k \times A/L \times (Pc–Pm)$, where k is the diffusion coefficient for oxygen, a function of the diffusibility and solubility of oxygen in the tissue substance, Pc is the pressure point in the capillary, Pm the pressure point in the mitochondria, A is the surface area (degree of capillary hyperaemia), and L is the diffusion distance (capillary to mitochondria) [13].

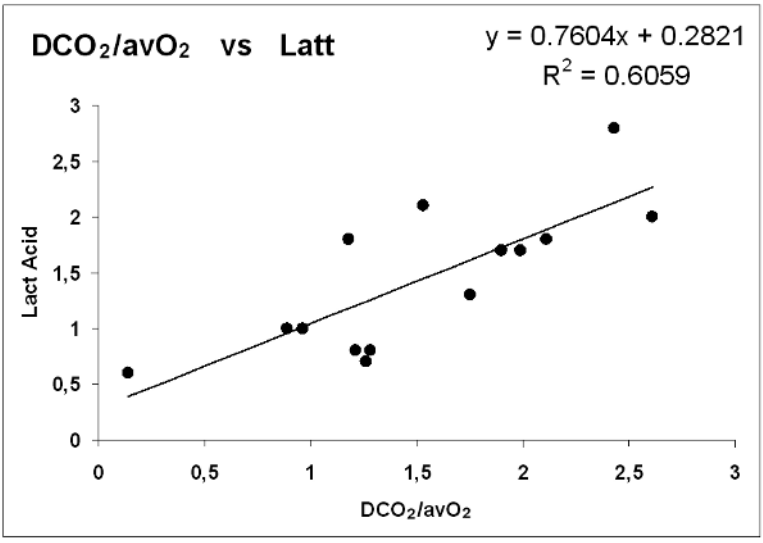

Fig. 4. Correlation between lactic acid values and the $DPCO_2/Da\text{-}vO_2$ ratio calculated at ICU admission. As shown, seven patients had a $DCO_2/avO2$ ratio of > 1.4. Among these subjects, 85% had a lactic acid level greater than 1.5 (see text for further details)

Conclusions

Pulse wave analysis and ventilatory parameters play key roles in the continuous monitoring of intensive care patients. Moreover, with these approaches, the patient does not require additional invasive procedures nor is extra time needed since peripheral arterial catheter insertion or mechanical ventilation are common procedures in the ICU. Undoubtedly, continuous CO measurements, together with the pulse oximetry are considered valuable methods to acquire information regarding oxygen delivery. However, even if CO constitutes the main indicator of low output syndrome (LOS), and subsequently of low oxygen delivery, the stroke volume should be considered a more precise 'marker' of LOS because it better reflects the pathophysiologic status of cardiovascular system with respect to tissue demand.

An increase in lactic acid means that: (1) the AT during the endurance test, and (2) VO_2/DO_2 dependence in critically ill patients have been reached. Since the $DPCO_2/Da\text{-}vO_2$ ratio measurement and the VCO_2 slope assessment with respect to the oxygen consumption are directly related to arterial lactate levels, their combined monitoring could represent a useful continuous technique to quickly disclose tissue anaerobic metabolism.

References

1. Laszlo G (2004) Respiratory measurements of cardiac output: from elegant idea to useful test. J Appl Physiol 96:428–437
2. Pinsky MR (2003) Probing the limits of arterial pulse contour analysis to predict preload responsiveness. Anest Analg 96:1245–1247
3. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in Humans. Crit Care Med 30:1834–1841
4. Giomarelli P, Scolletta S, Romano SM (2004). Analysis of arterial pulse—clinical implication. In: Gullo A (Ed) APICE 19. Springer, Milan, pp 417–423
5. Romano SM, Lazzeri C, Chiostri M et al (2004) Beat-to-beat analysis of pressure wave morphology for presymptomatic detection of orthostatic intolerance during head-up tilt. J Am Coll Cardiol 44(9):1891–1897
6. Arnett DK, Evans GW, Riley WA (1994) Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol 140:669–682
7. Gitt AK, Wasserman K, Kilkowski C et al (2002) Exercice anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 106:3079–3084
8. Beaver WL, Wasserman K, Whipp BJ (1986) A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60:2020–2027
9. Kirklin JR, McGiffin DC (1987) Early complications following cardiac surgery. Cardiovasc Clin 17:321–343
10. Polonen P, Ruokonen E, Poyhonen M et al (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059
11. Van der Linden P, Rausin I, Deltell A et al (1995) Detection of tissue hypoxia by

arteriovenous gradient for PCO_2 and pH in anaesthetized dogs during progressive haemorrhage. Anesth Analg 80:269–275
12. Mekontso-Dessap A, Castelain V, Anguel N et al (2002) Combination of venoarterial PCO_2 difference with arteriovenous O_2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 28:272–277
13. Koike A, Kobayashi K, Adaki H et al (2001) Effects of dobutamine on critical capillary PO_2 and lactic acidosis threshold in patients with cardiovascular disease. Chest 120:1218–1225
14. Denault A, Belisle S, Babin D et al (2002) Difficult separation from cardiopulmonary bypass and delta PCO_2. Can J Anaesth 48(2):196–199

Chapter 27

The assessment of cardiac performance in critically ill patients

C. Sorbara, A. Rossi

Essential to the management of any haemodynamically unstable patient is rapid assessment of the determinants of cardiovascular insufficiency, followed by appropriate specific therapies aimed at stabilising cardiovascular status and reversing the initiating processes. It would be very useful in everyday clinical practice to be able to calculate those indexes that discriminate between changes in preload and afterload and changes in contractility. The management of severely septic patients would be enhanced if haemodynamic changes caused solely by changes in preload and afterload could be separated from those caused by alterations in contractility. Within this context, the goal of cardiovascular therapy is to create a physiological condition wherein blood flow and oxygen delivery to the tissues are adequate to meet the varying metabolic demands of the tissues, without inducing untoward cardiorespiratory complications.

The incidence of cardiac problems is more than 50% in ICU patients, and the most frequent cause of impaired cardiovascular failure in critically ill patients is pump failure. Several aetiologic factors of pump dysfunction have been studied: myocardial ischaemia, septic cardiomyopathy, inflammatory responses, right ventricular (RV) failure with pulmonary hypertension, and a combination of several factors. Although left ventricular (LV) function is the determining parameter in various pathophysiologic conditions, the role of the RV in critically ill patients should not be underestimated, both for its ventricular interdependence effect and for RV failure as the primary cause of cardiovascular failure.

Haemodynamic variables have been well-studied and validated, but the possibility of early and specific monitoring of these parameters improves the time factor and the quality of intervention. Quick assessment and early treatment, with the possibility of titration of adequate therapy, allow a greater physiological response to therapy, prevent secondary subcellular damage due to persistent hypoperfusion (mitochondrial dysfunction), and are likely associated with improved survival [1, 2]. In the clinical assessment of cardiac function, especially in critically ill patients in whom rapid fluid shifts occur, such as hypovolaemic or distributive shock, crucial is the early detection of LV/RV systolic and/or diastolic dysfunction, by sensitive, reliable, and simple cardiovascular monitoring systems.

In this direction, echocardiography and Doppler ultrasonography have become important tools for the diagnosis and monitoring of cardiovascular problems. The impact of echocardiography on changes in the therapy and management of hospi-

talised patients was found to be as high as 57%, although changes occurred more frequently in ICU patients than in those admitted to the hospital (54% vs 37%, respectively) [3]. Particularly, transoesophageal echocardiography (TEE) with Doppler imaging, owing to its bedside availability, facilitates the routine diagnosis and management of cardiovascular failure, both intraoperatively and in ICU patients.

Moreover, in combination with echocardiography imaging, technical developments have provided several additional tools, derived by arterial pulse contour analysis, for functional and dynamic cardiovascular monitoring with on-line, beat-to-beat information about the cardiovascular system, such as stroke volume variations (SVV), pulse pressure variations (PPV), systolic pressure variations (SPV), and aortic flow variation (AFV). This extensive monitoring ability allows the rapid and rationale evaluation of functional cardiovascular performance, and provides answers to these clinical questions: How and by how much do the positive or negative changes of preload influence cardiac output in my patient? In the presence of systemic hypotension, what is the contribution of a loss of vascular tone vs inadequate blood flow? To what extent can the cardiac pump maintain an effective blood flow with a good perfusion pressure without the patient going into failure (cardiac reserve) [4]?

To comply with this functional approach, haemodynamic monitoring must be integrated into a concept of volume, pressure, and flow monitoring, using a combination of several technologies, so that key information about haemodynamic assessment is significantly augmented.

Cardiac performance

Left ventricular systolic performance is governed by four major determinants: (1) the Frank-Starling mechanism (pump output vs preload), necessitating the measurement of pressures and volumes; (2) afterload; (3) contractility, independent of loading conditions; (4) heart rate.

Preload

There is clinical and physiologic evidence that cardiac performance is influenced by preload. In order to optimise ventricular performance, preload must be adjusted to the appropriate level, also in the failing heart. Traditionally, several pressures have been used to assess preload, such as central venous pressure (CVP), pulmonary artery diastolic pressure, and pulmonary artery wedge pressure (PAWP), as indexes of filling pressures, and therefore as an estimation of preload, although preload is defined as the end-diastolic fibre length. While these parameters, even if indexes, offer good approximation of preload under physiological conditions, in critically ill patients, with different cardiovascular status and modified intrathoracic pressures, such as occur in mechanically ventilated patients, they are poor guides to estimate LV preload and its changes, without simultaneous assessment

of volumetric parameters. However, although indirectly estimating filling pressures, TEE nonetheless offers relevant information in this respect by Doppler interrogation of pulmonary venous flow and transmitral flow, and the relationship between the systolic, diastolic, and atrial contraction components of these flows. Moreover, Doppler pulmonary and transmitral flow, together with tissue Doppler imaging (TDI) of the ventricular wall, provide other, specific information about diastolic LV function, which is a fundamental aspect of a comprehensive haemodynamic assessment.

TEE permits good qualitative and quantitative assessment of volumetric estimation of preload in patients with either normal ventricular function or dysfunction. Quantitative estimation can be done in different ways using two-dimensional echocardiography. In a mid-oesophageal long-axis view in a longitudinal plane, four- or two-chamber, it is possible to evaluate LV end-diastolic volume (LVEDV) in agreement with Simpson's rule (methods of discs), which is an extremely well-validated technique. The LV end-diastolic area (LVEDA), measured per definition at the mid-papillary level of the LV, in the transgastric short-axis view, correlates well with volumetric analogues. Suggestive for low filling status of the LV is the LVEDA index, which refers to a body surface area, of $\leq 5.5\ cm^2/m^2$, a 'kissing walls' sign, or a linear decline of LVEDA of 0.3 cm^2 per percentage blood loss in hypovolaemic patients with normal function [5].

However, several limits and drawbacks exist for measurement of LVEDA, especially as a single parameter, when there is impaired global or regional LV dysfunction or a valvular pathology. In this case, a more accurate assessment of volume loading may be possible only with multiple measurements of LVEDA, filling pressures, and cardiac output after a fluid challenge.

Over the last several years, the fluid responsiveness concept has underlined the dynamic aspect of the preload parameter: since the gold standard for preload-responsiveness is an increase in cardiac output in response to volume expansion, 'physiologic volume expansion' trials may be used to ascertain preload-responsiveness. According to this approach, obligatory small changes in ventricular filling, induced by positive-pressure ventilation, as well as the small increase in venous return induced by leg raising or Trendelenburg position can be evaluated using the dynamic changes of cardiac (stroke) volume to predict preload-responsiveness. Beat-to-beat changes in LV stroke volume can be easily monitored by arterial pulse contour analysis as beat-to-beat changes in SVV, changes in SPV, and beat-to-beat changes in arterial PPV, since the only other determinants of pulse pressure, arterial resistance, and compliance cannot change enough to alter the pulse pressure during a single breath. If SPP or SVV are 15% more than the baseline pulse pressure for a normal tidal breath, then an increase in cardiac output in response to fluid challenge could be predicted [6, 7]. Since the primary determinant of arterial pulse pressure is the phasic aortic flow, which is generated by the heart's contraction with each beat, AFV, measured by transoesophageal 2-D echocardiography pulsed Doppler of the aortic outflow tract (LVOT) [8], can also be used to determine preload responsiveness and subsequent change in cardiac output in response to treatment. The rationale of the concept of 'fluid responsiveness' implies

that the entire cardiac circuitry in the chest, from the RV and pulmonary circulation to the LV, will transpose all the variation in venous flow rate. If this were not the case, as will occur in patients with selective RV failure, tamponade or LV failure, then no change in pulse pressure can occur. Importantly, these are exactly the conditions in which intravascular fluid loading can cause worsening of clinical status.

Afterload

Systemic hypotension is always pathological, as physiologic mechanisms normally keep central arterial pressure constant to maintain coronary and cerebral perfusion, despite a widely varying cardiac output. Moreover, the relationship between arterial pressure and regional blood flow is both non-linear and different among vascular beds: a primary vasoplegia may induce blood flow redistribution and/or frank ischaemia in specific organs (brain, heart, gut, kidney), even with a normal or supranormal cardiac output [9]. Nonetheless, the presence of peripheral vasoconstriction with systemic normotension does not imply a stable cardiovascular state and could compensate a condition of unknown cardiac failure.

Clinically, it is common practice to use the indexed systemic vascular resistance (SVRI) as a steady-state global measure of afterload, with the 'physiologic' limitation that this approach fails to account for the effect that ventricular geometry has on the load imposed on the myocardium (stress wall). To assess the effective arterial tone, in order to titrate therapeutic approach, it is more useful to know the ratio between the beat-to-beat phasic changes in blood pressure (MAP) vs the beat-to-beat phasic changes in blood flow during the cyclic variation induced by positive-pressure ventilation. If arterial tone is increased, then for the same variation of stroke volume the increase in variation of blood pressure (MAP) would be proportionally greater; and the contrary holds in case of decreased arterial tone. If MAP is replaced by arterial pulse pressure, then the large-vessel arterial tone can be assessed with the beat-to-beat ratio between PPV and SVV (pulse contour analysis) or AFV (TEE) [10].

Ventricular function

With TEE and Doppler echocardiography, it is relatively easy to rapidly estimate load-dependent parameters of global ventricular function, such as ejection fraction (EF), stroke volume (SV), cardiac output and, in the presence of mitral regurgitation, the positive maximum first derivative of pressure, corrected for time (dP/dt_{max}).

Another Doppler-derived index of myocardial performance (MPI) has been described by Tei [11]. The MPI incorporates both systolic and diastolic indexes of ventricular performance, is independent of ventricular geometric dimensions, and is free from any necessity to link to pressures data. It is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT),

corrected for the ejection time (ET) [MPI = (ICT + IRT)/ET]. The great advantage of this index is the simplicity by which MPI can be obtained, although its preload and afterload independence is still under debate [12].

Unfortunately, none of the above indexes, arterial pressure included, gives a true and specific indication of the performance of the cardiac pump. The ideal measure of ventricular performance, as an independent parameter of cardiovascular function, must be performed by a beat-to-beat assessment of the systolic pump, independent from load conditions and useful both as an index of contractility and as an index of ventricular functional reserve, because knowing the degree of contractile reserve is important in preventing and assessing a subject's response to different conditions of haemodynamic stress (weaning from mechanical ventilation, surgery, sepsis, etc.).

Complex derived measures have been used in experimental medicine to assess cardiac contractility. These measures, although accurate, are impractical in the clinical routine monitoring and management of critically ill patients due to their complexity and invasiveness.

The slope of the LV end-systolic pressure–volume (P–V) relation (E_{es} or end-systolic ventricular elastance), measured during progressively altered cardiac loading conditions, is still considered as the gold standard for assessing LV contractility, independent of preload and afterload [13–15]. Its clinical application, however, is limited by technical difficulties associated with instantaneous volume measurements, by the necessity of complicated off-line analysis, and by medical and ethical limitations related to the required episodes of load alterations.

A more physiologic approach to haemodynamic assessment together with the innovative technology of new monitoring systems, specifically echocardiography and arterial pulse contour analysis, may provide better tools for a clinical on-line approach to the concept of cardiac performance [16, 17].

In the cardiovascular system, which can be considered as a hydraulic system, the heart works as a pump to circulate the blood into both the pulmonary and systemic circulation. In hydraulic systems, the force is usually measured as pressure, the work as the product of pressure and volume, and the power as the product of pressure and flow. The cardiac muscle provides the energy necessary for this circulation, dispersing more energy as the blood proceeds further, into peripheral vascular beds (hydraulic energy). The effort performed by the ventricle to pump the blood against gravity and to overcome the inertia and the viscosity of blood can be described as 'ventricular work'. Thus, cardiac hydraulic power output (PWR), i.e. the work per unit time, is the product of cardiac flow output and its pressure delivered in the arterial system [18, 19]. The PWR provides the best representation of the performance obtained in a single cardiac cycle to counterbalance the demand imposed by metabolising tissues on the cardiac pump. In cardiogenic shock, baseline cardiac power is obviously low; when there is a condition of heart failure, measurement of PWR at rest and after the administration of positive inotropic stimulation provides insight into the cardiac energetic reserve [20].

In clinical practice, combining arterial pressure tracing and flow (measured as velocity), obtained with continuous-wave Doppler echocardiography through the

aortic valve, allows acquisition of all the data necessary for beat-to-beat PWR estimation.

In the absence of mitral regurgitation, ventricular flow during systole equals aortic flow, hence PWR can be described as the product of instantaneous aortic pressure and instantaneous aortic flow, where the maximal value (PWRmax) is obtained by the analysis of instantaneous data of pressure and flow, and by their product during ventricular ejection ($PWR_{max} = P_{ao} \times V_{aomax} \times AVA \times 1.333 \times 10^{-4}$), where P_{ao} is instantaneous aortic pressure, and V_{aomax} is instantaneous maximum aortic blood flow velocity, AVA is the time-averaged aortic valve area and PWR_{max} is the maximum PWR (in Watts) [21]. Unfortunately, this index (PWR_{max}) is dependent on contractility; while it shows great stability concerning changes in afterload, it is otherwise highly dependent on preload. Therefore, several authors have proposed to decrease this load dependence by normalising PWR_{max} for the square of the end-diastolic volume (EDV), with the resulting index of contractility, 'preload-adjusted maximal power' (PAMP), independent from load status and available by beat-to-beat measurements [22]. In clinical conditions, instantaneous aortic pressure is arterial blood pressure at the time point at which the product of pressure and flow is at the maximum. Although PAMP has these appealing characteristics, there is still an important limitation to its use in clinical practice, because a series of off-line, time-consuming analyses are necessary to obtain PAMP.

In the practical clinical setting, it is possible to assess an index of contractility, load-independent, based on the same concepts, with the same value and validity but easier to compute. This is done by: (1) estimating the ventricular power not as the instantaneous maximal product of pressure and flow but as the product of peak systolic pressure and peak flow normalised for preload ($LVEDV^2$), with the resulting index 'preload-adjusted peak power' (PAPP), and (2) combining the following data from echocardiography and arterial pressure: the aortic valve area (Fig. 1a); the peak velocity of aortic flow and the peak systolic pressure or the mean arterial pressure (Fig. 1b); and the LVEDV, estimated as volume (Fig. 1d) or area (Fig. 1c) [23, 24].

The clinical attractiveness of determining cardiac power by PAPP, which seems to be the least invasive method, is high because the integrity of the heart in relation to the circulation (ventriculoarterial coupling) can be assessed on-line, beat-to-beat. Moreover, the peak power provides an objective parameter of the severity of heart failure, and it has been validated as a predictive index in patients with heart failure [25].

Conclusions

Cardiovascular insufficiency is a complex process in which several physiologic and pathophysiologic adaptive mechanisms are involved and correlate with each other.

An analysis of the recent literature shows that several promising advances have been made using new monitoring systems, such as arterial pulse contour analysis [26–28] and TEE. These can dissect out, in the assessment of beat-to-beat on-line

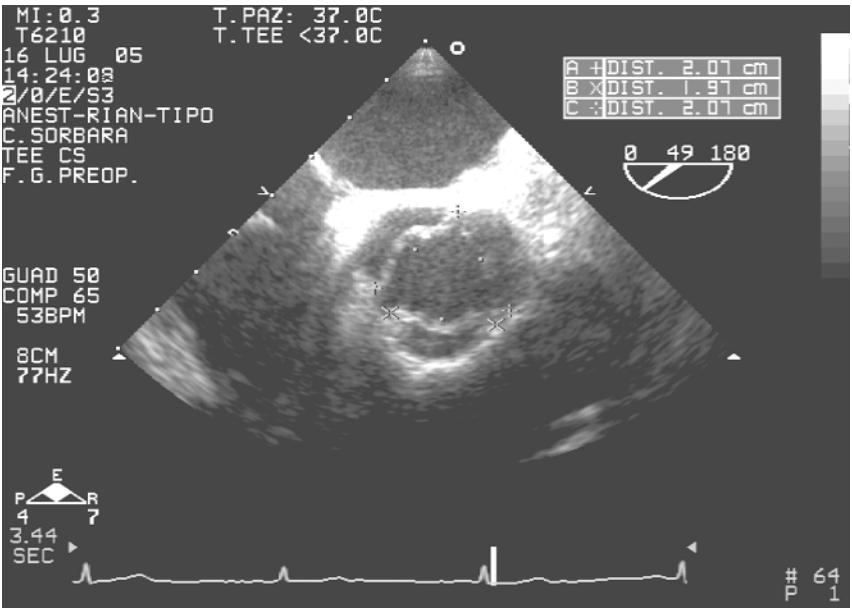
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Fig. 1a

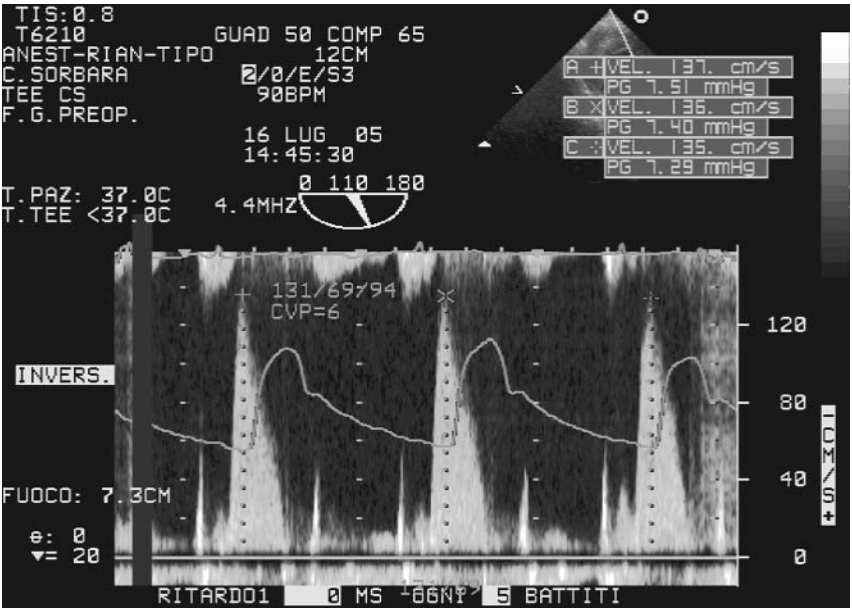
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Fig. 1b

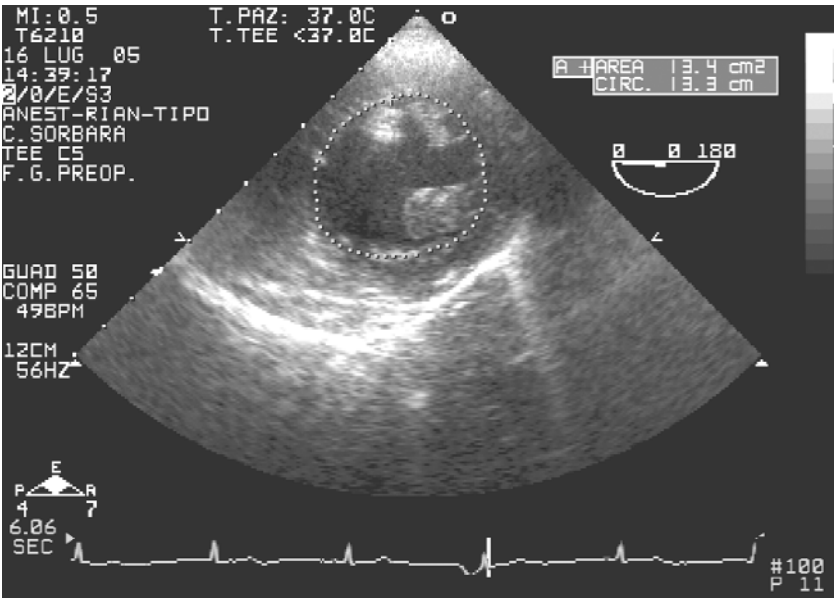


Fig. 1c

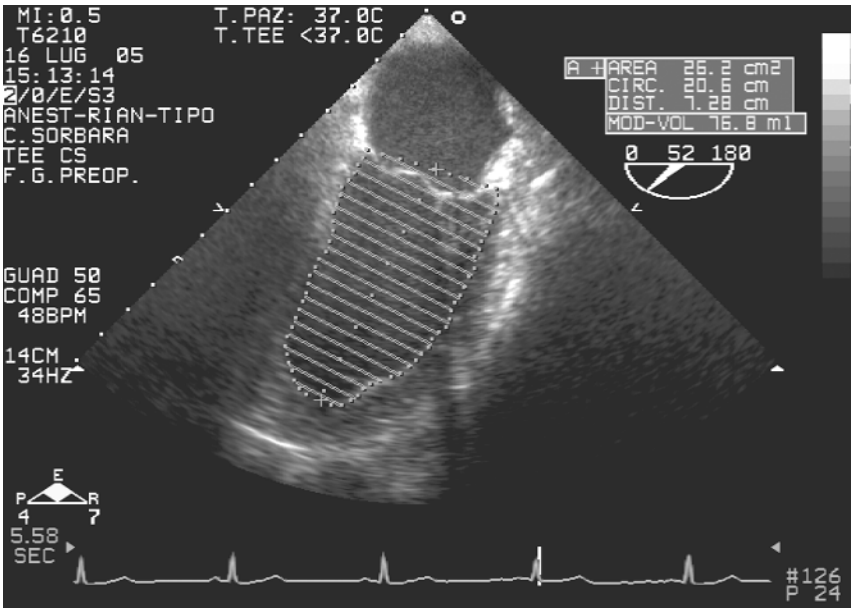


Fig. 1d

Fig. 1a–d. Transoesophageal echocardiography recordings from a sample patient. (**a**) Short-axis image of the aortic valve. The aortic opening appears as an equilateral triangle. (**b**) Continuous-wave Doppler echocardiography at the level of the aortic valve. The blood flow velocity is given in cm/s. (**c**) Short-axis view of the left ventricle: manual calculation of end-diastolic area. (**d**) Two-chamber view of the left ventricle in a longitudinal plane. Semi-automatic calculation of left ventricular volume according to Simpson's rule

cardiac performance, preload responsiveness, arterial tone, as well as load-independent cardiac performance and cardiac pumping reserve. It might be speculated that the endpoints of haemodynamic management, which have traditionally focused on improving cardiac output [29], will be integrated with both the enhancement of cardiac reserve, through a quick and specific diagnosis and an articulated treatment of the multiple aspects of cardiovascular performance, and the optimisation of perfusion at the tissue and cellular levels.

References

1. Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
2. Gattinoni L, Valenza F, Carlesso E (2005) 'Adequate' hemodynamics: a question of time? In: Pinsky MR, Payen D (eds) Functional hemodynamic monitoring, vol 42. Update in intensive care and emergency medicine. Springer, Berlin, pp 69–86
3. Vignon P, Mentec H, Terrè S et al (1994) Diagnostic accuracy and therapeutic impact of transthoracic and transesophageal echocardiography in mechanically ventilated patients in the ICU. Chest 106:1829–1834
4. Pinsky MR (2002) Functional hemodynamic monitoring: applied physiology at the bedside. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine 2002. Springer, Berlin, pp 537–552
5. Cheung A, Joseph S, Weiss S et al (1994) Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology 81:376–387
6. Michard F, Boussat S, Chemla D et al (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
7. Michard F, Teboul JL (2002) Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 121:2000–2008
8. Feissel M, Michard F, Mangin I (2001) Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 119:867–873
9. Schlichtig R, Kramer D, Pinsky MR (1991) Flow redistribution during progressive hemorrhage is a determinant of critical O2 delivery. J Appl Physiol 70:169–178
10. Pinsky MR (2005) Protocolized cardiovascular management based on ventricular-arterial coupling. In: Pinsky MR, Payen D (eds) Functional hemodynamic monitoring, vol 42. Update in intensive care and emergency medicine. Springer, Berlin, pp 381–395
11. Tei C (1995) New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 26:396–404
12. Tei C, Nishimura R, Seward JB et al (1997) A noninvasive Doppler-derived myocardial performance index : correlation with simultaneous measurements of cardiac catheterisation measurements. J Am Soc Echocardiogr 10:169–178
13. Sagawa K (1981) The end-systolic pressure-volume relation of the ventricle: definition, modification, and clinical use. Circulation 63:1223–1227
14. Suga H, Sagawa K (1974) Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 35:117–126
15. Suga H, Sagawa K, Shoukas AA (1973) Load independence of the instantaneous pres-

sure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 32:314–322
16. Snell R, Luchsinger P (1965) Determination of the external work and power of the left ventricle in intact man. Am Heart J 69:529–537
17. Stein P, Sabbah H (1976) Rate of change of ventricular power: an indicator of ventricular performance during ejection. Am Heart J 91:219–227
18. Milnor W (1990) The heart as a pump. In: Milnor W (ed) Cardiovascular physiology. Oxford University Press, New York, pp 111–139
19. Tan T (1991) Evaluation of cardiac dysfunction, cardiac reserve and inotropic response. Postgrad Med J 67:S10-S20
20. Marmor A, Raphael T, Marmor M, Blondheim D (1996) Evaluation of contractile reserve by dobutamine echocardiography: non-invasive estimation of the severity of heart failure. Am Heart J 132:1196–1201
21. Schmidt C, Roosens C, Struys M et al (1999) Contractility in humans after coronary artery surgery: echocardiographic assessment with preload-adjusted maximal power. Anaesthesiology 91:58–70
22. Kass DA, Beyar R (1991) Evaluation of contractile state by maximal ventricular power divided by the square of end-diastolic volume. Circulation 84:1698–1708
23. Amà R, Claessens T, Roosens C et al (2005) A comparative study of preload-adjusted maximal and peak power: assessment of ventricular performance in clinical practice. Anaesthesia 60:35–40
24. Armstrong GP, Carlier SG, Fukamachi K et al (1999) Estimation of cardiac reserve by peak power: validation and initial application of a simplified index. Heart 82:357–364
25. Marmor A, Schneeweiss A (1997) Prognostic value of noninvasively obtained left ventricular contractile reserve in patients with severe heart failure. J Am Coll Cardiol 29:422–428
26. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30:1834–1841
27. Giomarelli P, Biagioli B, Scolletta S et al (2004) Cardiac output monitorino by pressare recording analytical method in cardiac surgery Eur J Cardiothorac Surg 26:515–520
28. Scolletta S, Romano SM, Biagioli B et al (2005) Pressure recording analytical method (PRAM) for measurement of cardiac output during various haemodynamic states Br J Anaesth 95:159–165
29. Shoemaker W, Appel P, Kram H et al (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. Chest 94:1176–1186

Chapter 28

Haemodynamic monitoring of septic patients with pressure recording analytical method: preliminary observations

G. Tulli, S.M. Romano, R. Feminò

Sepsis is defined as a complex and dynamic inflammatory response of the host to a suspected, probable or actual infection [1, 2]. Severe sepsis is sepsis with one or more organ dysfunctions. The infectious stimulus provokes release of flogistic mediators, which determine activation of polymorphonuclear cells, macrophages and other cells involved in the different immuno-response pathways and induce modifications in endothelial and myocardial cell properties.

Since the mid 1950s, it has been known that sepsis induces profound derangements in cardiovascular function. More recently, information acquired on the functional state of the microcirculation in intestine, liver and skeletal muscle has shown that sepsis induces profound changes in microvascular geometry, haemodynamics and oxygen transport.

Cardiocirculatory dysfunction during sepsis is due to three main haemodynamic alterations: (1) relative hypovolaemia and consequent hypotension, (2) dysfunction of the cardiac pump (cryptic cardiac failure), (3) abnormal microvascular oxygen transport with dysfunctional regulatory mechanisms and dramatically altered cellular environments and mitochondrial dysfunction.

The profound vasodilatation of the peripheral circulation, in septic patients, may reduce the systemic vascular resistance (SVR) to a quarter of the normal value. This event is not uniform in all areas and cannot be due to a simple increase in vessel calibre.

The term 'vasoplegia' has been proposed to identify paralysis of the rhythmic vasomotion of smooth muscle cells. However, this definition seems to be inappropriate: small vessels, in septic patients, still exhibit vasomotion, even if its pattern is modified [3] and vascular beds are less responsive to sympathomimetic pressor agents (down-regulation).

Decreased microvascular flow results in a maldistribution of red blood cells (RBC) within the microcirculation and a mismatching of local oxygen delivery with oxygen demand. The remaining functional capillaries compensate for decreased functional capillary density by off-loading more oxygen to the surrounding tissue; nevertheless, increased oxygen flow heterogeneity seemingly impairs oxygen extraction by increasing critical oxygen delivery and decreasing the critical oxygen extraction ratio. The loss of capillary blood flow may strengthen the effects of

proinflammatory mediators by increasing their residence time in the microcirculation and tissue.

The potent vasodilator nitric oxide (NO) plays an important, complex [4] role in microvascular homoeo-dynamics. NO has been indicated as the main effector for vasodilatation during sepsis. NO is produced from l-arginine by the inducible form of nitric oxide synthase (iNOS), which is expressed after an inflammatory response to infection. During sepsis, over-production of NO has been associated with blood pressure decrease, impaired microvascular reactivity, abnormal RBC deformability, decreased functional capillary density and reduced oxygen consumption.

Beside vasodilatation, another relevant event is endothelial discontinuity (induced and maintained by inflammatory mediators), which contributes to modify hydrostatic and oncotic pressures, creating a more significant hypovolaemia by means of a fluid transfer from the circulation to the interstitium, with consequent oedema and hypovolaemia.

Systemic inflammatory response syndrome involves even the myocardium. In spite of a normal or increased cardiac index (CI), it has been demonstrated that contractility is altered with a severely depressed left ventricular ejection fraction (EF) [5]. Paradoxically, patients with a moderate or severe depression of EF showed a higher survival rate in comparison with other patients with only mild EF alterations [6]. Echocardiographic investigations identified an early diastolic dysfunction with a decreased filling time and altered relaxation of myocardial fibres [7].

The functional status of the pulmonary circulation is less well defined. Unlike the systemic circulation, pulmonary vascular resistances are increased due to hypoxic vasoconstriction and peribronchiolar oedema (non-cardiogenic oedema) during acute lung injury and acute respiratory distress syndrome [8]. However, it seems that dilatation and EF decrease (independently from afterload) are a characteristic pattern of right ventricle function (similar to the left ventricle) and the entity of such alterations is related to survival rate [9].

In summary, myocardial depression during sepsis is linked to a reversible dilatation involving both ventricles with decreased EF and decreased response to catecholamine administration (both in the presence of a hyperdynamic circulation). Sepsis is a dynamic and complex disease; the dynamism of sepsis can progress to septic shock (a severe cardiovascular dysfunction) and then death as the result of an irreversible process.

Therefore, in relation to death (end point) and the flowing time during the continuum of sepsis–severe sepsis and septic shock, three haemodynamic patterns can be defined: two patterns of early death and one of late death. Early deaths can be attributable both to a distributive shock with lowered SVR and refractory hypotension, even in the case of preserved CI, and to a cardiogenic form of septic shock (decreased CI). Late death is mainly caused by multiple organ failure (MOF) and, in spite of previous studies and observations, with a persisting hyperdynamic circulation [10, 11].

The intrinsic complexity and dynamic specificity of sepsis, together with consolidated evidence that early therapeutic interventions heavily determine survival

rates, require early diagnosis and dynamic and effective monitoring. This represents the only way to really 'tailor' a specific therapy for each patient.

Haemodynamic monitoring using thermodilution

Haemodynamic monitoring during sepsis needs to be reviewed in depth. Still today, thermodilution (ThD) is the most commonly used method of determining cardiac output (CO). It has been used for 20 years since its development with the catheter described by Ganz and Swan [12] .

The catheter can provide the measurement of pulmonary artery pressure and pulmonary capillary wedge pressure, really a better measurement of filling pressure in respect to central venous pressure (CVP). CVP can be considered neither as a reliable volaemic status index nor a fluid response parameter, expecially in the presence of heart and lung co-morbidities. To date, haemodynamic monitoring with a pulmonary artery catheter (PAC) has been shown to be inadequate, static, and not to contribute to substantially modify therapeutic strategies and the prognosis of septic patients [13, 14]. The insertion of a PAC involves an invasive procedure associated with several risks and complications [15]. Moreover, PAC and its ThD method-derived measures have been criticised because of their poor reliability and invasivity [16]. Errors in measurements may be introduced by rewarming the injectate before injection and by heat loss during measurement [17–20].

Collectively, these factors have prompted efforts to develop alternatives to the ThD technique and to measurement of pulmonary capillary wedge pressure. Several authors have investigated transoesophageal echo Doppler and pulse-contour methods (PCMs) [21–24].

Pressure recording analytical method

More recently, a system of pulse-contour analysis that is completely new in its developmental philosophy and less invasive has been developed and tested: beat-to-beat values of CO can be obtained using the pressure recording analytical method (PRAM) [25, 26]. As a particular analysis of the pressure wave recorded in radial or femoral arteries, PRAM represents a promising and interesting opportunity for haemodynamic monitoring in the intensive care unit (ICU).

Through a complex mathematical analysis of each arterial pressure waveform, PRAM obtains a beat-to-beat evaluation of CI, SVR, stroke volume index (SVI) and stroke volume variation (SVV%). The latter, together with pulse pressure variation, is considered a more reliable index of volaemic status. Further to CI, SVR, SVI and SVV%, PRAM titrates two completely new parameters: cardiac cycle efficiency (CCE) and dP/dt_{max} (linked to maximal intraventricular pressure increase/ms).

In contrast with bolus ThD, PRAM is quick and simple to use, has minimal risks, provides continuous data and does not need calibration.

PRAM has been used in volunteers, during cardiac surgery and in a study comparing PRAM with the ThD technique under hyperdynamic or hypodynamic laboratory conditions [25–27].

In comparison with alternative CI evaluation using PCMs (i.e. PiCCO and LiDCO based on the Modelflow method), PRAM does not require any calibration, it is operator independent and minimally invasive (all data can be easily obtained through radial or femoral cannulation, obviously with a good transduction and management of these arterial catheters).

Measurement of cardiac output by PRAM

A standard arterial catheter is inserted into the radial or femoral artery. A Baxter Truwave PX-600 F transducer (Baxter-Edwards, Irvine, CA, USA) is connected to the monitoring system (Hewlett Packard, Andover, MA, USA) for continuous recording of the systemic arterial pressure waves and subsequent computation of CO. The pressure signals are acquired at 1 000 Hz by means of an analogue–digital multifunction card (DAQ Card-700; National Instruments Corporation, Austin, TX, USA) working on the tension signals with 12 bits from –2.5 to 2.5 volts. All the signals are recorded on a personal computer (Travel Mate 507-DX; Acer, Taipei Hsien, Taiwan, ROC). The pressure signal is filtered at 25 Hz to avoid resonance effects caused by the catheter transducer system without degrading the pressure wave amplitude. PRAM-CO values are displayed on a dedicated instrument at each time point and recorded. The instrument provides arterial pressure (systolic, diastolic and mean) and beat-by-beat CO values continuously; other calculated parameters are also monitored on the display.

Basic physical principles of PRAM

Changes in volume that occur in all arterial vessels are mostly due to radial expansion of the wall in response to blood pressure changes. This depends on various physical factors, such as the force of cardiac contraction, arterial impedance and compliance, and resistance of peripheral vessels. These variables are closely interdependent and need to be evaluated simultaneously. A variable called Z, representing the relationship between changes in pressure and changes in volume with time, is taken into account for the evaluation of stroke volume (SV) in the various approaches to determine CO by PCMs.

Pulse pressure is converted to SV by calculating the area under the pulsatile portion of the pressure wave, and Z (mmHg x scm^{-3}) is calculated as a factor retrospectively approximated from the results of in vitro experiments or by calibration with an independent measure of SV (i.e. ThD bolus).

Differently from other PCMs, PRAM is the practical application of a model developed completely a priori. The model does not require adjustments based on experimental data.

The concept behind PRAM is based on the physical theory of perturbations [28] by which each physical system under the effects of a perturbing term tends to react to reacquire its own condition of stability (i.e. the situation of minimal energy required).

With PRAM, the whole area, instead of only the pulsatile systolic area under the pressure curve, is measured in each cardiac cycle. At the same time, Z is obtained directly from the morphological analysis of both the pulsatile and continuous components of the pressure waveform. The derivation of Z requires no predicted data apart from the expected mean arterial pressure (MAP). According to PRAM, Z is equal to (P/t) × K, and SV is calculated as follows (cm^3):

$$SV = A/(P/t \times K),$$

where A (mmHg × s) is the whole area under the systolic portion of the pressure curve, P/t (mmHg × s^{-1}) is a description of the pressure wave profile expressed as the variation in pressure (P) over time (t) during the real entire cardiac cycle (systolic and diastolic portion, without any mathematical artefacts) and K is a factor inversely related to the instantaneous acceleration of the vessel's cross-sectional area ($c^2 \times cm^{-1}$) ´ ($1 \times cm^{-2}$). The variables A, P/t and K are closely interdependent in each cardiac cycle. The value of K is obtained from the ratio between expected and measured mean blood pressures. The numerator of the relationship is constant (theoretical mean pressure) and the denominator is measured. As a consequence, K may change from cardiac cycle to cardiac cycle, and the constant value at the numerator is taken as a reference to gauge the deviation from normality of MAP. Because MAP is lower peripherally with respect to central arteries [29], PRAM applies two different values of expected mean pressure for the computation of K at central (aorta) and peripheral levels (radial or femoral), namely the values originally indicated by Burton [29] and Guyton [30] (i.e. 100 mmHg centrally and 90 mmHg peripherally). The value of K will differ from unity in the presence of physical phenomena that may affect pressure wave transmission (low stroke output from the left ventricle or backward wave reflections from the peripheral vasculature). Since perturbations of the pressure wave are reflected in the instantaneous acceleration of the arterial vessel cross-sectional area, the correction of P/t by a value of K above or below unity yields a corrected value of Z that takes into account the effect of the wave reflection.

In summary, with PRAM the waveform is studied in the domain of time; the shape of the wave in the domain of time introduces a new 'aesthetic' dynamic monitoring that takes into account the complexity of the dynamic interactions between the complete heart cycle and the circulation (systemic and pulmonary).

Use of PRAM in septic patients: materials and methods

During the past 12 months, 41 critical patients with a confirmed diagnosis of sepsis, severe sepsis or septic shock were monitored with PRAM: 68% (28/41) were males with a median age of 61.2 years and 32% (13/41) were female with a median age of 51.2 years.

The aim of this first observational study of the use of PRAM in septic patients

was to understand whether a method that is quick and simple to use, less invasive, with minimal-risk monitoring would be useful and reliable in a complex and dynamic clinical contest with respect to classical monitoring (i.e. PAC), and if the new concept of PRAM, in comparison with the PCMs, could give us more or new information.

The new concept of this monitoring, as briefly explained before, and its peculiar dynamic vision of the pressure wave shape in the time domain, allow us to invert the method of study, beginning from the case observation and then to move to statistics. It is an error attributable to a reductionist view of medicine not to understand how monitoring can help clinical judgement, especially in sepsis, and how the interactions of clinical judgement with metabolic and haemodynamic monitoring data are fundamental to this complex logic process.

For these reasons, we prefer to show how better to analyse the contribution of PRAM to the haemodynamic monitoring of septic patients; in a few words, what should we consider to increase our understanding and not only collect numbers.

Paradigmatic case report

We report data from a classic case of severe sepsis, which correlates quite well with haemodynamic patterns and trends in other septic patients.

A 30-year-old female with a previous history of idiopathic thrombocytopenia, refractory to conventional drug therapy, treated surgically (splenectomy) during childhood, apparently in a healthy state, after a mild fever episode treated at home with paracetamol, was transferred to the ICU because of severe dyspnoea (SaO_2 90% and FiO_2 0.5), purpura fulminans with a haemorrhagic red rash over the whole body, metabolic acidosis (lactate 13.4 mmol/l) and septic shock.

The patient immediately received ventilatory (sedation, curarisation, orotracheal intubation and volume-controlled ventilation—lung-protective ventilation—with positive end-expiratory pressure, PEEP) and cardiovascular support (tempestive fluid therapy with colloids and haemotransfusion, norepinephrine, dobutamine and levosimendan). Echocardiography at admission showed a severe hypokinesia with estimated EF between 20 and 25%.

Haemodynamic monitoring was performed with PRAM and metabolic assessment was investigated with sequential arterial and venous ($ScvO_2$) blood gas analysis and sequential lactate measurements.

After admission, a massive and critical bleeding from the airways, vascular accesses, digestive and genito-urinary tracts was associated with a severe septic shock and MOF with a constant platelet count $< 10\,000/mm^3$. Sequential haemocultures confirmed a *Streptococcus pneumoniae* infection.

Critical bleeding was temporarily stopped on the fifth day after administration of recombinant factor VII and activated protein C, and continuous renal replacement therapy (CRRT) was started. In spite of a mild improvement in pulmonary gaseous exchange and bleeding control, the patient's condition became very critical and death occurred on the 12th day because of MOF after a massive melena and

subarachnoid haemorrhage. Autopsy confirmed MOF, subarachnoid haemorrhage and diffuse alveolar damage from pneumonia.

Results from the preliminary observations of dynamic monitoring with PRAM

The patient was continuously monitored with PRAM from the first hours in ICU until her death. Early haemodynamic monitoring of this classic severe septic patient with PRAM immediately detected the early cryptic cardiac pump dysfunction through interpretation of these two new parameters: CCE and dP/dt_{max} variations (Fig. 1). The cryptic cardiac pump dysfunction was confirmed by an early echocardiographic assessment.

Aggressive fluid therapy, and vasopressor and inotrope support successfully restored a typical septic circulatory pattern with higher CCE and higher dP/dt (Fig. 2). CCE and dP/dt_{max} variations can be considered as independent values of haemodynamic status interpretation.

CRRT settings were based upon and adjusted using data collected with PRAM. Further to a beat-to-beat evaluation of continuous venovenous haemodiafiltration, influence on haemodynamics, CCE evaluation, after dialysis circuit substitution, seemed to indicate a significant improvement of cardiac performance (Fig. 3).

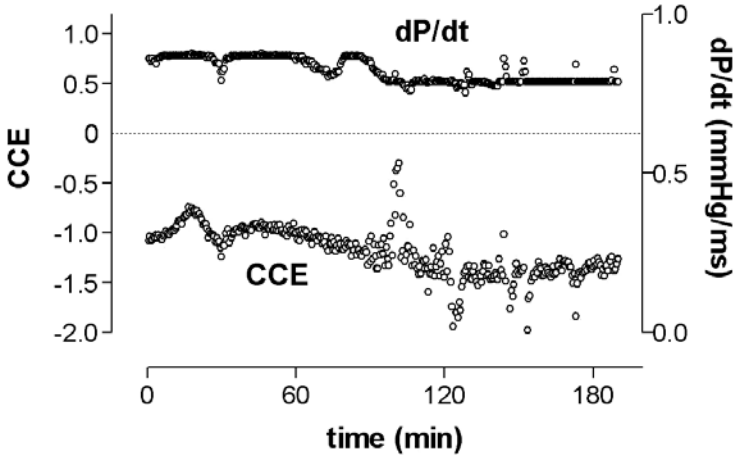


Fig. 1. Haemodynamic monitoring of a 30-year-old female with severe septic shock (*Streptococcus pneumoniae* detected with admission haemocultures). Data were collected with PRAM on 18.04.05 (first day in ICU). In consideration of the young age of the patient and no previous history of cardiocirculatory disease, CCE < -1.0 and dP/dt max < 1.0 are suggestive of a severe myocardial efficiency and contractility dysfunction. Echocardiographic evaluation estimated a 25% EF

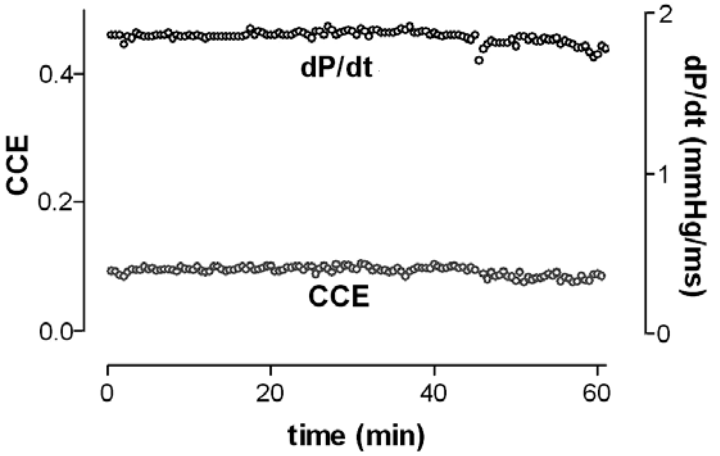


Fig. 2. Same patient as in Fig. 1. Data were collected with PRAM on 20.04.05 (third day in ICU). Intensive fluid therapy (blood and colloids) and continuous vasopressor and inotropic support (norepinephrine, dobutamine and levosimendan) allowed a better cardiac performance to be obtained. CCE changed from -1.0 to + 0.1 and dp/dt reached 1.7, confirming a typical hyperdynamic septic–shock pattern. Echocardiographic estimated EF was 50%

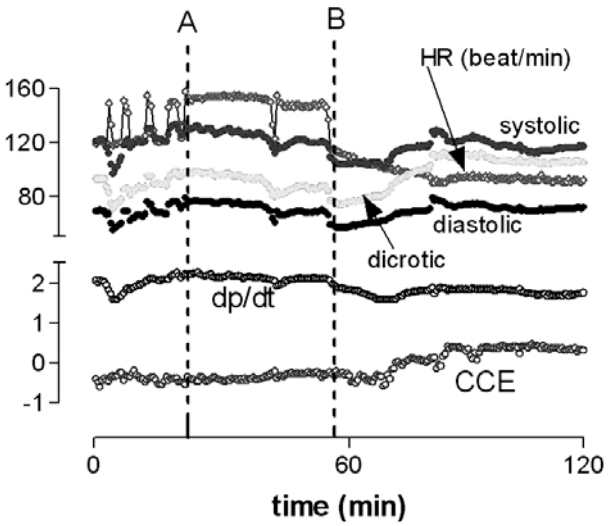


Fig. 3. Same patient as in Fig. 1. Data were collected with PRAM on 22.04.05 (fifth day in ICU). Continuous venovenous haemodiafiltration (CVVHDF) circuit substitution. An early and heavy renal replacement therapy was started. The efficiency of the cartridge filter of the haemodialysis circuit is decreased and the patient's haemodynamics (heart rate predominantly) are unstable. Marker *A* indicates disconnection of the haemodialysis machine to allow circuit substitution and marker *B* shows the CVVHDF cycle restart. It is worth noting that in spite of a relative arterial pressure stability, HR and CCE show significant variations, indicating that the external dialysis pump acts in synergy with the myocardium and HR response is decreased

Finally, beat-to-beat registration showed interactions between ventilatory settings, pulmonary and systemic circulation (Figs. 4, 5).

All these results confirm how PRAM, which is easy to use and minimally invasive, and without calibration procedures, fits well with the dynamic course of sepsis and how new parameters like CCE, dP/dt and SVV% can help us to understand better the complex and dynamically evolving haemodynamic condition of the septic patient.

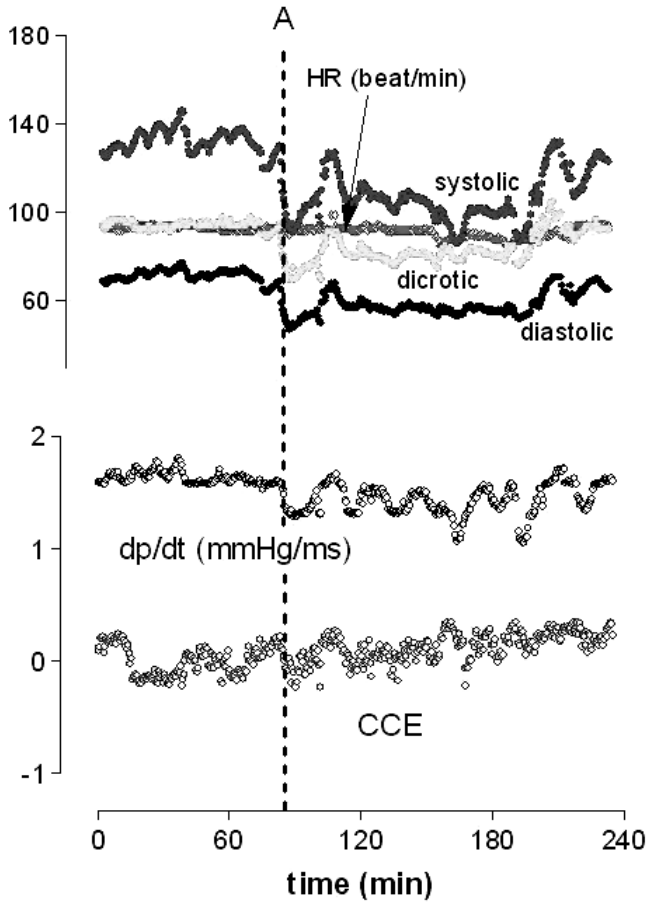


Fig. 4. Same patient as in Fig. 1. Data were collected with PRAM on 23.04.05 (sixth day in ICU). Ventilation setting–pulmonary circulation–systemic circulation interactions. Alveolar recruiting manoeuvres cause an alteration of hydrostatic and colloido–osmotic pressure within the lung circulatory bed, mimicking pump and fluid support. In fact, CCE and dP/dt_{max} values increase when recruiting is effective. Marker *A* indicates temporary recruiting interruption with significant simultaneous variations in haemodynamics, CCE and dP/dt_{max}

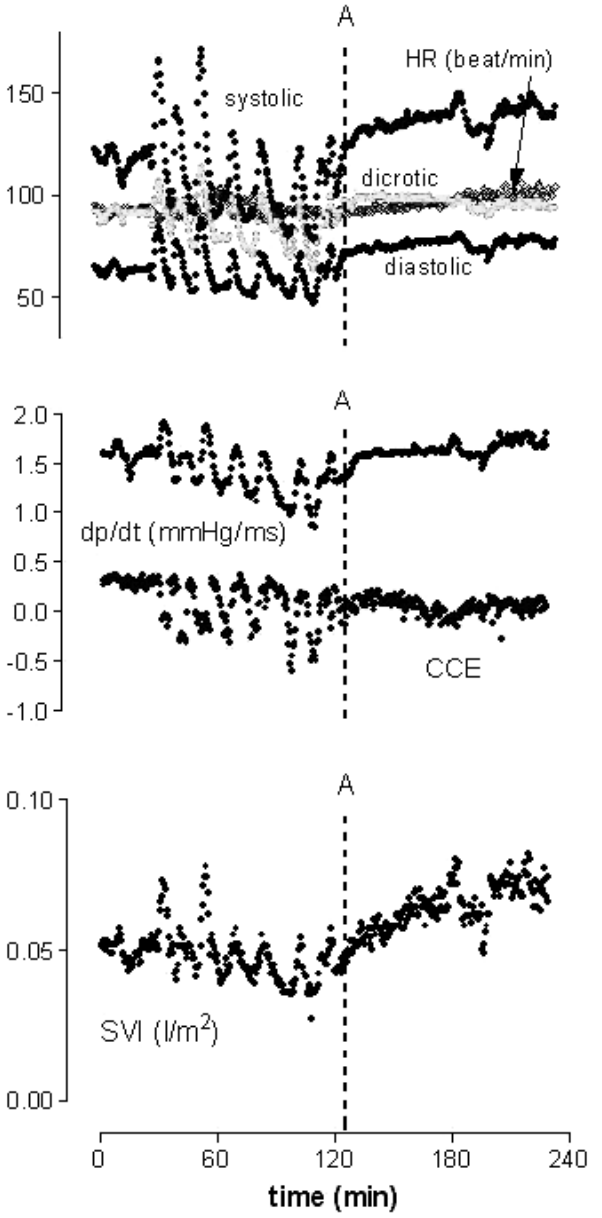


Fig. 5. Same patient as in Fig. 1. Data were collected with PRAM on 23.04.05 (sixth day in ICU). Ventilation setting–pulmonary circulation–systemic circulation interactions. Marker *A* indicates interruption of recruiting manoeuvres and a new ventilation setting with higher PEEP, tidal volume and airway peak pressure values. The new ventilatory setting caused a fluid transfer from the interstitium to the intravascular district with a significant increase of SVI (lower graph)

Conclusions

The PRAM method is based on the principle that, in any given vessel, volume changes occur mainly because of radial expansion in response to variations in pressure.

Similar approaches have been studied by several authors during the past three decades [31] and have led to the development of important clinical applications (PiCCO and LiDCO systems and the Modelflow method) [21, 22, 32, 33]. However, the PiCCO system does not start without a ThD-CO; moreover, even though both the LiDCO system and the Modelflow method start pulse-contour CO computations directly after connection to a radial artery pressure signal with a trending of CO, these two methods have a higher accuracy only after considering age, sex and external calibration data [21, 22, 31–33].

In contrast, PRAM can measure absolute values of SV, independently from calibration, by determining parameters able to characterise the elastic properties of the arteries from the objective analysis of the pressure wave profile.

The PRAM method seems easy to use. It provides a fast response time (beat-to-beat readout), and abrupt changes in CO resulting from blood loss or septic haemodynamics and changes in arterial resistance may be detected quicker than with PAC. More importantly, PRAM does not require external calibration by ThD and requires no other additional invasive procedure. Since it does not require injection of thermal solution, a PAC is not required, avoiding both time-consuming and potential complications due to insertion of the PAC.

To date, only three studies have provided an indication of the intrinsic accuracy of PRAM [25–27]. However, they do not give a direct answer to the questions arising from the accuracy of the method in measuring CO in various haemodynamic states.

This is the first observational report of the use of PRAM in the septic patient, the first remark and reflection of the possibility of the PRAM method to enter in the complex and dynamic evolution of septic haemodynamics. For example, it appears evident that further to CI, SVR, SVI and SVV%, PRAM titrates two interesting parameters: CCE and dP/dt. When associated with compatible and careful clinical investigations (clinical judgement drives numbers and not vice versa), an increase in their values—to be considered as efficiency of myocardial contractility status—allows us to detect a classic haemodynamic pattern. The cryptic cardiac failure during the early period of severe sepsis, well documented by Rivers et al. [34], will be evidenced by lower values of CCE and dP/dt. Meantime, together with an oxygen venous saturation from a central venous catheter ($ScvO_2$) and monitoring of lactate, base excess and strong ion gap from a bedside gas analyser, PRAM helps in tailoring an appropriate fluid, vasopressor and inotrope therapy for each therapy and modulating supportive ventilatory therapy without wasting time performing invasive procedures.

Our preliminary observations confirm that CCE and dP/dt are not affected by septic state-induced haemodynamic modifications (unlike SVI and SVV%, whose assessments strictly depend upon altered arterial tree compliance) and can detect early typical septic cardiac pump dysfunction.

Generally, dP/dt_{max} in septic patients is a difficult index to measure, but the 'point-to-point' analysis of arterial pressure waveform possible with the PRAM method demonstrates that contractility assessment with other methods is misleading. Simple identification of systolic and diastolic points of the curve cannot, in fact, reflect real dP/dt_{max} in the septic patient.

Being completely different from other PCMs, PRAM can detect and visualise the dicrotic notch, a crucial point indicating the effective blood flow pause [35]. Detection of the dicrotic notch in septic patients is extremely important because in these patients the percentage of variation of dicrotic pressure is augmented (dicrotic % >>).

Pressure waveform analysis and, particularly, reflected waves from the peripheral circulation (provoked by arterial tree branching) could be another useful instrument to identify vascular compliance alterations induced by the overproduction of nitric oxide in sepsis [36]. In septic patients, some arterial pressure waveforms seem to be modified up to mimic a real valvular dysfunction.

In sepsis, severe sepsis and septic shock, we believe that a new culture of monitoring has to be developed, a culture that considers time, complexity of interactions between heart and circulation and heterogeneity of patients. A dynamic vision, through the shape of the wave, of these interactions and the conceptualisation of the shape of the wave in the clinical context is the clue for this new philosophy. Another problem, with the continuum of sepsis, severe sepsis and septic shock, is that we do not know exactly at what stage we are beginning our haemodynamic observation of the patient. For example, if patients remain at home for 1 week with community-acquired pneumonia and then arrive at the emergency department with multiple organ dysfunction, are they in the early phase of shock or have they just entered into the stable phase for the domiciliary care (fluids and antibiotics)?

With PRAM monitoring (Fig. 6), we observed, in these few cases, that the early septic condition is often associated with a relative hypovolaemia (decreased SVI, increased SVV%, decreased CCE associated with an increased dP/dt_{max}), but the early septic condition can also be associated with a so-called (by Rivers) 'cryptic pump failure' (decreased SV and both decreased CCE and dP/dt). The late phase of sepsis is characterised by both increased CCE and dP/dt and increased SVI.

The clinical contest, to date, has to be in accordance with the Surviving Sepsis Campaign, which represents 20 years of efforts in defining and studying sepsis. In accordance with the Surviving Sepsis Campaign, haemodynamic treatment should be guided by CVP, MAP, $ScvO_2$ and haematocrit. Recent critical reviews recommend that treatment should be guided by CVP or airways peak pressure, MAP and CI (SVI x heart rate).

All these doubts about the numbers mean that the heterogeneity of patients in sepsis cannot allow us to believe in a generalisation, we must enter in the singular clinical contest, helped with reliable measurements that represent, not only with numbers, these complex and dynamic interactions. Target values on best values of these parameters are not enough and suggested goals in guidelines are not uniform [37, 38]; in general, a protocol is useful but not enough.

In order to re-interpret early goal-directed therapy by Rivers and colleagues, we considered the study that pointed out the importance of time in sepsis treatment (time is the issue, time is the tissue); using a more complete and reliable haemodynamic monitoring method such as PRAM, we tried to introduce new indices and their presumed cut-off values, which could help intensive-care specialists in their clinical judgement and therapeutic strategies during the whole course of sepsis (Table 1). These apparently rigid cut-off values must obviously be considered and reviewed through keen clinical observation (i.e. cut-off values should be adjusted for patients with previous cardiocirculatory disease).

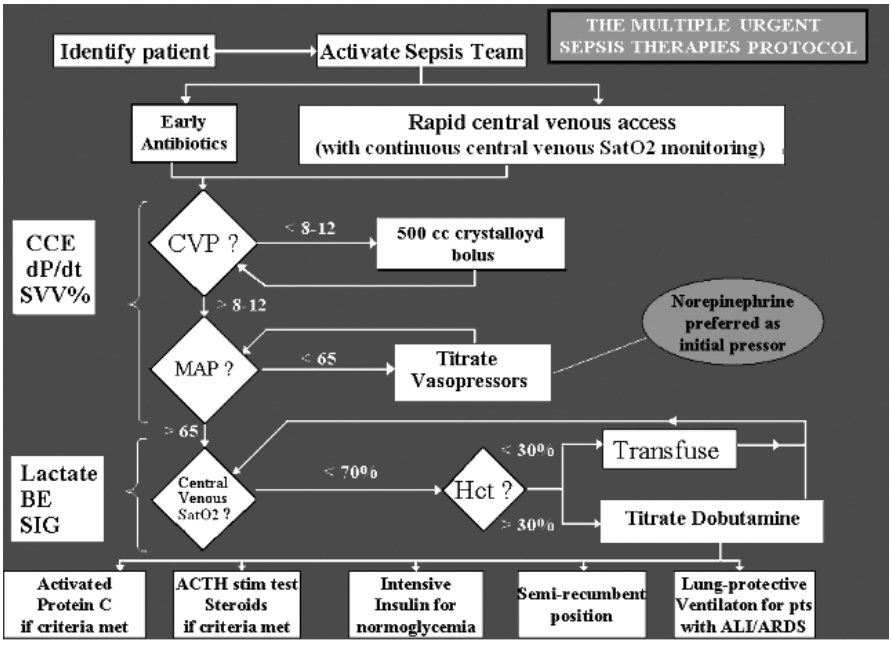


Fig. 6. The Multiple Urgent Sepsis Therapies (MUST) protocol. Haemodynamic assessment with PRAM offers the clinician the opportunity to understand in more depth the cardiac pump function and volaemic status of septic patients. CCE, dP/dt and SVV% are easy to measure and no time is wasted. Lowered values of CCE and dP/dt, in particular, could early detect myocardial dysfunction and foresee a presumable poor responsiveness to aggressive fluid therapy. Lactate, base excess and strong ion gap assessment provide a more complex view of metabolic status in septic patients than $ScvO_2$ only

Table 1. Combined PRAM haemodynamic and metabolic cut–off values for detecting septic conditions

Parameter	Early sepsis Cardiac cryptic dysfuntion	Early sepsis hypovolaemic	Late sepsis
CCE (cardiac cycle efficiency)	< 0	> 0	> 0.35
dP/DT MAX	< 1.0 mmhg/msec	> 1.0 mmHg/msec	> 1.5 mmHg/msec
HR	> 100 bpm	> 100 bpm	< 100 bpm
SVI	< 45 ml/m^2	< 45 ml/m^2	> 45 ml/m^2
CVP	< 16 mmHg	< 8-12 mmHg	> 16 mmHg
MAP	< 65 mmHg	< 65 mmHg	> 65 mmHg
SVV	> or > 15%	> 15/20%	< 15%
Warm feet	no	no	usually yes
Cold feet	yes	yes	usually not
$ScvO_2$	< 70%	< or > 70%	> 70%
Lactate	> 4.0 mmol/l	> 2.0 mmol/l	> 2.0 mmol/l
BE	< - 4 mmol/l	< - 4 mmol/l	< - 4 mmol/l (?)
SIG	> 3 mEq/l	> 3 mEq/l	> 3 mEq/l (?)

CCE ∝ a ratio that represents a measure of the rigidity of the wave and of the transmission line
CCE = wave without points of resonance ÷ wave with points of resonance
~ 0.2 ÷0.3 (CCE decreases with age and increasing rigidity)
CCE must diminish with increasing age because rigidity augments and reflected waves augment. In an old patient with a CCE around 0.3–0.4, we have to suspect a change in vascular tone and we can suspect a septic process (relatively high CCE values)
dP/dt ∝ a measure that represents the ventricular contractility, but pay attention to the heart rate (HR, normal value ~ 1, in sepsis >> 1.5)
SVV% ∝ a measure of the volaemia: (SV max – SV min) ÷ (SV max + SV min) ÷ 2
In hypovolaemic state SVV% 15–20%
Dicrotic notch % is severely augmented in sepsis

This new philosophy of monitoring with PRAM, more oriented to the dynamic interpretation of the wave shape, needs a clinically well-prepared intensive-care specialist. More experienced specialists should be able to identify different beat-to-beat shapes of arterial waveforms, having a clearer and dynamic clinical picture, in order: (1) to stage more precisely the haemodynamic septic pattern of each individual patient; (2) to identify more precisely the effective therapy; (3) to look more precisely at the effects of therapies; (4) finally, to avoid mitochondrial dysfunction, MOF and death (Fig. 7).

Of course, because of the originality of this method, further studies will be required to assess PRAM in the setting of extreme haemodynamic conditions and of severe haemorrhage. Further studies will be necessary to confirm that this new approach to septic haemodynamics is the next step to understand in depth the physiopathology of sepsis, severe sepsis and septic shock and more interesting findings could derive from parallel in vivo and in continuum cytokine–metabolic–endocrine–haemodynamic evaluation of septic patients.

Some disadvantages of PRAM remain to be addressed. Several factors could affect the accuracy of CO measurements based on the analysis of arterial waveforms

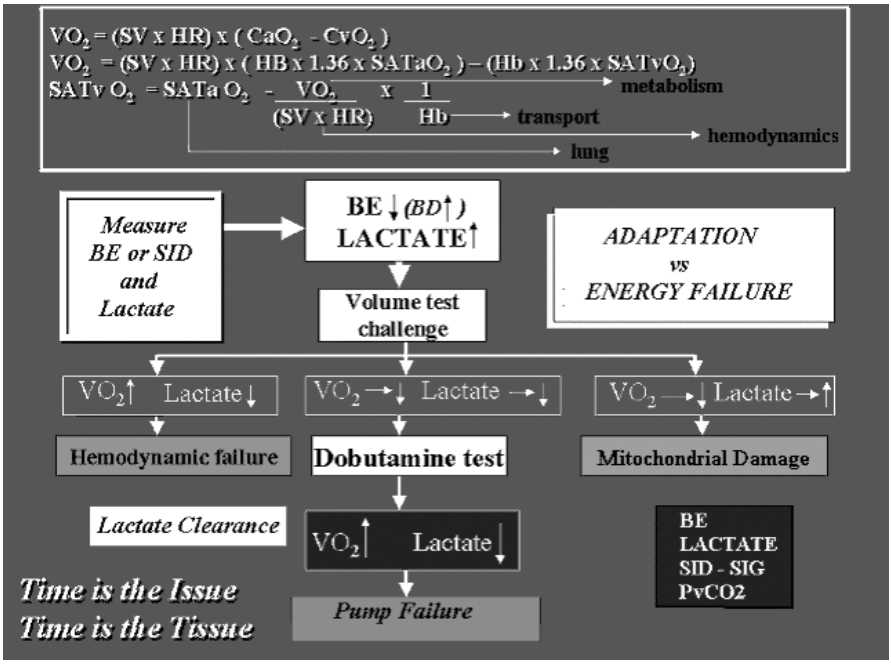


Fig. 7. Base excess, strong ion difference and lactate monitoring during sepsis can complete the haemodynamic profile, providing a picture of tissue metabolic status. VO_2 and lactate levels after volume test challenge could help in sepsis staging. Subsequent therapeutic efforts will be guided on SVV% (haemodynamic failure) or CCE and dP/dt (cardiac pump dysfunction). Decreasing VO_2 and increasing lactate levels after adequate fluid therapy are suggestive of mitochondrial damage as the end point of sepsis pathophysiology and MOF

[39], such as stenosis of the arterial tree, arterial pathology in the proximal segments, etc., which need to be further investigated and which can be present in the history of the septic patient.

Moreover, damped waveforms and inadequate pulse detection (severe arrhythmias, catheter dislodgement) or excessive resonance may influence the precision of the pressure wave analysis.

The additional data regarding the measurement of pressures (right atrium pressure, right ventricular pressure, pulmonary artery pressure and pulmonary capillary wedge pressure) are specific for PAC monitoring. The absence of direct preload measures may be a disadvantage of many PCMs. There are penalties we have to accept for being less invasive, but we must have enough brain to squeeze out data and clinical judgement from our functional monitors. PRAM permits this new kind of monitoring, moving to be not only a numerical monitoring but also an 'aesthetic' monitoring.

References

1. Anonymous (1992) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20(6):864–874
2. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS. International Sepsis Definition Conference. Crit Care Med 3:1250–1256
3. Young JD, Cameron EM (1995) Dynamics of skin blood flow in human sepsis. Intensive Care Med 21:669–674
4. Tsuneyoshi I, Kanmura Y, Yoshimura N (1996) Nitric oxide as a mediator of reduced arterial responsiveness in septic patients. Crit Care Med 24:1083–1086
5. Parrillo JE, Parker MM, Natanson C et al (1990) Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 113(3):227–242
6. Parker MM, Shelhamer JH, Bacharach SL et al (1984) Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 100:483–490
7. Court O, Kumar A, Parrillo JE, Kumar A (2002) Myocardial depression in sepsis and septic shock. Crit Care 6:500–508
8. Sibbald WJ, Paterson NA, Holliday RL et al (1978) Pulmonary hypertension in sepsis: measurement by the pulmonary artery diastolic pulmonary wedge pressure gradient and the influence of passive and active factors. Chest 73:583–591
9. Kimchi A, Ellrodt AG, Berman DS et al (1984) Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. J Am Coll Cardiol 4:945–951
10. Court O, Kumar A, Parrillo JE, Kumar A (2002) Myocardial depression in sepsis and septic shock. Crit Care 6:500–508
11. Young JD (2004) The heart and circulation in severe sepsis. Br J Anaesth 93:114–120
12. Ganz IU, Swan HJC (1972) Measurement of blood flow by thermodilution. Am J Cardiol 29:241–246
13. Sandham JD, Hull RD, Brant RF et al; Canadian Critical Care Clinical Trials Group (2003) A randomized, controlled trial of the use of pulmonary–artery catheters in high-risk surgical patients. N Engl J Med 348(1):5–14
14. Connors AF Jr, Speroff T, Dawson NV et al (1996) The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 276(11):889–897
15. Pater C, Laboy V, Venus B et al (1986) Acute complications of pulmonary artery catheter insertion in critically ill patients. Crit Care Med 14:195–197
16. Pinsky MR (2002) Functional hemodynamic monitoring. Intensive Care Med 28:386–388
17. Bazaral MG, Petre J, Novoa R (1992) Errors in thermodilution cardiac output measurements caused by rapid pulmonary artery temperature decreases after cardiopulmonary bypass. Anesthesiology 77:31–37
18. Latson TN, Nhitthen CW, O'Flaherty D (1993) Ventilation, thermal noise and errors—cardiac output measurements after cardiopulmonary bypass. Anesthesiology 79:1233–1243
19. Nishikawa T, Dohi S (1993) Errors in measurements of cardiac output by thermodilution. Can J Anesth 40:142–153
20. Dhingra VK, Fenwick JC, Nally KR et al (2002) Lack of agreement between thermodilution and Fick cardiac output in critically ill patients. Chest 122:990–997
21. Gödje O, Hoke K, Goetz AE et al (2002) Reliability of a new algorithm for continuous

cardiac output determination by pulse-contour analysis during hemodynamic instability. Crit Care Med 30:52–58
22. Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ (1993) Computation of aortic flow pressure in humans using a nonlinear, three-element model. J Appl Physiol 74:2566–2573
23. Jansen JRC, Schreuder JJ, Mulier JP et al (2001) A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. Br J Anaesth 87:212–222
24. Remmen JJ, Aengevaeren WR, Verheugt FW et al (2002) Finapres arterial pulse wave analysis with Modelflow is not a reliable non–invasive method for assessment of cardiac output. Clin Sci 103:143–149
25. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30:1834–1841
26. Giomarelli P, Scolletta S, Biagioli B (2004) Cardiac output monitoring by pressure recording analytical method in cardiac surgery. Eur J Cardiothorac Surg 26:515–520
27. Scolletta S, Romano SM, Biagioli B et al (2005) Pressure recording analytical method (PRAM) for measurement of cardiac output during various hemodynamic states. Br J Anaesth 95:159–165
28. Messiah A (1985) Change of representation and perturbation treatment of a part of the Hamiltonian. In: Quantum mechanics, vol. 2. North Holland Physics Publishing, Amsterdam, pp 722–760
29. Burton AC (1962) Physical principles of circulatory phenomena. The physical equilibrium of the heart and blood vessels. In: Hamilton WF (ed) Handbook of physiology, vol 1. American Physiological Society, Washington, pp 85–106
30. Guyton AC (1991) Textbook of medical physiology, 8th edn. WB Saunders, Philadelphia, p 151
31. Linton NW, Linton RA (2001) Estimation of changes in cardiac output from the arterial blood pressure waveform in the upper limb. Br J Anaesth 86:486–496
32. Jonas MM, Tansen SJ (2002) Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat–by–beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8:257–261
33. Hamilton TT, Huber LM, Jessen ME (2002) Pulse CO: a less invasive method to monitor cardiac output from arterial pressure after cardiac surgery. Ann Thorac Surg 74:S1408–S1412
34. Rivers E, Nguyen B, Havstad S et al (2001) Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
35. Romano SM, Lazzeri C, Chiostri M et al (2004) Beat-to-beat analysis of pressure wave morphology for pre–symptomatic detection of orthostatic intolerance during head-up tilt. J Am Coll Cardiol 44:1891–1897
36. McVeigh GE, Allen PB, Morgan DR et al (2001) Nitric oxide modulation of blood vessel tone identified by arterial waveform analysis. Clin Sci (Lond) 100(4):387–393
37. Dellinger RP, Carnet JM, Masur H et al; Surviving Sepsis Campaign Management Guidelines Committee (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32(3):858–873
38. Dellinger RP (2003) Cardiovascular management of septic shock. Crit Care Med 31(3):946–955
39. Van Lieshout JJ, Wesseling KH (2001) Continuous cardiac output by pulse contour analysis? Br J Anaesth 86:467–469

Chapter 29

The dark side of the moon: in-hospital cardiopulmonary resuscitation

E. Cerchiari, N. Cilloni, F. Semeraro

The increased awareness and training in cardiopulmonary resuscitation (CPR), the widespread introduction of automated external defibrillators (AED), and the use of AED by lay rescuers, together with the high level of attention in strengthening the chain of survival have opened a new era of hope of surviving out-of-hospital cardiac arrest.

Survival of in-hospital cardiac arrest, however, remains unaltered by the innovations introduced in resuscitation: a meta-analysis [1] conducted on literature published over the past 20 years reports a survival to discharge constant at 14%, i.e. one of eight patients who undergo CPR survives to discharge and one of three patients resuscitated from cardiac arrest survives to discharge.

The need to adapt the 'chain of survival' to the needs of in-hospital resuscitation was reported in 1996 [2], identifying five links—resuscitation appropriate, recognition, rapid defibrillation, CPR and advanced life support—and foremost suggesting that attention be devoted to the system of in-hospital resuscitation with attention on prevention and on the appropriateness of the response system with training, organisation and AEDs. In 2000, the ILCOR recommendations [3] for in-hospital resuscitation required that defibrillation was provided within 3 minutes in all areas of the hospital, that AEDs were made available and that accurate data collection was started. The data that can be collected from standard recordings of diagnosis-related groups were considered inadequate; standardised data to be collected for reporting of in-hospital resuscitation had been identified by a task force in the 'Utstein style', which has recently been revised and unified with out-of-hospital reporting [4].

Several interventions have been proved to improve outcome after in-hospital cardiac arrest:

- AED made available on wards and nurses trained to use it decreased the interval prior to defibrillation and improved outcome [5].
- The undertaking of permanent resuscitation training for in-hospital personnel, which led to the mandatory recommendation in UK hospitals that one full-time resuscitation training officer be appointed every 300 acute beds [6]. The relevance of correct performance of CPR manoeuvres on outcome has been extensively studied both in animals and humans. The quality of in-hospital CPR has been recently analysed by utilising a monitor recording including chest compression rate, compression depth, ventilation rate, and the fraction of arrest

time without chest compressions (no-flow fraction) [7]. Analysis of the first 5 minutes of each resuscitation by 30-second segments revealed that chest compression rates were often less than the recommended 100/min (< 90/min in 28.1% of segments); compression depth was more shallow than the minimum 38 mm for 37.4% of compressions; ventilation rates were higher than the recommended 12–16/min (> 20/min in 60.9% of segments). Additionally, the mean (SD) no-flow fraction was 0.24 (0.18), longer than adherence to recommendations might allow (a 10-second pulse check every minute of CPR would yield a no-flow fraction of 0.17). These data confirm other investigations [8, 9], suggesting that CPR quality may be highly variable in actual practice and confirming the need for permanent in-hospital CPR training.

- Introduction of a formally structured resuscitation team [10].

A recent [11] prospective, multisite, observational study, involving 207 hospitals and 14 720 cardiac arrests, with an emergency team present in 86% of hospitals, reported a 17% survival to discharge despite 86% of arrests reported to be monitored and an average interval prior to defibrillation of 1.5 minutes (0 median). This can be partially explained by the 25% incidence of ventricular tachycardia/fibrillation (VT/VF). The same study reported that 63% of resuscitated patients were 'do not attempt resuscitation (DNAR)' orders post-resuscitation and 43% had life support withdrawn.

Survey of in-hospital response

It is well known that focus on strengthening the in-hospital chain of survival is needed to improve outcome, but the attention hospitals and hospital personnel devote to organising the in-hospital response can still be improved.

A survey conducted in Finland showed that only 75% of hospitals have an organised system of response, CPR training involves only 50% of physicians and 70% of nurses, and only 55% of hospitals systematically collect data on in-hospital response (only 11% according to Utstein) [12].

A similar survey conducted in Italy in 2002 showed an even lower level of attention to in-hospital response to emergencies, with 52% having an organised response system, 56% performing CPR training for personnel and only 7% systematically collecting data on in-hospital response and outcome.

Identification of 'resuscitation appropriate'

One of the important issues is to identify, prior to cardiac arrest, patients in whom resuscitation is appropriate. It is well accepted that patients die in hospital (about 3% of admissions) and not all patients are candidates for resuscitation (resuscitation attempts are 1.4% of admissions) [13]. A fraction of patients admitted to hospital are DNAR because of underlying disease, and procedures vary according to local ethical and legislative policies [14].

The issue of identifying the predictors of survival after in-hospital cardiac arrest is difficult. Factors associated with survival are younger age, absence of comorbidities, respiratory arrest, ventricular arrhythmias, witnessed arrest, short-duration CPR and fast restoration of spontaneous circulation. A frequently utilised score for predicting survival after cardiac arrest is the pre-arrest morbidity index developed by George et al. [15] in 1989. Another score utilised more recently is that developed by van Walraven [16] in 2001.

Recently, the factors associated with survival after in-hospital cardiac arrest have been analysed in 219 consecutive adult attempted resuscitations in a large urban teaching hospital over a 3-year period [17]. The main outcome measures were survival to discharge, 1 and 3 months. Survival rates at discharge, 1 and 3 months were 15.1, 13.3 and 11.5%. Meaningful neurological status (cerebral performance score of 1) at discharge was achieved in 61% of survivors. Independent predictors of survival were: higher body-mass index, presence of chronic renal insufficiency, respiratory arrest, VT/VF as initial rhythm and arrest early during the hospital stay. A risk model based on these variables demonstrated a significant fit between predicted and observed survival at discharge with goodness of fit test p-value of 0.87.

However, all these scores are difficult to apply when responding to patients in cardiac arrest and the best strategy is that of evaluating appropriateness of resuscitation prior to the acute event, applying a DNAR strategy and periodically reviewing all in-hospital deaths.

New models

It is widely known that the chances of survival, despite the severity of disease, are much higher if the arrest occurs in monitored areas, compared to non-monitored areas [18]. The finding that almost two thirds of in-hospital cardiac arrests are announced by symptoms and avoidable [19] led to the hypothesis that in-hospital cardiac arrest could be prevented rather than treated. The symptoms that announce cardiac arrest have been extensively studied and include threatened airway, alteration of respiratory rate, pulse rate, blood pressure and neurologic function, and can be divided into early and late symptoms [20, 21]. One example of the attempt to respond to critical patients prior to the occurrence of cardiac arrest is the development of the medical emergency team (MET), introduced in Liverpool Hospital, NSW, Sydney, Australia in 1990; this is a development of the traditional 'crash team', composed of at least a doctor and a nurse trained in advanced life support, available 24 hours a day, providing immediate response. The difference from the traditional crash team is that the MET team responds to a request from the wards based on the alteration of one physiologic parameter or even to a subjective criterion of 'seriously worried' (Table 1) [22]. The introduction of a MET should be accompanied by training of hospital personnel in the recognition of signs and symptoms announcing the patient at risk for cardiac arrest. The aim is to improve patient handling by earlier recognition of acute deterioration, i.e. taking intensive care expertise to the wards [23].

Table 1. Criteria for calling the medical emergency team

Acute changes in:	Physiology
Airway	Threatened
Breathing	All respiratory arrests
	Respiratory rate < 5
	Respiratory rate > 36
Circulation	All cardiac arrests
	Pulse rate < 40
	Pulse rate > 140
	Systolic blood pressure 90 mmHg
Neurology	Sudden fall in level of consciousness (fall in GCS of 2 points)
	Repeated or prolonged seizures
Other	Any patient whom you are seriously worried about who does not fit the above criteria

Several groups have studied the effect of MET introduction to assess whether it could decrease the incidence and/or improve survival of in-hospital cardiac arrest. Buist et al. [24] analysed cardiac arrest survival before and after introduction of a MET team between 1996 and 1999 in a single 300-bed hospital; after adjustment for case mix, the intervention was associated with a 50% reduction in the incidence of unexpected cardiac arrest. Bellomo et al. [25], after a similar analysis, concluded that the incidence of in-hospital cardiac arrest and death following cardiac arrest, bed occupancy related to cardiac arrest and overall in-hospital mortality decreased after introducing an intensive-care-based MET. Bristow et al. [26] compared data from three Australian hospitals (one with a MET team versus two with traditional crash teams) and reported that no significant difference in the rates of cardiac arrest or total deaths between the three hospitals could be identified: however, the MET hospital had fewer unanticipated intensive care unit (ICU)/high-dependency unit admissions, with no increase in in-hospital arrest rate or total death rate, and the non-DNAR deaths were lower compared with one of the hospitals with a conventional cardiac arrest team.

The MET is a very young concept and there is not a wealth of literature available or level 1 studies providing a definitive answer. That said, the available evidence is loosely in favour of the hypothesis that MET implementation improves survival from in-hospital cardiac arrests:

1. It has been recognised that cardiac arrest is preceded by clinical signs of deterioration in 50% of in-hospital cases.
2. The MET has been empirically trialled since 1990 as a means of responding in an appropriate and timely fashion to patients who are at risk of cardiac arrest—the evidence is predominantly supportive of an improvement in outcome following cardiac arrest in association with the use of the MET.
3. Evidence that is not supportive is neutral, with other positive benefits associated (e.g. reduction in unanticipated ICU admission).
4. There is no documented evidence of harm from the MET.
5. There is no documentation of the costs of implementing and maintaining a MET system.

Given the fact that the primary goal of MET is to prevent cardiac arrest, the

finding of improved survival once an arrest has occurred is an advantageous 'downstream result' and thus, the conclusions of the specific subcommittee of the development of the 2005 ILCOR guidelines is that for adults the use of MET teams could be classified as a class IIb recommendation.

Parallel to the development of the MET team, the need to reduce readmissions to ICU, providing extended ICU care even in patients on the wards, stimulated the development of the critical care outreach (CCO) team. This system offers the assistance of a critical care expert (a nurse or a doctor) to help with the plan of care of patients dismissed from the ICU [27]. The survey is planned in given hours and a model for identifying patients at risk has been developed by attributing a weighted value to physiologic parameters (Early Warning score). The effect of introduction of the CCO team has been analysed in few studies and the results are even less clear cut than with the MET team. Ball et al. [28] analysed the effect of introducing a CCO team on survival of critical patients in a 1 200-bed hospital and reported a 6.8% (risk ratio 1.08) improvement of survival to hospital discharge of patients discharged from ICU and a 6.4% (risk ratio 0.48) decrease in readmission to ICU. After the introduction of the CCO service, Pittard [29] reported a significant impact on critical care utilisation: the emergency admission rate to intensive care fell from 58 to 43% ($p = 0.05$). These emergency patients had shorter lengths of stay (4.8 vs 7.4 days) and lower mortality (28.6 vs 23.5%, $p = 0.05$); and the re-admission rate also fell from 5.1 to 3.3% ($p = 0.05$).

The validation of the Modified Early Warning score as a means to identify patients at risk was conducted by Subbe et al. [30], by a prospective analysis of 1 695 acute medical admissions to ICU, compared to admissions the previous year to the same ICU: no change in mortality of patients with low, intermediate or high Modified Early Warning scores was recorded, and rates of cardiopulmonary arrest, and admission to ICU or the high-dependency unit were similar. Data analysis confirmed respiratory rate as the best discriminator in identifying high-risk patient groups.

The use of early warning scoring systems to decrease the number of in-hospital cardiac arrests is a very young concept and most of the literature available for review is tangential to this specific topic. There were only three supportive studies to evaluate and only the study by Pittard directly addressed the question at hand. The remainder of the studies were neutral or weak but there are no negative studies on the use of early warning scores. Given the minimal and tangential evidence, the conclusion of the specific subcommittee for the development of the 2005 ILCOR guidelines was that the level of recommendation for the introduction of the CCO system is indeterminate.

These systems represent two faces of the same need of making intensive care available to patients 'at risk' on the wards: the MET responds to patients who are admitted to a ward and develop an alteration of physiologic parameters that needs to be evaluated by intensive care, and the CCO helps evaluate patients dismissed from ICU to ward who may still be in need of intensive care periodical re-evaluation.

Although both these models respond to the patient at risk on the wards, they

are difficult to compare because the systematic response is different in terms of composition and availability of the teams, method of activation and activation criteria [27]. Differences include:

1. The MET is generally composed of at least one doctor (with advanced life support skills) and nurse and is available 24 hours a day. An outreach team may be as little as one nurse and may only be available for specific hours during the day.
2. The criteria for calling the MET is a yes/no system for any of the criteria (e.g. is the systolic blood pressure 90 mmHg?). The criteria for an outreach team is usually a graded system, where a patient has to be scored as reaching a certain threshold before the team can be called (e.g. a systolic blood pressure of 85 mmHg = 1 point; a heart rate of 105 = 1 point; a respiratory rate of 25 = 1 point). The threshold is three points, therefore a patient with all three of these vital signs can have an outreach team call [29]. This is obviously a more complex procedure.
3. In the MET system any member of staff can activate the team. In some outreach systems only a doctor of registrar grade or above can activate the team.
4. A MET is sent to review the patient immediately upon receiving a call. The outreach team may respond immediately, or may review patients as part of a planned ward round of the hospital, therefore constituting a delayed response.
5. The MET criteria usually incorporate a subjective 'seriously worried' criterion, which can be used to activate the team for non-specific or life-threatening emergencies not covered by the other criteria. The early warning scores generally have no subjective component, and no facility for calling the team if the set threshold is not attained by the designated criteria.
6. Although variations to the MET calling criteria do exist, they generally conform broadly to heart rate, systolic blood pressure, respiratory rate, level of consciousness and worried criteria. The outreach teams and variants have a profusion of complex calling criteria and grading of responses. Criteria include urine output, oxygen saturation, respiratory support, temperature and sometimes biochemical markers, as well as specific symptoms such as chest pain.

The team approaches presented in the literature are numerous and, according to the response modality, broadly fit under the MET/outreach classification (Table 2).

Table 2. Modalities of response to in-hospital emergencies

Medical emergency team	Outreach/Early Warning score
Medical crisis response team	Modified Early Warning score (MEWS)
Condition C	Early warning scoring system (EWSS)
Code Blue	Patient-at-risk team (PART)
Medical emergency team	Patient early response team (PERT)
	Assessment score for sick patient identification and step-up in treatment (ASSIST)
	Critical care outreach team (CCOT)

In conclusion, these models all respond to the need to provide intensive care expertise to patients on the wards. In our opinion, they should be unified in an

emergency in-hospital team, providing different and escalating modalities of response to the variable intensive care needs of patients on the wards:

1. Immediate resuscitation for patients in cardiac arrest
2. Timely intensive care assistance to patients on wards judged at risk for cardiac arrest
3. Planned intensive care evaluation for patients discharged from ICU.

Our experience

In our hospital an emergency team is organised to treat in-hospital emergencies including cardiac arrest. The team is composed of an intensive care physician and nurse, who respond to emergencies with a chart with all emergency equipment. All wards have an AED and a chart for basic life support with adjunct equipment, and ward personnel are trained in CPR and AED use.

Activation is by a centralised number with a message on the pages of the team members, CPR and defibrillation if indicated should be performed by ward personnel and ALS is provided by the emergency team.

With the purpose of evaluating the incidence of in-hospital cardiac arrest and the quality of response, the collection of data according to Utstein was started in March 2004. The analysis of results provided information on age, aetiology, ward requesting intervention, presenting rhythm and outcome. All response times and utilisation of AED if indicated were analysed.

Parallel analysis of the discharge reports allowed us to verify in what percentage of patients the team was called compared to deaths and to compare the incidence of calls with the incidence of deaths for wards, hours of the day and days of the week.

In 10 months of 2004, the team responded to 204 emergency calls, of which 38 were cardiac arrests. Presenting rhythms were VF/VT in 23% of cases, and a non-shockable rhythm in 77% of cases. In 63% of cases CPR was unsuccessful, in 15% of cases it was interrupted because considered futile and in 22% it was successful; 8% of patients survived CPR and 5% survived to discharge.

Response time intervals were very long, with an average time from collapse to beginning of CPR 5.7 min and collapse to shock 7.09 min. The AED was positioned in 12% of cases and utilised only in 5% of cases.

The comparison of emergency team calls with death occurrence showed that 62% of deaths occurred during the daily hours (08.00-20.00) compared to 53% of team calls with a rate of emergency calls/deaths of 38.7%, which decreased dramatically during the night hours to a rate of 19.5%.

The data collection allowed us to identify the weak areas of the chain of response for in-hospital emergencies: (1) lack of formalised procedure for identification of DNAR patients; (2) difference in rate of calling between wards; (3) under-utilisation of emergency team and AEDs; (4) long response times for the emergency team. We were able to implement interventions to correct the weak areas.

Conclusions

The data collection of response and outcome of emergencies should be implemented in all hospitals in order to evaluate the quality of in-hospital care and design system interventions.

References

1. Ebell MH, Becker LA, Barry HC, Hagen M (1998) Survival after in-hospital cardiopulmonary resuscitation: a metanalysis. J Gen Intern Med 13:805–816
2. Kaye E, Mancini ME (1996) Improving outcome from cardiac arrest in the hospital with a reorganized and strengthened chain of survival—an American view. Resuscitation 31:181–186
3. Anonymous (2000) From science to survival. Strengthening the chain of survival in every community. ILCOR guidelines Part 12. Resuscitation 46:417–430
4. Jacobs I, Nadkarny V, Bahr J et al (2004) Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for health care professionals from a task force of ILCOR. Resuscitation 63:233–249
5. Spearpoint KG, Mc Lean P, Zideman DA (2000) Early defibrillation and the chain of survival in 'in-hospital' adult cardiac arrest: minutes count. Resuscitation 44:165–169
6. McGowan J, Graham CA, Gordon M (1999) Appointment of a resuscitation training officer is associated with improved survival from in-hospital ventricular fibrillation/tachycardia cardiac arrest. Resuscitation 41:169–173
7. Abella BS, Alvarado JP, Myklebust H et al (2005) Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. JAMA 293:363–365
8. Aufderheide TP, Sigurdsson G, Pirrallo RG et al (2004) Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation 109:1960–1965
9. Milander MM, Hiscok PS, Sanders AB et al (1995) Chest compression and ventilation rates during cardiopulmonary resuscitation: the effects of audible tone guidance. Acad Emerg Med 2:708–713
10. Henderson SO, Ballesteros D (2001) Evaluation of a hospital-wide resuscitation team: does it increase survival for in-hospital cardiopulmonary arrest? Resuscitation 48:111–116
11. Peberdy MA, Kaye W, Ornato JP et al (2003) Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. Resuscitation 58:297–308
12. Skrifvars MP, Rosenberg PH, Finne P et al (2003) Evaluation of the in-hospital Utstein template in cardiopulmonary resuscitation in secondary hospitals. Resuscitation 56:275–282
13. Parish DC, Dane FC, Montgomery M (2002) Resuscitation in the hospital: relation of year and rhythm to outcome. Resuscitation 47:219–229
14. Aune S, Herlitz J, Bang A (2004) Characteristics of patients who die in hospital with no attempt at resuscitation. Resuscitation 65:366–379
15. George Jr AL, Folk III BP, Crecelius PL et al (1989) Pre-arrest morbidity and other correlates of survival after in-hospital cardiopulmonary arrest. Am J Med 87:28–33
16. van Walraven C, Forster A, Parish DC et al (2001) Validation of a clinical decision aid

to discontinue in-hospital cardiac arrest resuscitations. JAMA 285:1602–1606
17. Danciu SC, Klein L, Hosseini MM et al (2004) A predictive model for survival after in-hospital cardiopulmonary arrest. Resuscitation 62:35–42
18. Herlitz J, Bang A, Aune S et al (2001) Characteristics and outcome among patients suffering in-hospital cardiac arrest in monitored and non-monitored areas. Resuscitation 48:125–135
19. Hodgetts TJ, Kenward G, Vlackoni Kolis I et al (2002) Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. Resuscitation 54:115–123
20. Harrison GA, Jacques TC, Kilborn G et al (2005) The prevalence of recording of the signs of critical conditions and emergency responses in hospital wards—the SOCCER study. Resuscitation 65:149–157
21. Krause J, Smith G, Prytherch D et al (2004) A comparison of antecedents of cardiac arrest, death and emergency intensive care admissions in Australia and New Zealand and in the United Kingdom—the Acadaemia Study. Resuscitation 62:275–282
22. Hillman K, Parr M, Flabouris A (2001) Redefining in-hospital resuscitation: the concept of the medical emergency team. Resuscitation 48:105–110
23. Mercer M, Fletcher SJ, Bishop GF (1999) Medical emergency teams improve care. Br Med J 318:54
24. Buist MD, Moore GE, Bernard SA et al (2002) Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. Br Med J 324:387–390
25. Bellomo R, Goldsmith D, Uchino S et al (2003) A prospective before-and-after trial of a medical emergency team. Med J Aust 179:283–287
26. Bristow PJ, Hillman KM, They C (2000) Rates of in-hospital cardiac arrests, deaths and intensive care admissions: the effect of the medical emergency team. MJA 173:236–240
27. Mc-Arthur Rouse F (2001) Critical care outreach services and early warning scoring systems: a review of the literature. J Adv Nurs 36:696–704
28. Ball C, Kirkby M, Williams S (2003) Effect of the critical care outreach team on patient survival to discharge from hospital and readmission to critical care: non-randomised population based study. Br Med J 327:1014
29. Pittard AJ (2003) Out-of reach? Assessing the impact of introducing a critical care outreach service. Anaesthesia 58:874–910
30. Subbe CP, Davies RG, Williams et al (2003) Effect of introducing the Modified Early Warning score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions. Anaesthesia 58:797–783

LUNG

Chapter 30

Physiopathology of atelectasis during anaesthesia

G. Hedenstierna

The oxygenation of blood is impaired during anaesthesia, even in the patient with perfectly healthy lungs. Standard treatment of the patient includes a moderate increase in the oxygen supply, so that the oxygen concentration is around 30–40%. The mechanisms behind the impairment of gas exchange were poorly understood until the last 15 years and have since been mainly attributed to the collapse of lung tissue, i.e. atelectasis. In the following, the formation of atelectasis during anaesthesia and measures to prevent it or decrease its extent will be described.

Anaesthesia and atelectasis

Some 15 years ago, atelectasis was described in anaesthetised patients, neonates, and adults [1, 2]. While it can be demonstrated by computed X-ray tomography (CT), it is usually invisible on a conventional chest radiograph. This may be explained by the location of the atelectasis, in the most dependent parts of both lungs, where it may be difficult to distinguish from the chest wall and the spine on X-ray. The atelectatic tissue causes attenuation of X-rays corresponding to an attenuation number of ± 0 Hounsfield units (HU) (water has an attenuation factor of 0 HU) on a scale that ranges from + 1000 HU (bone) to – 1000 HU (air). In practice, lung tissue that has attenuation numbers between +50 and –100 HU is considered to be atelectatic, after subtraction of mediastinal organs and larger vessels [3].

Atelectasis appears in almost 90% of all patients who are anaesthetised [4]. It develops whether the anaesthesia is intravenous or inhalational and whether the patient is breathing spontaneously or is paralysed and mechanically ventilated [5]. Atelectasis is largest near the diaphragm in the supine patient and decreases in size towards the apex [6] (Fig. 1). It covers approximately 5% of the transverse pulmonary area near the diaphragm, with a large variation from 0 to 10–15%. In the average patient, atelectasis may not look very impressive. However, it should be remembered that the collapsed area consists of four times more lung tissue than the aerated regions. Thus, in the average patient atelectasis comprises about 15–20% of the lung tissue near the diaphragm and about 10% of the total lung tissue [6]. In extreme cases, almost half the lung can be collapsed during anaesthesia, before any surgery has taken place!

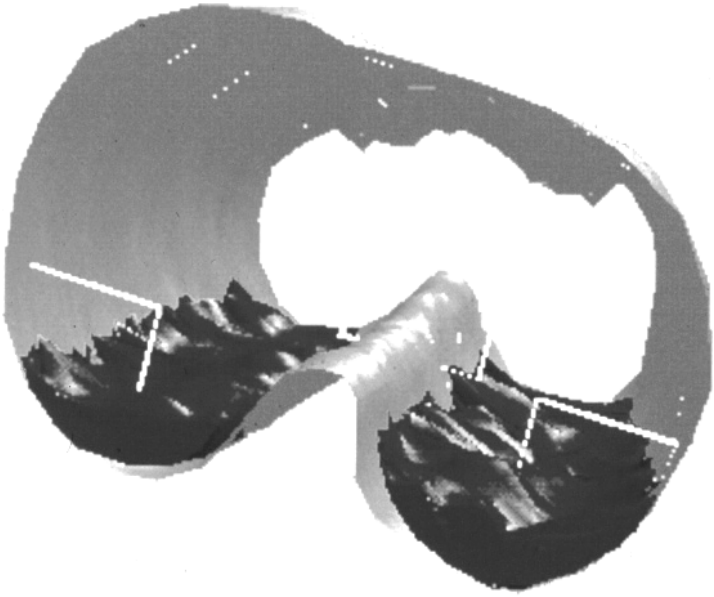


Fig. 1. Atelectasis during anaesthesia as shown in a three-dimensional reconstruction. The chest wall is shown, with atelectasis in *dark* in the dorsal parts of the lung space. Note the slight irregularity of the atelectasis and the larger size at the basal parts, near the diaphragm, than at the apex, indicating local forces that affect the distribution of atelectasis

Atelectasis may appear promptly after induction of anaesthesia, or may be first seen on a CT scan [2]. Moreover, although positive end-expiratory pressure (PEEP) can reopen collapsed lung tissue, as soon as the PEEP is discontinued atelectasis reappears within 1 min [7]. The rapid formation of atelectasis after induction of anaesthesia and discontinuation of PEEP suggests that a major cause of atelectasis is compression of lung tissue rather than slow adsorption of gas behind occluded airways. Patients who are anaesthetised with ketamine, which does not reduce respiratory muscle tone, do not develop atelectasis. It does not appear until the patient is paralysed and mechanically ventilated [8]. Tensing the diaphragm by phrenic nerve stimulation reduces atelectasis during anaesthesia [7]. All these findings fit with the concept of compression- or gravity-dependent atelectasis, a consequence of loss of muscle tone, and a decrease in FRC.

However, two recent observations have offered a more complex explanation of atelectasis formation during anaesthesia. First, collapsed lung tissue can be re-expanded by a vital capacity manoeuvre [9], but if the lungs are ventilated with pure oxygen, they rapidly re-collapse within 5 min after the manoeuvre [10]. If, however, the lungs are ventilated with 40% O_2 in nitrogen after the re-expansion, the lungs remain open with no or only little atelectasis formation for half an hour or longer.

Second, if anaesthesia is induced without 'pre-oxygenation' and ventilation is given with 30% O_2 in nitrogen, no or little atelectasis is formed [11]. These observations underscore the importance of the inspired oxygen fraction, and suggest that the rate of adsorption of gas from the alveoli plays an important role in the formation of atelectasis. Atelectasis is thus an effect of both compression of lung tissue and adsorption of gas, and both factors must be present simultaneously.

Prevention of atelectasis

Several different procedures can be carried out in order to prevent atelectasis or to re-open collapsed tissue. Some of the procedures have already been touched upon above. The procedures that will be discussed in the following sections are: (1) PEEP, (2) maintenance or restoration of respiratory muscle tone, (3) recruitment manoeuvres, and (4) minimisation of pulmonary gas adsorption.

PEEP

The effect of PEEP of 10 cmH_2O on atelectasis, as assessed by CT, has been tested in anaesthetised patients. As expected, it will consistently reopen collapsed lung tissue [2], although some atelectasis persists in most patients. Further increases in the PEEP level may have reopened this tissue. However, PEEP appears not to be the ideal procedure. Firstly, shunt is not reduced and arterial oxygenation is not improved on average in larger groups. This was demonstrated already in 1974 by Hewlett and co-workers, who warned against the 'indiscriminate use of PEEP in routine anaesthesia' [12]. The maintenance of shunt may be explained by the redistribution of blood flow towards the most dependent parts when intrathoracic pressure is increased, so that any persisting atelectasis in the bottom of the lung receives a larger share of the pulmonary blood flow than without PEEP [13]. The increased intrathoracic pressure will also impede venous return and lower cardiac output. This results in a lower venous oxygen tension for a given oxygen uptake which will augment the desaturating effect of shunted blood and perfusion of poorly ventilated regions on the arterial oxygenation [14]. Secondly, the lung re-collapses rapidly after discontinuation of PEEP. Within 1 min after the cessation of PEEP, the collapse is as large as it was before the application of PEEP [7].

Maintenance of muscle tone

The use of an anaesthetic that allows maintenance of respiratory muscle tone will prevent atelectasis formation. Ketamine does not impair muscle tone and does not cause atelectasis. However, if muscle relaxation is required, atelectasis will appear as with other anaesthetics, as mentioned above [8].

Another attempt is to restore respiratory muscle function. This can be achieved, at least partly, by diaphragm pacing by means of phrenic nerve stimulation, which

reduces the atelectatic area [7]. However, the effect is small and it can be argued that the technique is too complicated to become routine treatment during anaesthesia and surgery.

Recruitment manoeuvres

The use of a sigh manoeuvre, or a double tidal volume, has been advocated to reopen any collapsed lung tissue during anaesthesia [15]. However, atelectasis is not affected by an ordinary tidal breath or by a deep sigh with an airway pressure of up to + 20 cmH_2O [9]. Not until an airway pressure of 30 cmH_2O is reached does atelectasis decrease to approximately half the initial value. For complete reopening of all collapsed lung tissue, an inflation pressure of 40 cm H_2O is required, with the breath held for 15 s [9] (Fig. 2). Such a large inflation and subsequent expiration,

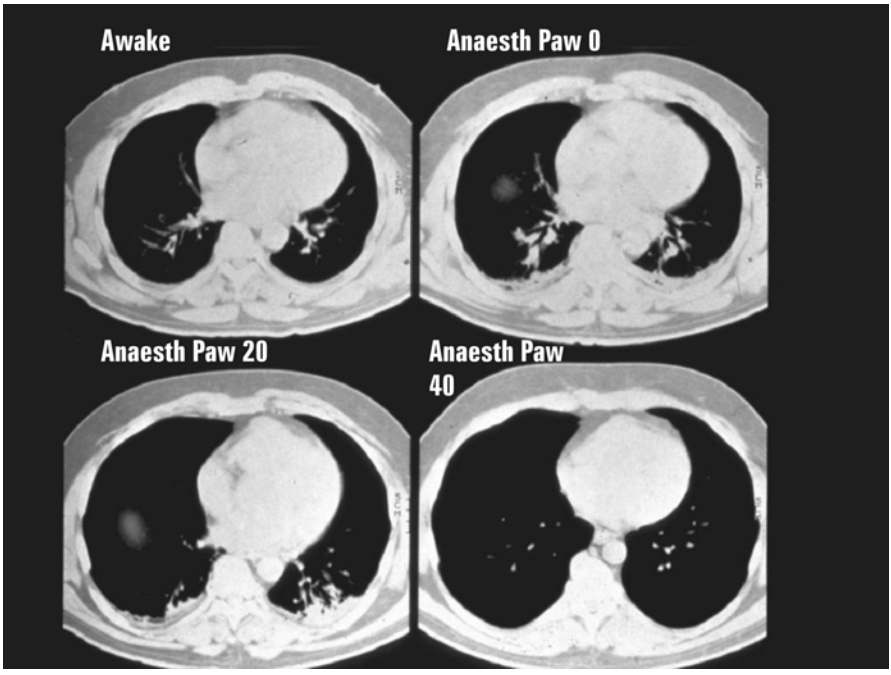


Fig. 2a–d. Atelectasis during anaesthesia and the effects of inflating the lung to different airway pressures. The CT cuts have been positioned so as to cover the same lung tissue at different lung inflations. **a** An awake patient, before anaesthesia; the lungs are well-aerated with no signs of atelectasis. Larger vessels can be seen in the lower half of the lung. **b** During anaesthesia at end-expiration (zero, atmospheric, airway pressure); atelectasis can be seen in the bottom of both lungs. **c** During anaesthesia after 15 s at an airway pressure of 20 cmH_2O, corresponding to a sigh or double tidal volume; there is no effect at all on atelectasis, which remains as large as at end-expiration. **d** During anaesthesia, after 15 s at an airway pressure of 40 cmH_2O, corresponding to a vital capacity manoeuvre; atelectasis has been eliminated. (From [9])

down to - 20 cm H_2O, corresponds to a vital capacity measured during spontaneous breathing with the patient awake. Although approved for lung function studies in anaesthetised subjects [16], it may be argued that such a manoeuvre can be dangerous and cause barometric/volumetric trauma [17]. Another procedure has been tested, in which the lung is repeatedly inflated to an airway pressure of + 30 cmH_2O. However, this causes only minor further opening of lung tissue after the first manoeuvre [15]. A full vital capacity manoeuvre of + 40 cmH_2O therefore seems necessary to completely reopen the lung in the anaesthetised patient.

Minimisation of gas adsorption

Ventilation of the lungs with pure oxygen after a vital capacity manoeuvre that reopened previously collapsed lung tissue results in a rapid reappearance of atelectasis [10]. If, however, the lung is ventilated with 40% O_2 in nitrogen, atelectasis reappears slowly, and 40 min after the vital capacity manoeuvre only 20% of the initial atelectasis re-appear (Fig. 3). Thus, ventilation during anaesthesia should be

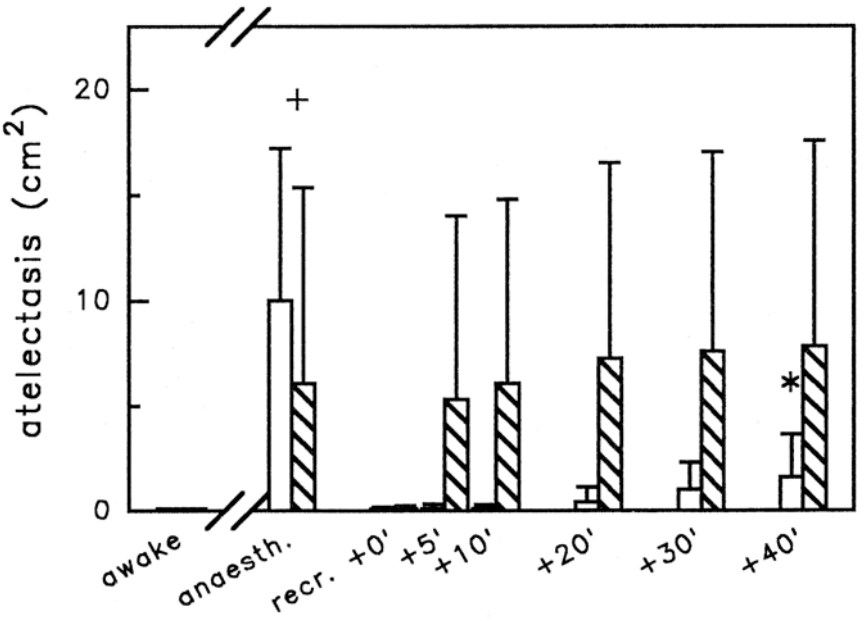


Fig. 3. The effects of a vital capacity manoeuvre (inflation of the lung to an airway pressure of 40 cmH_2O) on atelectasis, and influence of the inspired oxygen concentration. *Open bars* Ventilation with 40% oxygen in nitrogen, *stippled bars* ventilation with 100% oxygen). Note the disappearance of atelectasis after the vital capacity manoeuvre and its very slow reappearance when ventilating with 40% oxygen. Only 20% of the initial atelectasis has reappeared 40 min after the manoeuvre. When ventilating with 100% oxygen, atelectasis returns already within 5 min and tends to increase over the following 30 min. (From [10])

done with a moderate inspired oxygen fraction (e.g. 0.3–0.4) and be increased only if arterial oxygenation is compromised.

Moreover, avoidance of the pre-oxygenation procedure during induction of anaesthesia more or less eliminates atelectasis formation during anaesthesia [11]. If the pre-oxygenation period is prolonged from a standard 2–3 min to 4–5 min, atelectasis increases further in size [18]. A recent study showed that in patients breathing either 80% or 60% O_2 during the induction of anaesthesia, atelectasis was much smaller in the 80% O_2 group than in patients receiving 100% O_2, and was almost absent in the 60% O_2 group [19].

That rather subtle changes in the preoxygenation procedure and anaesthesia regime might prevent substantial atelectasis formation, with a potential decrease in post-operative lung complications, is likely but requires further study.

References

1. Damgaard Pedersen K, Qvist T (1980) Pediatric pulmonary CT-scanning. Anaesthesia-induced changes. Pediatr Radiol 9(3):145–148
2. Brismar B, Hedenstierna G, Lundquist H et al (1985) Pulmonary densities during anesthesia with muscular relaxation: a proposal of atelectasis. Anesthesiology 62(4):422–428
3. Lundquist H, Hedenstierna G, Strandberg Å et al (1995). CT-assessment of dependent lung densities in man during general anaesthesia. Acta Radiol 36:626–632
4. Hedenstierna G (2000) Anesthesia and gas exchange. In: Roca J, Rodriguez-Roisin R, Wagner PD (eds) Pulmonary and peripheral gas exchange in health and disease. Taylor & Francis, Oxford, pp 177–198
5. Strandberg A, Tokics L, Brismar B et al (1986) Atelectasis during anaesthesia and in the postoperative period. Acta Anaesthesiol Scand 30(2):154–158
6. Reber A, Engberg G, Sporre B et al (1996) Volumetric analysis of aeration in the lungs during general anaesthesia. Br J Anaesth 76(6):760–766
7. Hedenstierna G, Tokics L, Lundquist H et al (1994) Phrenic nerve stimulation during halothane anesthesia. Effects of atelectasis. Anesthesiology 80(4):751–760
8. Tokics L, Strandberg A, Brismar B et al (1987) Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. Acta Anaesthesiol Scand 31(8):684–692
9. Rothen HU, Sporre B, Engberg G et al (1993) Re-expansion of atelectasis during general anaesthesia: a computed tomography study. Br J Anaesth 71(6):788–795
10. Rothen HU, Sporre B, Engberg G et al (1995) Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. Anesthesiology 82(4):832–842
11. Rothen HU, Sporre B, Engberg G et al (1995) Prevention of atelectasis during general anaesthesia. Lancet 345:1387–1391
12. Hewlett AM, Hulands GH, Nunn JF et al (1974). Functional residual capacity during anaesthesia III: Artificial ventilation. Br J Anaesth 46(7):495–503
13. West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung: relations to vascular and alveolar pressure. J Appl Physiol 19:13–24
14. West JB (1977). State of the art: ventilation-perfusion relationships. Am Rev Respir Dis 116(5):919–943

15. Nunn JF (1993) Applied respiratory physiology. Butterworths, Oxford, pp 43–44
16. Leith DE (1976) Barotrauma in human research. Crit Care Med 4(3):159–161
17. Dreyfuss D, Saumon G (1992). Barotrauma is volutrauma, but which volume is the one responsible? Intensive Care Med 18(3):139–141
18. Reber A, Engberg G, Wegenius G et al (1996) Lung aeration. The effect of preoxygenation and hyperoxygenation during total intravenous anaesthesia. Anaesthesia 51:733–737
19. Edmark L, Kostova-Aherdan K, Enlund M et al (2003) Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 98:28–33

Chapter 31

Effect of mechanical ventilation on right ventricular afterload

D. Reis Miranda, D. Gommers, B. Lachmann

Mechanical ventilation has become a life-saving therapy in the treatment of patients with impaired pulmonary function. However, the dark side of mechanical ventilation has also emerged with the development of ventilator-induced lung injury [1], pneumonia, sepsis [2], and elevation of right ventricular (RV) afterload ultimately leading to a cor pulmonale [3, 4].

The right ventricle is very sensitive to changes in afterload [5]. It is anatomically adapted for the generation of sustained low-pressure perfusion. RV contraction occurs in three phases, as described by Mebazaa et al. [5]: contraction of the papillary muscles, the movement of the right ventricular wall towards the interventricular septum, followed by 'wringing' of the RV by contraction of the left ventricle. Because of the compliant upper region of the RV, peak pressure is reduced and ejection is prolonged. Therefore, the normal RV is able to increase peak systolic pressure to approximately 60 mmHg before RV contractile failure and systemic hypotension occur [6].

This review focuses on the influence of mechanical ventilation on RV afterload. First, the measurement of RV afterload is discussed, thereafter the influence of mechanical ventilation on RV afterload, and finally the effect of ventilation—according to the open lung concept (OLC)—on RV afterload.

How to measure right ventricular afterload

There is much discussion about measuring RV afterload by means of a pulmonary artery catheter (PAC). The most frequently used parameters obtained from a PAC that would estimate RV afterload are RV ejection fraction and pulmonary vascular resistance (PVR). Calculation of the PVR has been controversial ever since Versprille published an editorial (20 years ago) explaining why it is meaningless [7]; a year later, this claim was underscored by McGregor et al. [8]. The main criticism of the calculation of PVR is the assumption that the vessels have rigid walls. Because of the recruitable nature of the pulmonary circulation, PVR has a variable relationship to the Poiseuille resistance. Therefore, since PVR cannot express oscillatory and kinetic power components, RV power is underestimated by approximately 50% [9]. To assess pulmonary vascular resistance, Naeije [10] proposed using a pressure–flow diagram. On the vertical axis, the pressure drop through the pulmo-

nary circulation (mean pulmonary artery pressure minus wedge pressure) is displayed, and on the horizontal axis the cardiac index (CI). Changes in pressure drop through the pulmonary circulation and the CI are compared with baseline values, indicating pulmonary vasoconstriction or dilatation. Whether this dynamic pressure–flow plot reflects RV afterload adequately is not yet known.

There have been attempts to relate the end-systolic pressure–volume relationship (ESPVR) to ventricular afterload. The ESPVR is the relationship between each end-systolic volume and the concomitant pressure while changing the preload. The ESPVR defined area (consisting of the ESPVR, end-systolic volume, and diastolic compliance) plus the stroke work (Fig. 1), is proportional to myocardial oxygen consumption [11]. It is conceivable that myocardial oxygen consumption, and thus ESPVR, are related to ventricular afterload, but also to contractility. Pinsky [12] hypothesised that contractility and afterload could be distinguished by the ESPVR. Increases in contractility would increase the ESPVR slope, while changes in the afterload would co-vary end-systolic pressure and volume, but along the line described by the ESPVR [12]. However, the relation between this co-variation of end-systolic pressure and volume along the ESPVR line and RV afterload has, to our knowledge, never been established.

Echo-Doppler measurements of blood velocity and acceleration have been used as indices of ventricular afterload. For example, left ventricular afterload seems to be adequately reflected by acceleration of the aortic flow [13, 14], which is reduced by afterloading [13] and increased by unloading [14]. Similarly, RV afterload could be assessed by measuring the acceleration of the pulmonary flow (Fig. 2). Accele-

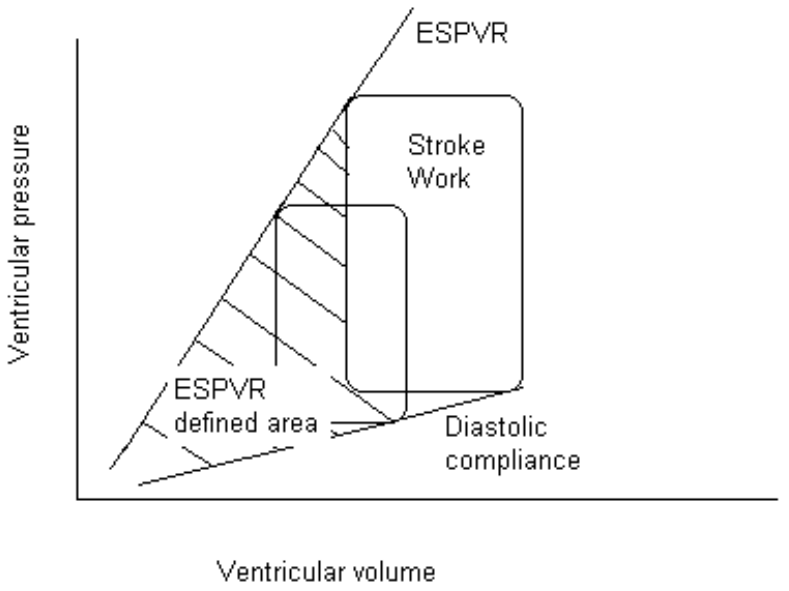


Fig. 1. Ventricular pressure-volume curve before (upper right rectangle) and after (lower left rectangle) preload reduction. *ESPVR* = end systolic pressure-volme relationship

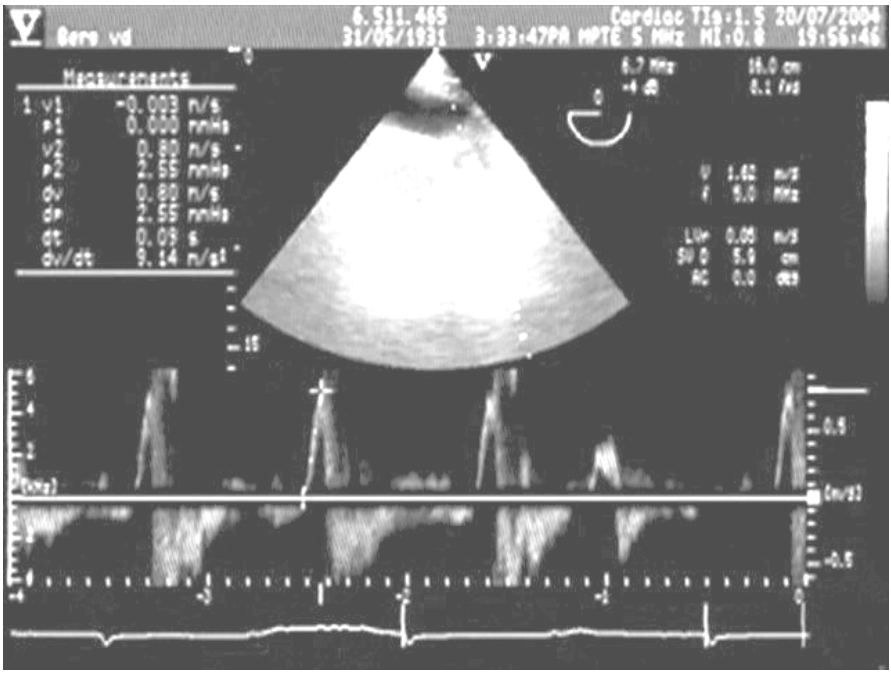


Fig. 2. Echo-Doppler of the pulmonary artery. *Bottom line* represents airway pressure, *Dotted line* in the second beat indicates acceleration of the pulmonary flow during inspiration

ration of the latter has been successfully assessed in several papers studying heart–lung interactions during mechanical ventilation [15–17].

Right ventricular afterload during expiration

It has been shown that positive end-expiratory pressure (PEEP) affects RV afterload. Biondi et al. [18] have shown that PEEP levels above 15 cm H_2O increased RV volume and decreased elastance, indicating an increase in RV afterload and a decline in RV contractility. Spackman et al. [19] have shown that, during high frequency ventilation, mean airway pressure above 12 cmH_2O results in a decrease in the RV ejection fraction and is associated with an increase in the RV end-systolic volume. The authors attributed these findings to an increase in the RV afterload due to increased mean airway pressure. Dambrosio et al. [20] found that RV ejection fraction and the RV stroke work/RV end-diastolic volume ratio started to decrease at PEEP levels higher than 10 cmH_2O in acute respiratory failure patients. Schmitt et al. [15] used echo-Doppler data obtained by transoesophageal echocardiography (TEE) to assess the effect of PEEP on the RV outflow impedance. In their study, high PEEP levels (13 ± 4 cmH_2O) caused an increased RV afterload. These studies clearly showed that RV afterload is elevated during mechanical ventilation with high PEEP levels.

Two factors that may have a role in increasing the RV afterload during high PEEP ventilation are direct compression of the pulmonary vascular bed, and atelectasis. Atelectasis can increase the RV afterload by two mechanisms: producing hypoxic pulmonary vasoconstriction [21–23], and high tidal volume ventilation. This use of large tidal volumes increases RV outflow impedance as assessed by Doppler TEE [16]. Moreover, large tidal volume ventilation is more likely to occur in the presence of atelectasis because of the so-called baby-lung effect [24]: if one imagines a lung with 50% atelectasis, then a pre-set tidal volume of 10 ml/kg would result in a tidal volume of 20 ml/kg in aerated lung areas [24]. Therefore, atelectasis may cause an increase in the RV afterload due to an increase in the tidal volume in aerated lung areas (baby-lung effect), and to hypoxic pulmonary vasoconstriction in non-aerated lung areas. This atelectasis cannot be reversed with the use of high PEEP ventilation, but only by the application of recruitment manoeuvres [25].

Right ventricular afterload during inspiration

RV afterload is not only increased by high PEEP levels; but also during inspiration RV afterload increment is observed [16, 26]. Poelaert et al. [26] showed that inspiration rather than expiration with high levels of PEEP caused RV afterload increment in cardiac surgery patients. Vieillard-Baron et al. [16] also showed that RV afterload is mainly increased during inspiration in patients with acute respiratory distress syndrome (ARDS). These authors separated the effects of peak inspiratory pressure (PIP) and tidal volume by chest trapping and application of PEEP. They found that tidal volume, and not PIP or PEEP, increased RV afterload. Although these results were very clear, theoretically this is hard to explain. Only intra-thoracic pressure, but not volume, generates a force that could compress pulmonary capillaries, increasing RV afterload. In addition, of course volume changes require pressure changes. The physiological explanation for the finding that tidal volume, not PIP, increases RV afterload is not yet known. However, this is more than a semantic discussion: if PIP and not tidal volume increases RV afterload, then elevated PEEP levels should increase RV afterload because of the increased PIP.

Open lung concept and RV afterload

The OLC is a ventilation strategy that entails short periods of high inspiratory pressures to open up collapsed alveoli followed by a relatively high level of PEEP to keep the alveoli open with (very) low tidal volume ventilation (4–6 ml/kg). The aim of this ventilation strategy is to avoid atelectasis, thereby attenuating ventilator-induced lung injury [27]. In cardiac surgery patients, this ventilation strategy attenuates reduction of lung volume and improves oxygenation after extubation [28]. One concern with the use of OLC is its effect on RV afterload due to the use

of relatively high PEEP levels. When RV afterload during OLC is assessed, care must be taken that RV preload is kept constant. In volume-loaded patients after cardiac surgery, Dyhr et al. [29] found no decrease in cardiac output by applying recruitment manoeuvres followed by a mean of 15 cmH_2O PEEP. Our group assessed RV afterload during OLC ventilation in cardiac surgery patients, using a PAC. We found that after a recruitment manoeuvre (mean pressure 45 cmH_2O) followed by a mean PEEP of 17 cmH_2O, RV afterload was not increased compared to conventional ventilation using 5 cmH_2O PEEP [30]. This suggests that when atelectasis is avoided, RV afterload is not increased by OLC ventilation. This also could explain the results of Huemer et al. [17], who found no increased RV afterload using 12 cmH_2O continuous positive airway pressure in healthy volunteers (without atelectasis), assessed by echo-Doppler. The separate effects of PEEP and tidal volume on RV impedance during OLC ventilation remained, however, unknown.

In a sequential study, the separate effect of PEEP during expiration while ventilating according to the OLC was found not to increase RV afterload, as assessed by echo-Doppler. In this (yet unpublished) study, OLC ventilation with a mean PEEP level of 14 cmH_2O was compared with conventional ventilation using 5 cmH_2O PEEP in cardiac surgery patients. That PEEP during OLC ventilation does not increase RV afterload is probably explained by the avoidance of atelectasis. As explained above, atelectasis may increase RV afterload due to local hypoxic pulmonary vasoconstriction, and the avoidance of atelectasis may therefore attenuate RV afterload increment during high PEEP ventilation.

Furthermore, during conventional ventilation, RV afterload increased during inspiration, as described by Vieillard-Baron et al. [16]. This phenomenon did not occur during OLC ventilation, as assessed by echo-Doppler in the study described above. Ventilation according to the OLC in this latter study was accompanied by a lower tidal volume but a higher inspiratory pressure than occurred with conventional ventilation. The low tidal volume used during OLC ventilation may explain the lack of increase in RV afterload during inspiration. Also, alveolar overdistention during inspiration could be reduced by application of OLC ventilation, despite the use of high PEEP levels. Namely, the group of Amato [25] demonstrated in ARDS patients using a CT-scan that tidal recruitment and degree of overdistention during inspiration decreased when a recruitment manoeuvre was performed compared with pre-recruitment with 25 cmH_2O PEEP. This implies that during OLC ventilation RV afterload is not increased during inspiration due to: (1) the reduction of tidal volume ventilation in aerated lung areas due to homogenisation of pulmonary gas distribution, and (2) the use of lower tidal volume, set on the ventilator. Furthermore, these two effects of OLC ventilation act in synergy: homogenisation of pulmonary gas distribution reduces tidal volume ventilation of aerated lung areas, which is reduced even further by the lower tidal volume ventilation set on the ventilator.

Conclusions

While high PEEP appears to increase RV afterload, the use of a ventilation strategy that avoids atelectasis, combined with low tidal volume ventilation might attenuate the effect of airway pressure on RV afterload.

References

1. Pinhu L, Whitehead T, Evans T et al (2003) Ventilator-associated lung injury. Lancet 361:332–340
2. Verbrugge SJ, Sorm V, van Veen et al (1998) Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental Klebsiella pneumoniae inoculation. Intensive Care Med 24:172–177
3. Vieillard-Baron A, Schmitt JM, Augarde R et al (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 29:1551–1555
4. Vieillard-Baron A, Prin S, Chergui K et al (2002) Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166:1310–1319
5. Mebazaa A, Karpati P, Renaud E et al (2004) Acute right ventricular failure—from pathophysiology to new treatments. Intensive Care Med 30:185–196
6. Greyson C, Xu Y, Lu L et al (2000) Right ventricular pressure and dilation during pressure overload determine dysfunction after pressure overload. Am J Physiol Heart Circ Physiol 278:H1414-H1420
7. Versprille A (1984) Pulmonary vascular resistance. A meaningless variable. Intensive Care Med 10:51–53
8. McGregor M, Sniderman A (1985) On pulmonary vascular resistance: the need for more precise definition. Am J Cardiol 55:217–221
9. Gorback MS (1990) Problems associated with the determination of pulmonary vascular resistance. J Clin Monit 6:118–127
10. Naeije R (2003) Pulmonary vascular resistance. A meaningless variable? Intensive Care Med 29:526–529
11. Suga H, Hayashi T, Shirahata M (1981) Ventricular systolic pressure-volume area as predictor of cardiac oxygen consumption. Am J Physiol 240:H39-H44
12. Pinsky MR (1997) The hemodynamic consequences of mechanical ventilation: an evolving story. Intensive Care Med 23:493–503
13. Harrison MR, Clifton GD, Berk MR et al (1989) Effect of blood pressure and afterload on Doppler echocardiographic measurements of left ventricular systolic function in normal subjects. Am J Cardiol 64:905–908
14. Bedotto JB, Eichhorn EJ, Grayburn PA (1989) Effects of left ventricular preload and afterload on ascending aortic blood velocity and acceleration in coronary artery disease. Am J Cardiol 64:856–859
15. Schmitt JM, Vieillard-Baron A, Augarde R et al (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29:1154–1158
16. Vieillard-Baron A, Loubieres Y, Schmitt JM et al (1999) Cyclic changes in right ventri-

cular output impedance during mechanical ventilation. J Appl Physiol 87:1644–1650
17. Huemer G, Kolev N, Kurz A et al (1994) Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography. Chest 106:67–73
18. Biondi JW, Schulman DS, Soufer R et al (1988) The effect of incremental positive end-expiratory pressure on right ventricular hemodynamics and ejection fraction. Anesth Analg 67:144–151
19. Spackman DR, Kellow N, White SA et al (1999) High frequency jet ventilation and gas trapping. Br J Anaesth 83:708–714
20. Dambrosio M, Fiore G, Brienza N et al (1996) Right ventricular myocardial function in ARF patients. PEEP as a challenge for the right heart. Intensive Care Med 22:772–780
21. Barer GR, Howard P, McCurrie JR et al (1969) Changes in the pulmonary circulation after bronchial occlusion in anesthetized dogs and cats. Circ Res 25:747–764
22. Yamaki S, Abe A, Sato K et al (1997) Microatelectasis in patients with secundum atrial septal defect and its relation to pulmonary hypertension. Jpn Circ J 61:384–389
23. Pirlo AF, Benumof JL, Trousdale FR (1981) Atelectatic lobe blood flow: open vs. closed chest, positive pressure vs. spontaneous ventilation. J Appl Physiol 50:1022–1026
24. Verbrugge SJ, Lachmann B (1999) Mechanisms of ventilation-induced lung injury: physiological rationale to prevent it. Monaldi Arch Chest Dis 54:22–37
25. De Matos GFJ, Borges JBS, Stanzani F et al (2004) Tidal recruitment decreases after stepwise recruitment maneuver: Multislice thoracic CT analysis. Am J Respir Crit Care Med 169:A720
26. Poelaert JI, Visser CA, Everaert JA et al (1994) Doppler evaluation of right ventricular outflow impedance during positive-pressure ventilation. J Cardiothorac Vasc Anesth 8:392–397
27. Lachmann B (1992) Open up the lung and keep the lung open. Intensive Care Med 18:319–321
28. Reis Miranda D, Struijs A, Koetsier P et al (2005) Open lung ventilation improves functional residual capacity after extubation in cardiac surgery. Crit Care Med (in press)
29. Dyhr T, Laursen N, Larsson A (2002) Effects of lung recruitment maneuver and positive end-expiratory pressure on lung volume, respiratory mechanics and alveolar gas mixing in patients ventilated after cardiac surgery. Acta Anaesthesiol Scand 46:717–725
30. Reis Miranda D, Gommers D, Struijs A et al (2004) The open lung concept: effects on right ventricular afterload after cardiac surgery. Br J Anaesth 93:327- 332

Chapter 32

Computed tomography evaluation of lung collapse and recruitment manoeuvres during anaesthesia

L.M.S. Malbouisson, J.O.C. Auler jr.

It has been long recognised that general anaesthesia procedures induce profound alterations upon the respiratory system. Since the beginning of the twentieth century, clinicians have recognised that lung collapse resulting from incapacity to deeply inspire after abdominal surgery is an important cause of postoperative lung complications [1]. In the late 1950s and 1960s, some authors suggested that the worsening of pulmonary gas exchange was due to shunt and uneven pulmonary ventilation/perfusion ratio during spontaneous ventilation general anaesthesia, and proposed the use of increased inspired oxygen concentration to treat oxygenation impairment related to general anaesthesia [2, 3]. After introduction of mechanical ventilation in clinical anaesthesia practice, in order to maintain gas exchange in patients undergoing major surgical procedures, impaired oxygenation and a progressive fall in pulmonary compliance were described as frequent perioperative complications, even in patients with normal preoperative pulmonary function [2, 4–7]. Bendixen et al. proposed that the progressive fall in lung compliance was caused, in part, by changes in surface tension in the lungs, but collapse of air spaces was likely to account for a large part of the fall in compliance, a condition they referred to as intraoperative atelectasis [5]. In the same year, Bergman reported a decrease in functional residual capacity (FRC) in patients undergoing anaesthesia and mechanical ventilation [8]. The decrease in FRC was attributed to atelectasis and was found to be associated with pulmonary ventilation/perfusion mismatch. These two components were suspected to be the main mechanisms explaining hypoxaemia during anaesthesia [9, 10]. In the same report, Bendixen showed that consecutive lung hyperinflations during anaesthesia were able to restore adequate arterial oxygenation and lung compliance. During the last decades, several studies have been conducted in order to elucidate the mechanisms involved in lung collapse and in its treatment. Since the mid-1980s, thoracic computed tomography (CT) has been used in research and clinical practice, enabling in vivo evaluation of lung morphology and quantitative assessment of regional gas and tissue distribution within the lung parenchyma. The objective of this chapter is to review the mechanisms associated with lung collapse and the use alveolar recruitment manoeuvres during the intraoperative period, in the light CT findings.

Definition and incidence of intraoperative atelectasis

Intraoperative atelectasis has been defined as lung collapse occurring after anaesthesia induction and is clinically characterised by a decrease in lung compliance and impairment of arterial oxygenation. The occurrence of atelectasis during anaesthesia is high, with an estimated incidence of 50–90% of all adult patients undergoing general anaesthesia, either with spontaneous breathing or mechanical ventilation [11, 12]. According to Moller et al., mild to moderate hypoxaemia, defined as arterial oxygen saturation between 85% and 90%, occurs in about half of patients undergoing general anaesthesia for elective surgery, despite the use of an inspired oxygen concentration as high as 40% [11]. Using thoracic CT, Lundquist et al. studied 109 patients scheduled for elective abdominal surgery during general anaesthesia. They reported that dependent pulmonary densities, interpreted as atelectasis, were seen in 95 patients (87%) [12]. Two different types of atelectasis were described: pulmonary densities homogeneously distributed in 78% of patients and nonhomogeneously in 9% [12].

Patients undergoing cardiac surgery frequently develop intraoperative atelectasis, a long-lasting postoperative complication. In our institution, mild to moderate hypoxaemia in the immediate postoperative period was detected in 52% of 461 patients undergoing elective CABG (unpublished data). According to Magnusson et al., atelectasis is a major cause of hypoxaemia and shunt after cardiopulmonary bypass (CPB) [13]. Gale et al. investigated the incidence of pulmonary complications after heart operations with CPB and found radiological evidence of atelectasis on radiographic chest plates in 64% of 50 consecutive patients [14]. On the first postoperative day, Tenting et al. obtained thoracic CT scans at three levels of the thorax from 18 patients submitted to CABG or mitral valve surgery. They found pulmonary bilateral dependent densities, corresponding to a fraction of collapsed lung tissue of about 20%, in all patients but one [15]. Vargas et al. studied late pulmonary complications in 125 patients undergoing CABG. Thirty patients had normal chest radiographs, 38 had atelectasis, and 57 had pleural changes after 6 days. In 11 patients, only atelectasis was observed in the radiograph, and in 27 it was combined with pleural changes [16]. These authors observed a mean decrease in functional vital capacity (FVC) and forced expired volume in 1 s (FEV_1) of 33.4% and 33.5%, respectively, in patients with atelectasis. According to the same group, the nadir of FVC occurs immediately after surgery and improves gradually thereafter. However, on the tenth postoperative day, FVC remains more than 30% below preoperative values [17].

Mechanisms of intraoperative lung collapse

Intraoperative lung collapse begins to occur within the first several minutes after anaesthetic induction. Brismar et al. used CT to study 20 patients undergoing general anaesthesia with muscle relaxation for abdominal surgery. They found that, 5 min after induction, all subjects had developed crest-shaped changes of increased

density in the dependent regions of both lungs. These authors also reported that densities did not increase after 20 min of anaesthesia and were not affected by the inspiratory oxygen fraction, neither was the size of densities correlated with age [18]. However, the impact of anaesthesia duration on the behaviour of intraoperative atelectasis is still controversial. Other studies have found that, during abdominal and thoracic surgery, arterial oxygenation progressively worsened during the course of surgery [19, 20]. Furthermore, none of these studies were able to discriminate whether this progressive deterioration in pulmonary gas exchanges was secondary to anaesthesia with muscle relaxation or to a combination of anaesthesia and surgical manipulation.

The mechanisms involved in atelectasis formation and decrease in FRC are multifactorial, and can be divided into three main groups: mechanical compression of lung parenchyma, absorption of alveolar gas contents, dysfunction of the surfactant system. From a mechanical point of view, the degree of lung aeration depends on the transpulmonary pressure, which is exposed to anteroposterior and cephalocaudal gradients. When the patient is placed in a supine position, the anteroposterior gradient is related to gravity and to the superimposed lung pressure, which imposes increments of 0.25 g cm^2 from nondependent to dependent lung regions in patients with nonoedematous lungs and 1 g cm^2 or more in patients with acute inflammatory lung processes, such as acute lung injury and ARDS [21, 22]. The cephalocaudal gradient results from the transmission of abdominal pressure to the thoracic cavity [23, 24]. Physiologically, the most caudal and dependent parts of the lung, i.e. the lower lobes, are exposed to a lower transpulmonary pressure than the most cephalic and nondependent parts of the lung, i.e. the upper lobes. Even in the awake state, supine positioning is associated with a decrease in FRC of 0.5–1 l [25]. An upward shift of the diaphragmatic cupola secondary to anaesthesia and muscle paralysis is associated with a further reduction in FRC of 0.5–1 l [26–28]. In obese patients or patients undergoing upper abdominal or laparoscopic surgery, diaphragm shift may have a magnified effect on atelectasis formation in the lower lobes of the lung [29]. Another factor contributing to the decrease in transpulmonary pressure in caudal and dependent lung regions is compression of the lower lobes by the heart and mediastinal contents [30–33]. All of these mechanisms contributing to a decrease in transpulmonary pressure in caudal and dependent lung regions are in accordance with reports from other authors [30, 34–36]. As expected, in patients undergoing general anaesthesia, lung collapse is usually observed in the most caudal and dependent regions of the lungs. In patients submitted to general anaesthesia for abdominal surgery using thoracic CT, Brismar et al. found that the largest lung densities were in the most caudal segments, with smaller ones in the cephalad regions [18]. The same results were described by Warner et al. in healthy volunteers undergoing general anaesthesia with halothane [37], by Tenling et al. in patients undergoing cardiac surgery [15] and by Puybasset et al. in patients developing acute lung injury postoperatively [27, 38, 39]. Absorption of alveolar gas contents is also implicated in the formation of intraoperative atelectasis, even in the absence of airway obstruction. The use of high inspiratory oxygen concentrations has often been reported as an important

factor contributing to lung collapse. Joyce and Williams postulated that the normal lung functioned as an ideal lung compartment but, after anaesthetic induction, the airways of the dependent lung areas closed up and behaved as a closed collapsible cavity. Using a mathematical model, the authors proposed that preoxygenation and use of high inspiratory oxygen concentrations increased the rate of gas uptake from the unventilated area of the lung and were the most important determinants in initiating collapse [40]. Rothen et al. showed in 12 elective surgical patients undergoing general anaesthesia that when a $FiO_2 = 1$ was used after a vital capacity recruitment manoeuvre, atelectasis reappeared within 5 min. When the patients were ventilated using a lower inspired oxygen concentration of 40% after the recruitment manoeuvre, atelectasis did not recur for at least 40 min [41]. Rothen et al. also described surgical patients with previously normal lungs whose pulmonary shunt increased from 0.3 to 2.1%, and a small amount of atelectasis was detected when patients were ventilated with $FiO_2 = 0.3$. When $FiO_2 = 1$ was used instead, the shunt fraction increased to 6.5% and a greater proportion of lung parenchyma became nonaerated [42]. This association between high inspired oxygen concentrations and lung collapse has been described for at least 50 years [9].

While some beneficial effects can be attributed to the use of a high oxygen concentration during anaesthesia, such as reduction of postoperative nausea and vomiting [43], increase in antimicrobial and proinflammatory responses of alveolar macrophages [44], possible decrease in postoperative surgical-wound infections [45], and prevention of hypoxaemic episodes, these may be counteracted by atelectasis formation. Atelectasis that was not promptly reverted in the postoperative period may persist for several days postoperatively, increasing the length of time of mechanical ventilation, respiratory therapy, and hospital stay, and the medical costs.

A third factor related to the development of intraoperative atelectasis is dysfunction of the surfactant system, which plays a pivotal role in preventing alveolar collapse by decreasing alveolar-wall surface tension and stabilising alveolar structure [46]. Experimental evidence obtained from deflation pressure–volume curves in the dog isolated lung model showed a reduction in percent maximal lung volume that was proportional to the increase in inhalational anaesthetics [47]. Studying tracheal aspirates from children undergoing cardiac surgery before and after CPB, Friedrich et al. observed that the procedure induced profound changes in the surfactant system involving both phospholipid and protein components [48]. Griese et al. also observed prolonged surfactant system dysfunction in children after open heart surgery with CPB [49]. However, the role played by the surfactant dysfunction in the development of intraoperative atelectasis is controversial, since surfactant protein turnover is about 14 h, time enough to complete the majority of surgical procedures.

Some other factors involved in the dynamics of atelectasis formation and maintenance during the intraoperative period should be discussed. Atelectasis has been described in patients undergoing most of types of general anaesthesia, whether intravenous or inhalational, and combined general-regional anaesthesia in patients spontaneously breathing or mechanically ventilated [5, 50]. The influence of regional

anaesthesia on lung collapse is still controversial. Earlier reports did not describe a significant decrease in arterial oxygenation, closing capacity, or FRC [51, 52]. Conversely, Freund et al. reported that regional blockades at a higher thoracic level were associated with a decrease in inspiratory capacity and might lead to development of atelectasis [53]. Airway suctioning, by degasifying the lungs is another factor that could theoretically induce atelectasis. Lu et al. studied the effects of airway suctioning in an experimental model consisting of a mechanically ventilated animal, with $FiO_2 = 0.3$. CT examination revealed that endotracheal suctioning resulted in atelectasis, a 29% reduction in the cross-sectional surface area of the bronchi, a decrease in arterial oxygen saturation from 95 to 87%, an increase in shunt from 19 to 31%, and an increase in lung tissue resistance. According to the data of these authors, an increase in FiO_2 would interact synergistically with airway suctioning, resulting in worsening of airway-suctioning-induced atelectasias, despite the protection conferred against transitory-suctioning-induced hypoxaemia [54]. Low tidal volumes used in the context of protective ventilation strategy in order to decrease ventilator-induced lung injuries would also be listed as a possible cause of atelectasis if adequate levels of PEEP had not been used. CPB during cardiac surgery has been described as a major factor contributing to the formation of intraoperative atelectasis, independent of general anaesthesia and thoracotomy [13]. Mediastinal manipulation during cardiac surgery is another cause of intraoperative lung collapse.

Clinical consequences of intraoperative atelectasis on patient outcome

The presence of atelectasis may predispose the lung to the deleterious effects of mechanical ventilation or aggravate already existing lung injuries. Some studies have shown that lung injury can be induced by mechanical overstretching of the aerated parenchyma. Since tidal ventilation is distributed to aerated lung parenchyma, the greater the volume of collapsed lung, the greater the tidal ventilation volume delivered to the noncollapsed lung regions, promoting sustained tidal hyperinflation of these regions and possibly volutrauma/barotrauma and inflammation with harmful consequences for lung tissue [55–57]. This effect of relatively increased tidal volumes on normally aerated lung parenchyma is well-established in patients with acute lung injury [58, 59] and may also be true for patients undergoing general anaesthesia. Ventilation-induced lung injury may increase the amount of time that the patient requires mechanical ventilation, as it evolves to postoperative respiratory failure and ARDS [60]. Other perioperative pulmonary complications associated with atelectasis are the necessity of intensive respiratory therapy, prolonged ICU stay, and postoperative pneumonia [61].

Clinical evaluation of atelectasias and alveolar recruitment

An impairment in arterial oxygenation and a decrease in pulmonary compliance are the first physiologic alterations suggesting the presence of atelectasis after anaesthesia induction. The pressure–volume curve of the respiratory system also give some clues as to the presence of atelectasis, such as a decrease in quasistatic compliance and the appearance of a lower inflection point. Conventional chest radiographs may present lines or opacifications, displacement of interlobar fissures, or loss of volume of the affected segment or lobe. Hemidiaphragm or mediastinal shift and a decrease in intercostal space are other radiological signs suggesting atelectasis. Conventional chest radiographs may not adequately detect collapse in small lung regions or in zones where images are superposed.

CT evaluation of alveolar collapse and recruitment

Compared to plain radiograph, there are several advantages in the use of CT to assess lung collapse: such as the ability to visually analyse lung morphology and to quantitatively assess lung volume (gas and tissue), either in the entire lung or regionally [27]. CT analysis also measures the CT attenuation coefficient from specific voxels, the CT volume unit, which enables the quantification voxel gas and tissue volumes. The calculations are based on the following principles of measurement: the volume of the total lung is measured as the total number of voxels present in a given region of interest multiplied by the volume of the voxel. The respective volumes of tissue and gas are calculated using simple mathematical equations and rely on the principle that the CT attenuation coefficient and physical density are closely correlated [62]. The CT attenuation coefficient characterising each voxel is expressed in Hounsfield units (HU) and is defined as the attenuation coefficient of the X-ray by the material being studied minus the attenuation coefficient of water divided by the attenuation coefficient of water. By convention, the CT number of water is 0 HU. The CT attenuation is scaled by a factor 1000, the CT number of gas being -1000 HU. According to the exact linear relationship existing between physical density and CT attenuation coefficient [63, 64], a lung area characterised by a mean CT number of -600 HU is considered as being composed of 60% gas and 40% water. A lung area characterised by a mean CT number of -300 HU was comprised between 30% gas and 70% water. In this analysis, water refers to lung tissue, extravascular lung water, cells, and blood. Based on this analysis, it is simple to compute the volume of gas and tissue present in the lung. CT also enables characterisation of lung regions according to their degree of aeration. Lung regions with a CT attenuation between -1000 and -900 HU are considered as overdistended, those between -900 and -500 HU as normally aerated, those between -500 and -100 HU as poorly aerated, and those between -100 and +100 HU as nonaerated or atelectatic [65]. CT assessment of alveolar recruitment was initially described as the decrease in nonaerated lung parenchyma according to a single juxtadiaphragmatic CT section. Since the transpulmonary pressure is nonhomogeneouly distributed within the lung, this approach may misevaluate the alveolar recruitment occurring in the

entire lung as well as possible recruitment-induced lung overdistension [66]. The use of fast helicoidal CT scanners in clinical practice enables assessment of alveolar recruitment of the entire lung within a few seconds. Another CT method to assess alveolar recruitment in patients with ARDS is to compute the volume of gas penetrating poorly and nonaerated lung regions [65].

Due to technical difficulties involved in the transportation of postoperative patients to CT scan facilities, the use of CT to diagnose lung collapse and measure alveolar recruitment is reserved for study protocols, clinical cases involving hypoxaemia, or patients who are difficult to treat. In the last few years, a newer method to assess lung collapse, electrical impedance tomography at bedside, has been proposed to assess regional ventilation in the context of ARDS [67]. Changes in intrathoracic gas volume distribution are detected by alterations in electrical impedance signals obtained through electrodes placed in the chest wall. This promising but still experimental method enables detection of regional ventilation alterations in real time, aiding in the diagnostic of atelectasis [68, 69].

Use of intraoperative alveolar recruitment manoeuvres

Mead et al. and Ferris et al., were the first to report worsening of arterial oxygenation and decrease in lung compliance in animal models of general anaesthesia with mechanical ventilation using 'normal tidal ventilation'. Since then, recruitment manoeuvres in the form of deep inspirations have been described as a means to revert the decrease in oxygenation and compliance [70, 71]. Bendixen and coworkers observed that the progressive decrease in lung compliance and arterial oxygenation in surgical patients undergoing general anaesthesia and controlled mechanical ventilation were restored to normal values by implementing hyperinflation of the lungs until total lung capacity was reached. The authors described a recruitment manoeuvre using three sustained inspiratory inflations with an anaesthesia rebreathing bag, the first inflation at a pressure of 20 cmH_2O during 10 s, the second with a pressure of 30 cmH_2O during 15 s, and the third with a pressure of 40 cmH_2O during 20 s [5]. From these initial reports describing the effects of hyperinflation manoeuvres to counteract the deleterious effects of atelectasis on gas exchange and respiratory mechanics, recruitment manoeuvres have become an important adjunct to mechanical ventilation during general anaesthesia. Other lung-recruiting protocols to reverse intraoperative lung collapse have been described by different authors. Among these, the use of three consecutive sustained hyperinflations with inspiratory pressure of 40 cmH_20 has been shown to virtually reexpand all collapsed lung areas in patients with normal lungs who undergo general anaesthesia for abdominal and cardiac surgery [72, 73]. Another recruitment manoeuvre that could be used in the intraoperative period was described by Tusman et al. These authors increased PEEP in a stepwise manner using increments of 5–15 cmH_2O, adjusted the respiratory rate to 8 breaths per minute, and prolonged the inspiratory pause to 20% of respiratory cycle time. In a second step, tidal volume was increased until 18 ml kg^{-1} or a peak inspiratory pressure of 40 cm H_2O

was reached. These settings were maintained for at least ten breaths, after which tidal volume was reduced to baseline levels and a PEEP of 5 cm H_2O was then maintained [74].

An important issue related to opening the lungs after performing a recruitment manoeuvre is the prevention of recollapse. The same factors predisposing to loss of lung aeration and atelectasis formation will be present after implementation of alveolar recruitment manoeuvres, and will probably endure until the end of anaesthesia, thus again necessitating the use of PEEP to prevent recollapses of the lungs. The level of PEEP that should be used is still a matter of debate. As described in a study by Brismar et al., a PEEP of 10 cmH_2O prevented or reduced the appearance of new lung densities after recruitment manoeuvres [18]. However, a fixed PEEP level may not be enough or may produce deleterious effects on haemodynamics without promoting the expected response on arterial oxygenation [75, 76]. PEEP level should be individualised and titrated according to oxygenation, respiratory mechanics, and haemodynamic behaviour during surgery. Another point to be highlighted is that after a recruitment manoeuvre the lowest possible inspired oxygen concentration should be used in order to decrease the rate of atelectasis formation due to gas reabsorption.

Nevertheless, a few questions concerning the use of intraoperative recruitment manoeuvres in anaesthetised patients, especially those undergoing cardiac surgery, are not yet resolved: (1) What kind of patient will benefit most by the recruitment manoeuvres? (2) Based on what criteria should the alveolar recruitment protocol be initiated? (3) How many recruitment manoeuvres should be realised during surgery?, and (4) What is the adequate interval time between manoeuvres? Recruitment manoeuvres will probably be well-tolerated by the majority of patients developing progressive worsening of oxygenation during surgery, and should not produce deleterious short- or long-term effects in lung function. In our institution, an ongoing study using CT is being developed to assess the effects of intraoperative recruitment on the first postoperative day in patients undergoing on-pump and off-pump CABG. Nonetheless, this manoeuvre might be harmful in patients presenting with important right ventricular dysfunction, severe pulmonary hypertension, untreated low cardiac output states, or shock. Although not frequently observed in clinical practice, another concern to be kept in mind after implementation of recruitment manoeuvres is the possibility that the patient develops complications, such as air leak syndrome in its various forms. Except for contraindications, any patient whose oxygenation worsens during surgery should be recruited and should receive PEEP at adequate levels shortly thereafter. The recruitment manoeuvres may be repeated as many times as considered necessary by the attending anaesthesiologist. However, the need of repeated manoeuvres may be an indication that the PEEP levels adjusted after previous recruitments are not enough to prevent lung recollapse. For the moment, monitoring of intraoperative recruitment efficacy involves only functional pulmonary parameters. In the near future, an imaging method such as high-resolution electrical impedance tomography will be available to intraoperatively monitor the distribution of regional ventilation. This will allow patient-by-patient determination of the level of inspiratory pressure necessary to

open up the lungs and the adequate level of PEEP needed to keep the lung open without producing regional overinflation.

The presumable beneficial effects of recruitment manoeuvres go beyond the reversion of oxygenation and the mechanical effects of atelectasis. Homogenising the distribution of ventilation after the opening of collapsed areas is associated with a reduction in ventilation-induced lung injury and a decrease in the necessity of postoperative mechanical ventilation. Despite the absence of clear evidence linking the presence of atelectasis to postoperative pneumonia, a reduction in the duration of postoperative mechanical ventilation is associated with a lower incidence of postoperative pulmonary infections, shorter ICU length of stay, and lower hospital costs.

References

1. Pasteur W (1910) Active lobar collapse of the lung after abdominal operations. Lancet 2:1080–1083
2. Nunn JF, Payne JP (1962) Hypoxaemia after general anaesthesia. Lancet 2:631–632
3. Grigor KC (1954) Atelectasis during anaesthesia (spontaneous atelectasis). Anaesthesia 9:185–189
4. Hallam J (1950) Collapse of the right lung following dental extractions under nitrous oxide anesthesia. Br J Anaesth 22:123
5. Bendixen HH, Hedley-Whyte J, Laver MB (1963) Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. a concept of atelectasis. N Engl J Med 269:991–996
6. Conway CM, Payne JP (1964) Hypoxaemia associated with anaesthesia and controlled respiration. Lancet 41:12–14
7. Tibbs DJ (1965) Hypoxaemia after anaesthesia. Lancet 14:1105–1106
8. Bergman NA (1963) Distribution of Inspired gas during anesthesia and artificial ventilation. J Appl Physiol 18:1085–1089
9. Dery R, Pelletier J, Jacques A et al (1965) Alveolar collapse induced by denitrogenation. Can Anaesth Soc J 12:531–557
10. Bendixen HH (1964) Atelectasis and shunting. Anesthesiology 25:595–596
11. Moller JT, Johannessen NW, Berg H et al (1991) Hypoxaemia during anaesthesia – an observer study. Br J Anaesth 66:437–444
12. Lundquist H, Hedenstierna G, Strandberg A et al (1995) CT-assessment of dependent lung densities in man during general anaesthesia. Acta Radiol 36:626–632
13. Magnusson L, Zemgulis V, Wicky S et al (1997) Atelectasis is a major cause of hypoxemia and shunt after cardiopulmonary bypass: an experimental study. Anesthesiology 87:1153–1163
14. Gale GD, Teasdale SJ, Sanders DE et al (1979) Pulmonary atelectasis and other respiratory complications after cardiopulmonary bypass and investigation of aetiological factors. Can Anaesth Soc J 26:15–21
15. Tenling A, Hachenberg T, Tyden H et al (1998) Atelectasis and gas exchange after cardiac surgery. Anesthesiology 89:371–378
16. Vargas FS, Cukier A, Terra-Filho M et al (1993) Influence of atelectasis on pulmonary function after coronary artery bypass grafting. Chest 104:434–437
17. Vargas FS, Terra-Filho M, Hueb W et al (1997) Pulmonary function after coronary artery bypass surgery. Respir Med 91:629–633

18. Brismar B, Hedenstierna G, Lundquist H et al (1985) Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. Anesthesiology 62:422–428
19. Lundh R, Hedenstierna G (1983) Ventilation-perfusion relationships during anaesthesia and abdominal surgery. Acta Anaesthesiol Scand 27:167–173
20. Jonmarker C, Nordstrom L, Werner O (1986) Changes in functional residual capacity during cardiac surgery. Br J Anaesth 58:428–432
21. Pelosi P, D'Andrea L, Vitale G et al (1994) Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149:8–13
22. Tomiyama N, Takeuchi N, Imanaka H et al (1993) Mechanism of gravity-dependent atelectasis. Analysis by nonradioactive xenon-enhanced dynamic computed tomography. Invest Radiol 28:633–638
23. Agostini E, D'Angelo E, Bonanni MV (1970) The effect of the abdomen on the vertical gradient of pleural surface pressure. Respir Physiol 8:332–346
24. Agostini E, D'Angelo E, Bonanni MV (1970) Topography of pleural surface pressure above resting volume in relaxed animals. J Appl Physiol 29:297–306
25. Nunn JF (1987) Respiratory aspects of anaesthesia. In: Nunn JF (ed) Applied respiratory physiology. Butterworths, London, pp 350–370
26. Froese AB, Bryan AC (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242–254
27. Puybasset L, Cluzel P, Chao N et al (1998) A computed tomography scan assessment of regional lung volume in acute lung injury. Am J Respir Crit Care Med 158:1644–1655
28. Reber A, Nylund U, Hedenstierna G (1998) Position and shape of the diaphragm: implications for atelectasis formation. Anaesthesia 53:1054–1061
29. Eichenberger A, Proietti S, Wicky S et al (2002) Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. Anesth Analg 95:1788–1792, table of contents
30. Hyatt RE, Bar-Yishay E, Abel MD (1985) Influence of the heart on the vertical gradient of transpulmonary pressure in dogs. J Appl Physiol 58:52–57
31. Hoffman EA (1985) Effect of body orientation on regional lung expansion: a computed tomographic approach. J Appl Physiol 59:468–480
32. Hubmayr RD, Walters BJ, Chevalier PA et al (1983) Topographical distribution of regional lung volume in anesthetized dogs. J Appl Physiol 54:1048–1056
33. Malbouisson LM, Busch CJ, Puybasset L et al (2000) Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. Am J Respir Crit Care Med 161:2005–2012
34. Strandberg A, Hedenstierna G, Tokics L et al (1986) Densities in dependent lung regions during anaesthesia: atelectasis or fluid accumulation? Acta Anaesthesiol Scand 30:256–259
35. Yang QH, Lai-Fook SJ (1991) Effect of lung inflation on regional lung expansion in supine and prone rabbits. J Appl Physiol 71:76–82
36. Yang QH, Kaplowitz MR, Lai-Fook SJ (1989) Regional variations in lung expansion in rabbits: prone vs. supine positions. J Appl Physiol 67:1371–1376
37. Warner DO, Warner MA, Ritman EL (1996) Atelectasis and chest wall shape during halothane anesthesia. Anesthesiology 85:49–59
38. Puybasset L, Cluzel P, Gusman P et al (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. Intensive Care Med 26:857–869
39. Puybasset L, Cluzel P, Chaw N et al (1997) Distribution of volume reduction in post

operative acute lung injury- factors influencing peep-induced alveolar recruitment. Br J Anaesth 78:supplement 1: 116:A380 (abs)
40. Joyce CJ, Williams AB (1999) Kinetics of absorption atelectasis during anesthesia: a mathematical model. J Appl Physiol 86:1116–1125
41. Rothen HU, Sporre B, Engberg G et al (1995) Reexpansion of atelectasis during general anaesthesia may have a prolonged effect. Acta Anaesthesiol Scand 39:118–125
42. Rothen HU, Sporre B, Engberg G et al (1996) Atelectasis and pulmonary shunting during induction of general anaesthesia — can they be avoided? Acta Anaesthesiol Scand 40:524–529
43. Goll V, Akca O, Greif R et al (2001) Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesth Analg 92:112–117
44. Kotani N, Hashimoto H, Sessler DI et al (2000) Supplemental intraoperative oxygen augments antimicrobial and proinflammatory responses of alveolar macrophages. Anesthesiology 93:15–25
45. Greif R, Akca O, Horn EP et al (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. N Engl J Med 342:161–167
46. Nunn JF (1987) Applied Respiratory Physiology. Butterworths, London
47. Woo SW, Berlin D, Hedley-Whyte J (1969) Surfactant function and anesthetic agents. J Appl Physiol 26:571–577
48. Friedrich B, Schmidt R, Reiss I et al (2003) Changes in biochemical and biophysical surfactant properties with cardiopulmonary bypass in children. Crit Care Med 31:284–290
49. Griese M, Wilnhammer C, Jansen S et al (1999) Cardiopulmonary bypass reduces pulmonary surfactant activity in infants. J Thorac Cardiovasc Surg 118:237–244
50. Bendixen HH, Bullwinkel B, Hedley-Whyte J et al (1964) Atelectasis and Shunting During Spontaneous Ventilation in Anesthetized Patients. Anesthesiology 25:297–301
51. McCarthy GS (1976) The effect of thoracic extradural analgesia on pulmonary gas distribution, functional residual capacity and airway closure. Br J Anaesth 48:243–248
52. Ward RJ, Bonica JJ, Freund FG et al (1965) Epidural and subarachnoid anesthesia. Cardiovascular and respiratory effects. Jama 191:275–278
53. Freund FG, Bonica JJ, Ward RJ et al (1967) Ventilatory reserve and level of motor block during high spinal and epidural anesthesia. Anesthesiology 28:834–837
54. Lu Q, Capderou A, Cluzel P et al (2000) A computed tomographic scan assessment of endotracheal suctioning-induced bronchoconstriction in ventilated sheep. Am J Respir Crit Care Med 162:1898–1904
55. Dreyfuss D, Basset G, Soler P et al (1985) Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Resp Dis 132:880–884
56. Dreyfuss D, Soler P, Saumon G (1995) Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations. Am J Resp Crit Care Med 151:1568–1575
57. Dreyfuss D, Saumon G (1996) Synergistic interaction between alveolar floading and distention during mechanical ventilation. Am J Respir Crit Care Med 153 (Suppl)A12 (abs)
58. Gattinoni L, Pelosi P, Pesenti A et al (1991) CT scan in ARDS: clinical and physiopathological insights. Acta Anaesthesiol Scand Suppl 95:87–94; discussion 94–86
59. Gattinoni L, Pesenti A (2005) The concept of 'baby lung.' Intensive Care Med 31:776–784

60. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
61. Brooks-Brunn JA (1995) Postoperative atelectasis and pneumonia. Heart Lung 24:94–115
62. Mull RT (1984) Mass estimates by computed tomography: physical density from CT numbers. Am J Roentgenol 143:1101–1104
63. Denison DM, Morgan MD, Millar AB (1986) Estimation of regional gas and tissue volumes of the lung in supine man using computed tomography. Thorax 41:620–628
64. Malbouisson LM, Preteux F, Puybasset L et al (2001) Validation of a software designed for computed tomographic (CT) measurement of lung water. Intensive Care Med 27:602–608
65. Malbouisson LM, Muller JC, Constantin JM et al (2001) Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1444–1450
66. Lu Q, Malbouisson LM, Mourgeon E et al (2001) Assessment of PEEP-induced reopening of collapsed lung regions in acute lung injury: are one or three CT sections representative of the entire lung? Intensive Care Med 27:1504–1510
67. Kunst PW, Vonk Noordegraaf A, Hoekstra OS et al (1998) Ventilation and perfusion imaging by electrical impedance tomography: a comparison with radionuclide scanning. Physiol Meas 19:481–490
68. Kunst PW, Bohm SH, Vazquez de Anda G et al (2000) Regional pressure volume curves by electrical impedance tomography in a model of acute lung injury. Crit Care Med 28:178–183
69. Kunst PW, de Vries PM, Postmus PE et al (1999) Evaluation of electrical impedance tomography in the measurement of PEEP-induced changes in lung volume. Chest 115:1102–1106
70. Mead J, Collier C (1959) Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. J Appl Physiol 14:669–678
71. Ferris BG Jr, Pollard DS (1960) Effect of deep and quiet breathing on pulmonary compliance in man. J Clin Invest 39:143–149
72. Rothen HU, Sporre B, Engberg G et al (1993) Re-expansion of atelectasis during general anaesthesia: a computed tomography study. Br J Anaesth 71:788–795
73. Magnusson L, Zemgulis V, Tenling A et al (1998) Use of a vital capacity maneuver to prevent atelectasis after cardiopulmonary bypass: an experimental study. Anesthesiology 88:134–142
74. Tusman G, Bohm SH, Vazquez de Anda GF et al (1999) 'Alveolar recruitment strategy' improves arterial oxygenation during general anaesthesia. Br J Anaesth 82:8–13
75. Pelosi P, Caironi P, Bottino N et al (2000) Positive end expiratory pressure in anesthesia. Minerva Anestesiol 66:297–306
76. Pelosi P, Ravagnan I, Giurati G et al (1999) Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. Anesthesiology 91:1221–1231

Chapter 33

Mechanisms of repair and remodelling in ARDS

C. Dos Santos, P.R.M. Rocco

Ashbaugh et al. [1] first described acute respiratory distress syndrome (ARDS) in 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on chest radiograph. ARDS is not defined by a specific pathogenesis, but reflects the lung's nonselective response to numerous insults and precipitating factors. Based on these observations, the term 'syndrome,' defined as a 'group of symptoms and signs of disordered function related to one another by means of some anatomic, physiologic, or biochemical peculiarity' was used. Although the term acute respiratory distress syndrome is often used interchangeably with acute lung injury (ALI), by strict criteria ARDS should be reserved for the most severe end of the spectrum [2].

The exact incidence of ARDS is difficult to measure, in part because of the lack of a clinical diagnostic test and in part because ARDS remains largely undiagnosed [3]. Overall, approximately 7% of patients admitted to the intensive care unit will develop ALI/ARDS, and among mechanically ventilated patients with acute respiratory failure the incidence varies from 11% to 23% [4]. The majority of recent studies report mortality to be in the 35–60% range when all patients who meet the American European Consensus Conference definitions are included [4].

Interstitial and intra-alveolar fibrosis are hallmarks of the more advanced stages of ARDS and are characterised by the abnormal and excessive deposition of extracellular matrix proteins, in particular collagen fibres [5]. The decrease in pulmonary compliance and progressive hypoxia resulting from fibrosis leads to ventilator dependence. As a result, progressive fibrosis is a direct cause of respiratory death [6], but it is also an indirect cause of death due to nosocomial infection and progressive multiorgan failure [7–9].

This chapter will focus on the histopathology and mechanisms of lung parenchyma remodelling and repair in ARDS.

Histopathology

There is a general belief that ARDS is the extreme form of a spectrum of lung injuries caused by a uniform inflammatory mechanism that is independent of the precipitating disease. This assumption mainly originates from pathology studies, which have consistently indicated that the lung response to injury is stereotyped, with transition from acute alveolar capillary damage to a late proliferative phase,

quite independently of the initial cause [10]. Unfortunately, most of the studies have described late or terminal events, since the pathologic features of the early phases of ARDS, such as interstitial oedema and alveolar collapse, are not easily recognised.

The pathologic features of the lung in ARDS are derived from severe injury to the alveolo-capillary unit. ARDS is described typically as passing through three phases: an inflammatory or exudative phase, a proliferative phase, and a fibrotic phase. However, recent evidence suggests that there are three overlapping phases of ARDS, with the underlying pathological process being termed diffuse alveolar damage (DAD), which itself is the result of severe injury to the alveolar-capillary unit [11, 12].

The exudative phase involves an acute inflammatory response with injury to endothelial and epithelial cells. The histologic features of the exudative phase are dense, eosinophilic hyaline membranes, and alveolar collapse. The endothelial cells swell, the intercellular junctions widen, and pinocytotic vesicles increase, causing the capillary membrane to be disrupted, resulting in capillary leak and oedema formation. Type I pneumocytes also become swollen with cytoplasmic vacuoles, which eventually detach from the basement membrane. At the same time, there is elaboration of a proliferative response. During the proliferative phase, type II cells migrate and begin to proliferate along the alveolar septa, in an attempt to cover the denuded basement membrane and re-establish continuity with the alveolar epithelium. Interstitial fibroblasts migrate into the alveolar clot, thereby initiating the fibroproliferative phase. Interstitial fibroblasts differentiate into myofibroblasts, which contain abundant actin and vinculin. Myofibroblasts proliferate and migrate through breaks in the alveolar membrane into the fibrinous intra-alveolar exudate, forming a cellular granulation tissue. Sparsely cellular, dense fibrous tissue, consisting mostly of collagen is deposited. Interestingly, myofibroblasts assume and maintain an enhanced proliferative phenotype, enabling them to proliferate with minimal exogenous stimulation [13]. If the fibrinous exudates can be resolved, restoration of normal lung architecture may be achieved. However, if epithelial cells migrate over the surface of the organising granulation tissue and transform the intra-alveolar exudate into interstitial tissue, interstitial fibrosis of the lung may develop. Fibroproliferation is also seen in the microcirculation, which contributes to the narrowing of the pulmonary circulatory cross-sectional area and subsequent pulmonary hypertension. The third or fibrotic phase may not occur in all patients with ARDS; it begins with extensive lung remodelling and develops into extensive fibrosis. Air spaces are irregularly enlarged and there is alveolar duct fibrosis. Initially, there is an increase in type III collagen, which is more flexible and susceptible to breakdown. Later, however, this is remodelled to the thicker and more resistant type I collagen, leading to a stiff lung [14].

Extracellular matrix organisation

The extracellular matrix (ECM) is not only a scaffold—with a mechanical role in supporting and maintaining tissue structure—but it is also a complex and

dynamic meshwork that influences many biological cell functions such as development, migration, and proliferation. The macromolecules that constitute the ECM are secreted locally, the composition of which depends on the cell types, their state of differentiation, and their metabolic status. Molecules comprising ECM consist of fibrous proteins (collagen, elastin) and structural or adhesive proteins (fibronectin and laminin) embedded in a hydrated polysaccharide gel containing several glycosaminoglycans, including hyaluronic acid. When the fibres are deformed, they carry stress and store energy that depends on their size, quantity, and organisation. In all vertebrates, collagen acts as a source of tensile strength to the tissue, whilst elastin and proteoglycans are essential to matrix resiliency. Collagen fibres constitute the main component of the ECM. There are several different types of collagen in connective tissue, with types I, II, III (fibrillar) and IV, V, VI (nonfibrillar or amorphous) representing the most abundant constituents. The turnover of collagen fibres is a dynamic process that is necessary to the maintenance of normal lung architecture [15]. The amount of collagen deposition depends on the extent of alveolar injury and on the intensity of the release of inflammatory mediators in lung parenchyma. Some reports suggested that type III collagen fibres, which are more flexible and susceptible to breakdown, predominate in the early proliferative stage, whereas type I collagen (made up of thicker, more cross-linked fibrils) is more prevalent in the fibrotic stage [14, 16]. The final amount of collagen accumulation depends not only on its synthesis, but also on its degradation [17]. Consequently, the ECM is a dynamic structure, and an equilibrium between the synthesis and degradation of ECM components is required for the maintenance of its homoeostasis [18]. The finding of an increased number of myofibroblasts and of cells producing procollagen types I and III early in the course of ARDS suggests that the proliferative phase begins much sooner than had been previously appreciated [19–23]. In this context, Rocco et al. observed that collagen and elastic fibres were elevated as early as 24 h after tissue damage in an animal model of ALI induced by paraquat [12, 16, 24]. Furthermore, Menezes et al. observed an increase in collagen fibre content in a murine model of pulmonary and extrapulmonary ARDS with similar mechanical compromise; thus indicating that the biochemical processes implicated in the synthesis of collagen fibres react very quickly to the injurious stimulus [25].

Elastic fibres, which are synthesised by chondroblasts, myofibroblasts, and smooth muscle cells, represent another component of the ECM. Due to their mechanical properties, elastic fibres provide recoil tension to restore the parenchyma to its previous configuration after the stimulus for inspiration has ceased. Elastic fibres comprise three components, defined according to their amount of elastin and fibril orientation: (1) oxytalan fibres, composed of bundles of microfibrils; (2) elaunin fibres, made up of microfibrils and a small amount of elastin; and (3) fully developed elastic fibres, consisting of microfibrils and abundant elastin [26, 27]. In normal alveolar septa, a subepithelial layer of elastic fibres made up mainly of fully mature elastic fibres, confers great elasticity to the alveolar tissue in normal situations [28]. The occurrence of elastosis has been well-studied and demonstrated in animal models of pulmonary fibrosis, and recent studies suggest

that elastin gene expression is increased following injury in certain animal models [29]. In ARDS, increased elastin destruction takes place due to the release of powerful elastolytic proteases by inflammatory cells. Elastosis could be a result of repair and remodelling following septal inflammation and fibre fragmentation but resulting in derangement of the alveolar wall architecture [30]. Reactivation of elastin synthesis is observed in response to the increased destruction, but in a highly disordered manner with deleterious consequences for the mechanical properties of the lung [12, 16]. Thus, the elastic component of the ECM could be one of the structures potentially involved in alveolar remodelling in patients with ARDS.

In the connective tissue, proteoglycans (PGs) form a gelatinous and hydrated substance embedding the fibrous proteins. PGs consisting of a central protein bound to one or more polysaccharides are referred to as glycosaminoglycans (GAGs). Due to their hydrophilic structure, GAGs can attract water into the ECM, thereby altering tissue turgor and the viscoelastic properties of the matrix. PGs interact with various cytokines and growth factors and affect cell migration and proliferation. Furthermore, PGs influence the formation of collagen fibres, and are frequently bound to collagen and elastic fibres participating in ECM organisation. In the fibroproliferative phase of ARDS, there is increased deposition of PGs on the pulmonary interstitium [31].

Although many proteases can cleave ECM molecules, the family of Zn^{2+} matrix metalloproteinases (MMPs) and their inhibitors are likely to be the normal, physiologically relevant mediators of ECM degradation [32–34]. Several subclasses of MMPs (23 enzymes) have been identified, including interstitial collagenases, gelatinases, stromelysins, and membrane-type MMPs. These can degrade many proteins, such as collagens, fibronectin, laminin, proteoglycans, entactins, and elastin. MMPs are secreted in a latent form, as inactive proenzymes, and are activated by the loss of propeptide under physiologic conditions. The amounts of at least two matrix metalloproteinases (MMP-2 and MMP-9) are elevated in the lungs of ARDS patients. The proteolytic activity of MMPs is precisely controlled by endogenous physiologic inhibitors, which include the broad-spectrum serum inhibitor $alpha_2$-macroglobulin and a special class of tissue inhibitors of metalloproteinases (TIMPs). Four members of the TIMP family have been characterised, and are designated as TIMP-1, TIMP-2, TIMP-3, and TIMP-4. The major role of MMPs is basement membrane and ECM breakdown in tissue remodelling and angiogenesis. TIMP-1 and TIMP-2 are capable of inhibiting the activities of all known MMPs and as such play a key role in maintaining the balance between ECM deposition and degradation in different physiologic processes. Loss of coordination in the expression of proteinases and inhibitors is believed to generate tissue degradation in inflammatory diseases [35]. The restoration of functional connective tissue is a major goal in the wound-healing process. This regenerative event requires the deposition and accumulation of collagenous and noncollagenous ECM molecules as well as the remodelling of ECM by MMPs.

Mechanisms of remodelling

Remodelling is defined in the Concise Oxford Dictionary (10th edn, 1999) as: 'model again or differently reconstruct.' This is a critical aspect of wound repair in all organs, representing a dynamic process that associates matrix production and degradation in reaction to an inflammatory insult with either a normal reconstruction process (model again) or a pathologic one (model differently). The process of fibrosing alveolitis begins early in the course of ARDS [12, 15, 19–23, 36] and results from complex interaction between fibroblasts, other lung parenchymal cells, and macrophages. Fibroblasts migrate into areas of acute lung injury and are stimulated to secrete collagen and other matrix proteins. These cells also release various proteases that have the capacity to degrade and remodel matrix proteins. Macrophages are thought to be important in the progression of ALI to fibroproliferative ARDS, as they are present in high numbers and secrete numerous proinflammatory mediators (IL-1b, IL-4, and IL-13) and growth factors [transforming growth factor (TGF)-β, TGF-α, transforming nuclear factor (TNF)-α] platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF)-I] [37–39]. These peptide growth factors influence mesenchymal cell migration, proliferation, and ECM deposition, thus implicating them in the progression of fibroproliferative lung disorders. The stimuli that activate fibroblasts to remodel the lung are not well-defined but likely include components of blood (fibrin), matrix degradation products, and mediators (TGF-β) that are released from macrophages and lung parenchymal cells. Fibrin provides a provisional matrix for both inflammatory cells and fibroblasts to migrate into the inflamed site, and by binding mediators it acts as a reservoir of fibroproliferative growth factors. Factors and circumstances that determine whether areas of the lung heal with minimal injury or progress to irreversible injury need to be defined.

In contrast, other mediators have been identified as purported mitigators of the pulmonary fibrotic process. Interferon-γ (IFN-γ) was shown to inhibit fibroblast collagen synthesis in a murine model of pulmonary fibrosis [40]. Prostaglandin E2 (PGE2) inhibits the response of mesenchymal cells to profibrotic cytokines, and is diminished in the lungs of patients with pulmonary fibrosis [41]. This has recently been linked to E prostanoid (EP) receptor loss following fibrotic lung injury. Lack of EP2 expression was correlated with an inability of fibroblasts from bleomycin-treated mice to be inhibited by PGE2 [42] (Tables 1–3).

Primary vs secondary acute lung injury

In experimental models of ALI/ARDS, different responses and morphological alterations of lung parenchyma have been reported as a consequence of direct or indirect insult to the alveoli [25, 43]. There are many triggers of ALI, but its precise pathophysiology needs to be clarified. An understanding of the range of pathways that lead to pulmonary dysfunction may allow assessment of novel treatments targeted to specific areas of the pathologic cascade in an attempt to modify lung

Table 1. Processes required for repair and remodelling: pro-fibrotic effects

	IL-1β	TGF-β	PDGF A/B	TNF-α	IGF-I	TGF-α	KGF	EGF	FGF	HGF	VEGF
Adhesion	Promotes cell adhesion	Promotes cell adhesion	Promotes cell adhesion	Promotes cell adhesion		Promotes cell adhesion	Yes	Yes	Yes	Yes	Yes
Migration	Promotes cell	Promotes migration fibroblast recruitment	Promotes cell migration	Promotes cell migration		Promotes cell migration	Yes	Yes	Yes	Yes	Yes
Proliferation	Promotes cell proliferation	TGF-b plays a critical role in the fibroproliferative responses	Fibroproliferative growth factor	Promotes cell proliferation	Powerful mitogenic activity for fibroblasts	Promotes cell proliferation	Yes	Yes	Yes	Yes	Yes
Differentiation		Differentiation of myofibroblasts									
Matrix/collagen deposition	Stimulates deposition of PCI and PCIII from fibroblasts and type IV from epithelial cells	Promotes matrix deposition	Yes	Induces alveolar septal thickening, disruption in alveolar architecture. TNF-α inhibition promotes reduction in fibrosis		Indirectly via regulation of fibroblast cellular processes	Yes	Yes	Yes	Yes	Yes
Fibrin deposition/ fibrinolysis	By regulating fibroblast proliferation, regulates matrix deposition										
Apoptosis				Involved in death and anti-death signals, or through its TNF related Rc Fas and FasL							May serve to promote survival (survival factor)
Angiogenesis											Angiogenic factor
Inflammatory/ anti-inflammatory mediators	Induces the synthesis of other cytokines, MMPs, PGE_2, gelatinase; leads to sustained levels of TGFβ			Powerful pro-inflammatory cytokine			Yes				

IL-1β, Interleukin-1β; *TGF-β*, Transforming growth factor-β; *PDGF*, platelet derived growth factor; *TNF-α*, tumour necrosis factor-α//I//; *IGF-I*, insulin-like growth factor; *TGF-α*, transforming growth factor-α//I//; *KGF*, keratinocyte growth factor; *EGF*, epithelial growth factor; *FGF*, fibroblast growth factor; *HGF*, hepatocyte growth factor; *VEGF* vascular endothelial growth factor; *PC*, procollagen; *FASL*, FAS ligand; *MMP*, matrix metalloproteinase; *PC*, pneumocyte

Table 2. Processes required for repair and remodelling: pro-fibrotic effects

	Elastases	APC and thrombomodulin	PAR1	MMPs	ACE/AGII
Differentiation					ANG II stimulates fibroblast/collagen production
Matrix/collagen deposition		Decreases in APC levels are associated with increased collagen deposition	Thrombin and factor Xa exert potent pro-fibrotic effects via PAR1		ACE inhibitors attenuate fibrosis
Fibrin deposition/fibrinolysis					
Apoptosis					ACE may have an inhibitory effect on apoptosis, while AGII may be pro-apoptotic
Coagulation/anti-coagulation		Anti-coagulants			
Matrix/protein degradation	Neutrophil elastases destroy matrix and cell membranes			The major role of MMPs is basement membrane and ECM breakdown in tissue remodelling and angiogenesis. Main MMP implicated in ARDS: MMP-2 and MMP-9	
Inflammatory/anti-inflammatory mediators	Involved in tissue destruction during inflammation	Yes		Possibly involved in innate immune response	

APC, Activated protein C; *PAR1*, protease-activated receptor 1; *MMPs*, tissue metalloproteinases; *ACE/ANGII*, angiotensin converting enzyme/angiotensin II

Table 3. Processes required for repair and remodelling: anti-fibrotic effects

	IFNγ	PGE_2	NO and its derivatives	Urokinase/plasmin
Adhesion			NO has an effect on cellular aggregation, and leukocyte adhesion	Urokinase promotes the ligand-like binding of its receptor to integrins, affecting signalling and cell migration
Migration				Alters Cell migration
Proliferation		PGE_2 inhibits fibroblasts	NO promotes cellular proliferation	
Matrix/collagen deposition	Interferon-g inhibits fibroblast collagen synthesis	PGE_2 inhibits the response of mesenchymal cellsby to profibrotic cytokines	May have an effect on matrix deposition regulating expression of MMPs	Depression of fibrinolytic activity occurs as a result of inhibition of urokinase plasminogen activator (uPA) by plasminogen activators
Fibrin deposition/fibrinolysis				Plasminogen activator urokinase are continuously released along alveolar surfaces to facilitate timely resolution of extensive fibrin deposition
Apoptosis			May have an effect on cell death at denuded edges of wounds	
Coagulation/anti-coagulation				Potent fibrinolytic agents
Matrix/protein degradation		PGE2 inhibits the response of mesenchymal cells to profibrotic cytokines		
Inflammatory/anti -inflammatory mediators	Involved in innate/ acquired immune responses	Anti-inflammatory mediator	Yes	Yes

IFN-γ, interferon-γ; *PGE_2*, Prostaglandin E_2; *NO*, nitric oxide

injury. Although various causes of ARDS result in a uniform pathology in the late stage, evidence indicates that the pathophysiology of early ARDS may differ according to the type of primary insult [43].

Primary ARDS or primary pulmonary epithelial injury

After a direct insult, the primary structure injured is the pulmonary epithelium. The normal alveolar epithelium is composed of two types of cells: flat type I cells, and cuboidal type II cells. Type I cells make up 90% of the alveolar surface area and are highly vulnerable to injury, whereas type II cells, which make up 10% of the alveolar surface area, are more resistant and function as progenitor cells for regeneration of the alveolar epithelium after injury [44]. Type II cells have many functions: surfactant production, ion transport, and proliferation and differentiation to type I cells after injury. Disruption of the alveolar epithelial integrity is a major contributor to increased alveolar–capillary permeability. Loss of integrity of this membrane leads to an influx of protein-rich oedema fluid, which is ultimately responsible for inciting a breakdown in the gas exchange and epithelial barrier functions of the lung. Associated with this process is the disruption in the function and production of endogenous surfactant within the epithelium. Additionally, injury to the alveolar epithelium leads to the activation of alveolar macrophages and the inflammatory cascade, determining the onset of pulmonary inflammation.

Epithelial cells produce cytokines in response to various stimuli, such as lipopolysaccharide (LPS) or lung stretch [45], but the regulatory features are not completely defined. Epithelial damage leads to: (a) alveolar flooding (the epithelial barrier is much less permeable than the endothelial barrier) [46]; (b) a reduction in the removal of oedema fluid from the alveolar space (loss of epithelial integrity and injury of type II cells disrupt normal epithelial fluid transport) [47]; (c) a decrease in the production and turnover of surfactant (lesion of type II cells) [48]; and (d) fibrosis (due to severe and disorganised injury of the alveolar epithelium) [49]. The factors determining whether pulmonary fibrosis or restoration of the normal pulmonary architecture will occur after ARDS remain unknown. One important step is the rapid and efficient restoration of the denuded basement membrane. Efficient alveolar epithelial repair may reduce the development of fibrosis, since the presence of an intact alveolar epithelial layer suppresses fibroblast proliferation and matrix deposition [50]. Epithelial repair involves close coordination of several complex molecular mechanisms, including interactions between alveolar type II cells and the matrix, and are coordinated by a variety of soluble mediators released into the alveolar space in ARDS [51].

Optimal repair also requires that a provisional fibrin matrix on the basement membrane provide a platform for cell adhesion, spreading, and migration. This provisional matrix is formed in the context of injury and emits signals to activate an inflammatory response, provoking an expansion of connective tissue elements that leads to persistent and sometimes permanent matrix reordering [52]. The alveolar proteinaceous exudate acts as a substrate to thrombin activation and fibrin formation. Concurrently, low but significant levels of plasminogen activator uro-

kinase are continuously released along alveolar surfaces to facilitate the timely resolution of extensive fibrin deposition on the basement membrane [53]. Therefore, the insoluble matrix accumulated in alveolar spaces contains both haemotactic compounds and growth factors to support an influx of fibroblasts and fibroproliferation. Epithelial growth factor (EGF), TGF-α, keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), and FGF regulate epithelial repair in vivo and in vitro [54].

Secondary ARDS or primary pulmonary endothelial cell injury

When the insult is indirect, pulmonary lesions are caused by circulating mediators released from extrapulmonary foci into the blood (e.g. peritonitis, pancreatitis). The main target for damage is the pulmonary endothelial cell [55, 56]. The vascular endothelium is a highly specialised metabolically active organ that possesses numerous physiological, immunological, and synthetic functions. The endothelium also holds numerous enzymes, receptors, and transduction molecules, which interact with other vessel wall constituents and circulating blood cells [57]. Increased pulmonary vascular permeability is a hallmark of ARDS pathogenesis. This may occur as a consequence of biochemical injurious events, such as those promoted by circulating cytokines, or biophysical events that act on cytoskeleton-related mechanisms, such as thrombin or mechanical stretch [58]. The lung endothelium, in concert with the epithelial barrier, mediates the initial change in permeability and is also critical for the repair and remodelling of the alveolar capillary membrane [57]. Each short segment of lung capillary possesses functionally distinct endothelial cells, such that endothelial heterogeneity may also be a factor in the lung's response to pathological stimuli.

Effectors cells in repair and remodelling and their mediators

The activated neutrophil and its by-products

The importance of endothelial cell membrane disruption as a key event in the loss of endothelial membrane integrity is supported by accumulating evidence. Moreover, it appears that the activated neutrophil and its by-products play a modulatory role in this process. Evidence that supports the involvement of neutrophil elastase in the pathophysiology of acute lung injury includes: (1) neutrophil elastase levels are increased in both clinical and animal models of acute lung injury; (2) topical or systemic administration of neutrophil elastase produces typical symptoms of acute lung injury both in vitro and in vivo, and (3) inhibition of increased neutrophil elastase activity reduces symptoms of acute lung injury in animal models [59]. In humans, the data are more controversial. Three recent studies examined the effects of ONO-5046 (sivelestat, a specific inhibitor of neutrophil elastase; sodium *N*-[2-[4-(2,2-dimethylpropionyloxy) phenylsulfonylaminobenzoyl] amino-acetate tetrahydrate]) on pulmonary function improvement, 28-day mortality, and ventilator-

free days. While one trial reported a purported benefit to the clinical use of this drug [60], the two double-blind randomised controlled trials did not report an improvement in mortality or ventilator-free days [61, 62].

Neutrophil elastases seem to also be involved in directly destroying endothelial cells [63]. Soluble cadherin (an endothelial junction protein) has been identified in the serum of ARDS patients, suggesting elastase-mediated proteolysis of the endothelial cell and disruption of the endothelial cell junction. This is further supported by the presence of thrombomodulin (an endothelial-cell-surface anticoagulant protein) in the serum of patients with ARDS, indicating proteolytic release of an endothelial cell membrane protein [64].

IL-1β and IL-6

Although the fibroproliferative response to lung injury occurs with high frequency in patients with clinical acute lung injury, the mechanisms that initiate this response are largely unknown. Transient overexpression of IL-1β, as compared with TNF-α, has a greater effect in promoting fibrosis [65, 66]. Both IL-1β and TNF-α lead to acute/subacute and chronic inflammation that evolves into pulmonary fibrosis [65, 66]. TGF-β is expressed in conjunction with these cytokines, and the presence of TGF-β is associated with fibrosis. The persistent expression of TGF-β occurs in the context of IL-1β-induced inflammation and marked alveolar–capillary wall and basement membrane destruction [65]. Disrupting the integrity of the alveolar–capillary wall and basement membrane leads to: (1) failure of normal re-epithelialisation and re-endothelialisation and (2) a loss of alveoli and fibrosis. The concomitant and subsequent expression of TGF-β in this context results in the fibrogenic response with failure of normal resolution [67].

To further elucidate the potential role of IL-1β in early fibroproliferative changes in ARDS, Olman et al. examined the oedema fluid obtained from patients with early lung injury [68]. Oedema fluid from these patients had a higher concentration of IL-1β and an increased IL-1β-dependent mitogenic effect on cultured fibroblasts than fluid obtained from control patients with hydrostatic pulmonary oedema. Furthermore, fibroblasts incubated with oedema fluid derived from patients with ALI produced soluble mediators that possess an autocrine mitogenic effect. Gene array analysis demonstrated that ALI oedema fluid induces several inflammation-modulating and proliferation-related genes in fibroblasts, whose inductions are similarly dependent on bioactive IL-1β, as demonstrated by blocking IL-1β studies. This induction appears to occur through an IL-1β-dependent up-regulation of IL-6 [68]. Although these data confirm that IL-6 plays an important role in tissue injury and repair, the net action of IL-6 cannot be easily inferred. Direct in vivo studies have shown that IL-6-deficient mice exhibit enhanced neutrophil recruitment and enhanced induction of pro-inflammatory cytokines (i.e. TNF-α, MIP-2, and GM-CSF) in response to exogenous LPS, suggesting that IL-6 acts to limit acute pulmonary inflammation [69]. However, overexpression of IL-6 along with IL-6 receptor in rat lungs or in transgenic mice induces an interstitial lymphocytic alveolitis, in keeping with its known stimulatory effects on lymphocytes [70]. Further studies

are clearly needed to elucidate the role of IL-6 as a mediator of pro-fibrotic changes in early fibroproliferative ARDS.

The coagulation cascade and lung remodelling

Decreased circulating protein C and increased circulating thrombomodulin are markers of the prothrombotic, antifibrinolytic state associated with poor outcomes in patients with ARDS [71]. Activated protein C (APC), a natural anticoagulant, is formed from protein C by the action of thrombin bound to thrombomodulin on the endothelial cell surface. APC regulates the coagulation system by inactivating the activated form of factors V and VIII in the presence of protein S. Recent evidence has implicated APC, and consequently thrombomodulin, in the regulation of innate immune responses by virtue of this molecule's ability to inhibit endotoxin-induced TNF-α production in human monocytes [72]. It has also recently been shown that the protein C pathway may be involved in the mechanism of lung and airway remodelling. Decreases in APC levels are associated with increased collagen deposition in the lung [73, 74]. Moreover, in vitro APC can prevent increased endothelial cell permeability and restore vascular integrity after administration of oedema-producing chemical agonists. This appears to occur through ligation of a novel endothelial cell receptor and transactivation of sphingosine-1-phosphate receptor and cytoskeletal rearrangement [75]. Moreover, thrombin and factor Xa exert potent pro-fibrotic effects via proteolytic activation of protease-activated receptor 1 (PAR-1) and the production of potent pro-fibrotic mediators [76, 77]. Another report has indicated that PAR-1 expression is increased in response to lung injury and that direct thrombin inhibition attenuates the fibrotic response to bleomycin in vivo [78]. This is in keeping with novel evidence suggesting a fundamental role of the coagulation pathway in determining the repair and remodelling of lung tissue.

The pulmonary endothelium is also actively involved in the fibrinolytic process, expressing plasminogen activators as well as their inhibitors. Endothelial cell fibrinolytic activity appears to be affected by several ARDS-related mediators, including endotoxin, IL-1β, TNF-α, and thrombin [79]. Depression of fibrinolytic activity occurs as a result of inhibition of urokinase plasminogen activator (uPA) by plasminogen activators, or series inhibition of plasmin by antiplasmins. Locally increased amplification of plasminogen activator inhibitor-1 (PAI-1) is largely responsible for this fibrinolytic defect [80–82]. Newly described pathways by which lung epithelial cells regulate expression of uPA, its receptor uPAR, and PAI-1 at the posttranscriptional level have been identified. These pathways operate by *cis–trans* interactions between mRNA binding proteins, and regulatory sequences within these mRNAs control their stability [83–87]. For the purpose of this review, our primary interest is in the role of the uPAR/PAI1 system in the regulation of cell–cell matrix interactions. Adhesion receptors and proteolytic enzymes are absolutely required to regulate a cell's interaction with and response to ECMs. Cooperation between integrins and proteases operates at several levels: integrin signalling induces proteases, proteases co-localise with integrins, and proteases regulate the

interface between integrins and the intracellular cytoskeleton. Recent studies indicate urokinase promotes the ligand-like binding of its receptor to a set of β1 and β2 integrins, this binding in turn affects integrin signalling and cell migration [88, 89]. The glycolipid anchor of uPAR associates with cholesterol-rich membrane rafts [90]. Binding of uPAR to integrins may enrich integrin clusters with signalling molecules, such as src-family kinases that localise to rafts and are important to integrin function. Signals derived from integrin/uPAR complexes promote the function of other integrins [91]. Thus, the urokinase/plasmin system coordinates with integrins to regulate cell–cell matrix interactions.

Growth factors

Vascular endothelial growth factor

Another clinically relevant molecule involved in pulmonary repair and remodelling is vascular endothelial growth factor (VEGF). VEGF plays an important role by directly regulating vascular permeability to water and proteins. Systemic expression of VEGF causes widespread multiorgan capillary leakage, suggesting that the overexpression of VEGF plays a pivotal role in the development of pulmonary oedema [92]. Furthermore, VEGF and related molecules determine profound effects on endothelial cell biology by regulating cell proliferation, angiogenesis, and monocyte recruitment.

Although endothelial cells stand out as primary targets of VEGF, the growth factor can also stimulate the production of surfactant by alveolar type II cells [93] and the growth of lung airway epithelial cells in vitro [94]. Hence, VEGF has been also characterised as an endothelial survival factor, since it prevents microvascular apoptotic cell loss. The expression and function of VEGF in ARDS vary, depending on the pathophysiological conditions, timing, and degree of epithelial and endothelial damage. The theory is that, in the early phase of lung injury, VEGF released by alveolar epithelial cells and leukocytes as part of the acute inflammatory response causes an increase in the permeability of the endothelial layer, thus contributing to the formation of interstitial oedema. Ensuing fluid exudation may extend the damage to the alveolar epithelial layer leading to a reduction in the production of VEGF. During the recovery period, VEGF may participate in the angiogenesis process, which is an important component of lung repair [92].

Transforming growth factor β

TGF-β consists of a family of several peptide members secreted in a latent form that must be activated by cleavage for function. Animal studies have shown that expression of several TGF-β-inducible genes is dramatically increased as early as 2 days after the induction of injury. The integrin a(v)b(6) activates latent TGF-β in the lungs, where it plays a critical role in fibroproliferative responses (recently reviewed in [95, 96]). Mice lacking this integrin are completely protected from pulmonary oedema in a model of bleomycin-induced ALI [97]. Once TGF-β binds

to its receptor, it stimulates signal transduction cascades, including the SMAD and mitogen-activated protein kinase pathways [98]. The processes stimulated by TGF-β include a reduction in cytokine production, fibroblast recruitment, differentiation of myofibroblasts, and stimulation of ECM proteins [99, 100], all of which are critical to wound repair. In ARDS, TGF-β can: (a) directly affect the expression of genes encoding ECM molecules in stroma cells to induce collagen synthesis and inhibit collagenase production; (b) induce fibroproliferation of fibroblasts, most probably indirectly through the induction of other growth factors, such as PDGF; (c) establish an apparent state of autocrine stimulation in structural cells, including fibroblasts, resulting in activation and possible differentiation to a more aggressive phenotype, consistent with the expression of disease [95, 101]. Whereas TGF-β has an essential role in the genesis of inflammation and fibroproliferation after ALI, the importance of this cytokine in the maintenance of fibroproliferation is uncertain. Recent studies report that fibroblasts from fibroproliferative lesions can display an enhanced proliferative or synthetic phenotype independent of continuous exogenous stimulation [102].

The significance of TGF-β in the regulation of the fibroproliferative phase of ARDS can be further inferred from experimental data demonstrating that pharmacologic inhibition of TGF-β protected wild-type mice from pulmonary oedema induced by bleomycin or *Escherichia coli* endotoxin [103]. In animal models, adenoviral-mediated transfer of soluble TGF-β type II receptor ameliorated fibroproliferative change in irradiated rat lungs [104].

The renin–angiotensin system in lung remodelling

Angiotensin II (ANG II), generated by activation of local renin–angiotensin sys tems (RASs), has recently gained much attention as an important mediator in tissue repair and remodelling, in part via a TGF-β-mediated mechanism. Angiotensin converting enzyme (ACE) levels have been shown to be elevated in the bronchoalveolar lavage fluid (BALF) and/or serum in patients with many potentially fibrotic lung diseases, including ARDS [105, 106]. In addition, mutations in this gene are associated with the development of, and outcome from ARDS, suggesting a pathogenic role for RAS in ALI [107]. ACE inhibitors attenuate endothelial activation [108], TNF activation [109], and collagen deposition [110] during experimental lung injury, possibly via a reduction in epithelial cell apoptosis [111, 112]. Moreover, ANG II could influence the progression of lung injury via a number of mechanisms; evidence suggests that the protein acts as a pro-apoptotic factor for alveolar epithelial cells in vitro [113] via the AT_1 receptor [114]. ANG II is also mitogenic for human lung fibroblasts via activation of the same receptor [115], implicating ANG II in the fibroproliferative response to lung injury. In vascular smooth muscle cells, the cellular actions of ANG II have been linked to the autocrine release of growth factors, such as PDGF, FGF, and TGF-β [116].

More recently, Marshall et al. have unambiguously implicated ANG II in the fibroproliferative response to lung injury [117]. In vitro, ANG II is a potent stimulator of lung fibroblast collagen production via the AT_1 receptor and this appears

to be, in part, mediated by TGF-β [117]. After bleomycin-induced lung injury, increased ANG II concentrations preceded a doubling of the amount of lung collagen. While lung ACE activity remained unchanged, administration of an ACE inhibitor attenuated lung ACE activity, increases in ANG II concentrations, and increased collagen deposition. Treatment with an AT_1 receptor antagonist also reduced lung collagen deposition and increased ANG II levels. Together, these data support the hypothesis that ANG II, possibly generated within the lung during acute injury, contributes directly to lung collagen deposition via fibroblast activation. However, the efficacy of ACE inhibition in this model may also involve actions unrelated to ANG II generation [117].

Nitric oxide, NO donors, and reactive nitrogen species

Nitric oxide (NO), NO donors, and reactive nitrogen species (RNS) have also been implicated in the process of lung remodelling. The pulmonary endothelium releases NO, a free radical with a very short half-life. NO can exert either pro- or anti-oxidative effects, depending on the type and the quantity of oxygen radicals present. In addition to vascular smooth muscle cell relaxation, NO inhibits platelet aggregation, and leukocyte adhesion, and promotes cellular proliferation. Furthermore, NO may modulate hypoxic pulmonary vasoconstriction (HPV), a protective feature of lungs to hypoxia. Since hypoxia reduces NO synthesis [118], HPV is lost in ARDS. An in vitro model of matrix contraction using three-dimensional collagen gels was used to explore the effects of different mediators on normal healing and remodelling after tissue injury. Based on this model, Zhu et al. were able to show that prostaglandin (PGE_2) and NO appear to function in parallel as autocrine/paracrine mediators of cytokine-driven fibroblast inhibition of the contraction of collagen gels, and that both agents may contribute to remodelling during repair and inflammation in lung disorders [119]. Moreover, *S*-nitrosothiols (RSNOs) are thought to represent a circulating endogenous reservoir of NO and may have potential as donors of NO that can dramatically inhibit cytokine induced up-regulation of MMP-9 via an NF-κB-related pathway [120]. Moreover, the lung can be exposed to nitrogen dioxide (NO_2), a reactive nitrogen intermediate produced during inflammation by the decomposition of peroxynitrite (ONOO-) or through peroxidase-catalysed reactions. Injury to the lung epithelial cells following exposure to NO_2 is characterised by airway denudation followed by compensatory proliferation. In wound healing experiments, NO_2-induced cell death occurred primarily in cells localised in the leading edge of the wound [121], and in a Fas- and c-Jun N-terminal kinase (JNK)-dependent manner. RNS are characteristic of chronic inflammatory diseases; consequently, treatment strategies aimed at preventing the interaction of RNS with Fas may attenuate the tissue damage characteristic of chronic inflammatory diseases that are accompanied by high levels of RNS [122].

The role of apoptosis in repair and remodelling

Recent studies state that apoptosis contributes to the pathogenesis of lung fibrosis as well as to its resolution [123, 124]. Apoptosis can be detrimental or beneficial, depending on the cell type, the circumstances, and the timing. Stimulation of apoptosis in myofibroblasts and fibroblasts in the fibrotic lung, for example, could be beneficial because these cells are the major source of excess ECM. Apoptosis of inflammatory cells might also be beneficial [125], but excessive epithelial cell apoptosis could lead to the destruction of alveolar septa and a fibrotic response [126].

Apoptotic epithelial cells have been found in the damaged alveolar epithelium of patients with ARDS. In the resolution phase, apoptosis of type II pneumocytes largely accounts for the disappearance of excess epithelial cells [127]. BALF from patients with ARDS contains elevated concentrations of soluble Fas and Fas ligand [128], suggesting that the Fas system plays a role in apoptosis.

Apoptosis of neutrophils probably plays an important role in attenuating lung injury and may ultimately benefit the outcome of patients with ARDS [129]. Furthermore, apoptosis of epithelial cells and neutrophils are interrelated events. In response to Fas ligand or TNF-α, bronchiolar epithelial cells undergo apoptosis and secrete IL-8 and NF-κB [130], which in turn suppresses the apoptosis of neutrophils, increasing lung injury.

A comprehensive understanding of the mechanisms of apoptosis and necrosis in the initial injury and repair of lung epithelial and endothelial cells and other key cells involved in ALI/ARDS is crucial. These cellular processes are likely to be central to imbalances between resolution and repair vs persistence and progression, and can be influenced by biomechanical, inflammatory, and thrombotic stimuli [131, 132].

It is not known how lung endothelial and epithelial injury modifies the fibrogenic response in ALI/ARDS or if apoptosis and necrosis affect the fibrotic process differently. In this context, Menezes et al. developed a murine model of pulmonary and extrapulmonary ALI with similar mechanical compromise early in the course of the lung injury. They observed that, given the same pulmonary mechanical dysfunction, insult to the pulmonary epithelium yielded more pronounced inflammatory responses with a greater degree of neutrophilic apoptosis. Although an exaggerated inflammatory response underlies the pathogenesis of pulmonary ALI at the early phase, the amount of collagen fibre was similar in pulmonary and extrapulmonary ALI [25]. These experimental models will enable us to test novel treatment modalities inhibiting the fibroproliferative process.

Conclusions

Acute respiratory distress syndrome is a devastating condition characterised by exudation, inflammation, and often fibrosis throughout the lung. The remarkable fact is that, despite this extensive damage, ARDS can fully resolve by a process that requires the clearance of inflammatory cells and mediators together with a reversal

of pulmonary fibrosis. Regulation of the remodelling of ECM results in a complex integrative mechanism comprising elements that degrade matrix proteins and which produces activation/inhibition of several lung-tissue cell types. Identification of the mechanisms regulating repair and remodelling may allow development of therapeutic targets for patients with fibrosis as a result of ALI/ARDS.

References

1. Ashbaugh DG, Bigelow DB, Petty TL et al (1967) Acute respiratory distress syndrome. Lancet 2:319–323
2. Bernard GR, Artigas A, Bringham KL et al (1994) The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
3. Ware LB (2005) Prognostic determinants of acute respiratory distress syndrome in adults: impact on clinical trial design. Crit Care Med 33:S217–S222
4. Vincent JL, Sakr Y, Ranieri VM (2003) Epidemiology and outcome of acute respiratory failure in intensive care unit patients. Crit Care Med 31:S296–S299
5. Marshall R, Bellingan G, Laurent G (1998) The acute respiratory distress syndrome: fibrosis in the fast lane. Thorax 53:815–817
6. Montgomery AB, Stager MA, Carrico CJ et al (1985) Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–489
7. Davidson TA, Caldwell ES, Curtis JR et al (1999) Reduced quality in life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 281:354–360
8. Herridge MS, Cheung AM, Tansey CM et al (2003) One-year outcome in survivors of acute respiratory distress syndrome. N Engl J Med 384:683–693
9. Piantadosi CA, Schwartz DA (2004) The acute respiratory distress syndrome. Ann Intern Med 141:460–470
10. Tomashefski JF Jr (2000) Pulmonary pathology of acute respiratory distress syndrome. Clin Chest Med 21:435–466
11. Rinaldo JE, Rogers RM (1982) Adult respiratory distress syndrome: changing concepts of lung injury and repair. N Engl J Med 306:900–909
12. Rocco PR, Negri EM, Kurtz PM et al (2001) Lung tissue mechanics and extracellular matrix remodeling in acute lung injury. Am J Respir Crit Care Med 164:1067–1071
13. Chen B, Polunowsky V, White J et al (1992) Mesenchymal cells isolated after acute lung injury manifests an enhanced proliferative phenotype. J Clin Invest 90:1778–1785
14. Raghu G, Striker LJ, Hudson LD et al (1985) Extracellular matrix in normal and fibrotic human lungs. Am Rev Respir Dis 131:281–289
15. Armstrong L, Thickett DR, Mansell JP et al (1999) Changes in collagen turnover in early acute respiratory distress syndrome. Am J Respir Crit Care Med 160:1910–1915
16. Rocco PR, Souza AB, Faffe DS et al (2003) Effect of corticosteroid on lung parenchyma remodeling at an early phase of acute lung injury. Am J Respir Crit Care Med 168:677–684
17. Raghow R (1994) The role of extracellular matrix in postinflammatory wound healing and fibrosis. FASEB J 8:823–831
18. Murphy G, Docherty AJ (1992) The matrix metalloproteinases and their inhibitors. Am J Respir Cell Mol Biol 7:120–125

19. Chesnutt AN, Matthay MA, Tibayan FA et al (1997) Early detection of type III procollagen peptide in acute lung injury. Pathogenetic and prognostic significance. Am J Respir Crit Care Med 156:840–845
20. Liebler JM, Qu Z, Buckner B et al (1998) Fibroproliferation and mast cells in the acute respiratory distress syndrome. Thorax 53:823–829
21. Meduri GU, Tolley EA, Chinn A et al (1998) Procollagen types I and III aminoterminal propeptide levels during acute respiratory distress syndrome and in response to methylprednisolone treatment. Am J Respir Crit Care Med 158:1432–1441
22. Pugin J, Verghese G, Widmer MC et al (1999) The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 27:304–312
23. Marshall RP, Bellingan G, Webb S et al (2000) Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. Am J Respir Crit Care Med 162:1783–1788
24. Rocco PRM, Facchinetti LD, Ferreira HC et al (2004) Time course of respiratory mechanics and pulmonary structural remodelling in acute lung injury. Respir Physiol Neurobiol 143:49–61
25. Menezes SL, Bozza PT, Neto HC et al (2005) Pulmonary and extrapulmonary acute lung injury: inflammatory and ultrastructural analyses. J Appl Physiol 98:1777–1783
26. Montes GS (1996) Structural biology of the fibres of the collagenous and elastic systems. Cell Biol Int 20:15–27
27. Starcher BC (2000) Lung elastin and matrix. Chest 117:S229–S234
28. Mercer RR, Crapo JD (1990) Spatial distribution of collagen and elastin fibres in the lungs. J Appl Physiol 69:756–765
29. Raghow R, Lurie S, Seyer JM et al (1985) Profile of steady state levels of RNAs coding for type I procollagen, elastin, and fibronectin in hamster lungs undergoing bleomycin-induced interstitial pulmonary fibrosis. J Clin Invest 76:1733–1739
30. Negri EM, Montes GS, Saldiva PHN et al (2000) Architectural remodelling in acute and chronic interstitial lung disease: fibrosis or fibroelastosis? Histopathology 37:393–401
31. Ebihara T, Venkatesan N, Tanaka R et al (2000) Changes in extracellular matrix and tissue viscoelasticity in bleomycin-induced lung fibrosis. Temporal aspects. Am J Respir Crit Care Med 162:1569–1576
32. Corbel M, Boichot E, Lagente V (2000) Role of gelatinases MMP-2 and MMP-9 in tissue remodeling following acute lung injury. Braz J Med Biol Res 33:749–754
33. Parks WC (2003) Matrix metalloproteinases in lung repair. Eur Respir J 44:S36–S38
34. Shapiro SD, Senior RM (1999) Matrix metalloproteinases: matrix degradation and more. Am J Respir Cell Mol Biol 20:1100–1102
35. Lanchou J, Corbel M, Tanguy M et al (2003) Imbalance between matrix metalloproteinases (MMP-9 and MMP-2) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) in acute respiratory distress syndrome patients. Crit Care Med 31:536–542
36. Clark JG, Millberg JA, Steinberg KP et al (1995) Type III procollagen peptide in the adult respiratory distress syndrome: association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death. Ann Intern Med 122:17–23
37. Henke C, Marineili W, Jessurun J et al (1993) Macrophage production of basic fibroblast growth factor in the fibroproliferative disorder of alveolar fibrosis after lung injury. Am J Pathol 143:1189–1199
38. Krein PM, Sabatini PJB, Tinmouth W et al (2003) Localization of insulin-like growth factor-I in lung tissues of patients with fibroproliferative acute respiratory distress syndrome. Am J Respir Crit Care Med 167:83–90

39. Madtes DK, Rubenfeld G, Klima LD et al (1998) Elevated transforming growth factor-alpha levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 158:424–430
40. Gurujeyalakshmi G, Giri SN (1995) Molecular mechanisms of anti-fibrotic effect of interferon gamma in bleomycin-mouse model of lung fibrosis: down regulation of TGF-beta and procollagen I and III gene expression. Exp Lung Res 21:791–808
41. Wilborn J, Crofford LJ, Burdick MD et al (1994) Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have diminished capacity to synthesis prostaglandin E2 and to express cyclooxygenase-2. J Clin Invest 95:1861–1868
42. Moore BB, Ballinger MN, White ES et al (2005) Bleomycin-induced E prostanoid receptor changes alter fibroblast responses to prostaglandin E2. J Immunol 174:5644–5649
43. Rocco PRM, Zin WA (2005) Pulmonary and extrapulmonary acute respiratory distress syndrome: are they different? Curr Opin Crit Care 11:10–17
44. Uhal B (1997) Cell cycle kinetics in the alveolar epithelium. Am J Physiol Lung Cell Mol Physiol 272:L1031–L1045
45. Slutsky AS, Tremblay LN (1998) Multiple system organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
46. Wiener-Knonish JP, Albertine KH, Mattahay MA (1991) Differential response of the endothelial and epithelial barriers of the lung in sheep to Escherichia coli endotoxin. J Clin Invest 88:864–875
47. Modelska K, Pittet JF, Folkesson HB et al (1999) Acid-induced lung injury: protective effect of anti-interleukin-8 pretreatment on alveolar epithelial barrier function in rabbits. Am J Respir Crit Care Med 160:1450–1456
48. Greene KE, Wright JR, Steinberg KP et al (1999) Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 160:1843–1850
49. Bitterman PB (1992) Pathogenesis of fibrosis in acute lung injury. Am J Med 92:39S–43S
50. Adamson IY, Young L, Bowden DH (1988). Relationship of alveolar epithelial injury and repair to the induction of pulmonary fibrosis. Am J Pathol 130:377–383
51. Geiser T (2003) Idiopathic pulmonary fibrosis—a disorder of alveolar wound repair? Swiss Med Wkly 133:405–411
52. Chapman HA (2004) Disorders of lung matrix remodeling. J Clin Invest 113:148–157
53. Marshall BC, Brown BR, Rothstein MA et al (1991) Alveolar epithelial cells express both plasminogen activator and tissue factor. Potential role in repair of lung injury. Chest 99:S25–S27
54. Panos RJ, Rubin JS, Csaky KG et al (1993) Keratinocyte growth factor and hepatocyte growth factor/scatter factor are heparin-binding growth factors for alveolar type II cells in fibroblast-conditioned medium. J Clin Invest 92:969–977
55. Wort SJ, Evans TW (1999) The role of the endothelium in modulating vascular control in sepsis and related conditions. Br Med Bull 55:30–48
56. Zimmerman GA, Albertine KH, Carveth HJ et al (1999) Endothelial activation in ARDS. Chest 116:18S–24S
57. Orfanos SE, Mavrommati I, Korovesi I et al (2004) Pulmonary endothelium in acute lung injury: from basic science to the critically ill. Intensive Care Med 9:1702–1714
58. Dudek SM, Garcia JG (2001) Cytoskeletal regulation of pulmonary vascular permeability. J Appl Physiol 91:1487–1500
59. Kawabata K, Hagio T, Matsuoka S (2002) The role of neutrophil elastase in acute lung injury. Eur J Pharmacol 451:1–10

60. Tamakuma S, Ogawa M, Aikawa N et al (2004) Relationship between neutrophil elastase and acute lung injury in humans. Pulm Pharmacol Ther 17:271–279
61. Zeiher BG, Artigas A, Vincent J-L et al (2004) Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. Crit Care Med 32:1695–1702
62. Kadoi Y, Hinohara H, Kunimoto F et al (2004) Pilot study of the effects of ONO-5046 in patients with acute respiratory distress syndrome. Anesth Analg 99:872–877
63. Carden D, Xiao F, Moak C et al (1998) Neutrophil elastase promotes lung microvascular injury and proteolysis of endothelial cadherins. Am J Physiol 275:385–392
64. MacGregor IR, Perrie AM, Donnelly SC et al (1997) Modulation of human endothelial thrombomodulin by neutrophils and their release products. Am J Respir Crit Care Med 155:47–52
65. Kolb M, Margetts PJ, Anthony DC et al (2001) Transient expression of IL-1beta induces acute lung injury and chronic repair leading to pulmonary fibrosis. J Clin Invest 107:1529–1536
66. Sime PJ, Marr RA, Gauldie D et al (1998) Transfer of tumor necrosis factor-alpha to rat lung induces severe pulmonary inflammation and patchy interstitial fibrogenesis with induction of transforming growth factor-beta1 and myofibroblasts. Am J Pathol 153:825–832
67. Striter RM (2002) Inflammatory mechanisms are not a minor component of the pathogenesis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 65:1206–1207
68. Olman MA, White KE, Ware LB et al (2004) Pulmonary edema fluid from patients with early lung injury stimulates fibroblast proliferation through IL-1 beta-induced IL-6 expression. J Immunol 172:2668–2677
69. Xing Z, Gauldie J, Cox G et al (1998) IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest 101:311–320
70. Yoshida M, Sakuma J, Hayashi S et al (1995) A histologically distinctive interstitial pneumonia induced by overexpression of the interleukin 6, transforming growth factor beta 1, or platelet-derived growth factor B gene. Proc Natl Acad Sci US A92:9570–9574
71. Ware LB, Fang X, Matthay MA (2003) Protein C and thrombomodulin in human acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L514–L521
72. Yuksel M, Okajima K, Uchiba M et al (2002) Activated protein C inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production by inhibiting activation of both nuclear factor-kappa B and activator protein-1 in human monocytes. Thromb Haemost 88:267–273
73. Yasui H, Gabazza EC, Taguchi O et al (2000) Decreased protein C activation is associated with abnormal collagen turnover in the intraalveolar space of patients with interstitial lung disease. Clin Appl Thromb Hemost 6:202–205
74. Suzuki K, Gabazza EC, Hayashi T et al (2004) Protective role of activated protein C in lung and airway remodeling. Crit Care Med 32:262–265
75. Finigan JH, Dudek SM, Singleton PA et al (2005) Activated protein C mediates novel lung endothelial barrier enhancement: role of sphingosine 1-phosphate receptor transactivation. J Biol Chem 280:17286–17293
76. Chambers RC, Leoni P, Blanc-Brude OP et al (2000) Thrombin is a potent inducer of connective tissue growth factor production via proteolytic activation of protease-activated receptor-1. J Biol Chem 275:35584–35591
77. Blanc-Brude OP, Archer F, Leoni P et al (2005) Factor Xa stimulates fibroblast procollagen production, proliferation, and calcium signaling via PAR1 activation. Exp Cell Res 304:16–27
78. Howell DC, Goldsack NR, Marshall RP et al (2001) Direct thrombin inhibition reduces

lung collagen, accumulation, and connective tissue growth factor mRNA levels in bleomycin-induced pulmonary fibrosis. Am J Pathol 159:1383–1395
79. Block ER (1992) Pulmonary endothelial cell pathobiology: implications for acute lung injury. Am J Med Sci 304:136–144
80. Jesmin S, Gando S, Matsuda N et al (2004) Temporal changes in pulmonary expression of key procoagulant molecules in rabbits with endotoxin-induced acute lung injury: elevated expression levels of protease-activated receptors. Thromb Haemost 92:966–979
81. Horton MR, Olman MA, Noble PW (1999) Hyaluronan fragments induce plasminogen activator inhibitor-1 and inhibit urokinase activity in mouse alveolar macrophages: a potential mechanism for impaired fibrinolytic activity in acute lung injury. Chest 116:17S
82. Idell S, James KK, Coalson JJ (1992) Fibrinolytic activity in bronchoalveolar lavage of baboons with diffuse alveolar damage: trends in two forms of lung injury. Crit Care Med 20:1431–1440
83. Hasegawa T, Sorensen L, Dohi M et al (1997) Induction of urokinase-type plasminogen activator receptor by IL-1 beta. Am J Respir Cell Mol Biol 16:683–692
84. Tran H, Maurer F, Nagamine Y (2003) Stabilization of urokinase and urokinase receptor mRNAs by HuR is linked to its cytoplasmic accumulation induced by activated mitogen-activated protein kinase-activated protein kinase 2. Mol Cell Biol 23:7177–7188
85. Solberg H, Ploug M, Hoyer-Hansen G et al (2001) The murine receptor for urokinase-type plasminogen activator is primarily expressed in tissues actively undergoing remodeling. J Histochem Cytochem 49:237–246
86. Shetty S, Idell S (2004) Urokinase receptor mRNA stability involves tyrosine phosphorylation in lung epithelial cells. Am J Respir Cell Mol Biol 30:69–75
87. Shetty S, Pendurthi UR, Halady PK et al (2002) Urokinase induces its own expression in Beas2B lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 28:L319–L328
88. Wei Y, Eble JA, Wang Z et al (2001) Urokinase receptors promote beta1 integrin function through interactions with integrin alpha3beta1. Mol Biol Cell 12:2975–2986
89. Zhu S, Gladson CL, Stewart J et al (2002) Adenovirally mediated expression of urokinase receptor binding site on integrin alpha-chain blocks adhesion and migration of human lung fibroblasts. Chest 121:34–35
90. Sitrin RG, Johnson DR, Pan PM et al (2004) Lipid raft compartmentalization of urokinase receptor signaling in human neutrophils. Am J Respir Cell Mol Biol 30:233–241
91. Chapman HA, Wei Y (2001) Protease crosstalk with integrins: the urokinase receptor paradigm.Thromb Haemost 86:124–129
92. Mura M, dos Santos CC, Stewart D et al (2004) Vascular endothelial growth factor and related molecules in acute lung injury. J Appl Physiol 97:1605–1617
93. Compernolle V, Brusselmans K, Acker T et al (2002) Loss of HIF-2alpha and inhibition of VEGF impair fetal lung maturation, whereas treatment with VEGF prevents fatal respiratory distress in premature mice. Nat Med 8:702–710
94. Brown SB, Savill J (1999) Phagocytosis triggers macrophage release of Fas ligand and induces apoptosis of bystander leukocytes. J Immunol 162:480–485
95. Dhainaut J-F, CHarpentier J, Chiche J-D (2003) Transforming growth factor-beta: a mediator of cell regulation in acute respiratory distress syndrome. Crit Care Med 31:258–264
96. Krein PM, Winston BW (2002) Roles for insulin-like growth factor I and transforming growth factor-beta in fibrotic lung disease.Chest 122:289S–293S
97. Munger JS, Huang X, Kawakatsu H et al (1999) The integrin alpha v beta 6 binds and

activates latent TGF-beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell 96:319–328
98. Letterio JJ, Roberts AB (1998) Regulation of immune responses by TGF-beta. Annu Rev Immunol 16:137–161
99. Lasky JA, Brody AR (2000) Interstitial fibrosis and growth factors. Environ Health Perspect 108:751–762
100. Krein PM, Winston BW (2002) Roles for insulin-like growth factor I and transforming growth factor-beta in fibrotic lung disease. Chest 122:289–293
101. Gauldie J, Jordana M, Cox G (1993) Cytokines and pulmonary fibrosis. Thorax 48:931–935
102. LeRoy EC (1974) Increased collagen synthesis by scleroderma skin fibroblasts in vitro: a possible defect in the regulation or activation of the scleroderma fibroblast. J Clin Invest 54:880–889
103. Pittet JF, Griffiths MJ, Geiser T et al (2001) TGF-beta is a critical mediator of acute lung injury. J Clin Invest 107:1537–1544
104. Nishioka A, Ogawa Y, Mima T et al (2004) Histopathologic amelioration of fibroproliferative change in rat irradiated lung using soluble transforming growth factor-beta (TGF-beta) receptor mediated by adenoviral vector. Int J Radiat Oncol Biol Phys 58:1235–1241
105. Fourrier F, Chopin C, Wallaert B et al (1985) Compared evolution of plasma fibronectin and angiotensin-converting enzyme levels in septic ARDS. Chest 87:191–195
106. Idell S, Kueppers F, Lippmann M et al (1987) Angiotensin converting enzyme in bronchoalveolar lavage in ARDS. Chest 91:52–56
107. Marshall RP, Webb S, Bellingan GJ et al (2002) Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med. 166:646–650
108. Ward WF, Molteni A, Ts'ao CH, Hinz JM (1990) Captopril reduces collagen and mast cell accumulation in irradiated rat lung. Int J Radiat Oncol Biol Phys 19:1405–1409
109. Ortiz LA, Champion HC, Lasky JA et al (2002) Enalapril protects mice from pulmonary hypertension by inhibiting TNF-mediated activation of NF-kappaB and AP-1. Am J Physiol Lung Cell Mol Physiol 282:L1209–L1221
110. Wang R, Ibarra-Sunga O, Verlinski L et al (2000) Abrogation of bleomycin-induced epithelial apoptosis and lung fibrosis by captopril or by a caspase inhibitor. Am J Physiol Lung Cell Mol Physiol 279:L143–L151
111. Ward WF, Molteni A, Ts'ao CH (1989) Radiation-induced endothelial dysfunction and fibrosis in rat lung: modification by the angiotensin converting enzyme inhibitor CL242817. Radiat Res 117:342–350
112. Ward WF, Molteni A, Ts'ao CH et al (1992) Radiation pneumotoxicity in rats: modification by inhibitors of angiotensin converting enzyme. Int J Radiat Oncol Biol Phys 22:623–625
113. Wang R, Zagariya A, Ibarra-Sunga O et al (1999) Angiotensin II induces apoptosis in human and rat alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 276:L885–L889
114. Wang R, Zagariya A, Ang E et al (1999) Fas-induced apoptosis of alveolar epithelial cells requires ANG II generation and receptor interaction. Am J Physiol 277:L1245–L1250
115. Marshall RP, McAnulty RJ, Laurent GJ (2000) Angiotensin II is mitogenic for human lung fibroblasts via activation of the type 1 receptor. Am J Respir Crit Care Med 161:1999–2004
116. Weber H, Taylor DS, Molloy CJ (1994) Angiotensin II induces delayed mitogenesis and

cellular proliferation in rat aortic smooth muscle cells. Correlation with the expression of specific endogenous growth factors and reversal by suramin. J Clin Invest 93:788–798
117. Marshall RP, Gohlke P, Chambers RC et al (2004) Angiotensin II and the fibroproliferative response to acute lung injury. Am J Physiol Lung Cell Mol Physiol 286:L156–L164
118. Liu SF, Crawley DE, Barnes PJ et al (1991) Endothelium-derived relaxing factor inhibits hypoxic pulmonary vasoconstriction in rats. Am Rev Respir Dis 143:32–37
119. Zhu YK, Liu XD, Skold MC et al (2001). Cytokine inhibition of fibroblast-induced gel contraction is mediated by PGE(2) and NO acting through separate parallel pathways. Am J Respir Cell Mol Biol 25:245–253
120. Okamoto T, Valacchi G, Gohil K et al (2002) S-nitrosothiols inhibit cytokine-mediated induction of matrix metalloproteinase-9 in airway epithelial cells. Am J Respir Cell Mol Biol 27:463–473
121. Persinger RL, Poynter ME, Ckless K et al (2002) Molecular mechanisms of nitrogen dioxide induced epithelial injury in the lung. Mol Cell Biochem 234–235:71–80
122. Shrivastava P, Pantano C, Watkin R et al (2004) Reactive nitrogen species-induced cell death requires Fas-dependent activation of c-Jun N-terminal kinase. Mol Cell Biol 24:6763–6772
123. Martin TR, Nakamura M, Matute-Bello G (2003) The role of apoptosis in acute lung injury. Crit Care Med 31:184–188
124. Uhal BD (2002) Apoptosis in lung fibrosis and repair. Chest 122:293–298
125. Li HP, Li X, He GJ et al (2004) The influence of dexamethasone on the proliferative and apoptosis of pulmonary inflammatory cells in bleomycin-induced fibrosis in rats. Respirology 9:25–32
126. Li X, Shu R, Filippatos G et al (2004) Apoptosis in lung injury and remodeling. J Appl Physiol 91:1535–1542
127. Wang HC, Shun CT, Hsu SM et al (2002) Fas/Fas ligand pathway is involved in the resolution of type II pneumocyte hyperplasia after acute lung injury: evidence from a rat model. Crit Care Med 30:1528–1534
128. Albertine KH, Soulier MF, Wang Z et al (2002) Fas and Fas ligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. Am J Pathol 161:1783–1796
129. Sookhai S, Wang JJ, McCourt M et al (2002) A novel therapeutic strategy for attenuating neutrophil-mediated lung injury in vivo. Ann Surg 235:285–291
130. Hagimoto N, Kuwano K, Kawasaki M et al (1999) Induction of interleukin-8 secretion and apoptosis in bronchiolar epithelial cells by Fas ligation. Am J Respir Cell Mol Biol 21:436–445
131. Matthay MA, Zimmerman GA, Esmon C et al (2003) Future research directions in acute lung injury. Am J Respir Crit Care Med 167:1027–1035
132. Huynh ML, Fadok VA, Henson PM (2002) Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF-beta 1 secretion and the resolution of inflammation. J Clin Invest 109:41–50

Chapter 34

Corticosteroids in ARDS: back to the future

A.B. Souza-Fernandes, W.A. Zin, P.R.M. Rocco

The first descriptions of acute respiratory distress syndrome (ARDS) were published in 1967, when Ashbaugh et al. [1] described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on chest radiograph. ARDS is thought to be a uniform expression of a diffuse and overwhelming inflammatory reaction of the pulmonary parenchyma to a variety of serious underlying diseases. In 1994, the American-European Consensus Conference [2] defined two pathogenetic pathways leading to ARDS: a direct ('primary' or 'pulmonary') insult that directly affects lung parenchyma, and an indirect ('secondary' or 'extrapulmonary') insult that results from an acute systemic inflammatory response (Table 1).

Table 1. Recommended criteria for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [2]

	Timing	Oxygenation	Chest radiograph	Pulmonary artery wedge pressure
ALI criteria	Acute onset	$PaO_2/FiO_2 \leq 300$ (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	$\leq$ 18 mmHg when measured or no clinical evidence of left atrial hypertension
ARDS criteria	Acute onset	$PaO_2/FiO_2 \leq 200$ (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	$\leq$ 18 mmHg when measured or no clinical evidence of left atrial hypertension

The pathologic features of the lung in ARDS derive from severe injury to the alveolocapillary unit. The morphologic picture of the lung in ARDS has been labelled diffuse alveolar damage, and seepage of intravascular fluid dominates the onset of the disease [3]. Microscopic findings are dependent on the stage of the illness. Traditionally, ARDS has been divided into three stages in which an initial inflammatory phase (exudative) is followed by fibroproliferation, which can lead to established interstitial and intraalveolar fibrosis, the final phase. The histologic features of exudative phase are: (a) hyaline membranes, (b) alveolar collapse, and (c) swollen type I pneumocytes with cytoplasmic vacuoles. The endothelial cells swell, the intercellular junctions widen, and pinocytic vesicles increase, causing disruption of the capillary membrane and resulting in a capillary leak and oedema

formation. The proliferative phase was described as beginning as early as the third day and reaching a peak in the second and third weeks after the onset of symptoms. However, recently, some authors have reported that fibroproliferation is an early response to lung injury [4–9]. Thus, inflammatory and repair mechanisms occur in parallel rather than in series. Despite recent advances in our understanding of the pathophysiology of ARDS, improvements in supportive care, and multiple therapeutic efforts directed at modifying the course of the condition, the mortality rates of 30–60% persist [10, 11].

The recognition that neutrophils, macrophages, and other components of the inflammatory cascade participate in the progression of ARDS has resulted in the use of anti-inflammatory agents, particularly corticosteroids [12–16]. Corticosteroids, by virtue of their ability to attenuate cell-mediated immunity and decrease cytokine release and activation, seem to be ideal agents to interrupt the detrimental cascade of immunologic events that accompany ARDS. Corticosteroids inhibit NF-κB (the central transcription factor that drives the inflammatory response to insults) and consequently the expression of NF-κB-dependent pro-inflammatory genes [17]. Thus, they inhibit the transcription of several cytokines that are relevant to ARDS, including interleukin (IL)-1, IL-3, IL-4, IL-5, IL-6, IL-8, tumour necrosis factor (TNF)-a, and granulocyte-macrophage colony stimulating factor (GM-CSF). Corticosteroids also have an inhibitory effect on fibrogenesis [18, 19], and act on the antagonist of IL-1 receptor and on the anti-inflammatory cytokines IL-4, IL-10, and IL-13 [20] to synergistically control the host defence response (HDR). Corticosteroids stimulate apoptosis of T-cells, eosinophils, and monocytes, and inhibit neutrophil activation. In addition, they are important in maintaining endothelial integrity and vascular permeability [21, 22].

Corticosteroids are mainly transported in the blood complexed to transcortin (corticosteroid-binding globulin) and albumin, although a small portion is in a free, metabolically active state. The free corticosteroid molecules cross the plasma membrane into the cytoplasm, where they bind to a specific receptor, the glucocorticoid receptor (GR) [23]. When not bound to its ligand, GR is sequestered in the cytoplasm as an inactive complex with two molecules of heat-shock protein (HSP-90) and other cytosolic proteins. Upon binding glucocorticoids, the GR undergoes a conformational change, which allows it to dissociate from HSP-90. The hormone-bound GR translocates to the nucleus, where it transiently associates with another heat-shock protein, HSP-56, and later dissociates from it and binds as a dimer to a conserved palindromic DNA sequence, the glucocorticoid response element (GRE) [23, 24].

Activated GR mediates transcriptional interference via the following mechanisms: (a) by physically interacting with NF-κB and forming an inactive GRa–NF-κB complex, (b) by inducing transcription of the gene encoding inhibitory protein IκBα, which traps NF-κB in inactive cytoplasmic complexes in a process catabolised by the ubiquitin–proteasome pathway, (c) by blocking degradation of IκBα, via enhanced synthesis of IL-10, (d) by impairing TNF-α-induced degradation of IκBα, and (e) by competing for limited amounts of GR co-activators [17, 24]. GR may also interact directly with protein transcription factors in the cytoplasm and

nucleus, and thereby influence the synthesis of certain proteins independently of an interaction with DNA in the cell nucleus.

Corticosteroid therapy in ARDS has been studied in three different situations: (1) prevention in high-risk patients; (2) early treatment with high-dose, short-course therapy; and (3) prolonged therapy in unresolving cases.

Prevention in high-risk patients

Based on results of animal research, methylprednisolone (MP) was subjected to clinical trials as adjunctive therapy for patients with ARDS. Sibbald et al. used the clearance of iodinated human serum albumin (I-HSA) to demonstrate increased pulmonary capillary permeability in 19 patients with ARDS [25]. Their study reported that treatment with MP at 30 mg/kg was associated with a 50% reduction in I-HSA clearance in 14 out of 19 patients, whereas the other five patients showed no change. Responders and nonresponders to MP were identified on the basis of the mean pulmonary artery pressure and intrapulmonary shunt fraction at admission to the study, with a lower mean pulmonary artery pressure and intrapulmonary shunt fraction characterising the steroid responders. The mortality rate was 21% in the responders vs 100% in nonresponders (Table 2).

Table 2. Clinical trials of corticosteroid for ARDS prevention or at the early phase of ARDS

Author (year)	Population	Dose	Results
Sprung et al. (1984)	Septic shock	MP 30 mg/kg or dexamethasone 6 mg/kg or placebo	No survival benefit from steroid
Bone et al. (1987)	Septic shock	MP 30 mg/kg every 6 h for 4 days	MP failed to reverse ARDS and increased the mortality rate
VA (1987)	Septic shock	MP 30 mg/kg bolus, 5mg/kg/h during 9 h	No survival benefit
Luce et al. (1988)	Septic shock	MP 30 mg/kg every 6 h for 4 days	Similar progression to ARDS and overall mortality rate for MP and placebo groups
Weigelt et al. (1985)	Risk for ARDS, not necessarily septic shock	MP 30 mg/kg every 6 h for 2 days	Greater progression to ARDS with no change in mortality
Schonfeld et al. (1983)	Fat embolism syndrome	MP 7.5 mg/kg every 6 h for 12 doses	Reduced the risk of respiratory failure
Gagnon et al. (1990)	*Pneumocystis carinii* pneumonia	MP 40 mg every 6 h for 7 days	Reduced mortality and the risk of respiratory failure
Bozzette et al. (1990)	*Pneumocystis carinii* pneumonia	Prednisone 40 mg twice daily for 5 days, 40 mg daily for 5 days, 20 mg daily for 10 days	Reduced mortality and the risk of respiratory failure
Montaner et al. (1990)	*Pneumocystis carinii* pneumonia	Prednisone 60 mg/day for 7 days, taper over 14 days	Reduced deterioration in oxygenation
Bernard et al. (1987)	Early ARDS	MP 30 mg/kg every 6 h for 1 day	Similar mortality rate for MP and placebo groups

ARDS, Acute respiratory distress syndrome; *MP*, methylprednisolone

Two prospective clinical trials subsequently evaluated MP as prophylaxis against ARDS in high-risk trauma patients. In an open study of 92 trauma patients, Van der Merwe et al. reported fewer cases of ARDS in corticosteroid-treated patients, but this study had no placebo control and did not provide mortality data. They suggested that MP-treated patients with injury scores less than 50 developed ARDS at a significantly lower rate than control patients with similar scores [26]. In another study, Weigelt et al. carried out a prospective, double-blind, randomised study of early corticosteroid therapy in acutely ill, mechanically ventilated patients felt to be at high risk for ARDS [27]. Patients received intravenous MP (30 mg/kg every 6 h for 48 h) or placebo. The results showed that ARDS developed more frequently in MP-treated patients (51%) than in those receiving placebo (33%), and no significant differences in mortality were observed between these two groups [27].

At least four subsequent randomised controlled trials (RCTs) have failed to show any protective effects of high-dose corticosteroids in patients with sepsis or septic shock at risk for ARDS [28–31]. Bone et al. did a multicentre, double-blind, RCT to determine whether corticosteroid therapy could prevent the development of ARDS in high-risk patients [30]. They randomised 382 patients with sepsis to either MP (30 mg/kg) or placebo infusions every 6 h for a total of four doses. Treatment was initiated within 2 h of the onset of sepsis. There was a trend toward an increased incidence of ARDS in the MP group (32% vs 25%, $P = 0.10$). Overall mortality was not reported; however, in those patients developing ARDS, 14-day mortality was significantly higher in the MP group (52%) than in the placebo group (22%). A study from the members of the Veterans Administration Systemic Sepsis Cooperative Study Group comprised 223 patients treated with antibiotics and MP (30 mg/kg bolus, then 5 mg/kg/h for 9 h) or placebo [29]. Mortality at 14 days was similar in both groups and there was no evidence that corticosteroids were harmful to septic patients. Similar to the studies of Bone et al., the results of a clinical trial carried on by Luce et al. failed to demonstrate any benefit of MP on ARDS development or subsequent death [31]. They conducted a prospective, double-blind, randomised trial evaluating the efficacy of MP to prevent ARDS in patients with septic shock. Patients received four doses of methylprednisolone (30 mg/kg every 6 h) or placebo. Steroid therapy did not decrease the incidence or the mortality rate. Thus, it is clear that there is no evidence to support the use of corticosteroids for the prevention of ARDS in all patients at high risk.

Early treatment with high-dose, short-course therapy

In 1987, Bernard et al. carried out a double-blind, RCT to determine the effect of high-dose, short-course corticosteroid on mortality and several physiologic variables in early ARDS [32]. The study population comprised adult patients who met ARDS criteria [2] while those with recent corticosteroid use, evidence of active infection, other indications for corticosteroid therapy, extensive burns, or pregnancy were excluded. Ninety-nine patients were randomised, within 30 h of the onset of ARDS, to receive high-dose MP (30 mg/kg every 6 h for 24 h) or placebo.

The results of the trial showed no differences between the placebo and corticosteroids groups with respect to mortality or reversal of ARDS. In addition, there was a trend toward increased prevalence of infections in the corticosteroid group, as well as significantly more frequent treatment-related hyperglycaemia. A recent meta-analysis pooled the patients from the study of Weigelt et al. [27] and Bernard et al. [32] (180 patients), and confirmed no survival benefit with early corticosteroids [33].

However, corticosteroids have been shown to reduce mortality in two groups of patients with ARDS or at risk for developing the syndrome. The first comprised patients at risk for fat embolism syndrome (e.g. long-bone fractures) in whom corticosteroids given prophylactically decreased the risk of respiratory failure [34]. Schonfeld et al. randomly assigned 64 consecutive patients who had one or more lower-extremity long-bone fractures to receive intravenous placebo or MP (7.5 mg/kg every 6 h for 12 doses, total dose of 90 mg/kg) [34]. None of the patients who received MP died. The second group enrolled patients with AIDS and *Pneumocystis carinii* pneumonia (PCP). Three randomised trials assessed the efficacy of adjunctive therapy with corticosteroids in patients with AIDS and PCP [35–37]. Patients in these studies received placebo or a combination of intravenous and oral corticosteroids when PCP initially was treated with antibiotics. The active drugs were associated with a lower risk of respiratory failure, improved survival, or both, in all three studies. An acute lung lesion that fulfils the diagnostic criteria for ARDS and does benefit from steroid therapy is acute eosinophilic pneumonia, which most likely denotes a manifestation of acute eosinophilic alveolitis [38]. Hence, patients that present large numbers of eosinophils in the bronchoalveolar lavage (BAL) fluid should be treated with high doses of steroids.

The absence of beneficial effects of corticosteroid at the early phase of acute lung injury (ALI) could be due to the population studied, in particular to the fact that those studies were multicentric ones, i.e. very heterogeneous in terms of the case mix and management of the patients. In addition, negative effects owing to the profound immunodepression or other side effects induced by high doses of steroids could counterbalance positive outcomes, so that the overall result appears to show a neutral or even deleterious effect of corticosteroids. Furthermore, corticosteroid therapy would seem to be ineffective if many of the patients considered to have ARDS based on clinical definitions did not have activation of inflammatory cascades in their lungs. The failure of the beneficial effect of steroid in ALI could also be related to the activation of macrophage inhibitor factor (MIF) early in the course of lung injury. MIF has been shown to override corticosteroid-mediated inhibition of cytokine secretion, whereas it enhances both TNF-a and IL-8 secretion from alveolar macrophages, thus maintaining the inflammatory process [39].

Steroids in the late phase of ARDS

In contrast to early ARDS, there is evidence that corticosteroids may be beneficial in the late phase of the disease (Table 3). Ashbaugh and Maier described ten patients

with ARDS that did not respond to conventional therapy [40]. These patients underwent open-lung biopsies, and at the histological examination all of them had cellular proliferation, obliteration of alveoli, and fibrosis without infection. Intravenous MP (125 mg every 6 h) was administered to these patients 6–22 days after onset of ARDS, followed by oral prednisolone tapered over 3–6 weeks. Eight patients recovered and two died of sepsis. Hooper and Kearl treated another ten patients with severe ARDS treated with long-term adrenocortical steroids (21 days) [41]. The initial dose of MP (12–250 mg every 6 h) was based on the severity of the respiratory damage, and was maintained for 72–96 h. All patients showed improvement in ventilatory requirements, oxygenation, and chest radiographs, and the survival rate was 81%. In this context, six patients with refractory late ARDS were treated with MP (1–2 mg/kg every 6 h) in a study by Biffl et al. [42]. Steroids were instituted after 16 days of mechanical ventilatory support. By day 7 of steroid therapy, there was clinically significant improvement in the PaO_2/FiO_2 ratio and a lower lung injury score (LIS). Overall survival corresponded to 83% and the mean duration of corticosteroid therapy was 21.3 days (Table 3).

Table 3. Clinical trials of corticosteroids at the late phase of ARDS

Author (year)	Population	Dose	Results
Ashbaugh and Maier (1985)	Pulmonary fibrosis	MP 125 mg every 6 h followed by oral prednisone for 3–6 weeks beginning 6–22 days	MP increased the survival
Hooper et al. (1990)	Established ARDS > 3 days with cause resolved	MP 125–250 mg every 6 h for 3–4 days reducing by 50% every 2–3 days	MP improved the respiratory parameters, 81% survival
Biffl et al. (1995)	Prolonged ARDS not responding to conventional therapy	MP 1–2 mg/kg every 6 h for 16 days	MP improved PaO_2/FiO_2 ratio and decreased LIS, 83% survival
Meduri et al. (1994)	Late ARDS	MP 200 mg followed by 2–3 mg/kg/day every 6 h until extubation	MP increased PaO_2/FiO_2 ratio and decreased LIS
Meduri et al. (1995)	Late ARDS	MP 200 mg bolus, 2–3 mg/kg/day until extubation (mean: 6 weeks)	MP reduced plasma and BALF inflammatory cytokines
Meduri et al.(1998)	Late ARDS	MP 2 mg/kg followed by 2 mg/kg/day every 6 h for 14 days followed by progressively lower doses until day 32	MP improved PaO_2/FiO_2 ratio, decreased LIS and MODS, reduced mortality
ARDS network (2005)	Late ARDS	MP 2 mg/kg/day every 6 h for 14 days	MP did not improve survival rate, muscle weakness and neuropathy.

ARDS, Acute respiratory distress syndrome; *MP*, methylprednisolone; *LIS*, lung injury score; *MODS*, multiple organ dysfunction syndrome

A large uncontrolled series of patients with late ARDS was treated with corticosteroids as part of a study reported by Meduri et al. [43]. All patients had progressively worsening respiratory failure 7 days or more after the onset of ARDS. Patients were treated with MP (200 mg in bolus followed by 2–3 mg/kg/day in divided doses every 6 h until extubation, after which the steroid was tapered slowly). By day 7 of treatment, the PaO_2/FiO_2 ratio had increased and the LIS had decreased [43]. Three patterns of response were noted: (1) rapid responders showed improvement by day 7, (2) delayed responders showed improvement by day 14, and (3) nonresponders exhibited no improvement by day 14. Intensive care unit (ICU) survival was 87% in rapid responders, 83% in delayed responders, and 25% in nonresponders. The average duration of corticosteroid treatment was 36 days. Pneumonia developed in 38% of responders and 75% of nonresponders.

In 1998, Meduri et al. speculated that the early removal of high-dose corticosteroid treatment in the previous randomised trials, which used short-term corticosteroid treatment, may have reversed any early beneficial effect of treatment or overturned the ability to detect a beneficial effect. In order to determine the effects of prolonged steroid therapy on lung function and mortality in nonresolving ARDS, the group conducted a randomised, double-blind, placebo-controlled trial in four medical ICU's [44]. In 24 patients with unresolving ARDS, randomised on day 7 of mechanical ventilation, treatment with a lower dose of MP for a longer treatment course (0.5 mg/kg every 6 h for 14 days, then tapering doses to day 32) reduced hospital mortality from 62% in the placebo group to 12% in the steroid group. However, the major criticism of this study has rested on its early termination [45, 46]. It was originally calculated that the study needed 99 patients to show an absolute survival benefit of 30% with a power of 0.95, but the study was stopped early, with just 24 patients. Therefore, the results must be interpreted carefully. Furthermore, the study design required a crossover of those patients that did not respond to the initially prescribed treatment. This reflects the researchers' conviction that every patient should be given corticosteroids, which further confounds interpretation of the results [47].

In another study, Meduri et al. analysed the effects of corticosteroid (initial bolus of 200 mg MP i.v. every 6 h at a dosage of 2–3 mg/kg/day until extubation) on plasma and BALF cytokine levels in patients with late ARDS [48]. Baseline plasma and BALF cytokine levels were similar in both groups. The surviving patients treated with corticosteroids were found to have a significant reduction in plasma and BALF TNF-α, IL-1β, IL-6, and IL-8 concentrations. The decrease in various cytokine levels was seen only after 5–14 days of steroid administration. ARDS nonsurvivors have been reported to have higher initial and persistent elevation of plasma and BALF cytokines than measured in survivors. These findings mandate a reappraisal of the role of anti-inflammatory treatment of ARDS [48].

Steroids also prevent excessive collagen deposition and increase collagen breakdown [18, 19]. In this context, Meduri et al. also examined the effects of corticosteroids on plasma and BALF levels of procollagen amino-terminal propeptide type I (PINP) and type III (PIIINP) in patients with nonresolving ARDS [49]. PINP and PIIINP are secreted by fibroblasts and reflect collagen synthesis at the site of the

disease. Previous studies reported that nonsurvivors of ARDS had persistent elevations of plasma and BALF PIIINP levels [7, 50]. Meduri et al. found augmented plasma levels of PINP and PIIINP in their patients and observed that the concentrations of PINP and PIIINP increased over time in nonsurvivors, as opposed to survivors in whom the levels did not change significantly. BALF concentrations of PINP and PIIINP were also noted to be higher in nonsurvivors than in survivors, although the differences were not statistically significant [49]. In that study, patients who had not shown an improvement in LIS greater than 1 point were randomised to receive MP using the same protocol as in the previous randomised trial of this group [44], or placebo. Patients treated with MP had significant decreases in plasma and BALF PINP and PIIINP levels, whereas there were no changes in patients receiving placebo. Decreases in plasma and BALF PINP and PIIINP levels correlated with improvements in LIS and PaO_2/FiO_2 ratio [49].

Meduri et al. investigated whether unresolving ARDS is associated with systemic inflammation-induced corticosteroid resistance and whether prolonged MP administration accelerates the suppression of systemic inflammatory indices and normalises the sensitivity of the immune system to steroids [51]. Patients with unresolving ARDS were treated with MP (2 mg/kg/day from day 1 to day 14, followed by progressively lower doses until day 32). Patients treated with corticosteroid had progressive and sustained reductions of TNF-α IL-1β, IL-6, and endogenous cortisol concentrations over time. Normal peripheral blood leukocytes exposed to plasma samples collected during MP treatment also exhibited rapid, progressive, and significant increases in GR-mediated activities and significant reductions in NF-kB binding and transcription of TNF-α and IL-1β. These findings provide support for the presence of endogenous glucocorticoid inadequacy in the control of inflammation and systemic-inflammation-induced peripheral glucocorticoid resistance in ARDS. Prolonged MP administration accelerated the resolution of both systemic inflammation and peripheral acquired glucocorticoid resistance in patients with ARDS [52].

To definitively answer this question, the ARDS network designed the Late Steroid Rescue Study (LaSRS), a multicentre RCT comparing steroid with placebo in late phase (> 7 days) ARDS [53]. In that trial, MP is initially dosed at 2 mg/kg/day for 14 days, and then tapered up to day 25. Outcomes are 60-day mortality, ventilator-free days, organ-failure-free days, and a subgroup analysis comparing steroid responsiveness in patients with high initial serum and BAL markers of inflammation and fibroproliferation to those with low initial levels. The group observed that steroids do not seem to improve survival in patients with ARDS. Furthermore, there is increasing evidence of long-term morbidity, including disabling muscle weakness and neuropathy associated with steroid use [54–56].

Future perspectives on the basis of experimental models

The use of steroids in the late phase of ARDS was based on the assumption that the fibroproliferative phase began 7–10 days after the onset of the insult. However,

some authors have observed an increased number of myofibroblasts and cells producing procollagen types I and III during the early phase of ALI [4–9], suggesting that the proliferative phase begins much sooner than had been previously appreciated. Thus, inflammatory and repair mechanisms occur simultaneously rather than subsequently. As a complement to this finding, Rocco et al. observed pronounced mechanical changes at the tissue level and fibroelastogenesis at an early phase of ALI, even in mildly abnormal lung parenchyma [9, 57]. This same group then analysed the effects of administering corticosteroids at the early phase of paraquat-induced ALI [58]. Corticosteroids were found to act differently depending on the degree of ALI, leading to a complete maintenance of normal tissue mechanics and collagen content in mild lesion, and minimising changes in tissue impedance and the accumulation of extracellular matrix components in severe lesions. In addition, the early beneficial effects of corticosteroids with respect to extracellular matrix formation remained unaltered 30 days after paraquat-induced ALI [58].

On the basis of the previous experimental study [58], Lee et al. tested the efficacy of low-dose MP administration in patients with postoperative ARDS immediately after the syndrome was confirmed, and compared this treatment with conventional therapy [59]. It was observed that early administration of low-dose MP significantly reduced mortality due to ARDS after thoracic surgery. Certainly, further multicentre, prospective, clinical RCTs are needed to confirm these results.

Two distinct forms of ARDS/ALI are described, since there are differences between pulmonary (direct lung injury) and extrapulmonary (reflecting lung involvement in a more distant systemic inflammatory response) ALI. These differences can be detected radiographically, functionally, and by analysing the responses to therapeutic intervention. In this respect, we studied the effects of corticosteroids in an experimental model of primary and secondary ALI induced by intratracheal or intraperitoneal injection of lipopolysaccharide (LPS) of *Escherichia coli,* respectively [60, 61]. MP (2 mg/kg) was intravenously injected 1 and 6 h after the induction of ALI. Pulmonary and extrapulmonary ALI exhibited similar degrees of lung injury, as indicated by lung mechanics and histology, the amount of collagen fibre in the alveolar septa, and tissue cellularity, but corticosteroid attenuated these changes only in pulmonary ALI [90]. BALF levels of IL-8, IL-6 and neutrophils increased more in pulmonary than in extrapulmonary ALI. Corticosteroid reduced IL-8, IL-6, and neutrophils in the BALF only in pulmonary ALI. Thus, corticosteroid acted differently depending on the aetiology of ALI, with complete maintenance of normal lung mechanics and histology in ALI caused by pulmonary disease [62].

Although prolonged steroid therapy is associated with side effects, such as muscle weakness and neuropathy and increased risk of infection [40, 41, 55, 56], Meduri et al. reported that early cessation of corticosteroid treatment could reverse any early beneficial effect of treatment or overturn the ability to detect a beneficial effect [44, 51]. Thus, we decided to compare the effects of only one low-dose of steroid with prolonged small doses of steroid therapy at an early phase of ALI. To that end, acute lung injury was induced by instilling intratracheally *E. coli* LPS in BALB/c mice. These animals were treated with either only one dose of MP (2mg/kg, i.v.) at 6 or 24 h after LPS administration or daily (7 days duration, starting at day

1). One, 3, and 8 weeks after ALI induction, respiratory mechanics, lung histology (light and electron microscopy), and the amount of collagen and elastic fibres in the alveolar septa were evaluated. MP led to a complete maintenance of respiratory mechanical parameters and avoided fibrosis independently of the steroid treatment design. Thus, short-duration, small-dose steroid therapy is as effective as prolonged therapy for early ARDS in this model of lung injury [63, 64].

Based on these results, there is a potential role for corticosteroids in the treatment of inflammatory complications of pneumonia. Recently, Confalonieri et al. hypothesised that hydrocortisone infusion (bolus of 200 mg i.v., followed by infusion at a rate of 10 mg/h for 7 days) in severe community-acquired pneumonia attenuates systemic inflammation and leads to earlier resolution of pneumonia and a reduction in sepsis-related complications [65]. In addition, a 7-day course of low-dose hydrocortisone infusion was associated with a significant reduction in duration of mechanical ventilation, hospital length of stay, and hospital mortality. These findings support the hypothesis that modulation of systemic inflammation with early introduction of prolonged low-dose corticosteroids administration hastens resolution of pneumonia and prevents development of life-threatening sepsis-related complications [65]. Specifically, it would be interesting to evaluate in a prospective, controlled, randomised trial aimed at determining whether small doses of corticosteroids administered throughout a short period influence survival in patients with severe acute pneumonia.

Conclusions

Improving the course and outcome of patients with ARDS presents a considerable challenge. A more comprehensive understanding of the heterogeneous pathophysiology of ARDS and the biologic response of the individual patient represents an important component to meet this challenge. By understanding the immune status of a given patient at a given point in the disease process, the physician can consider manipulating proinflammatory systems more rationally. In this context, corticosteroids inhibit a host of potent inflammatory mediators and could be a therapeutic tool in the armamentarium against ARDS. The use of corticosteroid in the treatment of ALI/ARDS remains a subject of great controversy; however, it is clear that there is no evidence to use high-dose corticosteroids routinely in patients at risk for or in the exudative phase of ALI/ARDS. Corticosteroids may be indicated for ARDS of suspected allergic origin, fat embolism syndrome, *Pneumocystis carinii* pneumonia, and for those with inadequate adrenal reserve, even in the early phase. Despite a study by the National Institutes of Health that failed to show an improvement in mortality of patients with ARDS, numerous important factors need to be taken into account when corticosteroid is used as a strategy to treat ARDS, such as disease definitions, intervention timing, and dosing regimen. Recently, there has been a resurgent enthusiasm for their use in specific conditions, including small doses early in the course of ARDS, and in specific subgroups of patients who respond to steroid therapy.

References

1. Ashbaugh DG, Bigelow DB, Petty TL et al (1967) Acute respiratory distress syndrome. Lancet 2:319–323
2. Bernard GR, Artigas A, Bringham KL et al (1994) The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
3. Tomashefski JF Jr (2000) Pulmonary pathology of acute respiratory distress syndrome. Clin Chest Med 21:435–466
4. Liebler JM, Qu Z, Buckner B et al (1998) Fibroproliferation and mast cells in the acute respiratory distress syndrome. Thorax 53:823–829
5. Pugin J, Verghese G, Widmer MC et al (1999) The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 27:304–312
6. Chesnutt AN, Matthay MA, Tibayan FA et al (1997) Early detection of type III procollagen peptide in acute lung injury: pathogenetic and prognostic significance. Am J Respir Crit Care Med 156:840–845
7. Clark JG, Milberg JA, Steinberg KP et al (1995) Type III procollagen peptide in the adult respiratory distress syndrome. Ann Intern Med 122:17–23
8. Marshall RP, Bellingan G, Webb S et al (2000) Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. Am J Respir Crit Care Med 162:1783–1788
9. Rocco PRM, Negri EM, Kurtz PM et al (2001) Lung tissue mechanics and extracellular matrix in acute lung injury. Am J Respir Crit Care Med 164:1067–1071
10. Gong MN, Thompson BT, Williams P et al (2005) Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med 33:1191–1198
11. Kallet RH (2004) Evidence-based management of acute lung injury and acute respiratory distress syndrome. Respir Care 49:793–809
12. Crimi E, Slutsky AS (2004) Inflammation and the acute respiratory distress syndrome. Best Pract Res Clin Anaesthesiol 18:477–492
13. Luce JM (2002) Corticosteroids in ARDS. An evidence-based review. Crit Care Clin 18:79–89
14. Brower RG, Ware LB, Berthiaume Y et al (2001) Treatment of ARDS. Chest 120:1347–1367
15. Tasaka S, Hasegawa N, Ishizaka A (2002) Pharmacology of acute lung injury. Pulm Pharmacol Ther 15:83–95
16. Jantz MA, Sahn AS (1999) Corticosteroids in acute respiratory failure. Am J Respir Crit Care Med 160:1079–1100
17. Wissink S, van Heerde EC, van der Burg B, van der Saagt PT (1998) A dual mechanism mediates repression of NF-kappa B activity by glucocorticoids. Mol Endocrinol 12:355–363
18. Meduri GU, Belenchia JM, Estes RJ et al (1991) Fibroproliferative phase of ARDS: clinical findings and effects of corticosteroids. Chest 100:943–952
19. Hesterberg TW, Last JA (1981) Ozone-induced acute pulmonary fibrosis in rats. Prevention of increased rates of collagen synthesis by methylprednisolone. Am Rev Respir Dis 123:47–52
20. Hart PH, Whitty GA, Burgess DR et al (1990) Augmentation of glucocorticoid action on human monocytes by interkeukin-4. Lymphokine Res 9:147–153
21. Thompson BT (2003) Glucocorticoids and acute lung injury. Crit Care Med 31:5253–5257

22. Cronstein BN, Kimmel SC, Levin RI et al (1992) A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad Sci USA 89:9991–9995
23. Payne DNR, Adcock IM (2001) Molecular mechanisms of corticosteroid actions. Paediatr Respir Rev 2:145–150
24. Almawi WY, Melemedjian OK (2002) Negative regulation of nuclear factor-kappaB activation and function by glucocorticoids. J Mol Endocrinol 28:69–78
25. Sibbald WJ, Anderson RR, Reid B et al (1981) Alveolocapillary permeability in human septic ARDS. Chest 79:133–142
26. Van der Merwe CJ, Louw AF, Welthagen D, Schoeman HS (1985) Adult respiratory distress syndrome in cases of severe trauma: the prophylactic value of methylprednisolone sodium succinate. S Afr Med J 57:279–284
27. Weigelt JA, Norcross JR, Borman KR et al (1985) Early steroid therapy for respiratory failure. Arch Surg 120:536–540
28. Sprung CL, Caralis PV, Marcial EH et al (1984) The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. N Engl J Med 311:1137–1143
29. Anonymous (1987) Effects of high dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. The Veterans Administration Systemic Sepsis Cooperative Study Group. N Engl J Med 317:659–665
30. Bone RC, Fisher CJ Jr, Clemmer TP et al (1987) Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest 92:1032–1036
31. Luce JM, Montgomery AB, Marks JD et al (1988) Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 138:62–68
32. Bernard GR, Luce JM, Sprung CL et al (1987) High dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317:1565–1570
33. Adhikari N, Burns KEA, Meade MO (2004) Pharmacologic therapies for acute respiratory distress syndrome and acute lung injury. Systematic review and meta-analysis. Treat Respir Med 3:307–328
34. Schonfeld SA, Ploysongsang Y, DiLisio R et al (1983) Fat embolism prophylaxis with corticosteroids: a prospective study in high risk patients. Ann Intern Med 99:438–443
35. Bozzette SA, Sattler FR, Chiu J et al (1990) A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 323:1451–1457
36. Gagnon S, Boota AM, Fischl MA et al (1990) Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome: A double-blind, placebo-controlled trial. N Engl J Med 323:1444–1450
37. Montaner JSG, Lawson LM, Levitt N et al (1990) Corticosteroids prevent early deterioration in patients with moderately severe Pneumocystis carinii pneumonia and the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 113:14–20
38. Allen JN, Pacht ER, Gadek JE et al (1989) Acute eosinophilic pneumonia as a reversible cause of noninfections respiratory failure. N Engl J Med 321:569–574
39. Donnelly SC, Bucala R (1997) Macrophage migration inhibitory factor: a regulator of glucocorticoid activity with a critical role in inflammatory disease. Mol Med Today 3:502–507
40. Ashbaugh DG, Maier RV (1985) Idiopathic pulmonary fibrosis in adult respiratory distress syndrome. Diagnosis and treatment. Arch Surg 120:530–535
41. Hooper RG, Kearl RA (1990) Established ARDS treated with a sustained course of adrenocortical steroids. Chest 97:138–143

42. Biffl WL, Moore FA, Moore EE et al (1995) Are corticosteroids salvage therapy for refractory acute respiratory distress syndrome? Am J Surg 170:591–596
43. Meduri GU, Chinn AJ, Leeper KV et al (1994) Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS: patterns of response and predictors of outcome. Chest 105:1516–1527
44. Meduri GU, Headley S, Golden E et al (1998) Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomised controlled trial. JAMA 280:159–165
45. Marras T, Herridge M, Mehta S (1999) Corticosteroid therapy in acute respiratory distress syndrome. Intensive Care Med 25:1191–1193
46. Bosma K, Fanelli V, Ranieri VM (2005) Acute respiratory distress syndrome: update on the latest developments in basic and clinical research. Curr Opin Anesthesiol 18:137–145
47. Brun-Buisson C, Brochard L (1998) Corticosteroid therapy in acute respiratory distress syndrome: better late than never? JAMA 280:182–183
48. Meduri GU, Headley S, Tolley E et al (1995) Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. Chest 108:1315–1325
49. Meduri GU, Tolley EA, Chinn A et al (1998) Procollagen types I and III aminoterminal propeptide levels during acute respiratory distress syndrome and in response to methylprednisolone treatment. Am J Respir Crit Care Med 158:1432–1441
50. Entzian P, Huckstadt A, Kreipe H et al (1990) Determination of serum concentrations of type III procollagen peptide in mechanically ventilated patients: pronounced augmented concentrations in the adult respiratory distress syndrome. Am Rev Respir Dis 142:1079–1082
51. Meduri GU, Tolley EA, Chrousos GP et al (2002) Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome. Evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. Am J Respir Crit Care Med 165:983–991
52. Meduri GU, Carratu P, Freire AX (2003) Evidence of biological efficacy for prolonged glucocorticoid treatment in patients with unresolving ARDS. Eur Respir J 22:57S–64S
53. National Heart, Lung, and Blood Institute. NHLBI. ARDSnet website. Available online at: http://www.ardsnet.org
54. Herridge MS, Cheung AM, Tansey CM et al (2003) One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 348:683–6931
55. Bercker S, Weber-Carstens S, Deja M et al (2005) Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med 33:711–715
56. De Jonghe B, Sharshar T, Lefaucheur J-P et al (2002) Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 288:2859–2867
57. Rocco PR, Facchinetti LD, Ferreira HC et al (2004) Time course of respiratory mechanics and pulmonary structural remodelling in acute lung injury. Respir Physiol Neurobiol 143:49–61
58. Rocco PRM, Souza AB, Faffe DS et al (2003) Effect of corticosteroid on lung parenchyma remodeling at an early phase of acute lung injury. Am J Respir Crit Care Med 168:677–684
59. Lee HS, Lee JM, Kim MS et al (2005) Low-dose steroid therapy at an early phase of postoperative acute respiratory distress syndrome. Ann Thorac Surg 79:405–410
60. Menezes SLS, Bozza PT, Castro-Faria Neto HC et al (2005) Pulmonary and extrapulmonary acute lung injury: inflammatory and ultrastructural analyses. J Appl Physiol 98:1777–1783

61. Rocco PR, Zin WA (2005) Pulmonary and extrapulmonary acute respiratory distress syndrome: are they different? Curr Opin Crit Care 1:10–17
62. Rocco PRM, Leite-Junior JHP, Souza AB et al (2002) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: effects of corticosteroids. Eur Respir J 20:36S
63. Rocco PRM, Maronas P, Cagido V et al (2004) Short versus prolonged low dose steroid therapy early in the course of acute lung injury. Eur Respir J 24:263S
64. Fernandes ABS, Zin WA, Rocco PRM (2005) Corticosteroids in acute respiratory distress syndrome. Braz J Med Biol Res 38:147–157
65. Confalonieri M, Urbino R, Potena A et al (2005) Hydrocortisone infusion for severe community-acquired pneumonia. A preliminary randomised study. Am J Respir Crit Care Med 171:242–248

Chapter 35

Nitric oxide should be used in ARDS

H. Gerlach

Acute lung injury (ALI) or its aggravated form, acute respiratory distress syndrome (ARDS), is characterised by a sudden, mostly generalised inflammation of the lung, which further in its course induces; (1) a non-cardiogenic pulmonary oedema, (2) pulmonary arterial hypertension, (3) reduction of total compliance of the lung, and (4) progressive systemic hypoxaemia due to pulmonary ventilation/perfusion-mismatching leading to more areas of the lung exhibiting intrapulmonary right-to-left shunt. Pulmonary hypertension causes a rise in the microvascular filtration pressure in the lung and, hence, the development of interstitial pulmonary oedema as well as overstress and dysfunction of the right ventricle. Until recently, the only therapeutic means of re-establishing a safe level of oxygenation in patients with ARDS was mechanical ventilation with high inspiratory oxygen concentrations (FIO_2) and positive end-expiratory pressure (PEEP). Such an approach could be counter-productive in some patients, since high O_2 concentrations and high airway pressures could entail further lung damage due to O_2 toxicity and pulmonary barotrauma. The pharmacologic approach, which is emerging as an adjunct to conventional management, aims to decrease the need for high O_2 concentrations and high airway pressures, thereby attenuating the ventilator-induced lung injury. The objective of most of these newer modalities of therapy is to redistribute the pulmonary blood flow preferentially towards well-ventilated alveoli.

Again, ventilation/perfusion mismatch is one of the important hallmarks of ARDS. In the lung, regions with normal ventilation/perfusion (V/Q) ratios coexist along with regions having high or low V/Q ratios. A large proportion of the lung regions appearing ventilated on chest radiograph and computerised thoracic scan is not perfused at all or only poorly perfused; these regions constitute the alveolar dead space. At the same time, a good part of the non-ventilated zones continue to be perfused due to the failure of hypoxic pulmonary vasoconstriction (HPV), a reflex that tends to limit pulmonary blood flow perfusing poorly oxygenated alveolar spaces. High tidal volumes and consequently high airway pressures are needed to maintain normal $PaCO_2$ in the face of increased alveolar dead space.

Acute pulmonary hypertension is frequently observed in patients with ARDS. It is a result of pulmonary vasoconstriction, which characterises the early stages of ARDS, and anatomical remodelling of the pulmonary vasculature, observed in the late stages of the disease. In turn, pulmonary vasoconstriction could be due to HPV reflex or chemical mediators, such as thromboxane A_2 and platelet activating factor. Anatomical remodelling leads to muscular hypertrophy, microthrombosis,

fibrosis, and destruction of pulmonary vessels. Theoretically, selective constriction of the pulmonary vessels in the non-ventilated zones or selective vasodilatation in the ventilated zones should decrease the V/Q mismatch. The administration of selective pulmonary vasoconstrictors and vasodilators to achieve the above objective forms the basis of the pharmacologic approach to treating hypoxaemia during ARDS. Vasoactive drugs should have a predominant effect on the pulmonary circulation and minimal or no effects on the systemic circulation.

Nitric oxide (NO) is a multipotent endogenous messenger molecule that is extensively involved in the regulation of vascular tone. NO is also a well-known environmental pollutant emanating from the exhaust of cars and factories. It is toxic in higher concentrations and the upper limit for NO during occupational exposure is 25 parts per million (ppm). NO gas mixed in nitrogen can be used for medical purposes as an inhalational drug, administered together with inspiratory gas. NO passes over the alveolar membrane and reaches the blood in the pulmonary vasculature, where it is taken up and possibly eliminated by haemoglobin before it reaches the systemic circulation. Thus, inhaled NO (iNO) is considered to be a selective pulmonary vasodilator, as it dilates those regions of the pulmonary vasculature that are in contact with ventilated alveoli, whereas it has no effect on the resistance of the systemic vasculature.

Nitric oxide inhalation in acute respiratory distress syndrome: first trials

After Furchgott and Zawadzki first described the in vitro phenomenon that vascular relaxation requires the presence of an intact vascular endothelium [1], and after the first identification of the responsible, so-called 'endothelium-derived relaxing factor' (EDRF) as NO [2, 3], characterisation of the synthetic and pathophysiologic pathways that finally induce vasodilatation quickly followed [4, 5]. Meanwhile, NO was demonstrated to be also synthesised by brain cells, macrophages, epithelial cells, and platelets; it acts as a neurotransmitter, mediator of cellular immunological processes, and modulator of platelet aggregation and adhesion, e.g. during inflammation [6]. However, NO is not only a physiological mediator, but also an environmental gas that results from combustion reactions, and is quickly oxidised to NO_2. NO is extremely lipophilic and tends to bind to the ferruginous haeme group; after inhalation, exogenous NO freely diffuses into the alveolar capillaries and, within seconds, binds to the haeme group of haemoglobin with a 1500-fold higher affinity than carbon monoxide (CO) [7]. The resulting nitrosyl-haemoglobin is unstable, oxidised to methaemoglobin, and eventually transformed to nitrates, which are metabolised unspecifically and excreted through the kidneys.

When the biological relevance and physiological pathways of NO became apparent, the question arose whether gaseous NO could be used for controlled inhalation. Similar to endogenous, endothelium-derived NO, iNO should be able to induce vasodilatation. Based on the two features of NO—its vasodilatory activity and ability to bind haemoglobin within seconds after diffusion into the intravascular space—it could be potentially inactivated immediately, without influencing the

systemic circulation and thus resulting in 'selective pulmonary vasodilatation.' Preceding animal studies on the toxicity of iNO when administered for up to 6 months revealed no evidence of side effects using NO doses of less than 40 ppm [8, 9]. Early pilot-studies in humans by Higenbottam et al. in 1988 demonstrated that iNO was, indeed, able to reduce pulmonary hypertension in adult patients without major effects on the systemic circulation [10, 11]. Animal experiments by Frostell and Pison revealed that iNO was also able to reverse hypoxic pulmonary vasoconstriction without impairing pulmonary gas exchange [12, 13]. In parallel, two other groups concluded that the beneficial effect of iNO might also be useful in the therapy of persistent pulmonary hypertension of the newborn (PPHN) [14, 15]. In all these studies, NO doses between 5 and 80 ppm were inhaled, and no critical side effects, such as systemic hypotension or methaemoglobinaemia, were registered.

Falke et al. were the first to treat ARDS iNO, at doses of 18 and 36 ppm. The effects on haemodynamics and pulmonary gas exchange were compared with those after treatment of the same patients by intravenous infusion of prostacyclin (PGI_2), at a dose of 4 ng/kg/min [16]. Results of subsequent studies by Rossaint et al. revealed that both iNO and infused PGI_2 are able to reduce pulmonary resistance by about 20% [17]. However, in contrast to PGI_2, which simultaneously caused systemic hypotension and decreased arterial oxygen saturation, iNO did not induce any changes in systemic haemodynamics, but significantly improved arterial oxygenation. The V/Q ratio of these patients was measured by multiple inert-gas elimination technique (MIGET), which confirmed that the portion of intrapulmonary shunt areas was expanded by the infusion of PGI_2, but, in contrast, reduced by inhalation of 18 and/or 36 ppm NO, due to a redistribution of pulmonary blood flow towards areas with nearly normal V/Q ratios. Daily tests of iNO efficacy using a 20-min shut-off followed by readministration of iNO inhalation ('on-off-on measurements') demonstrated that the beneficial effect of iNO was also observed in long-term studies with doses of less than 20 ppm [17]. Severe side effects, especially the formation of toxic metabolites of NO, such as methaemoglobin or nitrogen dioxide (NO_2) were not observed, even when iNO therapy was administered for a long period of time.

iNO in ARDS: side effects

During several clinical trials it was reported that, especially after long-term treatment of patients with iNO, patients require a specific weaning procedure to terminate inhalation. In addition, rebound phenomena regarding systemic oxygenation and pulmonary hypertension point to an increasing dependency of patients on iNO [18]. These effects are probably due to feedback inhibition of endothelial NOS by exogenously supplied NO, as demonstrated in vitro using NO donors [19] and gaseous NO [20]. Thus, vasoconstriction in the ventilated areas may re-occur after a sudden shut-off of NO in ARDS patients, and is responsible for the rebound phenomenon [20]. These findings, combined with those of other studies showing

that the absolute level of the pulmonary arterial pressure (PAP) is a marker for the severity of pulmonary microvascular injury in ARDS [21], and that pulmonary hypertension is associated with impaired NO production [22] confirm the hypothesis that even low doses of NO might reduce PAP in most severe cases of acute lung injury, as also reported in previous studies [17, 18], since endogenous NO production by the pulmonary vascular endothelium is considerably impaired under these circumstances. This was underlined by the observation that intravenous administration of inhibitors of endogenous NOS increased systemic and pulmonary vascular resistance in septic patients with vasoplegia, but had more or less no effect in ARDS patients who had been treated with iNO for a longer time.

Additional studies demonstrated that inhalation of gaseous NO prolongs bleeding time in animals and healthy humans [23, 24], and inhibits platelet aggregation in patients with ARDS [25]. Other case reports pointed out the possible danger of bleeding disorders during iNO, which might lead to a fatal outcome due to intracerebral haemorrhages [26]. In vitro, NO released from endothelial cells inhibits platelet adhesion to endothelium [27] and platelet aggregation [28], and has disaggregating properties [29]. Endogenous NO, produced by Ca^{2+}- and NADPH-dependent cytosolic NO synthase (NOS) via the l-arginine/NO-pathway, down-regulates platelet aggregation. This was found to be due to an intra-platelet negative feedback mechanism that modulates platelet response after stimulation [30, 31]. Similar to smooth muscle cells, the inhibitory effect of NO on platelets is mediated through cGMP, which inhibits the phosphoinositide pathway regulating phospholipase C, and indirectly increases cyclic adenosine monophosphate (cAMP) levels by inhibiting cAMP-specific phosphodiesterase [32]. As a result of the interaction of NO with intracellular signal transduction, platelet aggregation decreases by the inhibition of a rise in Ca^{2+}, the release of granule contents, and the phosphorylation of proteins [33]. Thus, NO plays an important role in the regulation of vascular homeostasis by controlling vascular tone and platelet function.

Whereas NO–platelet interactions have been intensively studied by numerous investigators using functional assays, measurement of secreted granule contents, ligand binding to receptors, and analysis of intra-platelet activation-dependent metabolic pathways, only one study has reported the effects of NO on the expression of platelet cell-surface adhesion receptor during activation with _-thrombin, as measured by flow cytometry [34]. Keh et al. used flow cytometry to investigate the modulating effects of the NO-releasing compound SIN-1 [35] on the availability of different functional platelet adhesion receptors [36]. The reaction with a specific antibody (PAC) against the activated form of the fibrinogen receptor glycoprotein GP IIb-IIIa demonstrated the dose-dependent inhibitory effect of SIN-1 on GP IIb-IIIa activation. Furthermore, α-thombin induced platelet activation was inhibited by SIN-1 60 min after activation [36]. Thus, in vivo, iNO may induce bleeding disorders by disaggregating platelets even when bleeding does not occur initially after surgical interventions. This is probably an important finding in terms of defining inclusion and exclusion criteria for future clinical studies with iNO inhalation in ALI, although none of the controlled clinical studies with iNO in ARDS patients have thus far been able to show any increase in bleeding disorders (see below).

Experiences from controlled studies

Convincing data on the effect of iNO in ARDS patients in reducing pulmonary hypertension and increasing systemic oxygenation led to the question whether this therapeutic approach is able to improve patient outcome in terms of reducing mortality and/or ICU/ventilation time. A retrospective matched-paired analysis revealed that there was no difference in the survival rate of ARDS patients who received NO therapy or not (both 69%), and no differences were found for the duration of ventilation or ICU stay [37]. Recently, the first prospective randomised, double-blinded, placebo-controlled, phase II multicentre trial on 177 ARDS patients was published by Dellinger et al. The aim of that study was to evaluate the safety, physiologic response, and outcome parameters of different doses of iNO (1.25–80 ppm) [38]. To minimise the influence of different equipment in the participating centres, the same type of ventilator and NO delivery system was used, and NO treatment was administered according to a strict protocol. During the first 4 h after the initiation of treatment, ventilator settings were not changed, and an improvement of oxygenation reflected the acute effects of iNO; subsequent changes of ventilator settings were used to calculate the intensity of ventilation by the oxygenation index. While 60% of patients responded to iNO with an increase of $PaO_2 \geq 20\%$, which allowed a reduction of FIO_2, this was only significant on the first day of treatment, and the reduction of FIO_2 was only modest (0.71 ± 0.14 vs 0.69 ± 0.13). In the NO group, the oxygenation index remained lower during the first 4 days, and mean PAP remained lower (~2 mmHg) for 2 days. During the initial 4-h observation period, however, 24% of the placebo group also had an increase in $PaO_2 \geq 20\%$. There were no differences between the NO and placebo groups with respect to mortality and/or the number of days the patients survived after meeting oxygenation criteria for extubation. A post-hoc analysis revealed that in the group receiving 5 ppm NO, the percentage of patients alive as well as of patients weaned from mechanical ventilation at day 28 after study inclusion was higher than in the placebo group. However, when 56 additional patients, in whom NO treatment was discontinued before the patients had met the oxygenation threshold criteria (mainly due to death), were included into the analysis, the mortality of the NO group was even higher (38 vs 30%).

A randomised trial by Micheal et al. investigated the acute effects of iNO on oxygenation parameters in 40 patients with ARDS during the first 3 days of treatment [39]. Similar to the results of from Dellinger et al., NO therapy, compared to conventional therapy, increased PaO_2/FIO_2 only during the first day. After 24 h, the two groups had an equivalent improvement in PaO_2/FIO_2, and at 72 h following inclusion, the reduction of FIO_2 (≥ 0.15) was not different with or without NO. Another 30 ARDS patients were enrolled in a randomised, controlled pilot study by Troncy et al. [40]. Again, improvement of oxygenation and reduction of venous admixture were significant only during the first 24 h of NO inhalation, and there was no significant difference with regard to the 30-day mortality or days of mechanical ventilation between the NO group and controls. Furthermore, preliminary results of a European multicentre study in more than 200 patients with ALI showed

no improvement of survival or duration of ventilation with iNO [41]. Furthermore, there was a higher incidence of renal failure in the NO group (35 vs 16%), which was a major reason that the study was discontinued before the initial protocol was finished. This finding, however, was in contrast to those of the above mentioned studies [37–40], which did not demonstrate any adverse effect of iNO on either renal function or bleeding disorders.

In conclusion, when focusing on outcome, iNO seems to offer no advantage for ARDS patients. However, with respect to the primary target of NO therapy, i.e. selective pulmonary vasodilatation with subsequent improvement of systemic oxygenation and pulmonary hypertension, there was a sustained effect—probably more pronounced with low doses of NO—in the majority of patients within the first 24 h of treatment; this allows the reduction of ventilation settings in terms of FIO_2 and airway pressure.

Dosing of iNO in ARDS: the more, the better?

Early studies of iNO in ARDS patients [17] demonstrated no difference between 18 or 36 ppm NO in terms of pulmonary resistance and systemic oxygenation. Patients did not develop tachyphylaxis, but seemed to become 'dependent' on iNO, even when the course of the disease was positive. We tested the dose–response of selective pulmonary vasodilatation by NO in patients with severe ARDS, using NO doses between 10 ppb and 100 ppm. It was found that an improvement of systemic oxygenation by NO can be achieved with much lower doses of NO than were used in those earlier studies (the ED_{50} for increasing oxygenation was approximately 0.1 ppm). In addition, the best dose for improved oxygenation is different from that for optimal reduction of pulmonary resistance ($ED_{50} > 2$ ppm) [42]. Optimal improvement of systemic oxygenation usually occurs with 10 ppm NO; higher doses might reverse the beneficial effect. In some cases, however, ARDS patients had an impressive response to NO, achieving the best systemic oxygenation with 1 ppm NO, whereas higher doses, e.g. 100 ppm, exerted effects similar to those of systemic vasodilators, i.e. deteriorated systemic oxygenation due to increased intrapulmonary right-to-left shunt areas. Pulmonary resistance, in contrast, was continuously reduced, correlating with increasing NO doses.

The response to iNO varied both inter-individually between the patients and intra-individually during treatment. The optimal NO dose for systemic oxygenation was 0.5–100 ppm; however, some patients showed no or only moderate effects after induction of iNO ('non-responders'). In the case of long-term iNO, after an individual patient dose–response was established, it was possible to induce an improvement of systemic oxygenation in some patients for up to 2 weeks by administering 0.06–0.25 ppm NO [18]. These are NO concentrations similar to those produced in the upper airways and autoinhaled during normal ventilation [43, 44]. Thus, low-dose iNO might be considered as replacement therapy, since mechanical ventilation disrupts the patient from utilising his or her own NO!

We also carried out a prospective, randomised, placebo-controlled, monocen-

tre clinical trial on the time-dependent dose–response characteristics of long-term iNO in patients with severe ARDS [45]. Patients were evaluated according to a standard protocol. At the time of inclusion, none of the patients had received venovenous extracorporeal membrane oxygenation (vv-ECMO). After undergoing an initial dose–response analysis of iNO, using inhalatory concentrations from 0.01 up to 100 ppm NO, patients were randomised. The NO group received continuous inhalation of 10 ppm NO, regardless of whether they were considered as 'responders' or 'non-responders' with respect to systemic oxygenation or pulmonary hypertension. The effect of iNO inhalation was controlled every day (on-off-on tests). After 48 h, a second dose–response curve was obtained, as well as afterwards during a 48-h time course. iNO in the NO group was continued until FIO_2 could be reduced to 0.4 in order to keep the PaO2/FIO2 > 60 mmHg under pressure-controlled ventilation with a maximal PEEP of 10 cmH_2O.

A statistical analysis of 40 patients, 20 patients with, 20 without iNO, found no significant differences between the two groups at the time of inclusion with respect to the epidemiology of the patients, including initial catastrophic event, haemodynamics, gas exchange, and other parameters. The initial dose–response curves for systemic oxygenation and reduction of pulmonary hypertension were identical, demonstrating a peak effect for oxygenation at 10 ppm NO as described before [42]. In the following days, there was an overall tendency in terms of improved oxygenation and pulmonary hypertension. Interestingly, the PAP data obtained after 48 h demonstrated that a shut-off of NO resulted in a higher PAP baseline than in the control group, i.e. that patients were sensitised to iNO. Furthermore, the NO effect in the control group was no longer significant. This means that NO treatment might not be truly beneficial, since PAP in the NO group during iNO was not significantly different from the baseline PAP of the control group.

Similar data were found for systemic oxygenation. The initial reduction of FIO_2 in the NO group due to the positive effect of inhaled NO on systemic oxygenation was only significant compared to the control group at the day of inclusion; this is similar to the results of other published randomised studies [38–41]. Hence, the conclusion that iNO makes it possible to reduce aggressive ventilation must be reconsidered. Further studies are needed to clarify whether this phenomenon is due to feedback inhibition of endogenous NO synthesis by iNO or to a direct interaction of high oxygen concentrations with NO, possibly inducing toxic metabolites such as NO_2 or peroxynitrite. The outcome in terms of survival, ICU stay, or ventilation days (regardless of whether for all or only for surviving patients) was identical in the two groups. Patients from the NO group, however, required significantly less vv-ECMO than control patients. Although the total number of patients was very small, these data indicate that iNO should be considered as a bridging therapy for severe hypoxaemia, in order to bypass more invasive and expensive strategies.

Another interesting finding of this study was that the time course of the dose–response curves from the patients differed depending on the initial randomisation: Control patients generally demonstrated similar dose–response characteristics over time, with a peak effect of iNO on systemic oxygenation at 10 ppm

NO regardless of when the analysis was done. These findings are in accordance with already described data from previous studies [42]. Patients from the iNO group, however, had a shift of the dose–response curve for systemic oxygenation to the left within 96 h. After this time, the peak for oxygenation was obtained at 1 ppm NO, i.e. continuous inhalation of 10 ppm NO sensitised these patients. This finding is of potential importance since the administered NO concentration of 10 ppm was no longer in the ideal range compared to the initial data, and in some patients led to a decrease of PaO_2! This may explain why, in previous studies, oxygenation improved only during the first 24 h. For future protocols, a programmed reduction of iNO concentration over time might be indicated [45].

Possible reasons for iNO overdosing

In probably more than 80% of patients with ARDS, (a) lower doses of iNO improve systemic oxygenation, (b) higher doses, in contrast, lower the arterial oxygen content, and (c) improvement of systemic oxygenation and reduction of pulmonary artery pressure are not correlated during NO dose–response studies [42, 45]. This may be explained by two hypotheses:

1. The 'diffusion theory': NO is a very lipophilic substance, with a low molecular weight, that quickly diffuses into tissue, reaching a balance between the rate of diffusion and the rate of NO oxidation or binding to targets. Inhaling low doses of NO probably induces diffusion only into the near vessels, i.e. capillaries of the ventilated alveoli. Hence, with lower NO doses, there is a more or less 'strictly selective' vasodilatation in ventilated areas of the pulmonary vasculature, reducing intrapulmonary shunt areas and, thus, increasing systemic oxygenation. With higher NO doses, however, diffusion of lipophilic NO through the lung tissue also reaches nonventilated areas, i.e. shunt areas, still leading to a selective pulmonary vasodilatation with further reduction of pulmonary resistance, but reversing the beneficial effect on oxygenation by additional vasodilatation of shunt vessels.

2. The 'transport theory': This theory is based on the findings that iNO binds to albumin and haemoglobin and, in this way, may be transported through the pulmonary vessels before it affects extrapulmonary regions [46]. The vascular system of the lung, in contrast to other organs like the liver, is strictly dichotomous, i.e. from the pulmonary artery up to the final capillaries, each vessel divides into two smaller ones without transverse connections. After the capillary system, two vessels always re-join to form a larger one, until the pulmonary veins are reached. This means that vessels comprising shunt (i.e. non-ventilated) areas and areas with ideal V/Q ratios are finally united in the pulmonary venous system. Hence, if NO is inhaled in low doses, it causes a low local concentration that acts on the vascular smooth muscles of the vessel. Due to the low concentration, diffusion of iNO into the intravascular space and binding to albumin and/or haemoglobin may not occur before the venous vessel re-joins with a shunt vessel, thus inducing vasodilatation and increased flow only in the ventilated area. If, however, high doses of NO are inhaled, intracapillary concentrations increase. Thus, NO may be transported to

downstream regions, which can result in decreased 'afterload' for both ventilated and non-ventilated areas, since NO is active after rejoining of the vessels.

So far, both theories are speculative. The 'diffusion theory' might be favoured since NO is thought to act on the vascular smooth muscle cell of the capillary before it is resorbed into the intravascular space. The marked reduction of PAP by NO may also be an argument for the 'diffusion theory,' since the alveolar capillaries almost completely lack smooth muscle cells, i.e. there is only little effect on pulmonary resistance, while the arteries and arterioles are thought to be a regulating factor for pulmonary vascular resistance. How can NO reach the arteries if not per diffusion? If NO has to diffuse through the pulmonary tissue to achieve its effect, how is it possible to guarantee selectivity for ventilated areas with low doses of NO? This might be an argument in favour of the 'transport theory.' Furthermore, studies by Jia et al. revealed that NO binding to haemoglobin is not selective for the haeme group leading to nitrosyl-haemoglobin but also involves cysteine domains, preferably from oxygenated haemoglobin (oxyHb) forming S-nitrosohaemoglobin [46]. After reduction of oxyHb in the systemic capillaries, the affinity of haemoglobin for NO is reduced, thus leading to detachment of NO and peripheral vasodilatation [47]. These findings, by the group of Stamler et al., are in contradiction with the classic hypothesis that iNO has only local, intrapulmonary effects, since the NO is 'neutralised' by haemoglobin. Indeed, iNO seems to be taken up by haemoglobin and albumin in the lung, but it is probably transported to the systemic periphery, where it is delivered due to the oxygen gradient, leading to vasodilatation in small arteries. These findings are important to understand the dose-dependent, local, and systemic effects of NO, and thus merit further attention for future studies evaluating the clinical use of iNO.

Conclusions

Inhalation of NO in patients with severe ARDS or other forms of pulmonary hypertension is a new, and encouraging approach. However, there is no proof that iNO improves the outcome of patients. In addition, the individual effects are not predictable, i.e. it is necessary to test different NO doses in order to determine efficacy. However, it remains unclear whether optimal treatment for the patient consists of the best systemic oxygenation, or the most effective reduction of pulmonary resistance, or something in between. This insecurity and the varying effects of iNO in ARDS patients make it very difficult to perform prospective randomised controlled studies aimed at determining whether iNO is able to lower mortality due to ARDS.

Very low doses of NO that are similar to environmental concentrations were shown to exert beneficial effects in ARDS patients. Although this may imply that NO toxicity is a secondary problem, one important point for future research is the possible side effects of iNO, e.g. on immunological and neurological functions, which must be considered due to the complexity of NO as a biological mediator. Harmful effects have to be excluded before iNO can be accepted as a standard

therapy. Hence, iNO in the treatment of patients with severe ARDS should only be administered following clear protocols. Recommendations for the basic requirements of these protocols include: (1) ethical requirements (Helsinki Declaration, Good Clinical Practice, approval of the hospital's ethical committee, insurance for the patient, informed consent from a relative); (2) evaluation of patients (defined inclusion criteria, repeated dose–response studies, identification of 'responders' and 'non-responders,' strategy of dosing of iNO over time, primary and secondary targets); (3) NO/NO_2-measuring systems (continuous measurement of NO and NO_2 by electrochemical sensors for long-term use, chemiluminescence analysers for dose–response curves); and (4) standardised NO application systems (no self-made systems, feed-back controls, alarm systems). So far, iNO in ARDS patients still cannot be considered as a standard therapy; however, there is also no reason to completely abandon this approach.

References

1. Furchgott RF, Zawadzki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376
2. Ignarro LJ, Buga GM, Wood KS et al (1987) Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci USA 84:9265–9269
3. Palmer RM, Ferrige AG, Moncada S (1987) Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327:524–526
4. Palmer RM, Rees DD, Ashton DS et al (1988) L-arginine is the physiological precursor for the formation of nitric oxide in endothelium-dependent relaxation. Biochem Biophys Res Commun 153:1251–1256
5. Ignarro LJ (1989) Endothelium-derived nitric oxide: actions and properties. FASEB J 3:31–36
6. Moncada S, Palmer RM, Higgs EA (1991) Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 43:109–142
7. Gibson QH, Roughton FJW (1957) The kinetics of equilibria of the reactions of nitric oxide with sheep hemoglobin. J Physiol 136:507–526
8. Oda H, Nogami H, Kusumoto S et al (1976) Long-term exposure to nitric oxide in mice. J Jpn Soc Air Pollut 11:150–160
9. Hugod C (1979) Effect of exposure to 43 ppm nitric oxide and 3.6 ppm nitrogen dioxide on rabbit lung. Int Arch Occup Environ Health 42:159–167
10. Higenbottam T, Pepke-Zaba J, Scott J et al (1988) Inhaled 'endothelium-derived relaxing factor' (EDRF) in primary hypertension. Am Rev Respir Dis 137(Suppl I):107A (abs)
11. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT et al (1991) Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 338:1173–1174
12. Frostell C, Fratacci MD, Wain JC et al (1991) Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047
13. Pison U, Lopez FA, Heidelmeyer CF et al (1993) Inhaled nitric oxide selectively reverses hypoxic pulmonary vasoconstriction without impairing pulmonary gas exchange. J Appl Physiol 74:7287–7292

14. Roberts JD, Polander DM, Lang P et al (1992) Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 340:818–819
15. Kinsella JP, Neish SR, Shaffer E et al (1992) Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 340:819–820
16. Falke KJ, Rossaint R, Pison U et al (1991) Inhaled nitric oxide selectively reduces pulmonary hypertension in severe ARDS and improves gas exchange as well as right heart ejection fraction: a case report. Am Rev Respir Dis 143(Suppl I):248A (abs)
17. Rossaint R, Falke KJ, Lopez F et al (1993) Inhaled nitric oxide in adult respiratory distress syndrome. New Engl J Med 328:399–405
18. Gerlach H, Pappert D, Lewandowski K et al (1993) Long-term inhalation with evaluated low doses of nitric oxide for selective improvement of oxygenation in patients with adult respiratory distress syndrome. Intensive Care Med 19:443–449
19. Assreuy J, Cunha FQ, Liew FY et al (1993) Feedback inhibition of nitric oxide synthase activity by nitric oxide. Br J Pharmacol 108:833–837
20. Kiff RJ, Moss DW, Moncada S (1994) Effect of nitric oxide gas on the generation of nitric oxide by isolated blood vessels: implications for inhalation therapy. Br J Pharmacol 113:496–498
21. Villar J, Blazquez MA, Lubilio S et al (1989) Pulmonary hypertension in acute respiratory failure. Crit Care Med 17:523–526
22. Dinh-Xuan AT, Higenbottam TW, Clelland CA et al (1991) Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N Engl J Med 324:1539–1547
23. Högman M, Frostell C, Arnberg H et al (1993) Bleeding time prolongation and NO inhalation. Lancet 341:1664–1665
24. Högman M, Frostell C, Arnberg H et al (1994) Prolonged bleeding time during nitric oxide inhalation in the rabbit. Acta Physiol Scand 151:125–129
25. Samama CM, Diaby M, Fellahi JL et al (1995) Inhibition of platelet aggregation by inhaled nitric oxide in patients with acute respiratory distress syndrome. Anesthesiology 83:56–65
26. Joannidis M, Buratti T, Pechlaner C et al (1996) Inhaled nitric oxide. Lancet 348:1448–1449
27. Radomski MW, Vallance P, Whitley G et al (1993) Platelet adhesion to human vascular endothelium is modulated by constitutive and cytokine induced nitric oxide. Cardiovasc Res 27:1380–1382
28. Furlong B, Henderson AH, Lewis MJ et al (1987) Endothelium-derived relaxing factor inhibits in vitro platelet aggregation. Br J Pharmacol 90:687–692
29. Radomski MW, Palmer RM, Moncada S (1987) The anti-aggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. Br J Pharmacol 92:639–646
30. Radomski MW, Palmer RM, Moncada S (1990) An L-arginine/nitric oxide pathway present in human platelets regulates aggregation. Proc Natl Acad Sci USA 87:5193–5197
31. Radomski MW, Palmer RM, Moncada S (1990) Characterization of the L-arginine/nitric oxide pathway in human platelets. Br J Pharmacol 101:325–328
32. Maurice DH, Haslam RJ (1990) Molecular basis of the synergistic inhibition of platelet function by nitrovasodilators and activators of adenylate cyclase: inhibition of cyclic AMP breakdown by cyclic GMP. Mol Pharmacol 37:671–681
33. Nguyen BL, Saitoh M, Ware AJ (1991) Interaction of nitric oxide and cGMP with signal transduction in activated platelets. Am J Physiol 261:H1043-H1052
34. Michelson AD, Benoit SE, Furman MI et al (1996) Effects of nitric oxide/EDRF on

platelet glycoproteins. Am J Physiol 270:H1640-H1648
35. Gerzer R, Karrenbrock B, Siess W et al (1988) Direct comparison of the effects of nitroprusside, SIN-1, and various nitrates on platelet aggregation and soluble guanylate cyclase activity. Thromb Res 52:11–21
36. Keh D, Gerlach M, Kürer I et al (1996) The effects of nitric oxide (NO) on platelet membrane receptor expression during activation with human α-thrombin. Blood Coag Fibrinol 7:615–624
37. Rossaint R, Gerlach H, Schmidt-Ruhnke H et al (1995) Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest 107:1107–1115
38. Dellinger RP, Zimmerman JL, Taylor RW et al (1998) Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 26:15–23
39. Micheal JR, Barton RG, Saffle JR et al (1998) Inhaled nitric oxide versus conventional therapy:effect on oxygenation in ARDS. Am J Respir Crit Care Med 157:1372–1380
40. Troncy E, Collet JP, Shapiro S et al (1998) Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. Am J Respir Crit Care Med 157:1483–1488
41. Lundin S, Mang H, Smithies M et al for the European Study Group of Inhaled Nitric Oxide (1997) Inhalation of nitric oxide in acute lung injury: Preliminary results of a European multicenter study. Intensive Care Med 23(Suppl I):S 2 (abs)
42. Gerlach H, Rossaint R, Pappert D et al (1993) Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur J Clin Invest 23:499–502
43. Gustafsson LE, Leone AM, Persson MG (1991) Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun 181:852–857
44. Gerlach H, Rossaint R, Pappert D et al (1994) Autoinhalation of nitric oxide after endogenous synthesis in nasopharynx. Lancet 343:518–519
45. Gerlach H, Keh D, Semmerow A et al (2003) Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. Am J Respir Crit Care Med 167:1008–1015
46. Jia L, Bonaventura J, Stamler JS (1996) S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control. Nature 380:221–226
47. Stamler JS, Jia L, Eu JP et al (1997) Blood flow regulation by S-nitrosohemoglobin in the peripheral oxygen gradient. Science 276:2034–2037

Chapter 36

Formation and clearance of pulmonary oedema in acute lung injury/acute respiratory distress syndrome

B. Allaria

The presence of oedema is a constant in pictures of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and there is no doubt that its extent is correlated with the seriousness of the illness.

In the past 40 years, much progress has been made to identify the mechanisms underlying ALI/ARDS and focus on the best procedures to follow in artificial ventilation. However, little progress has been made in the search for drug treatment and the choice of an infusion strategy to reduce oedema.

This work revolves around this aspect of treatment and its goal is to examine the mechanisms that generate pulmonary oedema as well as those that should eliminate it but that, as we will see, are impaired in ALI/ARDS.

This knowledge is the basis for treatment proposals concerning the infusion strategies to be implemented and the drugs that can help reduce the formation of oedema and facilitate its clearance, such as diuretics and β2 agonists.

Forces that regulate fluid passage through the capillary membrane

The pulmonary capillary wall acts like a semi-permeable membrane and the passage of fluids from the vessel to the interstice takes place according to Starling's law [1]:

$Qf = Kf (Pc - PiF) - \delta (\pi c - \pi iF)$

Qf = fluid crossing the capillary membrane
Kf = coefficient of filtration through the capillary
Pc = capillary hydrostatic pressure
Pi_F = interstitial hydrostatic pressure
δ = oncotic reflection coefficient
πc = capillary colloidosmotic pressure
pc = interstitial colloidosmotic pressure

It is clear that the first part of this formula expresses the force that promotes flow from the vessel to the interstice, whereas the second one expresses the force that contrasts it.

It is equally clear that, given the same hydrostatic gradient, the greater the Kf

value, the greater the fluid passage; likewise, given the same oncotic gradient, the greater the reflection coefficient δ, the lower the fluid passage.

Therefore, interstitial pulmonary oedema will be antagonised by the reduction of the Pc–PiF gradient and by the increase of the πc–πiF gradient.

Nevertheless, another important factor intervenes in regulating interstitial fluid: lymphatic drainage (QLiNPH), which plays a key role in the human lung. In fact, if necessary it can increase up to 15-fold.

Though acute cardiogenic pulmonary oedema is considered a classic expression of oedema triggered by an increase in hydrostatic pressure, and oedema from ALI/ARDS is the fundamental expression of altered membrane permeability, in reality things are not quite this simple.

In acute cardiogenic pulmonary oedema as well, there have been documented cases of membrane alterations even long after the acute episode, explaining the recurrence of new episodes, although with left atrial pressures at much lower values than the ones that caused the initial episode. In this sense, the recent study by an Australian group is quite interesting. This study noted that the alveolar fluid of patients with cardiogenic pulmonary oedema had inflammation mediators such as TNFα at values similar to those observed in patients with ALI/ARDS [2].

Therefore, if it is true that, as demonstrated, left atrial pressure must exceed 24 mmHg to provoke pulmonary oedema in healthy subjects, it is equally true (and this has been known for years) that a drop in oncotic blood pressure can greatly lower this critical level. Guyton conducted experiments along these lines about half a century ago [3]. Alterations in membrane permeability play a similar role, allowing the formation of interstitial oedema even with normal hydrostatic and oncotic pressures.

In the past it was stated that the radiological picture of lung oedema without any increases in hydrostatic pressure was fundamental for establishing a diagnosis of ALI/ARDS. This statement is still valid, but it must not lead us to overlook the fact that the interaction of hydrostatic pressure, oncotic pressure and membrane alterations represents the true determining factor of oedema.

In ALI/ARDS, all it takes is a small increase in hydrostatic pressure, tied to a moderate overinfusion of fluids, to cause lung oedema. This is also because of the fact that haemodilution secondary to the infusions triggers a drop in oncotic pressure in the capillary that, though modest, contributes to the increase in hydrostatic pressure to favour the passage of fluids from the blood into the interstice, and the phenomenon is enhanced by alterations in permeability.

As we can see, the simplification 'cardiogenic pulmonary oedema = hydrostatic oedema; oedema from ALI/ARDS = oedema caused by the alteration of membrane permeability' is not tenable.

Moreover, an excellent review of the subject published recently by Lewis et al. [4] sustains that hypoproteinaemia and the ensuing drop in oncotic pressure play an important role in causing pulmonary oedema in ARDS, again supporting the utility of combined treatment with colloids and diuretics.

Considered from this standpoint, older works like those of Humphrey et al., observing a decrease in mortality among ARDS patients in whom wedge pressure

was successfully reduced with diuretics [5], and Simmons [6], who 20 years ago proposed limiting liquids and treating these patients with diuretics, take on renewed value.

Therefore, even if there is no question about the fundamental role that – above all in septic patients – the alteration of the permeability of the capillary membrane plays in determining interstitial oedema, we must also bear in mind the equally important role played by even modest changes in the hydrostatic and oncotic pressure of these patients.

The work by Mangialardi et al. [7] is enlightening: in 455 septic patients at risk for ARDS, this study demonstrated that proteinaemia < 6.0 g/dl is accompanied by an increase in weight, mortality and duration of artificial ventilation.

This observation certainly supports the conviction that oncotic pressure is of key importance in determining interstitial oedema in general and pulmonary oedema in particular.

Following what we have noted here, it seems clear that the most appropriate treatment approach for patients with ALI/ARDS or those at risk of ALI/ARDS must be managed with the fluid infusions that are as limited as possible and with the use of diuretics in order to minimise hydrostatic pressure and the drop in oncotic pressure caused by dilution.

This strategy also stems from knowledge of the fluid balance of artificially ventilated patients, who constantly tend to retain liquids: if managed properly, this will permit both a drop in hydrostatic pressure and an increase in plasma oncotic pressure.

Nevertheless, an approach involving drastic reduction of hydrostatic pressure is not devoid of problems. The first one is tied to the onset of iatrogenic hypovolaemia, which can lead to haemodynamic repercussions that, in turn, are accentuated by artificial ventilation. This aspect cannot be overlooked, because alterations in renal, splanchnic and coronary perfusion are always a risk in these patients. However, frequent monitoring of renal function (creatininaemia, urinary electrolytes), monitoring myocardial oxygenation (automatic monitoring of ST on D2, V4 and V5), SVO2 and DO2I will make it possible to maintain restricted infusion and diuretic treatment within clinically safe limits.

It will be more difficult to monitor the effect of this strategy on pulmonary circulation. In fact, a reduction in hydrostatic pressure can trigger an interruption in flow during the inspiratory phase of artificial ventilation, when the extravascular pressure at the alveolar capillaries increases, tending to collapse them. In fact, it is well known that during the inspiratory phase of artificial ventilation there is a tendency to divert flow from the alveolar vessels to the extra-alveolar ones, where extravascular pressure is reduced. The phenomenon is accentuated when hydrostatic pressure is reduced, and this diversion of flow towards areas that do not participate in respiratory exchanges ends up increasing VD/VT, worsening oxygenation and contributing further to alveolar and capillary damage. This phenomenon, which essentially involves passage of part of the lung from West's Zone 3 to Zone 2 or even Zone 1, has been known for over 40 years [8, 9], and must certainly be avoided in ALI/ARDS patients.

One of the ways to monitor this, and thus invert the direction when limited fluids and diuretic treatment start to cause unfavourable redistribution of pulmonary perfusion, is to use volumetric capnography to monitor VD/VT. A sudden increase in VD/VT means it is necessary to stop the strategy of reducing hydrostatic pressure.

We must also add that during artificial ventilation, excessive reduction of left atrial pressure leads to a sequence of collapse and distension of the alveolar capillaries, which can provoke endothelial damage and thus an increase in interstitial oedema. This unfavourable mechanism has been demonstrated experimentally by Broccard et al. on rabbit heart–lung preparations [10]. The authors measured the variations in the formation of pulmonary oedema and microvascular permeability (Kf) at different levels of left atrial pressure; they were able to demonstrate an increase in the formation of oedema and deterioration in the capillary permeability at lower levels of left atrial pressure. Obviously, caution is essential in transferring these experimental data to the clinical setting, but there is no question that this is something that cannot be overlooked.

Alveolar oedema: formation and clearance

Normally, the high level of efficiency of the lymphatic vessels is able to remove even large amounts of fluids that have passed from the vessels to the pulmonary interstices.

It ensues that minimum quantities of fluid can pass into the alveoli, which remain dry in order to permit normal gas exchange. However, when the possibility of draining interstitial fluid is exceeded and – above all – if the alveolar epithelium is damaged, interstitial fluids enter into the alveoli.

At this point, normality is restored only if the mechanism for removing water from the alveoli is maintained. What happens in ALI/ARDS patients is precisely a defect in the mechanisms that clear the alveoli of fluids, in a condition in which the passage of these fluids from the interstice to the alveolus is pathologically stimulated by an increase in interstitial hydrostatic pressure and damage to the alveolar epithelium.

Therefore, it is important to recall what these mechanisms are and how they can be influenced positively.

Water is transported from the alveolus to the interstice by the Na/K-ATPase pump, which by actively transporting sodium from the alveolus to the interstice, creates an ion gradient that forces water out of the alveolus [11] through transcellular channels located above all in Type I cells (aquaporins). Matthay et al. [12] demonstrated this active mechanism, which transports ions and removes water, over 20 years ago in ventilated sheep.

The authors showed that in 4 hours, the protein concentration of the alveolar fluid increased, whereas that of the lymphatic fluid decreased, demonstrating the passage of water from the alveoli to the interstices and, lastly, to the lymphatic vessels.

This mechanism, which is not influenced by the transpulmonary pressure of the air passages, was confirmed many years later by Sakuma et al. [13], who

pinpointed the fact that this was the essential determining factor in clearance of alveolar oedema, rather than pressure changes in the air passages.

Just as damage to the vascular endothelium arises in ALI/ARDS, the same thing happens to the alveolar epithelium. Consequently, a protein-rich fluid like the one accumulated in the interstices passes to the alveoli. The interstitial and alveolar fluids have the same protein content, and as a result there can be no movement of fluids between the two compartments for oncotic reasons. The only mechanism that can favour the passage of fluid from the alveolus to the interstice is the active ion mechanism we described, unless there is a drop in hydrostatic pressure in the interstice as a result of treatment (use of diuretics, continuous venovenous haemofiltration, etc.) that promotes circulatory refilling at the expense of interstitial fluid. However, above all in ARDS in septic patients, circulating toxins induce monocytes and alveolar macrophages to release mediators that activate polymorphonucleates. The activated granulocytes cross the alveolar epithelium and the capillary endothelium, promoting interstitial and alveolar oedema.

The damage that is produced on an alveolar level chiefly involves Type I cells (the cells that line the alveolus and represent 90% of the cells present), which are the most sensitive.

Type II cells, which are larger and more resistant to damage, multiply and are transformed into Type I cells, proceeding to repair the alveolus and restore active ion transport – and thus oedema clearance.

Considering the damage that occurs in ALI/ARDS involving the active ion system responsible for clearing oedema fluid, it seems useful to examine the body's ability to activate this system and the possibility of exploiting this mechanism for therapeutic purposes. In particular, we will examine the activating effect on the Na/K-ATPase pump that stimulates the β2 receptors.

The β adrenergic receptors are widely distributed throughout the air passages in the epithelia and bronchial smooth muscle, and are also present in the vascular epithelia of the bronchial muscles. There are divergent data regarding the alveolar and extravascular distribution of the β receptors, although according to certain studies 90% of the β receptors are on an alveolar level and, of these, 70% are composed of β2 receptors and 30% of β_1 receptors [14, 15]. According to Liebler et al. [16], only 5% of the β2 receptors are on the Type II alveolar cells, and the remainder are on the Type I cells.

The different studies examined thus lead to the conviction that β_2 receptors are located above all at the alveolar epithelial Type I cells. Nevertheless, though there are fewer of them, the β2 receptors of Type II cells are the ones that, by activating the Na/K-ATPase pump, stimulate the transportation of sodium from the alveolus to the interstice, and thus the passage of water in this same direction. The intracellular increase of cAMP produced by β2 stimulation enhances the transportation of sodium [17] and chlorine [18], a process that is indispensable for alveolar fluid clearance.

Proof of the importance of this mechanism comes from the observation that blocking the β receptors inhibits alveolar fluid clearance.

There is no sure data regarding the usefulness of stimulating the β1 receptors

in activating clearance; nevertheless, there have been positive experiences along these lines with denopamine, a β1 adrenergic antagonist [19]. Likewise, the effect of α adrenergic stimulation is still unclear vis-à-vis alveolar fluid clearance, although there have been favourable experiences along these lines in animals [20].

At this stage of knowledge, what still had to be verified was whether or not the positive effects of β2 adrenergic stimulation in activating the Na/K-ATPase, as observed in healthy animal lungs, could also be reproduced in man with ALI/ARDS, taking into account that several experimental models demonstrated that the alveolar epithelium is not as efficient in clearing fluid from damaged lungs [21] and that the adrenergic mechanism is likewise not as efficient in alveolar fluid clearance after haemorrhagic shock [22]. In effect, a block in ion transport, and thus alveolar clearance, is not entirely predictable in situations such as sepsis and hypovolaemic shock.

In fact, it seems that in the initial phase of these events there is even a compensatory increase in ion transport, thanks to the adrenergic response that accompanies these pathologies [23]. However, as the noxa persists, ion transport is inhibited or even blocked.

In experimental situations of lung damage, such as hypoxic lung damage, β2 stimulants have proven to be effective in restoring ion transport damaged by hypoxia [24]. The transition from experimental animals to man has essentially confirmed what was predicted. By introducing a 14G catheter through the orotracheal tube and wedging it into the smallest air passages in ALI/ARDS patients, it was possible to demonstrate that in these patients the alveolar clearance mechanism is damaged to varying degrees: the greater the damage, the worse the outcome [25].

Therefore, it seems we can state that impaired transport of sodium and fluids involving the alveolar epithelium is one of the main factors responsible for the acute condition of ALI/ARDS patients, and that β2 receptor stimulation could play a role in restoring it. According to McAuley et al., the authors of an excellent editorial on this subject [26], the most advisable dosage of albuterol aerosol seems to be 5 mg every 4 hours.

Conclusions

Drug treatment of pulmonary oedema in patients with ALI/ARDS is promising and is based on the use of diuretics associated with a restricted infusional strategy aimed to produce moderate hypovolaemia with a drop in capillary and interstitial hydrostatic pressure. Nevertheless, this hypovolaemia, which we will call 'permissive', must not be to such an extent that it can impair kidney function, myocardial oxygenation and the capillary flow involved in respiratory exchanges. Frequent checks of creatininaemia, as well as monitoring of alveolar VD/VT with volumetric capnography and the ST segment in ECG, can make it possible to achieve 'permissive hypovolaemia', exploiting only its advantages.

To guide this treatment, it may be useful to evaluate the amount of fluid present in the chest via a simple and inexpensive method that can be repeated at short

intervals, namely control of the initial distribution volume of glucose (IDVG). Glucose administered intravenously is distributed rapidly in the plasma and the interstices of highly perfused districts such as the thoracic cavity.

With the short method described by Ishihara et al. [27], the procedure is completed 7 min after the administration of 25 ml of a 20% glucose solution. The effectiveness of the anti-oedema treatment can be monitored easily by the increase in IDVG. Moreover, IDVG seems to be closely correlated with thoracic fluid content (TFC) in thoracic impedance, which expresses the inverse of the basic ohmic resistance of the chest, thereby rising as extravascular lung water increases [27]. Both IDVG and TFC are parameters that can be obtained non-invasively and they can be considered useful for monitoring the efficacy of the diuretic strategy that has been implemented.

The same methods can also be used to verify the efficacy of treatment with β2 agonists that, as we have noted, merit attention and further experimentation in humans.

References

1. Starling EH (1896) On the absorption of fluid from connective tissue spaces. J Physiol (London) 19:312–326
2. De Pasquale GC, Arnolde LF, Doyle IR et al (2003) Prolonged alveolocapillary barrier damage after acute cardiogenic pulmonary edema. Crit Care Med 31:1060–1067
3. Guyton AC, Lindsey AW (1959) Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649–657
4. Lewis CA, Martin G (2004) Understanding and managing fluid balance in patients with acute lung injury. Curr Opin Crit Care 10:13–17
5. Humphrey H, Hall J, Snaider I et al (1990) Improved survival in ARDS patients associated with reduction in pulmonary capillary wedge pressure. Chest 97:1176–1180
6. Simmons RS, Berdine GC, Seidenfeld JJ et al (1987) Fluid balance and the adult respiratory distress syndrome. Am Rev Resp Dis 135:924–929
7. Mangialardi RJ, Martin GS, Bernard GR et al (2000) Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain and death in patients with sepsis. Crit Care Med 28:3137–3145
8. Brower R, Wise RA, Hassafoyannes C et al (1985) Effect of lung inflation on lung blood volume and pulmonary venous flow. J Appl Physiol 58:954–963
9. Howell J, Pernnett D, Proctor DF et al (1961) Effect of inflation of the lung on different parts of the pulmonary vascular bed. J Appl Physiol 16:71–76
10. Broccard AF, Vannay C, Feihl F et al (2002) Impact of low pulmonary vascular pressure on ventilator-induced lung injury. Crit Care Med 30:2183–2190
11. Matthay MA, Flokesson HG, Clerici C (2002) Lung epithelial fluid transport and the result of pulmonary edema. Physiol Rev 82:569–600
12. Matthay MA, Landolt CC, Staub NC (1982) Differential liquid and protein clearance from the alveoli of anesthetized sheep. J Appl Physiol 53:96–104
13. Sakuma T, Pittet JE, Jayr C et al (1993) Alveolar liquid and protein clearance in the absence of blood flow in ventilated sheep. J Appl Physiol 74:176–185

14. Barnes PJ (1995) Beta adrenergic receptors and their regulation. Am J Resp Crit Care Med 152:838–860
15. Corstairs JR, Nirumo AJ, Barnes PJ (1985) Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. Am Rev Resp Dis 132:541–547
16. Liebler JM, Borok Z, Kim KJ et al (2001) Immunoreactive beta-2 adrenergic receptors are expressed in rat alveolar epithelial type I cells. Am J Resp Crit Care Med 163:A570 (abs)
17. Minakata Y, Suzuki S, Grygorczyk C et al (1998) Impact of beta adrenergic agonist on Na channel and Na/-ATPase expression in alveolar type II cells. Am J Physiol 275:L412–L422
18. Fang X, Fukuda N, Rarbzy P et al (2002) Novel role of CFTR in fluid absorption from the distal airspaces of the lung. J Gen Physiol 119:199–207
19. Sakuma T, Tuchihara C, Ishigaki M et al (2001) Denopamine, a B1 adrenergic agonist increases alveolar fluid clearance in ex-vivo rat and guinea pig lungs. J Appl Physiol 90:10–16
20. Azzam ZS, Crespo A, Cormellos A et al (2001) Role of α-adrenergic agonists in lung edema clearance. Am J Resp Crit Care Med 163:A451 (abs)
21. Frank JA, Pittet JF, Lee H et al (2003) High tidal volume ventilation induces NOS2 and impairs a AMP dependent airspaces fluid clearance. Am J Physiol 284:L791–L798
22. Modelska K, Matthay MA, Brown LA et al (1999) Inhibition of beta-adrenergic dependent alveolar epithelial clearance by oxidant mechanism after hemorrhagic shock. Am J Physiol 276:L844–L857
23. Pittet JF, Brenner JF, Modelska K et al (1996) Alveolar liquid clearance is increased by endogenous catecholamines in hemorrhagic shock in rats. J Appl Physiol 81:830–837
24. Vivona M, Matthay MA, Freidlander G et al (2001) Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: reversal by beta-2-adrenergic agonist treatment. Am J Resp Cell Mol Biol 25:554–561
25. Ware LB, Matthay MA (2001) Alveolar fluid clearance is impaired in the majority of patients with ALI and ARDS. Am J Resp Crit Care Med 163:1376–1383
26. McAuley DF, Frank JA, Matthay MM (2004) Lung fluid balance and pulmonary edema in ARDS: modulation by beta-adrenergic stimulation. In: Vincent J-L (ed) Yearbook of intensive care and emergency medicine. Springer Verlag New York, pp 453–462
27. Ishihara H, Suzuki A, Okawa H et al (2001) Comparison of initial distribution volume of glucose and plasma volume in thoracic fluid accumulated patients. Crit Care Med 29:1532–1538

FLUID, ELECTROLYTES AND ACID/BASE BALANCE

Chapter 37

Diabetic ketoacidosis: incidence, biochemical abnormalities, pathophysiology, and diagnosis

K. Hillman

The incidence of diabetes in industrial societies is increasing at an alarming rate, and the most common cause of mortality in individuals with type I diabetes, under the age of 40 years, is diabetic ketoacidosis (DKA).

The aetiology is often related to the onset of another acute disease, such as a severe infection, acute myocardial infarction or stroke [1]. Diabetic ketoacidosis can also be precipitated by lack of patient compliance with their normal insulin requirements.

There are many complex biochemical abnormalities in DKA [2, 3]. The primary problem is hyperglycaemia and ketosis due to a lack of insulin, particularly in the fat and muscle cells, and often exacerbated by increases in counter-regulatory hormones, such as cortisol, adrenaline, noradrenaline, and growth hormone. In DKA, liver cells contribute to hyperglycaemia by gluconeogenesis and glycogenolysis.

Lipolysis results in the formation of free fatty acids (FFAs), which are transformed into beta-hydroxybutyric acid and acetoacetic acid, known collectively as ketoacids, in the liver.

Hyperglycaemia results in glycosuria, with the excessive glucose in the urine causing osmotic diuresis [3]. The composition of electrolytes due to osmotic diuresis is approximately 70 mmol/l, for sodium and potassium, as well as for smaller concentrations of phosphate, magnesium, and calcium. The average fluid loss in an episode of DKA is between 5 and 10 l [4].

Initially water moves from the intracellular compartment (ICC) to the extracellular fluid (ECF), so that even though there is urinary loss of sodium, serum sodium levels actually decrease. This is exacerbated by the patient drinking large quantities of water to compensate for the fluid loss. As the relatively hypotonic urine losses continue, serum sodium increases. At the same time, potassium moves out of the cells and is washed out in the urine along with magnesium and phosphate.

Fluid losses occur from all three body fluid compartments—the ICC, the interstitial space (ISS), and the intravascular space (IVS) or circulating volume [5]. The most life-threatening of these is, of course, the latter.

Ketoacids produced as a result of DKA dissociate at physiologic pH, leading to the formation of high levels of hydrogen ions and anions [6]. The resulting acidosis is often worsened by lactic acidosis caused by hypovolaemia and tissue ischaemia. As hypovolaemia worsens, renal insufficiency can supervene, making the metabolic acidosis even worse.

The patient with DKA usually presents with a history of insulin-dependent diabetes (IDD), sometimes with a history of a precipitating cause, and a history of thirst, polyuria, polydipsia, and lethargy. Diffuse abdominal pain is present in about one-quarter of all patients [7].

On presentation to hospital, and depending on the severity of the DKA, the patient is dehydrated, with varying degrees of shock and Kussmaul's breathing as a result of the metabolic acidosis—typically manifesting as large tidal volumes and air hunger.

On physical examination, it is important to look for possible sites of infection and suggestions in the patient's history of possible precipitating causes.

The diagnosis is usually obvious from the history and examination and confirmed by a positive finger stick for glucose, together with a positive keto-diastix. Arterial blood gases; renal function tests; electrolytes; blood and urine ketosis; a 12-lead ECG, cardiac enzymes; and tests to exclude infection, such as white cell count and differential; microbiological cultures; and chest radiography, need to be measured in the patient upon admission.

Treatment

The immediate life-threatening aspects of DKA are usually related to hypovolaemia and complications of the precipitating factors. Lack of insulin and hyperglycaemia are not, in themselves, life-threatening [8]. Obviously if the patient's airway is compromised by, for example, a decreased level of consciousness, then the patient requires intubation. The adequacy of breathing and oxygenation is not often a problem in patients with DKA, as they usually have tachypnoea and hypocarbia. In fact, their oxygen levels are usually supranormal, partly as a result of the patient's dehydration and reduced ISS. Hypoxia may occur in elderly, obese and obtunded patients or as a result of an underlying chronic condition or an acute condition, such as severe infection, contributing to the DKA presentation.

Fluid replacement

Inadequate circulation is common in DKA and must be rapidly treated. The patient also has decreased ISS and ICC as a result of water and electrolyte losses. However, dehydration of these two spaces is not life-threatening and fluids should be replaced slowly in order to avoid excessive oedema [5]. Many sources still recommend the use of inflexible fluid replacement regimens, which do not take into account the variation in the volume lost or response of the individual patient [9]. Just as inflexible fluid replacement recipes are not recommended in hypovolaemic patients who have suffered severe trauma; it is just as inappropriate to suggest that each patient has the same degree of fluid loss, shock, and cardiac function.

Initial assessment of the circulation can be determined by simple vital signs, such as blood pressure, pulse rate, and peripheral perfusion. The most appropriate

replacement fluid could be, from a physiological perspective, a fluid with a concentration of approximately 70 mmol/l saline (1/2 'normal' saline), as this is what the patient is actually losing as a result of the glycosuria. While this may address the issue of correcting the dehydration, it would not result in rapid resuscitation of the IVS, resulting in uncorrected shock and ischaemia for unacceptable lengths of time [10]. Rapid correction of shock is a paramount principal in acute medicine, but especially so in patients with DKA, as they often have compromised underlying organ function which can be more vulnerable to the effects of prolonged ischaemia.

The most efficient fluid for resuscitating the IVS is a colloid, as more of it is actually retained in that space [10]. Isotonic saline, often used for fluid replacement in DKA, is less efficient since only approximately one third is retained in the IVS. The remainder is distributed to the ISS, which does not require immediate resuscitation. Resuscitation of the IVS with isotonic saline inevitably results in oedema due to excessive ISS expansion. Moreover, the isotonic saline does not address the issue of ICS dehydration.

Whether a crystalloid or colloid is used, the most important objective is to rapidly correct any shock and ischaemia. Rapid fluid challenges of 300–500 ml/h should also be infused until the patient's circulating volume returns to normal.

Hypovolaemia can be exacerbated when insulin therapy is commenced, as water moves from the ECF to the ICC. Monitoring of fluid resuscitation can be achieved with the same simple vital sign measurements that were used to initially assess the patient. Fine-tuning the circulation with more complex and invasive techniques, such as measurement of central venous pressure and blood volume, can be employed at a later stage.

If there is little or no hypovolaemia, fluid losses would be most effectively replaced by a fluid similar to what the patient is losing; that is, 0.45% saline or half-normal saline, with other electrolytes added as necessary. If hypovolaemia is significant, then a physiologically compatible approach would be to rapidly resuscitate the IVS with colloid and to simultaneously replace losses in the ISS and ICC with water in the form of 5% dextrose [8]. The amount of dextrose in this fluid is relatively small and would not contribute significantly to the hyperglycaemia which, by this stage, would gradually be controlled with insulin. The rate of replacement is empirical and would vary between 50 ml/h in mild cases of dehydration and up to 200 ml/h in severe cases. Fluid resuscitation can be ceased once the patient's biochemistry is relatively stable and he or she is tolerating oral fluids.

Electrolyte replacement

The amount of sodium in either the colloid or crystalloid used for fluid resuscitation is more than enough to replace the total sodium losses. It must be remembered that potassium losses are equal to, or greater than sodium losses. The initial potassium levels are usually within normal limits or even high [4, 7]. As the patient with DKA becomes more acidotic, potassium, which is mainly an intracellular ion, moves out of the cells into the ECF in order to maintain electrical neutrality. So,

while serum levels of potassium may be normal, total body losses are high. This loss becomes apparent as a result of dilution caused by fluid resuscitation as well as the shift of potassium back into the ICS when insulin therapy is commenced. Many of the avoidable deaths associated with DKA are a result of hypokalaemia [10]. Unless there is renal failure or another cause for hyperkalaemia, such as rhabdomyolysis, continuous infusion of potassium should be commenced at a rate between 5 and 3 mmol/h; the average requirement being around 10 mmol/h. As with fluid replacement, rather than follow inflexible recipes, serum potassium should be measured on admission and every hour until a trend becomes obvious. Continuous ECG monitoring is mandatory in all but the most benign cases of DKA.

Phosphate deficiency is also common and phosphate should be replaced as required to maintain normal levels [9]. Many phosphate mixtures also contain potassium, so that the potassium infusion may have to be reduced while phosphate is administered [9].

Like phosphate and potassium, magnesium is an intracellular ion and there are considerable losses of it during DKA. Therefore, magnesium levels should also be measured on admission and then regularly, especially during the first 24 h of treatment, and replaced as necessary.

There was a time when the metabolic acidosis associated with DKA was corrected with bicarbonate. We now understand that if the shock is adequately corrected and insulin commenced, then, even severe metabolic acidosis will reverse without any specific treatment. In fact, there are some suggestions that administration of bicarbonate causes an overshoot, leading to a metabolic alkalosis and possibly paradoxical intracellular acidosis.

Insulin

Insulin is not immediately life-saving and can, in fact, exacerbate or cause hypovolaemia and reduce serum electrolyte levels; thus, its commencement should be delayed until resuscitation has occurred.

Insulin should always be administered as a continuous intravenous infusion in all but the most uncomplicated presentations of DKA, as hypovolaemia causes vasoconstriction in muscular and subcutaneous tissue, resulting in unpredictable absorption. As well as facilitating glucose to move intracellularly; water, potassium, magnesium, and phosphate also follow glucose, correcting intracellular defects but at the same time decreasing ECF levels. Thus, initial boluses of insulin should be avoided [9]. Hyperglycaemia will be markedly reduced by the dilutional effect of fluid resuscitation even before any insulin is administered. Glucose should be slowly and smoothly reduced over 24–48 h, depending on the initial levels of glucose, and at a rate of less than 4 mmol/h. Even though insulin is adsorbed onto the plastic of syringes and administration sets, the amount lost in this way is not clinically relevant. Insulin infusion rates should commence at 1-2 units/h and can then be adjusted like any other infusion, according to regularly increased endpoints—in this case blood sugar levels.

General measures

Because of the many investigations that must take place during the treatment of DKA, an arterial line facilitates multiple blood tests, with less patient discomfort compared to multiple intravenous collections.

There is an increased risk of intravenous thrombus formation in DKA, leading to deep venous thrombolysis and other complications. Therapies such as low-dose heparin and anti-thrombosis stockings should be considered.

Finally, acute episodes of DKA treated in hospitals present an opportunity for educating the patient about compliance with therapy and related matters.

In summary, intravenous fluid resuscitation should be early and aggressive; electrolyte replacement should be provided according to regularly measured levels; bicarbonate should be avoided except in cases of life-threatening (pH ~6.9) or persistent acidosis; and insulin should be given to produce a slow reduction in blood sugar.

References

1. Johnson DD, Palumbo PJ, Chu CP (1980) Diabetic ketoacidosis in a community-based population. Mayo Clin Proc 55:83–88
2. Keller U (1986) Diabetic ketoacidosis: current views on pathogenesis and treatment. Diabetologia 29:71–77
3. Gennari FJ, Kassirer JP (1974) Osmotic diuresis. N Engl J Med 291:714–720
4. Atchley DW, Leob RF, Richards DW Jr et al (1933) On diabetic acidosis; a detailed study of the electrolyte balance following the withdrawal and re-establishment of insulin therapy. J Clin Invest 12:297–326
5. Hillman K (1987) Fluid resuscitation in diabetic emergencies – a reappraisal. Intensive Care Med 13:4–8
6. Foster DW, McGarry JD (1983) The metabolic derangements and treatment of diabetic ketoacidosis. Seminars in Medicine of the Beth Israel Hospital, Boston. N Engl J Med 309:159–169
7. Alberti KG, Hockaday TD (1977) Diabetic coma: a reappraisal after five years. Clin Endocrinol Metab 6:421–455
8. Hillman KM (1983) Resuscitation in diabetic ketoacidosis. Crit Care Med 11:53–54
9. Hillman K (1991) The management of acute diabetic emergencies. Clin Intensive Care 2:154–162
10. Twigley AJ, Hillman KM (1985) The end of the crystalloid era? A new approach to peri-operative fluid administration. Anaesthesia 40:860–871

Chapter 38

Endogenous metabolic acid–base abnormalities: lactate and other strong ions

K.J. Gunnerson, J.A. Kellum

Some of the most common clinical problems in critically ill and injured patients are disorders of acid–base equilibrium. Although alkalosis is also common and severe alkalosis may be life-threatening, acidosis appears to be the most frequently encountered acid–base abnormality and has a considerably larger differential diagnosis. Acidosis may occur as a result of increases in arterial partial pressure of carbon dioxide (pCO_2) (respiratory acidosis) or from a variety of organic or inorganic, fixed acids (metabolic acidosis). There appears to be a difference in physiological variables and outcomes in patients with either respiratory acidosis or metabolic acidosis [1, 2], leading some investigators to hypothesise that the cause of acidosis rather than the acidosis per se drives the association with clinical outcomes. Although the true cause–effect relationship between acidosis and adverse clinical outcome remains uncertain, metabolic acidosis remains a powerful marker of poor prognosis in critically ill patients [3–5].

Common aetiologies of metabolic acidosis include lactic acidosis, hyperchloraemic acidosis, renal failure, and ketones. All types of metabolic acidosis have a contributing anion responsible for the acidosis. In some case, the single contributing anion may be obvious, such as a pure lactate acidosis, whereas other complex disorders may not have a single, identifiable, causative anion, and only the anion gap (AG) or strong ion gap (SIG) are elevated. Importantly, there is recent evidence to suggest that clinical outcomes may be influenced by the type of metabolic acidosis. In other words, the clinical consequences of acidosis may be different depending on which predominant anion is responsible for the metabolic acidosis. In the critically ill, metabolic acidosis secondary to lactate and those cases secondary to unknown or unmeasured anions appear to be associated with the highest mortality [6]. In this review, we focus on these types of metabolic acidosis and consider how they occur and what their presence might mean. We also review the clinical methods of detection and identification of metabolic acidosis due to lactate and other strong anions.

Modern and traditional views of acid–base physiology

It is something of a misnomer to lump a variety of clinical approaches to understanding acid–base physiology into a single group and refer to them as 'traditional.'

Approaches that can now be classified as 'traditional' include those that built on the work of Henderson and Hasselbalch as well as those proposed by Siggaard-Andersen et al. These traditional approaches are able to identify the presence of a metabolic acidosis and categorise them based on the presence or absence of an AG. The shortcoming of these approaches lies in the fact that they are only semi-quantitative. A change in bicarbonate does not accurately map to the amount of metabolic acidosis in a given blood sample. Although base excess was developed precisely for this reason, and does map to the change in the amount of acidosis, it does not differentiate between types of metabolic acidosis. Similarly, the AG cannot easily be adapted to achieve a quantitative understanding. Thus a 'modern quantitative' or 'physicochemical' approach was developed to allow for a quantitative understanding of the causative ions [7]. The basic principle of the quantitative approach involves independent variables, such as pCO_2, strong ion difference (SID), and total weak acids (A_{TOT}), and dependent variables, which include pH and bicarbonate ions [8–11]. Although controversy has existed for many years over which of these approaches is superior, the results obtained from each of them are nearly identical [9, 10, 12].

Indeed, modern quantitative acid–base chemistry has its roots in some basic principles as the traditional approaches. For example, the SID is the resulting net charge of all the strong ions (primarily Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and lactate). This measurable difference is referred to as the 'apparent' SID (SIDa), with the understanding that not all ions may be accounted for. In healthy humans, this number is close to + 40 mEq/l [13]. Since the principle of electroneutrality states that there must be an equal and opposing charge to balance the positive charge, the + 40 mEq/l is balanced by an equal negative force comprised of mostly weak acids (A_{TOT}) and pCO_2. The weak acids include plasma proteins (predominately albumin), and phosphates, and their total amount must equal the SIDa. The sum of all the measurable anions contributing to the balancing negative charge is referred to as the effective SID (SIDe) and is in fact equal to the buffer base. Thus, a change in SID is equal to a change in buffer base and a change in buffer base is referred to as base excess (or deficit). In this way, SID and base excess are not only compatible but are equally quantitative.

The additional advantage of SID comes from using both SIDa and SIDe to quantify unmeasured ions. Theoretically, SIDa and SIDe should equal each other; however, they are often different and we refer to this difference as the SIG [14]. A small amount of unmeasured ions may be present even in health, so that in healthy humans SIG appears to be less than 2 mEq/l [13]. By convention, SIG is calculated from SIDa – SIDe so that a positive SIG denotes the presence of unmeasured anions while a negative SIG denotes unmeasured cations. SIG only measures the difference, so that both unmeasured anions and cations may be present.

Note that the SIG does not require that ions be 'strong'; in fact, weak ions may cause the SIG. This is notable especially since the role of plasma proteins, specifically albumin, in acid–base balance is curiously neglected in the traditional approaches. This has led to numerous controversies on the usefulness of the AG [15] and the classification of metabolic acid–base disorders [16]. Several studies have supported

the observation that a significant number of abnormal AGs go unrecognised without correction for the albumin level (which in the critically ill is usually low) [16–18]. The importance of correcting the AG for albumin is not limited to the adult population. Quite the contrary, there is a high incidence of hypoalbuminaemia in paediatric patients who are critically ill, and the effects on the AG measurements are similar to those in the adult population [19, 20]. When the AG is not corrected in critically ill paediatric patients, Hatherill and colleagues have demonstrated that approximately 10 mEq of acid and up to 50% of abnormally elevated AGs are missed [20].

Strong ion gap metabolic acidosis

The SIG and traditional AG differ in the sense that the traditional AG exists in a broad 'range' of normal values whereas the SIG takes into account the effect of a wider range of ions, including weak acids, and thus should approach zero. Even though this theoretical value of zero should exist for patients who have no known acid–base abnormalities, a wide range (0–13 mEq/l) has been reported in the literature [14, 16, 21–23]. In the United States, ranges for SIG in survivors tend to be low and are predictive of survival in critical illness [17, 24]. However, in England and Australia, countries that routinely use gelatins for resuscitation, values of SIG as high as 11 mEq/l have been reported in ICU survivors [21], and do not appear to be predictive of outcome [21, 25]. Gelatins are a class of colloid plasma expanders that are made up of negatively charged polypeptides (mean molecular mass between 20 000 and 30 000 Daltons) dissolved in a crystalloid solution commonly consisting of 154 mEq sodium and 120 mEq chloride. These negatively charged polypeptides have been shown to contribute to both an increased AG [26] and SIG [27], most likely due to their negative charge and long circulating half-life. Moreover, these high SIG levels may be seen in the absence of acid–base abnormalities using traditional acid–base measurements, e.g. pCO_2, standard base excess (SBE), pH.

We recently compared quantitative acid–base variables between healthy volunteers (control) and 'stable' ICU patients [13]. There were significant differences between these two groups. The control group had a SIDe of 40 mEq/l (± 3.8) and SIG of 1.4 mEq/l(± 1.8). The ICU patients had a SIDe of 33 mEq/l (± 5.6) and SIG of 5.1 mEq/l (± 2.9). The control group also had a higher albumin level 4.5 g/dl vs 2.6 g/dl in the ICU group. Interestingly, traditional acid–base variables (pH, pCO_2, SBE) were similar between the groups [13]. Controversy still remains, but it appears that a normal range of SIG in healthy patients is 0–2 mEq/l (± 2 mEq/l) and in stable ICU patients without renal failure, SIG appears to be slightly higher, at 5 mEq/l (± 3 mEq/l).

The SIG calculation is somewhat cumbersome to use at the bedside [14] and attempts have been made to simplify this technique based on normalising the AG for the serum albumin, phosphate, and lactate concentrations [9, 18, 22, 28]. By supplementing the corrected anion gap (AGc) in place of the SIG, we found a strong correlation between the two ($r^2 = 0.96$) [6]. The AGc was calculated as follows:

$[(Na^+ + K^+) - (Cl^- + HCO_3^-)]$ – 2.0 (g albumin/dl) – 0.5 (mg phosphate/dl) – lactate mEq/l [9]. An even simpler formula, $(Na^+ + K^+) - (Cl^- + HCO_3^-)$ – 2.5 (g albumin/dl) – mmol lactate/l, for the AGc without the use of phosphate can be used and still retains a strong correlation with SIG ($r^2 = 0.93$) [6, 9]. For international units, the following conversion can be substituted for albumin and phosphate: 0.2 (g albumin/l) – 1.5 (mmol phosphate/l).

There is still much debate as to what SIG means in terms of clinical significance [17, 21, 24, 25]. The association between high SIG and mortality in the critically ill is not as clear as that of lactate. There have been varying results as to the absolute values and the significance of all quantitative acid–base variables, especially SIG. It appears that a pattern is emerging in which studies conducted in different countries have shown different baseline levels of SIG and have noted differences in their clinical significance [17, 21, 24, 25, 29]. This may be related to technology used to measure acid–base variables [30–32] or administration of medications or fluid (e.g. gelatins) [26, 27] that alter the SIG.

Two recent prospective studies have controlled for the limitations noted above when evaluating the association between SIG and mortality [24, 29]. The findings of these two studies are unique in that they are the first reports of SIG in patients before treatment, i.e. prior to any significant amount of volume resuscitation. In the first study, Kaplan and Kellum evaluated the relationship of SIG to mortality in patients with major vascular injury requiring surgery. In this cohort, a SIG of 5 mEq/l was predictive of mortality. Interestingly, SIG outperformed lactate as a predictor of mortality based on receiver–operator characteristic curves. SIG was also a stronger predictor of mortality than the injury severity score based on multivariable regression analysis. Non-survivors had a mean SIG of 10 mEq/l. These levels of unmeasured anions were generated in the absence of resuscitative fluids known to contribute to unmeasured anions, such as gelatin-based solutions, which are not used for resuscitation in the United States. This study supports the hypothesis that SIG may be a rapidly accumulating biomarker reflecting severity of injury or illness, similar to other acute-phase responses.

Dondorp et al. evaluated the relationship of SIG to mortality in critically ill patients diagnosed with severe malaria. Severe *Falciparum malaria* infection is frequently associated with metabolic acidosis and hyperlactataemia. The aetiology of both has been thought to be based on hepatic dysfunction and hypoperfusion. The authors found that, even in fatal cases of this disease state, the predominant form of metabolic acidosis was not lactate, but rather unaccounted anions, or SIG. Mean lactate levels were surprisingly low in survivors (2.7 mEq/l) and nonsurvivors (4.0 mEq/l) [29]. However, SIG levels were elevated in both groups, 9.7 mEq/l and 15.9 mEq/l, respectively. SIG was also a strong predictor of mortality in this study.

Lactic acidosis

Lactic acidosis is a pathophysiologic state of great concern in critically ill patients, and there is a wealth of literature reporting the significance of the various aetiolo-

gies of elevated lactate as it pertains to the critically ill patient [33–35]. During basal metabolic conditions, arterial lactate levels exist in a range between 0.5 and 1 mEq/l. Levels may be higher in hypoperfused or hypoxic states. However, critically ill patients may have conditions other than hypoperfusion that can lead to lactate elevations, such as increased catecholamine production in sepsis or trauma [36], or from production by the acutely injured lung [37, 38].

Even though elevated lactate levels can be a sign of underlying pathology, most patients in the ICU do not have elevated lactate levels. Five recent outcome trials comparing various approaches in diagnosing acid–base disorders found relatively low mean lactate levels, Dondrop et al. (survivors) (2.7 mEq/l), Rocktaeschel et al. (1.88 mEq/l), Durwad et al. (1.0 mEq/l), Cusak et al. (survivors) (2.3 mEq/l), and Balasubramanyan et al. (3.1 mEq/l) [17, 21, 25, 29, 39]. In a cohort of 851 ICU patients with a suspected lactic acidosis, and using the highest lactate value if there were multiple values, the mean lactate level was still only 5.7 mEq/l [6]. Therefore, when an elevated lactate is present it should not be dismissed without further investigation as to the underlying aetiology.

Regardless of the aetiology, lactic acidosis has been associated with worse outcome in critically ill patients. Elevated lactate has been associated with oxygen debt since the 1930s [40] and with poor outcome since the 1960s [3, 41–43]. Elevated lactate on presentation [43] and in serial measurements [35, 44] are both associated with worse outcome. More importantly, the ability to rapidly clear lactate has been associated with improved mortality [45–47]. Although our understanding of the metabolism of lactate has greatly improved since these early studies [48], critically ill patients with elevated lactate levels continue to have worse outcomes than those who do not [34, 35, 47]. Recent goal-directed strategies incorporating lactate either as a marker for acuity [49] or as an endpoint for resuscitation [50] have been shown to improve mortality.

Conclusions

Acid–base disorders in critically ill patients are common. Traditional approaches used to measure these disorders may actually underestimate their presence. Currently, the relationship between metabolic acidosis and clinical outcome remains uncertain, but it appears that a difference in mortality may depend on the varying contribution of causative anions. Metabolic acidosis secondary to lactate or unmeasured anions (SIG) appear to be significant markers of adverse outcome in the critically ill.

References

1. Kellum JA, Song M, Subramanian S (2002) Acidemia: good, bad or inconsequential? In: Vincent JL (ed) Yearbook of intensive care and emergency medicine. Springer, Berlin, pp 510–516
2. Li J, Hoskote A, Hickey C et al (2005) Effect of carbon dioxide on systemic oxygenation, oxygen consumption, and blood lactate levels after bidirectional superior cavopulmonary anastomosis. Crit Care Med 33:984–989
3. Broder G, Weil MH (1964) Excess lactate: an index of reversibility of shock in human patients. Science 143:1457–1459
4. Hickling KG, Walsh J, Henderson S et al (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22:1568–1578
5. Stacpoole PW, Lorenz AC, Thomas RG et al (1988) Dichloroacetate in the treatment of lactic acidosis. Ann Intern Med 108:58–63
6. Gunnerson KJ, Saul M, Kellum JA (2003) Lactic versus nonlactic metabolic acidosis: outcomes in critically ill patients. Critical Care 7(Suppl 2):P017
7. Gunnerson KJ, Kellum JA (2003) Acid-base and electrolyte analysis in critically ill patients: are we ready for the new millennium? Curr Opin Crit Care 9:468–473
8. Corey HE (2003) Stewart and beyond: new models of acid-base balance. Kidney Int 64:777–787
9. Kellum JA (2000) Determinants of blood pH in health and disease. Critical Care 4:6–14
10. Stewart P (1983) Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 61:1444–1461
11. Stewart PA (1981) How to understand acid-base. In: Stewart PA (ed) A quantitative acid-base primer for biology and medicine. Elsevier, New York, pp 1–286
12. Sirker AA, Rhodes A, Grounds RM et al (2002) Acid-base physiology: the 'traditional' and the 'modern' approaches. Anaesthesia 57:348–356
13. Gunnerson KJ, Roberts G, Kellum JA (2003) What is a normal strong ion gap (SIG) in healthy subjects and critically ill patients without acid-base abnormalities? Crit Care Med 31(Suppl A111):12 (abs)
14. Kellum JA, Kramer DJ, Pinsky MR (1995) Strong ion gap: a methodology for exploring unexplained anions. J Crit Care 10:51–55
15. Salem MM, Mujais SK (1992) Gaps in the anion gap. Arch Intern Med 152:1625–1629
16. Fencl V, Jabor A, Kazda A et al (2000) Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med 162:2246–2251
17. Balasubramanyan N, Havens PL, Hoffman GM (1999) Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. Crit Care Med 27:1577–1581
18. Story DA, Poustie S, Bellomo R (2002) Estimating unmeasured anions in critically ill patients: anion-gap, base-deficit, and strong-ion-gap. Anaesthesia 57:1109–1114
19. Durward A, Mayer A, Skellett S et al (2003) Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap. Arch Dis Child 88:419–422
20. Hatherill M, Waggie Z, Purves L et al (2002) Correction of the anion gap for albumin in order to detect occult tissue anions in shock. Arch Dis Child 87:526–529
21. Cusack RJ, Rhodes A, Lochhead P et al (2002) The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. Intensive Care Med 28:864–869

22. Moviat M, van Haren F, van der Hoeven H (2003) Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. Crit Care 7:R41-R45
23. Wilkes P (1998) Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. J Appl Physiol 84:1740–1748
24. Kaplan LJ, Kellum JA (2004) Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med 32:1120–1124
25. Rocktaeschel J, Morimatsu H, Uchino S et al (2003) Unmeasured anions in critically ill patients: can they predict mortality? Crit Care Med 31:2131–2136
26. Sumpelmann R, Schurholz T, Marx G et al (1999) Alteration of anion gap during almost total plasma replacement with synthetic colloids in piglets. Intensive Care Med 25:1287–1290
27. Hayhoe M, Bellomo R, Liu G et al (1999) The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. Intensive Care Med 25:680–685
28. Figge J, Jabor A, Kazda A et al (1998) Anion gap and hypoalbuminemia. Crit Care Med 26:1807–1810
29. Dondorp AM, Chau TT, Phu NH et al (2004) Unidentified acids of strong prognostic significance in severe malaria. Crit Care Med 32:1683–1688
30. Burns RF, Russell LJ (1985) Ion-selective electrode technology: an overview. Contemp Issues Clin Biochem 2:121–130
31. Fogh-Andersen N, Wimberley PD, Thode J et al (1984) Determination of sodium and potassium with ion-selective electrodes. Clin Chem 30:433–436
32. Worth HG (1985) A comparison of the measurement of sodium and potassium by flame photometry and ion-selective electrode. Ann Clin Biochem 22(Pt 4):343–350
33. De Backer D (2003) Lactic acidosis. Minerva Anestesiol 69:281–284
34. Luft FC (2001) Lactic acidosis update for critical care clinicians. J Am Soc Nephrol 12:S15-S19
35. Vincent JL, Dufaye P, Berre J et al (1983) Serial lactate determinations during circulatory shock. Crit Care Med 11:449–451
36. James JH, Luchette FA, McCarter FD et al (1999) Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet 354:505–508
37. Bellomo R, Kellum JA, Pinsky MR (1996) Transvisceral lactate fluxes during early endotoxemia. Chest 110:198–204
38. De Backer D, Creteur J, Zhang H et al (1997) Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med 156:1099–1104
39. Durward A, Skellett S, Mayer A et al (2001) The value of the chloride: sodium ratio in differentiating the aetiology of metabolic acidosis. Intensive Care Med 27:828–835
40. Margaria R, Edwards R, Dill D (1933) The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. Am J Physiol 106:689–715
41. Cowley RA, Attar S, LaBrosse E et al (1969) Some significant biochemical parameters found in 300 shock patients. J Trauma 9:926–938
42. Schweizer O, Howland WS (1968) Prognostic significance of high lactate levels. Anesth Analg 47:383–388
43. Weil MH, Afifi AA (1970) Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41:989–1001
44. Bakker J, Gris P, Coffernils M et al (1996) Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 171:221–226

45. Abramson D, Scalea TM, Hitchcock R et al (1993) Lactate clearance and survival following injury. J Trauma 35:584–588
46. Bakker J, Coffernils M, Leon M et al (1991) Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 99:956–962
47. Nguyen HB, Rivers EP, Knoblich BP et al (2004) Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 32:1637–1642
48. Gladden LB (2004) Lactate metabolism: a new paradigm for the third millennium. J Physiol 558:5–30
49. Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
50. Rossi AF, Khan DM, Hannan R et al (2005) Goal-directed medical therapy and point-of-care testing improve outcomes after congenital heart surgery. Intensive Care Med 31:98–104

Chapter 39

Metabolic acidosis

F. Schiraldi, G. Esposito, E.G. Ruggiero

Starting from Arrhenius, in the 1880s, and continuing through Naunyn [1], Van Slyke, Bronsted and Lowry [2], and Henderson, Hasselbalch, researchers and clinicians have long been interested in the chemistry of acids and bases, and the physiological regulation of pH. The original Henderson-Hasselbalch equation relates pH to the ratio of the concentration of the coniugate anion A- to the concentration of undissociated acid HA. However, all weak acids in a given solution can be inserted into Henderson-Hasselbach-type equations to calculate pH. The reason for this is that, in a solution of several weak acids, all of the acids are in equilibrium with a single pool of hydrogen ions (isohydric principle). Indeed, the Henderson-Hasselbalch equation, e.g., for the "'phosphate pool,"' can be used to describe pH, as follows :

$$pH = pK\,(phos) + \log \frac{HPO_4^-}{H_2PO_4^-};$$

Everyone agrees on the superior buffering function of the phosphate system, which is characterised by a pK (dissociation constant) near 6.8, theoretically closer to that of normal blood pH (7.38–7.42), and so potentially useful to counteract acidic or basic derangements from the normal. Nevertheless, even if the bicarbonate system has a pK near 6.1 (theoretically disadvantageous), there are several good reasons as to why evolution has conferred upon the human body a bicarbonate-based system. In particular, bicarbonate comprises an 'open system,' allowing optimal matching between metabolism and ventilation.

$$pH = pK\,(bic) + \log \frac{HCO_3^-}{PCO_2 \times 0.03}$$

This is an important strong point, since an understanding of the bicarbonate system is essential to understanding the metabolic state of a given patient, regardless of his or her ventilatory function. In other words, any bicarbonataemia 'less than expected' in any setting implies some degree of metabolic acidosis.

One of the key points of the 'Great Trans-Atlantic Debate' [3, 4] is related to some slightly cumbersome 'rules of thumbs,' which are needed to understand the nature of a patient's 'primary' derangement (metabolic vs respiratory) and the body's 'expected' compensatory response. This pathophysiologic approach is the only one that provides complete insight into the clinical problems underlying acid–base derangements, particularly if combined with a precise evaluation of the anion and osmolal gaps, and, if needed, of the concentrations of urinary electrolytes.

Aiming to simplify the physiological concepts related to metabolic derange-

ments, Singer and Hastings, in 1948 [5], introduced the concept of 'buffer base' (BB), which is the sum of weak acid anions in plasma, including albumin anions and bicarbonate. Based on their approach, Siggaard-Andersen proposed the term 'base excess' (BE), defined as the amount of strong acid (mmol/l) to be added to a blood sample to reach a pH of 7.40 after equilibration, while maintaining the PCO_2 at 40 mmHg (in vitro). Unfortunately while the BE-targeted approach is useful for a simplistic approach to the problem, it does not offer an understanding of mixed disorders. Moreover, a clinician's reliance on the BE approach may be potentially dangerous for understanding a patient's metabolic derangements, e.g. in the case of metabolic alkalosis plus metabolic acidosis, two almost contemporary derangements in which BE may be normal [6, 7].

Based on the principles of physical chemistry (electroneutrality, mass conservation, dissociation of weak acids, albumin relevance), Stewart introduced, some 30 years ago, a third 'road map' which offered a more complete understanding of the biochemical derangements—produced by diseases and/or clinicians—that occur in acid–base disturbances [8–11]. The essentials of the Stewart approach start from the concept of an 'expanded' anion gap, which takes into account not only the usual electrolytes, but also Mg^{2+}, Ca^{2+}, lactate, albumin, and phosphate. Starting from this fully comprehensive approach, the relative specific responsibility of each term as a cause of suspected metabolic acidosis can be calculated according to the following three equations.

First, the 'apparent' strong ion difference (SIDa), in mEq/l, is determined:

$$SIDa = [Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}] - [Cl^-] - [lactate]$$

This SIDa is "apparent" because it does not consider the role of HCO_3^- albumin, and phosphate in the electrical balance in plasma water. Thus, the next step is to calculate the 'effective' strong ion difference (SIDe) using the rather cumbersome formula:

$$SIDe = 1000 \times 2.46 \times 10^{-11} \times PCO_2/10^{-pH} + [Alb] \times (0.12 \times pH - 0.631) + [phos] \times (0.309 \times pH - 0.469)$$

This SIDe formula quantitatively accounts for the contribution of weak acids and, more interestingly, shows that the difference between the SIDa and SIDe should be zero, unless there are unmeasured charges to explain this ion gap, referred to then as the 'strong ion gap' (SIG):

$$SIG = SIDa - SIDe$$

A positive value for SIG represents unmeasured anions (sulfate, ketoacids, citrate, pyruvate, acetate, gluconate) that must be included to account for the measured pH. This could, for example, explain some cases of light metabolic alkalosis due to hypoalbuminaemia, and is tightly linked to the otherwise puzzling acidifying effect of large infusions of saline. Indeed, the crystalloid effect from the Stewart perspective can help to disclose the mystery of dilutional acidosis. Many reports have pointed out that overzealous saline infusions can cause metabolic acidosis [12, 13]; this has been best documented during repletion of a deficit in extracellular fluids, acute normovolaemic haemodilution [14], and cardiopulmonary bypass. The mechanism is obviously not bicarbonate dilution since in this case the proton donors would also be diluted. The key explanation is that the SID of saline is zero, because the strong cation concentration $[Na^+]$ is exactly the same

as the strong anion concentration [Cl^-]; what is different is the 'percent' impact of the infusion on the respective starting concentrations, which are different. The net result, if more then 2000 ml of saline have been infused in less than 24 h, is an infusion-related metabolic acidosis; interestingly, hypertonicity makes solutions more acidifying, as more water is drained from the intracellular space, which becomes a participant in contributing to the final equilibrium. So what can be adopted from Stewart's cumbersome approach is an appreciation of the relevance of hypoalbuminaemia, on the one hand, and of the acidifying effect of massive saline infusions on the other.

Other diagnostic clues

Urinary anion gap

Since the normal concentration ranges of urinary electrolytes are very large, they should be assessed taking into account the clinical setting and the ongoing therapies. Nevertheless, as the electroneutrality principle must always be respected, some useful information can be derived from measuring Na^+, K^+, and Cl^- urinary concentrations. If the patient's blood gas analysis (BGA) suggests metabolic acidosis and the anion gap is near-normal, a measurement of urinary NH_4^+ excretion could be critical to define the origin of such metabolic acidosis. Due to the difficulty of directly evaluating urinary NH_4Cl, one can easily determine whether urinary acidification is functional in a patient as follows : if the urinary Cl^- is $\geq Na^+ + K^+$, it is very likely that urinary acidification is not directly responsible for the hypobicarbonataemia; instead, the cause of the bicarbonate loss should be sought extrarenally (enteric) [15].

Osmolal gap

One osmol of any substance is the presence of 6.023×10^{23} molecules of that substance in 1 kg of water. Therefore, osmolality is a function of the number of particles in a given weight of solvent and is independent of the size, shape, or weight of a substance. The only important factor is the number of molecules present, which is inversely proportional to the molecular weight. It should also be noted that the solutes that are present in the blood or serum are dissolved only in the aqueous phase. Normally, sodium and glucose determine serum osmolality, which can be calculated as:

$2 \times$ Na (mEq/l) + Gluc (mg/dl)/18 = plasma osmolality (Posm) 285 ± 5 mOsm/l

If an intoxicant of low molecular weight is added to serum, it may increase the measured osmolality, leaving the calculated one unchanged or actually reduced; this is referred to as the 'osmolal gap' (OG):

OG = meas Posm – cCalc Posm = normal value (n.v.) 5 ± 2

It can be easily argued that if any intoxicant, responsible for metabolic acidosis of unknown origin, is present, it will change the meas Posm, leaving unchanged the

calc Posm and increasing the OG. Interestingly, the lower the molecular weight of the intoxicant, the larger the OG.

Central venous BGA sample

Arieff, Weil, and many others [16–20] pointed out the paramount importance of a central venous, or mixed venous BGA in hypoperfused and/or hypoxic/dysoxic patients. Extensive information can be derived from pH and PCO_2 gradients between arterial BGA samples and central or mixed venous BGA. Admittedly, arterial BGA is a poor indicator of metabolic derangements, due to the respiratory adjustments of the primary disturbances. In contrast, it is easily appreciated that whenever tissue metabolism (oxygen consumption [VO_2] vs O_2 demand) is unsatisfied by poor oxygen delivery (DO_2) or cellular metabolic derangements (toxins, mediators), tissue and venous metabolic acidosis are very likely. The larger than normal pH or PCO_2 gradient, which is linked to the overproduction of venous PCO_2 due to tissue buffering of the produced acids and which arises from the insufficient presentation of such venous hypercarbia in the lungs, can be used as a valid monitoring tool in critically ill patients (so-called venous metabolic hypercarbic acidosis).

Lactic acidosis and hyperlactataemia

Another clinical marker of dysoxia, regardless of origin (hypoperfusion, mediators, toxins, etc.) is lactate monitoring; which has been in use since 1970. Weil demonstrated a strong correlation between the starting plasma lactate value and mortality in his medical ICU. Lactic acidosis is an 'elevated anion gap' acidosis, which reflects an evolving disease process. Lactate generated from dysoxia generates acidosis, as the vast amount of lactate produced results in a strong anion, decreases the SID, and generates protons. Resolution of lactic acidosis correlates well with survival in a time-dependent fashion [21]. Moreover, even when an occult hypoperfusion (near-normal vital signs, but persistent lactic acidosis) is present, reduced or absent lactate clearance directly correlates to infection risk and to mortality [22].

In order to avoid inappropriate therapy, it is important to differentiate lactic acidaemia from hyperlactataemia (= normal pH, elevated lactate level, and constant lactate/pyruvate ratio). Regarding the lactate/pyruvate ratio, lactic acid can be considered as a metabolic 'dead end,' as pyruvic acid, its only precursor, is also the only route of metabolic transformation:

$$H + PYR + NADH \leftarrow LDH \rightarrow LACTATE + NAD$$

When pyruvate is converted to lactate, NADH undergoes oxidation; conversely when lactate (LDH-catalysed) reverts to pyruvate, there is a reduction of NAD. Three factors are the key determinants of the reaction: the availability of pyruvate, the pH, and the redox state of the cell, so that the equilibrium constant (K_{eq}) is:

$$K_{eq} = \frac{LACT \times NAD}{PYR \times NADH \times [H]}$$

And:

$$LACT = K \times \frac{PYR}{NADH} \times [H].$$

As normally the ratio pyruvate/lactate is 1/4, a brisk increase of NAD and pyruvate are needed to increase lactate, which is strongly favoured by a low intracellular pH and a high NADH/NAD ratio. In summary, whenever DO_2 or O_2 metabolism is impaired, there will be more pyruvate, a higher NADH/NAD ratio, lower pH, less energy, and increased lactate production; moreover if any type of circulatory shock ensues, there will be less lactate presentation to the liver and the kidneys, and less lactate extraction [23]. These concepts have been strongly confirmed, from a prognostic point of view, by several well-performed studies based on so-called Early Goal-Directed Therapy [24–26].

Systemic effects of acidosis

Because protein function is sensitive to blood pH, acidosis exerts detrimental effects on a host of bodily functions. In critically ill patients, the tissue PCO_2 may increase and the intracellular pH decrease while the arterial blood pH remains near normal. Moreover, the effects of elevated $[H^+]$ may also be difficult to separate from the effects of the accompanying anion: lactate buffered to a pH of 7.4, for example, still causes a decrease in cardiac contractility in animal models. Nevertheless, lowering the arterial pH has convincingly been shown to decrease cardiac contractility, even if the net influence of acidosis on the cardiovascular system is associated with derangements resulting from concomitant stimulation of the sympathetic–adrenal axis. In contrast, a mild degree of acidosis has been shown to protect the heart, lung, brain, and liver against hypoxic injury [27, 28].

Immune activation has been intimately linked to the presence of acidosis, and activation of T-cell protein kinases and acute lung injury are provoked by intravascular acid infusion. These effects stem from acidosis-stimulated expression of inducible nitric oxide synthase, which is associated with elaboration of pro-inflammatory cytokine interleukin (IL)-6 in rat preparations [29, 30] (Table 1).

Table 1. Systemic effects of acidosis. *TNF* Tumor necrosis factor, *GH* growth hormone

↓ Myocardial contractility
Arterial vasodilatation
↑ Pulmonary resistance
↑ Work of breathing
↑ Insulin resistance
↓ Anaerobic glycolisis
Hyperkalaemia
↑ protein catabolism, ↑ TNF (?)
↓ Neuronal efficiency
↑ Peripheral resistance to GH

Therapeutic troubleshooting

In summary, there is no real *diagnostic* problem regarding metabolic acidosis, regardless of the three major approaches (Henderson-Hasselbalch, Singer-Hastings, or Stewart) used to assess metabolic acidosis. At our institution, we are more confident applying the pathophysiologic approach, which takes into account the expected physiological compensations, and modified based on information regarding lactate clearance, osmolality, urinary indexes, intravascular filling, etc. In addition, the pathophysiologic approach facilitates a complete evaluation of the impact of different bodily systems on acid–base metabolism.

An understanding of the patient's perfusional state is the cornerstone of the therapeutic approach, whatever the cause of metabolic acidosis. Of paramount importance, from this point of view, is the bulk of evidence against the indiscriminate use of i.v. bicarbonate during low/absent circulatory flow. First, bicarbonate infusion has been shown to stimulate the production of lactate in animal models of hypoxic lactic acidosis and haemorrhagic shock. Under such circumstances, the subsequent massive CO_2 production, in the setting of inadequate lung presentation/elimination, could have a devastating impact on cardiac and cerebral DO_2 (due to a leftward shift of Hb dissociation) and intracellular pH [31, 32]. In general, whole-animal studies failed to demonstrate any haemodynamic benefit of sodium bicarbonate over isotonic saline. Thus, the only successful way to correct hypoperfusional (lactic) acidoses is to improve circulation/oxygenation [33–35].

In almost every other acidaemic state, alkali therapy may be useful, particularly in the setting of chronic bicarbonate depletion (renal, enteric) or an acute toxic or hyperkalaemic state. If a choice must be made, alkalinising substances, other than bicarbonate, have not proven to be more useful (Table 2).

Table 2. Alkalinising substances and side effects

Substance	Name	Effects on CO_2	Possible side effects
Tris-OH-amino-methane	THAM	↓ ↓	Systemic vascular resistance Coronary perfusion
$NaHCO_3$ bicarbonate	Sodium	↓	Na overload; venous hypercarbia
Na2CO3 carbonate	Sodium	↓	Na overload
Na_2CO_3 + $NaHCO_3$	Carbicarb	=, ↓	Na overload
$NaHCO_3$ + THAM + Phosphate + acetate	Tribonate	↓	All of the above
Dichloroacetate	DCA	↑	Oxalate production

An alternative approach to rapidly correct an harmfully low pH may, in some cases, be a hyperventilatory trial, by non-invasive or invasive support. The goal is

to 'buy time' before starting a more strategic approach, i.e. one that is based on removal of the underlying causes of metabolic acidosis [36].

References

1. Narins G, Jones ER, Stom MC et al (1982) Diagnostic strategies in disorders of fluids, electrolytes and acid-base homeostasis. Am J Med 72:469–512
2. Kellum JA (2000) Determinants of blood pH in health and disease. Crit Care 4: 6–14
3. Adroguè HJ, Madias NE (1998) Management of life-threatening acid-base disorders. NEJM 338,1:26–34
4. Gabow P (1985) Disorders associated with an altered anion gap. Kidney Int 27:472–483
5. Schiraldi F (1994) Metabolic acidosis: diagnosis and treatment. In: Gullo A (ed) Anaestesia, pain, intensive care and emergency medicine 1994. APICE proceedings, Milan, pp 47–57
6. Schiraldi F (1995) Time to abandon base excess as a reliable index in the ICU? International Journal of Intensive CareInt J Intensive Care 2:23
7. Ishihara K, Szerlip HM (1998) Anion gap acidosis. Semin Nephrol 18(1):83–97
8. Stewart PA (1983) Modern quantitative acid-base chemistry: applications in biology and medicine. Respir. Physiol 91:1–16
9. Kaplan LJ, Frangos S (2005) Clinical review: Acid-base abnormalities in the intensive care unit. Critical Care ,9:198–203
10. Kellum JA, Song M, Subramanian S (2002) Acidemia: good, bad or inconsequential? In: Vincent J-L (ed) Yearbook of intensive care and emergency medicine. Springer Verlag, Berlin, pp 510–516
11. RJ Cusak RJ, A Rhodes A, P Lochhead P, et al (2002) The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. Intensive Care Med 28(7): 864–869
12. Morgan TJ (2005) The meaning of acid-base abnormalities in the intensive care unit: part III—effects of fluid administration. Crit Care 9(2): 204–211
13. Funk GC, Doberer D, Heinze G et al (2004) Changes of serum chloride and metabolic acid-base state in critical illness. Anaesthesia 59(11):1111–1115
14. Bruegger D, Bauer A, Rehm M et al (2005) Effect of hypertonic saline dextran on acid-base balance in patients undergoing surgery of abdominal aortic aneurysm. Crit Care Med 33:556–563
15. Lorenz JM, Kleinman LI, Markarian K et al (1999) Serum anion gap in the differential diagnosis of metabolic acidosis in critically ill newborns. J Pediatr 135(6): 751–755
16. Cavaliere F, Antonelli M, Arcangeli A et al (2002) Effects of acid-base abnormalities on blood capacity of transporting CO2: adverse effect of metabolic acidosis. Intensive Care Med 28(5):609–615
17. De Bakker D, Creteur J (2003) Regional hypoxia and partial pressure of carbon dioxide gradients : what is the link? Intensive Care Med 29:2116–2118
18. Mahutte CK, Jaffe MB, Sassoong CS et al (1991) Cardiac output from carbon dioxide production and arterial and venous oximetry. Crit Care Med 19(10):1270–1277
19. Bircher NG (1992) Acidosis of cardiopulmonary resuscitation: carbon dioxide transport and anaerobiosis. Crit Care Med 20(9):1203–1205
20. Zhang H, Vincent J-L (1993) Arterio-venous differences in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Resp Dis 148:867–871

21. Abramson D, Scalea TM, Hitchcock R et al (1993) Lactate clearance and survival following injury. J Trauma 35: 584–589
22. Claridge JA, Crabtree TD, Pelletier SJ et al (2000) Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. J Trauma 48: 8–14
23. Vitek V, Cowley RA (1971) Blood lactate in the prognosis of varius forms of shock. Ann Surg 173: 308–313
24. Bryant Nguyen H, Rivers EP (2004) Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 32: 1637–1642
25. Smith I, Kumar P, Molloy S et al (2001) Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 27(1):74–83
26. Kliegel A, Losert H, Sterz F et al (2004) Serial lactate determinations for prediction of outcome of cardiac arrest. Medicine 83:274–279
27. Yanos J, Wood LD, Davis K et al (1993) The effect of respiratory and lactic acidosis on diaphragm function. Am Rev Respir Dis 147: 616–619
28. Kitakaze M, Takashima S (1997) Temporary acidosis during riperfusion reperfusion limits myocardial infarction in dogs. Am J Physiol. 272:2071–2078
29. Laffey JG, Honan D, Hopkins N et al (2004) Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. Am J Respir Crit Care Med 168: 1383–1390
30. Wiederkerh M, Krapf R (2001) Metabolic and endocrine effects of metabolic acidosis in humans. Swiss Med Wkly 131: 127–132
31. Sun S, Weil MH, Tang W et al (1996) Effects of buffer agents on postresuscitation myocardial dysfunction. Crit Care Med 24: 2035–2041
32. Forsythe SM, Schmidt GA (2000) Sodium bicarbonate for the treatment of lactic acidosis. Chest 117:260–267
33. Kette F, Weil MH (1993) Intramyocardial hypercarbic acidosis during cardiac arrest and resuscitation. Crit Care Med 21(6):901–906
34. Hatherill M, Waggie Z, Purves L et al (2003) Mortality and the nature of metabolic acidosis in children with shock. Intensive Care Med 29(2): 286–291
35. Schiraldi F (1993) Acqua, elettroliti, equilibrio acido-base. Idelson, Naples
36. Idris AH, Staples ED, O'Brien DJ et al (1994) Effect of ventilation on acid-base balance and oxygenation in low blood-flow states. Crit Care Med 22:1827–1834

Chapter 40

Metabolic alkalosis

F. Schiraldi, E. Mirante, F. Paladino

It is beyond the objective of this short review to discuss in detail the many different causes of metabolic alkalosis. Nonetheless, a brief reminder of the pathogenesis and clinical effects of metabolic alkalosis is useful for the following reasons: (1) Metabolic alkalosis is the most common clinical acid-base abnormality observed in hospitalised patients (2) it is sometimes the most sensitive clue indicating a clinical or iatrogenic disorder, and (3) in intensive care unit (ICU) patients, an alkalaemic pH may have further detrimental effects, due to its influence on ventilatory drive and myocardial excitability.

The pathogenesis of metabolic alkalosis is considered under three broad categories:

1. Volume-depleted, chloride-responsive metabolic alkalosis (due to gastroenteric or renal fluid losses)
2. Volume-near-normal/expanded, chloride-unresponsive metabolic alkalosis (due to hyperaldosteronism, Cushing's syndrome, or exogenous steroids or drugs)
3. Post-hypercapnic (due to overzealous correction of chronic hypercapnia)

It is also of interest to note that the apparent bicarbonate space percentage (ABS %) is strictly correlated to the total body water (TBW), as elegantly demonstrated by studies carried out in patients before and after dialysis [1]—modelling a situation that may occur in the ICU setting, where patients undergo continuous fluid manipulation.

The 'expected' bodily response to acute metabolic alkalosis is predictable, but is usually less efficient than other compensatory mechanisms elicited in other, 'simple' acid-base disorders [2, 3].

Indeed, hypoventilation, induced through a chemoreceptor response, requires several hours to restore steady state, as at its maximum there is an increase of 0.5 mmHg PCO_2 for each 1 mEq/l of increased bicarbonate. Most importantly, as a general rule, a PCO_2 60 mmHg is never only due to metabolic alkalosis compensation; thus, in a patient with a history and clinical setting suggestive of metabolic alkalosis, and, for example, a PCO_2 > of 70 mmHg, a superimposed respiratory acidosis should always be suspected.

The renal handling of bicarbonate usually draws upon a tremendous functional reserve in normal subjects. Indeed, the kidneys filter over 4500 mEq of bicarbonate per day, which is normally completely reabsorbed, while roughly 80 mEq of net acid is excreted. If the total daily amount of bicarbonate is doubled, corresponding

to a plasma bicarbonate concentration of 48–50 mEq/l, the kidney could still manage the excretion of excess bicarbonate in order to maintain blood pH near-normal.

Unfortunately, many of the pathological conditions determining this renal alkali 'overload' are also responsible for 'paradoxical' urinary acidification, in order to preserve intravascular filling as the first priority of the body. If any uncertainty persists about central venous pressure (CVP) or more invasive haemodynamic evaluations, a useful diagnostic approach is to measure urinary secreted fraction of chloride, which is directly proportional to intravascular filling and renal perfusion. Whenever the fine servomechanisms of the kidney perceive an underperfusion, fractional chloride reabsorption is maximally elicited, with fractional excretion (FE)(Cl)< 0.7%, or FE(Na)> 1%. If a 24-h urinary collection cannot be obtained, a 'spot' value of urinary chloride ~20 mEq/l can be substituted [4, 5].

Whatever the cause of metabolic alkalosis, there are some common metabolic effects, which are elicited by the blood pH elevation per se; first, metabolic alkalosis shifts the oxyhaemoglobin dissociation curve to the left (Bohr effect). This is only important in acute alkalosis, as it is counteracted within 24 h by a compensatory increase of 2,3-DPG in red cells, which shifts the Hb curve back toward the right.

A second effect is the increased lactate production, resulting in a tentative compensation in pH and an increase in the anion gap. The overproduction is due to stimulation of the enzyme phosphofructokinase (PFK), which catalyses the rate-limiting step in glycolysis, i.e. the conversion of fructose 6-phosphate to fructose 1,6-diphosphate. This metabolic adaptive response usually raises the concentration of lactate in the blood, up to 5 mEq/l [6]. It should be noted that, with respect to Stewart's approach to assessing metabolic derangements, more than just organic acid production contributes to the elevated anion gap frequently seen in metabolic alkalosis. Titration of serum albumin due to the elevated pH results in a higher net negative charge of albumin and thus a greater anion gap [7, 8].

The role of the liver in acid-base regulation

As well-recognised among the experts in liver transplantation, multiple studies have underlined the risk of lactic acidosis during hepatic phases. In contrast, less is known about the role of the liver in maintaining metabolic alkalosis.

After Henderson and Hasselbalch, the concept became accepted that the constancy of the extracellular CO_2 and HCO_3^- concentrations was achieved solely by the equilibrium between ventilatory and renal/metabolic functions. While undoubtedly ventilation has a pivotal role in regulating CO_2 production to control the CO_2 level, the role of the kidney in acid-base balance should be re-evaluated, taking into account that one important function of the liver is to cooperate in maintaining bicarbonate [HCO_3^-] homeostasis in the body. The complete oxidation of proteins generates large amounts of HCO_3^- and thus a tendency toward alkalosis. The oxidation of amino acids produces equimolar amounts of the weak acid NH_4+ and of the strong base HCO_3. Mammals have developed a pathway to eliminate both

compounds during urea synthesis (which is an energy-consuming process):

$$2HCO_3^- + 2NH_4^+ \rightarrow \text{Urea} + CO_2 + 3H_2O$$

In this way, the daily production/excretion of 30 g urea is equivalent to the disposal of 1000 mmol HCO_3^- and 1000 mmol ofNH_4+ [9]; the alternative pathway is direct renal elimination of NH_4+, which produces a correspondent return of HCO_3^- to the blood (renal ammoniagenesis). In other words, increases or decreases of urea cycle flux relative to the rate of protein catabolism will diminish or expand the bicarbonate pool in the body, respectively. In the past, hyperaldosteronism, diuretics abuse, and antacid treatment were considered the main causes of metabolic alkalosis in liver dysfunction. Nowadays, a more satisfying explanation is offered by the concept of systemic pH regulation. By considering the implications of Eq. 1, it is clear that since the cirrhotic liver is unable to synthesise urea, metabolic alkalosis results from impaired HCO_3 disposal. This alkalosis in turn activates liver glutaminase to improve the mitochondrial ammonia production. Thus, ultimately, a near-normal urea level is achieved only in the presence of an alkalaemic pH. If acidosis develops (sepsis, heart failure, etc.), in a patient with encephalopathy and cirrhosis, there could be a worsening of hyperammonaemia. Therefore, any metabolic acidosis demands correction in this setting, even if bicarbonate treatment remains to be confirmed in controlled trials [10].

Metabolic alkalosis and gastric losses

A large volume of gastric fluid may be lost by severe and prolonged vomiting or excessive nasogastric suction (> 1000 ml/day and > 600 mmol HCl/day). Normally, the parietal gastric cells produce and secrete protons into the gastric lumen, thereby acidifying the gastric fluid. The protons are produced by the reaction: $CO_2 + H_2O \rightarrow H+ + HCO_3^-$; the bicarbonate crosses the basolateral cell membrane and enters the extracellular fluid (ECF), such that the gastric content becomes very acid (pH = 1–2).

During vomiting or nasogastric drainage, there is a direct loss of HCl, parietal cells increase the production of protons in the lumen, and the concentration of HCO_3^- increases in the ECF, producing metabolic alkalosis.

The persistence of metabolic alkalosis is due to three main processes:

1. The loss of gastric fluid and electrolytes, which in the early stage are less important because of urinary spillage of the HCO_3^- excess.
2. The loss of Na^+ and K^+ in the urine to maintain electroneutrality following HCO_3^- spillage. This increases the volume depletion and hypokalaemia.
3. Volume depletion leads to stimulation of aldosterone and of $NaHCO_3$ reabsorption in renal tubes, which is accompanied by increased potassium secretion.

Thus, severe hypokalaemia, aldosterone excess and volume depletion maintain metabolic alkalosis and HCO_3^- spillage ceases.

In the urine, the pH may initially be alkaline but then become acidic following the increased reabsorption of HCO_3^- (paradoxical aciduria). This response de-

pends on the extent of volume depletion of the patient; thus, the first goal of therapy is the restoration of adequate plasmatic volume, possibly restoring at the same time the electrolyte pool, which has disappeared [11].

Main systemic effects of metabolic alkalosis

Whatever the pathogenetic mechanisms, several risky consequences can be provoked by metabolic alkalosis per se, with direct effects on the cardiovascular, respiratory, and cerebral systems and secondary effects on body metabolism (Table 1).

Tab. 1 Major effects of metabolic alkalosis

Arterial constriction
Reduction in coronary blood flow
Ventricular life-threatening arrhythmias
Hypoventilation/hypoxaemia
Increased anaerobic glycolysis
Hypokalaemia
Reduced ionised fractions of Ca and Mg
Reduction in cerebral blood flow
Tetany, seizures

Some of these effects are self-limiting, but the increase in arrhythmogenicity in stressed ICU patients and the tendency toward delirium or seizures in neurological patients, whose respiratory compensation is likely to be minimal, could be extremely dangerous. Another side effect of metabolic alkalosis, potentially relevant to the patient outcome, is the increased difficulty in weaning patients from mechanical ventilation, due to the weak inspiratory drive induced by a high liquoral pH [12].

Therapeutic troubleshooting

There are several controversial points regarding the therapeutic strategy of volume-responsive metabolic alkalosis:

1. How will infused fluids be distributed, immediately and later?
2. How will they impact cardiovascular function?
3. The controversial therapeutic role of acetazolamide.

As stated before, patients affected by contraction alkalosis are said to be saline-responsive. Moreover, their neurohormonal homeostasis is deranged due to mechanisms involving renal tubular co-transport [13, 14]. In fact, from a physical/chemical perspective, any metabolic alkalosis is saline-responsive, provided sufficient saline (or any zero SID fluid) can be administered. Whatever the preferred form of crystalloid infusion, it must be kept in mind that after 30–90 min only 20% of the infused fluid will remain in the vessels, while most of it will move to the interstitium. This could become of paramount relevance, for example, in the

presence of concomitant acute lung injury or hypoalbuminaemia. Indeed, a brisk increase in the amount of lung water could affect O_2 diffusion, while reducing pulmonary compliance. Another type of problem relates to the electrolyte composition of the infused fluid. As frequently observed, some types of metabolic alkalosis are associated with hypokalaemia and/or total body potassium deficit [15]. In such cases, correcting the deficit with KCl is the first line therapeutic approach. Interestingly, from the Stewart perspective [16, 17], this practice is similar to infusing HCl; because potassium deficits are predominantly intracellular, so that much of the infused potassium ends up within cells during correction, while the retained accompanying anion, Cl^-, remains extracellular. This ultimately reduces plasma and extracellular SID. In fact, if 100 mmol of potassium are to be restored in 6 h, due to a high risk of life-threatening arrhythmias, and the plasma [K] is to increase by 3 mmol/l, then 75 mmol will cross into the cells, leaving 75 mmol of chloride in the extracellular space, unaccompanied by any strong cation. The SID will thus be lowered by about 5 mEq/l, thereby reducing the metabolic alkalosis.

The correction mechanism may be quite different if colloids are infused. In such circumstances, the intravascular compartment is replenished, blocking the vicious circle of underfilling hyperaldosteronism → HCO_3 resorption plus hypokalaemia → persistence of metabolic alkalosis, which allows the residual dyselectrolytaemia to be corrected. Interestingly, whatever the choice of fluids to be infused, it is mandatory that the electrolyte pattern be re-checked, as any pH correction is bidirectionally linked to the intra/extracellular shift of potassium and calcium and magnesium bioavailability (Table 2).

Tab. 2 Electrolytes bioavailability and blood pH

pH	$[K^+]$	$[Ca^{++}]$	$[Mg^{++}]$
↑	↓	↓	↓
=	=	=	=
↓	↑	↑	↑

Regarding cardiovascular function, two main aspects should be considered. Firstly, as described above, the metabolic alkalosis should be related to the apparent filling of the intravascular and interstitial spaces: the clinical features of dehydration, oliguria, hypotension, low CVP, dynamic evaluation by echo Doppler, etc. should guide the speed and total amount of the infusion. The main problem may be the sometimes unpredictable total cardiovascular compliance of the patient; from this point of view, applying Eq. 1 may provide a rough estimate of the total amount of deficit. Then, about half of the calculated deficit should be infused followed by monitoring the clinical state of the patient, and then reevaluating his or her condition.

$$\text{Total water deficit} = \text{TBW} \times \frac{85 - [\text{OSM}]_P}{[\text{OSM}]_P}$$

The major pitfall of this approach is its inherent limitation in patients with iso/hypotonic dehydration; in such cases, the clinician should rely on the patient's

haemodynamic index, and neurological state, to tailor the infusion strategy [18]. Indeed, some patients may have had fluid and electrolyte losses (renal diseases, diuretics, gastroenteric losses) that were replaced only by compulsive drinking of pure water, so that they are still somewhat dehydrated but have some degree of hypoosmolality.

Even if intravenous fluid administration is tailored to the patient, only dynamic evaluation of cardiovascular parameters could protect him or her from overenthusiastic corrections.

The other relevant aspect is the influence of some electrolyte derangements on myocardial excitability. As depicted in Tables 1 and 2, there is a close relationship between the bioavailability of calcium, magnesium, and potassium and blood pH. As a matter of fact, most of the cardiovascular and neuromuscular effects of alkalaemia are inter-related to the intra/extracellular potassium ratio, and the ionised fractions of calcium and magnesium concentrations. Whenever the blood pH rises, potassium enters the cells (shifting downward the K_e/K_i ratio), and the ionised fractions of calcium and magnesium drop [19, 20]. The total effect of these derangements is that in metabolic alkalosis it is very likely to observe a QT dispersion with some enhancement of the triggered myocardial activity, leading even to an increased risk of life-threatening ventricular arrhythmias [21, 22].

Indeed, in cases of dangerous ventricular arrhythmias in the setting of any form of metabolic alkalosis, it might be better to first correct any possible electrolyte disorder before administering drugs to treat any arrhythmia [23]. Moreover, the therapeutic safety of almost every antiarrhythmic drug is lowered by a deranged electrolyte pattern, as can easily be understood by considering the interference of many drugs with ionic conductances [24, 25] (Fig.1).

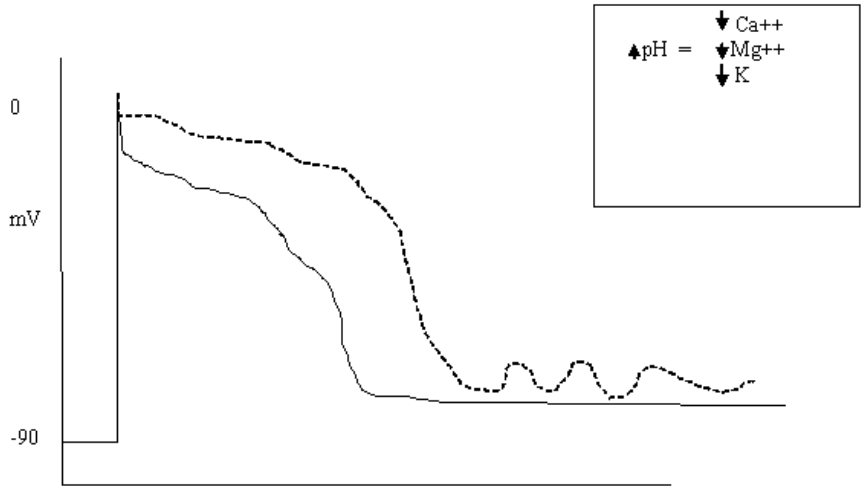


Fig. 1. QT dispersion, metabolic alkalosis, and dyselectrolytaemia

Acetazolamide is a weak diuretic, with marginal effects on urinary bicarbonate elimination. Its use is limited and someway controversial, as, at the same time, it stresses the kidney by forcing bicarbonaturia, while the water balance should be positive and, by definition, opposite to any diuretic effect.

Conclusions

Metabolic alkalosis in the critically ill is mostly found in volume-depleted, slightly hypoperfused patients, or as a temporary side effect of inappropriately fast weaning from mechanical ventilation. Far from being a biochemical bedside curiosity, metabolic alkalosis should be treated using a multifactorial approach. Indeed, there are potentially life-threatening cardiovascular, neurological, and metabolic effects resulting from the elevation of blood pH, particularly if the patient has drug-induced dispersion of the QT interval or a low threshold for seizures. Full monitoring and an integrated diagnostic and therapeutic strategy are always needed in order to avoid further derangements of the patient's fluid/electrolyte pattern, with deleterious effects on survival.

References

1. Tzanatos H, Dalamangas A, Retsa K et al (2005) Relation of interdyalitic water retention with apparent bicarbonate space, HCO3, and pH in hemodialyzed uremic patients. Ren Fail 27:235–238
2. Narins G, Jones ER, Stom MC (1982) Diagnostic strategies in disorders of fluids, electrolytes and acid-base homeostasis. Am J Med 72:469–512
3. Adroguè HJ, Madias NE (1998) Management of life-threatening acid-base disorders. NEJM 338:26–34
4. Adroguè HJ, Madias NE (1998) Medical progress: management of life-threatening acid-base disorders:second of two parts. N Engl J Med 338:107–111
5. Kaplan LJ, Frangos S (2005) Clinical review: Acid-base abnormalities in the intensive care unit. Critical Care 9:198–203
6. Wiederkehr M, Krapf R (2001) Metabolic and endocrine effects of metabolic acidosis in humans. Swiss Med Wkly 131:127–132
7. Haussinger D (1997) Liver and pH regulation.In: Bircher, Benhamou, McIntyre, Rodes (eds). Oxford textbook of hepatology
8. Gabow P (1985) Disorders associated with an altered anion gap. Kidney Int 27:472–483
9. Haussinger D (1990) Nitrogen metabolism in liver: structural and functional organization and physiological relevance. Biochem J 267:281–290
10. Funk GC, Doberer D, Heinze G et al (2004) Changes of serum chloride and metabolic acid-base state in critical illness. Anaesthesia 59(11):1111–1115
11. Kellum JA (2000) Determinants of blood pH in health and disease. Crit Care 4:6–14
12. Holland AE, Wilson JW, Kotsimbos TC et al (2003) Metabolic alkalosis contributes to acute hypercapnic respiratory failure in adult cystic fibrosis. Chest 124(2):490–493
13. Ishihara K, Szerlip HM (1998) Anion gap acidosis. Semin Nephrol 18(1):83–97
14. Lorenz JM, Kleinman LI, Markarian K et al (1999) Serum anion gap in the differential

diagnosis of metabolic acidosis in critically ill newborns. J Pediatr 135(6):751–755
15. Tsuji H, Venditti FJ, Evans JC (1994) The association of levels of serum potassium and magnesium with ventricular premature complexes. Am J Cardiol 74: 232–235
16. Morgan TJ (2005) The meaning of acid-base abnormalities in the intensive care unit: part III – effects of fluid administration. Crit Care 9(2):204–211
17. Funk GC, Doberer D, Heinze G et al (2004) Changes of serum chloride and metabolic acid-base state in critical illness. Anaesthesia 59(11):1111–1115
18. Schiraldi F (1993) Acqua, elettroliti, equilibrio acido-base. Idelson, Naples
19. Sun S, Weil MH et al (1996) Effects of buffer agents on postresuscitation myocardial dysfunction. Crit Care Med 24:2035–2041
20. Zaidenberg G, Mimouni FB, Dollberg S (2004) Effect of bicarbonate on neonatal serum ionized magnesium in vitro. Magnes Res 17(2):90–93
21. Roden DM (1993) Early afterdepolarizations and Torsade de Pointes: implications for the control of cardiac arrhythmias by controlling repolarization. Eur Heart J 14:56–61
22. Schiraldi F, Ferraro P, Paladino F (2000) Physiologic imbalance as a cause of cardiac arrhythmias. In: Atlee J, Vincent J-L (eds) Critical care cardiology in the perioperative period. Springer, Berlin, pp 101–114
23. Kerin N, Somberg J (1994) Proarrhythmia: definition, risk factors, causes, treatment, and controversies. Am Heart J 128:575–586
24. Avkiran M, Ibuki C (1992) Reperfusion-induced arrhythmias. A role for washout of extracellular protons. Circ Res 71:1429–1440
25. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350:1013–1022

Chapter 41

Blood-gas monitoring

R.G.G. Terzi

Why monitor blood gases?

Biochemical reactions of intermediary metabolism that respond for energy production occur within a narrow margin of temperature and acidity of the internal milieu. For this reason, temperature and pH of blood and tissues are kept constant. Normal pH of blood varies from 7.35 to 7.45. Blood pH and its metabolic (bicarbon ate, buffer base) and respiratory (carbon dioxide) components must be known in very ill patients. This evaluation must be obtained as soon as possible in the intensive care unit and, preferably, in the emergency room, because early correction of the underlying process may enhance outcome.

Normal blood gases and acid–base balance

Aerobic metabolism is accountable for most of the H^+ production, approximately 24 000 mM every 24 h. However, around 50–60 mM acid is produced daily as result of incomplete oxidative metabolism and catabolism. These fixed or non-volatile acids, as well as sulphuric and phosphoric acids, are excreted by the kidneys. This renal process is slow but no less important than the respiratory system to maintain homoeostasis of the internal milieu in healthy functioning organisms.

Carbonic acid, a weak acid, is related to carbon dioxide (CO_2), which is constantly produced by aerobic metabolism. Hydrogen ions (H^+) can be eliminated in huge quantities because the lungs act as an open system that can excrete carbon dioxide produced by the dehydration of carbonic acid.

$$H_2CO_3 \leftrightarrows H_2O + CO_2 \uparrow$$

Extreme variations of carbon dioxide or plasma bicarbonate are of little physiological impact if pH is kept within the normal range. For this reason, in acid–base disorders, renal compensation—in order to adjust blood bicarbonate—and respiratory compensation— in order to regulate carbon dioxide—are means to preserve the pH within normal limits.

The Henderson–Hasselbalch equation

The correlation among these variables was first suggested by Henderson in 1908, based on studies of pH determination in body fluids, and by Hasselbalch in 1916, in what has become the classic Henderson–Hasselbalch equation. The Henderson–Hasselbalch equation provides a simple relationship among acids and bases:

$$pH = pK + \log \frac{BASE}{ACID}$$

In the buffering system, bicarbonate/carbonic acid relates the respiratory parameter, PCO_2, the non-respiratory parameter, HCO_3^-, and the overall acidity parameter, pH.

$$pH = pK + \log \frac{HCO_3^-}{(\alpha)\, PCO_2}$$

The constant pK is specific for each buffer system. In the case of the buffer system bicarbonate/carbonic acid, pK is 6.1. In normal conditions, with a plasma bicarbonate of 24 mEq/l and a PCO_2 of 40 mmHg, the pH of blood can be calculated by the Henderson–Hasselbalch equation:

$$pH = pK + \log \frac{24}{0.03 \times 40}$$

$$pH = 6.1 + \log 20$$

As $\log 20 = 1.3$
and $pK = 6.1$

$$pH = 6.1 + 1.3$$
$$pH = 7.4$$

For the calculation of pH, it is necessary to calculate logarithms. In the example given above, the logarithm of 20 is 1.3. Logarithms are not familiar for professionals in biological areas. Siggaard-Andersen, the acid–base master of the Danish acid–base school, developed the alignment nomogram [1], by which, if two variables of the equation are known, it is possible to find graphically several other variables without the need to calculate logarithms. In this nomogram, from the pH and the PCO_2 measured in the blood, it is possible to calculate total CO_2 (TCO_2), plasma bicarbonate ($[HCO_3^-]$) and base excess of blood (BEb). It may be observed that for each pair of pH and PCO_2, BEb will be variable depending on the haemoglobin concentration of blood. As a matter of fact, haemoglobin is the second most important buffer system of the blood (Fig. 1). Observe that in anaemia, given the limited buffer capacity of haemoglobin, acidaemia results in a more negative BEb.

Today these calculations are performed digitally and are embedded in most modern commercially available blood-gas analysis equipment.

It can be appreciated in the Henderson–Hasselbalch equation that acidaemia may result from a reduction of bicarbonate $[HCO_3^-]$, which characterises a metabolic shift, or by an increase in PCO_2, which expresses a respiratory change. On the

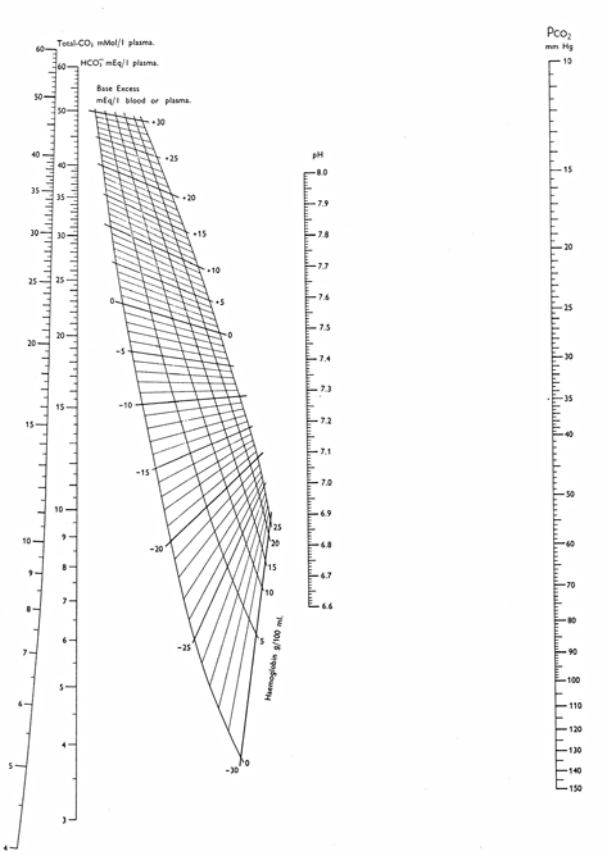


Fig. 1. Siggaard-Andersen alignment nomogram. Note that from any pair of pH (measured with a glass electrode) and PCO_2 values (measured with a Severinghaus electrode), it is possible to determine plasma bicarbonate (HCO_3^-), total CO_2 ($TCO_2 = HCO_3^- + H_2CO_3$) and base excess of blood. If the line of Hb = 5 g% is used in this alignment nomogram, it is possible to determine standard base excess of extracellular fluid

other hand, an increase in pH can be associated with an increase in [$HCO3^-$] or a fall in blood PCO_2.

A similar concept to evaluate deviations from normal acid–base equilibrium was proposed by Stewart [2]. The Stewart approach was proclaimed a revolutionary new approach as, to understand the causes of the acid–base disturbances, only three independent variables have to be analysed: strong ion difference, carbon dioxide partial pressure in arterial blood ($PaCO_2$) and total weak non-volatile acids (A_{TOT}). It was stated that 'many current models for ion movements through membranes will require modification on the basis of this quantitative analysis' [2].

These variables have been validated mathematically and they, supposedly, provide more clinical information than the 'old' variables, such as base excess and

anion gap. Siggaard-Andersen, however, has shown that the approach is anachronistic and the terminology misleading, confusing anions and cations with acids and bases [3]. He stressed that traditional methods of analysis are valid and should not be discarded because the acid–base status of blood and extracellular fluid is equivalent to the hydrogen ion status, not equivalent to the electrolyte status of the plasma.

It is possible that advances in mathematics, computer sciences and basic chemistry may shed light upon old problems. However, at this time, for clinical purposes, the three relevant acid–base quantities are the arterial pH, the arterial PCO_2, and the extracellular base excess. Determination requires an arterial blood sample and a modern pH-blood-gas analyser.

Carbon dioxide

Aerobic cell metabolism consumes oxygen and produces carbon dioxide, which is liberated from the tissues to the blood as gas in physical solution. Under steady-state conditions, normal adults produce approximately 200 ml of CO_2 per minute. The molecular weight of carbon dioxide is 44, so that 1 mol of CO_2 will be equivalent to 44 g, which will occupy 22.4 l. In this way, 22.4 ml correspond to 1 mM of the gas weighing 44 mg. As long as 200 ml of CO_2 are produced per minute, CO_2 production can be calculated:

$$200/22.4 = 9 \text{ mM/min}$$
$$\text{or } 44 \times 9 = 376 \text{ mg/min of } CO_2$$

This value multiplied by 1 440 (the number of minutes in 24 h) results in 12 960 mM or 570 g of CO_2 in 24 h, in steady-state conditions, that is, absolute rest. In normal conditions of active life, the output of CO_2 in 24 h is estimated as 24 000 mM or a little more than 1 000 g of CO_2. As soon as carbon dioxide produced by the tissues enters the bloodstream, a small quantity of CO_2 is hydrated to carbonic acid in plasma.

$$CO_2 + H_2O \rightarrow H_2CO_3$$

The equilibrium of this reaction is strongly dislocated to the left, so that the concentration of the dissolved carbon dioxide in plasma is around 1 000 times greater than the concentration of carbonic acid. When the blood reaches the peripheral capillary bed and becomes venous, the CO_2 concentration increases and the above reaction is forced to the right. A very small quantity of carbonic acid dissociates according to the equation:

$$H_2CO_3 \leftrightarrows H^+ + HCO_3^-$$

Hydrogen ions produced by ionisation of the carbonic acid are buffered by the weak buffer systems of plasma, with a resulting fall in the pH. The bicarbonate ions are then transported by plasma.

However, most of the produced carbon dioxide inflowing in the bloodstream moves through the red cell membrane and, once inside the erythrocyte, is transported in three forms:

1. A minimal fraction continues in physical solution within the red cell.
2. A small fraction of CO_2 produced by tissues combines with plasma proteins to form carbaminic compounds according to the following equation:

$$R\text{-}NH_2 + CO_2 \rightarrow R\text{-}NH\text{-}COO^- + H^+$$

The haemoglobin itself reduces, liberating oxygen and becoming capable of combining with a larger quantity of CO_2.

$$Hb\text{-}NH_2 + CO_2 \rightarrow Hb\text{-}NH\text{-}COO^- + H^+$$

When a molecule of haemoglobin combines with CO_2 it produces a hydrogen ion that is buffered inside the erythrocytes.

3. Most of the CO_2 that enters the erythrocytes is hydrated to form carbonic acid under the action of the enzyme carbonic anhydrase. The acid dissociates and produces bicarbonate and hydrogen ions. These ions are readily removed because haemoglobin buffers most of the hydrogen ions and most of the bicarbonate diffuses out to the plasma. Electric neutrality across the erythrocyte membrane is kept by inflow of calcium ions from the plasma, a phenomenon called 'chloride shift' (Fig. 2).

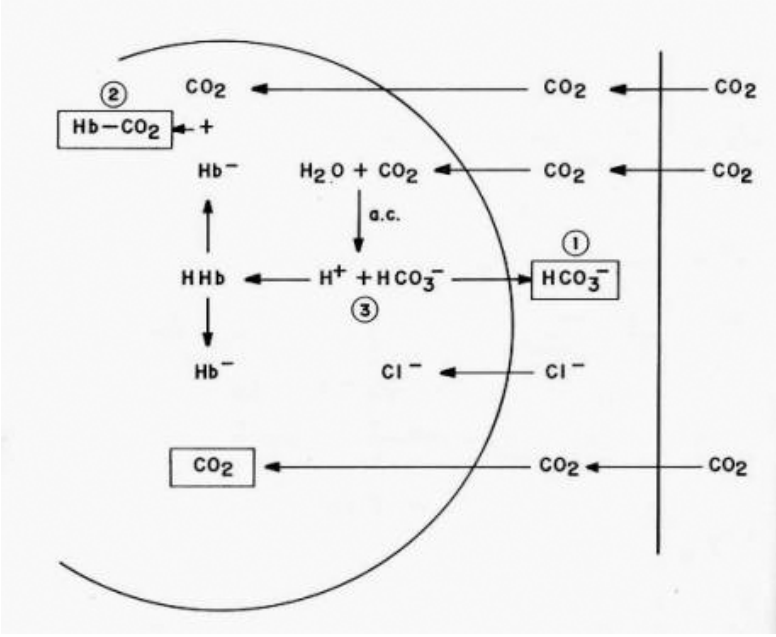


Fig. 2. Carbon dioxide transport in venous blood. A small fraction is transported as dissolved gas. Most of the CO_2 is transported as bicarbonate in plasma

Bicarbonate

A pure sodium bicarbonate solution with added salts may serve as a model of the body fluids. In this model, a decrease or increase in bicarbonate concentration directly reflects the amount of added non-carbonic acid or base, while the bicarbonate concentration is independent of changes in PCO_2.

Bicarbonate is the most important buffer in a biological system at constant PCO_2. The plasma total CO_2 concentration, also called CO_2 content, is only slightly higher than the bicarbonate concentration.

A pure bicarbonate solution is too simple as a model of blood and extracellular fluid. Due to non-bicarbonate buffers in blood, especially albumin and haemoglobin, a change in bicarbonate concentration no longer reflects the total amount of accumulated non-carbonic acid or base (Fig. 3).

This occurs because the bicarbonate concentration is no longer independent of variations in PCO_2. As PCO_2 increases, carbonic acid is buffered by non-bicarbonate buffers and the bicarbonate concentration increases. An elevated bicarbonate concentration may therefore erroneously be interpreted as a metabolic alkalosis when respiratory acidosis is the cause. One approach to solve this problem is to measure the bicarbonate concentration at a standard PCO2: standard bicarbonate.

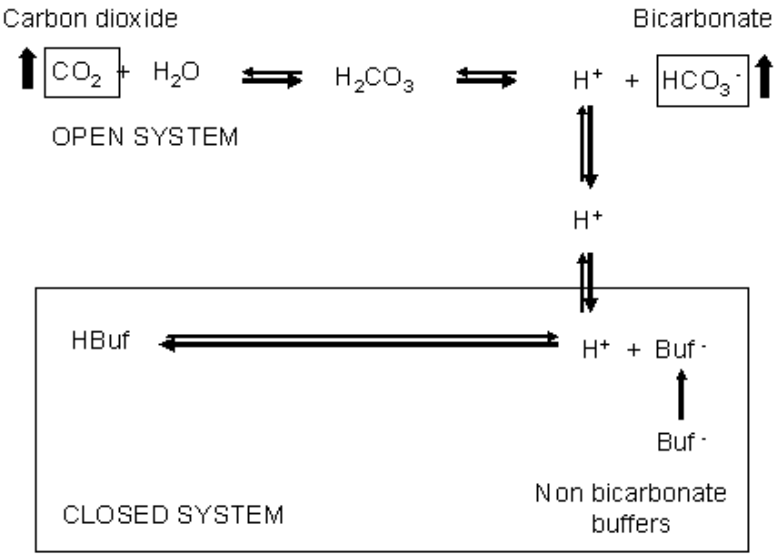


Fig. 3. Carbon dioxide when added to blood increases HCO_3^- because non-bicarbonate buffers are able to neutralise protons

Standard bicarbonate is the bicarbonate concentration of the plasma phase of whole blood equilibrated at 37°C with a CO_2–O_2 gas mixture of PCO_2 of 40 mmHg in appropriately designed apparatus with a pH electrode and tonometer, such as devised by Astrup [4].

CO_2 combining power was a previous attempt introduced by Van Slyke and Cullen [5] to eliminate the respiratory component from the total CO_2 content of plasma measured with the Van Slyke apparatus after the technician had blown expiratory air into the serum.

Finally, another approach was to use the sum of bicarbonate and non-bicarbonate buffer anions: buffer base [6].

Base excess of blood

The introduction of the base excess (BE) concept [7] came to define a pure metabolic parameter, because it corrects variations of bicarbonate induced by respiratory variations and because it takes into account the non-bicarbonate buffer component. This involves titration of blood to a partial pressure of carbon dioxide of 40 mmHg and to a pH of 7.4. Given the technical difficulty in carrying out this titration in the laboratory, BE was originally determined by a curved nomogram idealised by Siggaard-Andersen and Engel [8]. This nomogram was built thanks to the relatively linear relationship between pH and the logarithm of the carbon dioxide partial pressure in blood. This linear relationship permitted Astrup to develop the equilibration technique [7] for the determination of blood PCO_2. With the development of the specific electrode by Severinghaus [9], PCO_2 was measured directly, so that the alignment nomogram of Siggaard-Andersen (Fig. 1) published in 1960 [1] permitted calculation of plasma bicarbonate as well as the base excess of blood.

Today, the base excess parameter is essential for the correct interpretation and for the handling of the metabolic deviations found in clinical practice. The modern blood-gas apparatus reports both the base excess in blood (actual base excess) and the base excess in the extracellular space (standard base excess).

Base excess of extracellular fluid

Whole-blood base excess remains constant when PCO_2 is varied in a blood sample in vitro. However, when the PCO_2 is varied in vivo, by CO_2 inhalation or hyperventilation, not only blood, but all extracellular fluid is equilibrated with the new PCO_2.

Interstitial fluid is not as well buffered as blood because it has no haemoglobin. Remember that haemoglobin is the second most important buffering system of blood. Therefore, when PCO_2 increases in interstitial fluid, the pH tends to decrease more than in blood. Hydrogen ions then tend to diffuse from the interstitial fluid into the blood where they are buffered in the erythrocytes. As H^+ increases in blood, the BE lowers while the plasma BE rises slightly.

A blood sample diluted three-fold (1 + 2) with its own plasma may serve as a model of the extracellular fluid. Base excess of such a model of the extracellular fluid may be calculated using the Van Slyke equation and it now represents the most relevant measure of a metabolic acid–base disturbance. Modern pH-blood-gas analysers calculate the extracellular base excess [3] and present the result with the same ease as they present the actual bicarbonate concentration.

Metabolic acidosis

Metabolic acidosis is the most frequent deviation of the acid–base balance found in intensive care practice. The most frequent causes are:

1. Diabetic ketoacidosis
2. Lactic acidosis
3. Renal acidosis.

Independently of the kind of acid that accumulates in blood (lactic, aceto-acetic, beta-hydroxybutyric, sulphuric, etc.), the important fact is the build-up of protons (hydrogen ions). For this reason, ions of lactate, acetate, beta-hydroxybutyrate, among others, can be grouped under the general denomination of anion (A^-). In metabolic acidosis, there is an increase of H^+ and A^-. Strong acids added to blood are buffered by the bicarbonate/carbon dioxide system. The reaction of a strong acid with sodium bicarbonate generates an inert salt of sodium, which will depend on the type of anion. Carbonic acid is generated as well, which will produce carbon dioxide and water, which will be eliminated by the lungs and by the kidney.

$$H^+A^- + Na^+HCO_3^- \rightarrow Na^+A^- + H^+HCO_3^-$$
$$\downarrow \quad \nearrow$$
$$H_2O + CO_2$$
$$\downarrow$$

Excess strong acids abnormally produced in the body are neutralised by plasma bicarbonate. As bicarbonate is consumed in this reaction, the alkali reserve in blood decreases. The numerator of the Henderson–Hasselbalch equation will be reduced from a normal of 24 mEq/l to something like, let's say, 12 mEq/l.

$$pH = pK + \log \frac{12}{0.03 \times 40} \qquad = pK + \log \frac{12}{1.2}$$

As pK = 6.1
and log 10 = 1.0

$$pH = 6.1 + 1.0$$
$$pH = 7.1$$

In metabolic acidosis pH is diminished, as in the example above, to 7.1. However, the addition of 12 mEq of a strong acid to a litre of a solution without buffering capacity would produce a pH of 1.92, incompatible with life.

Treatment of metabolic acidosis

Treatment of diabetic ketoacidosis includes insulin, hydration and treatment of the immediate precipitating factors. Bicarbonate is not appropriate in patients with pH over 7.1. In cardiac resuscitation interventions, early defibrillation, adrenaline and oxygen therapy improve outcome. Bicarbonate is not appropriate and it is probably deleterious. Bicarbonate has been withdrawn from the recommendations of the American Heart Association since 1986 [14]. Reversible causes of shock should be corrected immediately. Remember that hypovolaemia may not be readily recognised. Improve coronary perfusion with vasoactive drugs. Eradicate eventual foci of infection. Give volume if central venous oxygen saturation is under 70%. Intubation and mechanical ventilation are priorities in the patient in shock. Consider hyperventilation, simulating the response of a healthy person to a similar degree of acidosis (Kussmaul). Hypocapnia with $PaCO_2$ below 25 mmHg is not recommended because of the risks of cerebral ischaemia. If the pH is below 7.1 and it is decided to order bicarbonate, initiate a slow infusion of 10–20 mM/h, to sustain pH above 7.0. In renal insufficiency, institute early dialysis or continuous haemofiltration. If the patient exhibits elevated blood potassium above 7 mEq/l, emergency infusion of sodium bicarbonate (1.0–1.5 mEq/kg) is mandatory to avoid cardiac arrest. Finally, if metabolic acidosis is due to renal loss of bicarbonate or gastrointestinal (GI) fistulae, handling is not controversial and includes infusion of bicarbonate and electrolytes to correct accumulated and ongoing losses.

Metabolic alkalosis

Metabolic alkalosis is an infrequent clinical situation and occurs essentially in two situations:

1. Excessive administration of sodium bicarbonate
2. Losses of chloride by upper GI obstruction.

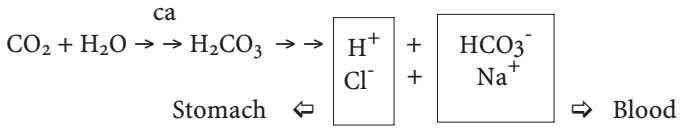
Excessive administration of sodium bicarbonate

This iatrogenic occurrence is due to indiscriminate administration of sodium bicarbonate, particularly without control of blood gases. The literature reports disastrous resuscitation manoeuvres due to excessive administration of bicarbonate leading to acute hyperosmolarity (350 mOsm/l), elevated plasma bicarbonate (over 50 mEq/l) and pH (up to 7.54). The outcome of patients with cardiac arrest is worse when acidaemia is corrected with sodium bicarbonate rather than with hyperventilation.

Upper gastrointestinal obstruction

Vomiting and the loss of hydrochloric acid in upper GI obstruction lead to metabolic alkalosis. Physiopathology of this disturbance starts in the parietal cells of the

stomach. There, under the action of the enzyme carbonic anhydrase (ca), carbonic acid is formed from water and carbon dioxide, which is further dissociated as hydrogen and bicarbonate ions.



Hydrogen and chloride ions migrate from the parietal cell to the lumen of the stomach. For each molecule of HCl formed and lost in the stomach, a molecule of bicarbonate exits from the parietal cell entering the bloodstream. After copious meals, the postprandial increase in plasma bicarbonate is called 'alkaline tide' and tends to resolve when pancreatic and biliary secretions, known to be alkaline, are produced in the following step of digestion. In obstruction of the upper GI tract (tumour of the head of the pancreas or stenosing pyloric ulcer), hydrochloric acid is lost by persistent vomiting and will not neutralise alkaline GI secretions, as well as blood alkalosis. The hypothetical increase of plasma bicarbonate from 24 to 48 mEq/l determines the following alterations in the equation of Henderson–Hasselbalch:

$$pH = pK + \log \frac{48}{1.2} = pK + \log 40$$

As pK = 6.1
and log 40 = 1.6

$$pH = 6.1 + 1.6$$
$$pH = 7.7$$

Alkalaemia in metabolic alkalosis is associated with an excess blood bicarbonate. As in severe metabolic acidosis, there is a respiratory compensation, now with alveolar hypoventilation, expressed by carbon dioxide retention, induced by shallow and slower breaths. However, respiratory compensation in metabolic alkalosis is not as intense and dramatic as seen in metabolic acidosis. Hypokalaemia is a prominent aspect associated with metabolic alkalosis.

Treatment of metabolic alkalosis

Ammonium chloride (NH_4Cl) administration corrects metabolic alkalosis. Once in the bloodstream, NH_4Cl is dissociated into ammonia (NH_3) and hydrochloric acid (HCl). The dose of NH_4Cl is calculated with the equation of Mellemgaard and Astrup [10]:

$$NH_4CI\ (mEq/l\ ) = Weight\ (kg) \times 0.3 \times [BE]$$

Ammonium chloride, when presented in the concentration of 5.3%, holds 1 mEq NH_4Cl per ml solution. It should be stressed that before any surgical intervention aiming to correct the upper GI obstruction, metabolic alkalosis must be corrected as well as the associated hypokalaemia.

Respiratory acidosis

Respiratory acidosis occurs whenever respiratory insufficiency determines alveolar hypoventilation and carbon dioxide retention. There is a substantial difference between the acute and chronic respiratory insufficiency in blood-gas analysis.

Acute respiratory insufficiency

Acute respiratory insufficiency occurs in normal individuals who, for some reason, develop alveolar hypoventilation, such as:

1. Extrapulmonary factors such as dysfunction of the central nervous system caused by traumatic brain injury, cerebral vascular accident and cardiac arrest, as well as dysfunction of the respiratory centre by drugs, such as in attempted suicide or action of strong sedatives in very sick, elderly or sensitive patients
2. Peripheral nervous system diseases, such as polyneuritis, Guillain–Barré syndrome
3. Myasthenia gravis
4. Myopathies
5. Loss of the integrity of the respiratory bellows, as occurs in expressive thoracic trauma, haemothorax, pneumothorax or hydrothorax
6. Mechanical dysfunction of the lungs (reduced pulmonary compliance, increased airway resistance or foreign bodies, tongue falling backwards obstructing the oropharynx in an unconscious patient or glottis oedema.

The list of the causes of acute respiratory insufficiency is extensive. In all of these cases, the result is foreseeable: carbon dioxide retention by alveolar hypoventilation. Increased carbon dioxide will affect the denominator of the Henderson–Hasselbalch equation. There is a direct linear relationship between PCO_2 and carbonic acid (H_2CO_3).

If the partial pressure of carbon dioxide in the arterial blood increases from 40 to 80 mmHg, the pH calculated by the Henderson–Hasselbalch equation would be:

$$pH = pK + \log \frac{HCO_3^-}{H_2CO_3} = pK + \log \frac{HCO_3^-}{(\alpha) \times PCO_2}$$

As (α) = 0.03

$$pH = pK + \log \frac{HCO_3^-}{0.03 \times 80}$$

$$pH = pK + \log \frac{24}{2.4}$$

As pK = 6.1
and log 10 = 1.0

$$pH = pK + \log 10$$
$$pH = 6.1 + 1.0$$
$$pH = 7.1$$

Treatment of acute respiratory insufficiency

The treatments consist in the immediate opening of the airways and installing mechanical ventilation. With this, the partial pressure of carbon dioxide in the arterial blood returns to a normal value of 40 mmHg and pH comes back to normality. It should be emphasised that mechanical ventilation should be instituted immediately; otherwise serious hypoxaemia may result in irreversible central nervous system damage.

Chronic respiratory insufficiency

This situation is found in patients with chronic obstructive pulmonary disease, when the reduced alveolar–capillary interface impairs gas exchange leading to hypoxaemia and, at later stages, to hypercarbia. As in acute respiratory insufficiency, the denominator of the Henderson–Hasselbalch equation is increased. However, as the chronic disease develops insidiously and progressively, a compensation mechanism leads to renal retention of bicarbonate, resulting in increased plasma bicarbonate. In this way, the effect of the increased carbon dioxide on blood pH is attenuated by the action of bicarbonate. Assuming a plasma bicarbonate increase from 24 to 36 mEq/l, in the Henderson–Hasselbalch equation the final pH will be 7.29 instead of 7.1. We must remember that the intermediate reactions of metabolism occur within a narrow band of acidity (pH = 7.4 ± 0.05) and not by isolated parameters such as carbon dioxide partial pressure or plasma bicarbonate.

$$pH = pK + \log \frac{24}{(\alpha) \times PCO_2}$$

$$pH = pK + \log \frac{36}{0.03 \times 80}$$

$$pH = pK + \log 15$$

As pK = 6.1
and log 15 = 1.19

$$pH = 6.1 + 1.19$$
$$pH = 7.29$$

In chronic respiratory insufficiency there is also a biochemical adaptation (increase in haemoglobin) to acclimatise the patient to significant levels of hypoxaemia.

Treatment of chronic respiratory insufficiency

Whenever possible, submitting patients with chronic respiratory insufficiency to mechanical ventilation must be avoided, since it is extremely difficult to wean them from the respirator. Palliative measures, such as oxygen therapy in reduced concentrations (FiO_2 26–28%), expectorants, bronchodilators, respiratory physiother-

apy and inhalations should be aggressively employed. The pH of chronic respiratory acidosis is limited due to the compensatory metabolic alkalosis. The increased plasma bicarbonate and the positive base excess should not be corrected, given the risk of clinical worsening due to acute, intense acidaemia.

Respiratory alkalosis

Respiratory alkalosis occurs in two circumstances:
1. Mechanical hyperventilation
2. Hysterical hyperventilation.

In both circumstances, there is a reduction of the carbon dioxide partial pressure within the alveolus and, consequently, in the arterial blood. For example, if alveolar hyperventilation determines an arterial PCO_2 of 20 mmHg (hypocapnia or hypocarbia), the Henderson–Hasselbalch equation calculates an alkaline pH.

$$pH = pK + \log \frac{HCO_3^-}{(\alpha) \times PCO_2}$$

$$pH = pK + \log \frac{24}{0.03 \times 20}$$

$$pH = pK + \log \frac{24}{0.6}$$

$$pH = pK + \log 40$$

As pK = 6.1
and log 40 = 1.6

$$pH = 6.1 + 1.6$$
$$pH = 7.7$$

One aspect that has been emphasised with respiratory alkalosis caused by mechanical hyperventilation is the possibility of the occurrence of hypokalaemia and potentially fatal ventricular arrhythmia. Although this eventuality is real, it is not observed in clinical practice. Intensive-care patients, when under controlled mechanical ventilation, are deliberately maintained in hypocapnia with the objective of avoiding spontaneous breathing that could interfere with the respirator. Arterial carbon dioxide partial pressures around 30–35 mmHg are perfectly acceptable in patients under mechanical ventilation. In neurological patients, to reduce brain oedema and intracranial pressure, a PCO_2 between 25 and 28 mmHg does not result in cardiac arrhythmia. Anyway, in those patients with chronic respiratory insufficiency and hypercarbia in need of mechanical ventilation, it is recommended that mechanical ventilation be initiated slowly and progressively. Theoretically, aggressive hyperventilation could lead to hypokalaemia with unforeseeable outcomes.

Emotional hyperventilation generally occurs in objectively anxious, young patients with facial blush who complain of a pricking sensation in the perioral region and at the finger tips.

Treatment of respiratory alkalosis

When hyperventilation is induced by excessive mechanical ventilation, adjust the minute volume, unless hyperventilation is necessary, such as in cases of intracranial hypertension.

When hyperventilation is hysterical, in general, a reassuring attitude is sufficient to correct this psychosomatic respiratory alkalosis.

Bicarbonate infusion

For more than 30 years, sodium bicarbonate had been employed routinely for the correction of metabolic acidosis, when the pioneering studies of Mattar et al. in 1974 [11] showed that the administration of large quantities of bicarbonate (mean 180 mEq) to resuscitated patients in cardiac arrest exhibited hypernatraemia, hyperosmolarity, increased lactic acidosis and 100% mortality. More recently, the use of bicarbonate has been questioned in the treatment of metabolic acidosis, not only in cases of anaerobiosis, but also diabetic ketoacidosis. Patients with lactic acidosis by anaerobiosis may have aggravated the oxygen delivery to tissues because the correction of acidosis with bicarbonate displaces the dissociation curve of the haemoglobin to the left. Finally, to neutralise fixed acid with bicarbonate, carbon dioxide is liberated, which cannot be removed in low flow states, thus aggravating the intracellular respiratory acidosis.

$$NaHCO_3 + HLac = H_2O + CO_2 + NaLac$$

The increased blood PCO_2 after administration of bicarbonate is translated into a fall in the intracellular pH (pHi,), because CO_2 crosses the cellular membrane more quickly than the bicarbonate ion. Experimental studies have shown a fall in pHi in liver and muscle of animals, after administration of bicarbonate [12]. In an animal model of lactic acidosis, mortality of the group treated with bicarbonate (89–100%) was higher compared to those treated with saline solution. Animals treated with dichloroacetate had a mortality of 22–33% [13]. The present recommendation of the American Heart Association is not to use bicarbonate in cardiopulmonary resuscitation unless the patient had metabolic acidosis prior to cardiac arrest, has hyperkalaemia or is intoxicated with tricyclic or barbituric agents [14].

Electrolyte changes associated with acid–base imbalances

Electrolytes and residual anions

Every time strong acids invade the bloodstream, bicarbonate is consumed in order to buffer these acids. In this way, calculated residual anions increase due to bicarbonate reduction (Table 1). In this case we call it residual anion acidosis (usually when greater than 12, but certainly when above 20 mEq/l).

Non-residual anion (non-anion gap) acidosis occurs with loss of bicarbonate, by external infusion of acids or by hyperchloraemia.

Table 1. Anions and cations in the blood (mEq/l)

Anions		Cations	
Proteins	15	Calcium	5
Organic acids	5	Magnesium	1.5
Phosphates	2	Potassium	4.5
Bicarbonate	24	Sodium	140
Sulphates	1		
Chloride	104		
Total	151	Total	151

Anions
$Cl^- + HCO_3^- = 128$

Cations
$Na^+ = 140$

Residual anions (anion gap) = 140 – 128 = 12

Increased residual anions (anion gap) acidosis

In metabolic acidosis, with an increase in organic acids, such as lactic and beta-hydroxybutyric acids, or an increase in unexcreted acids due to renal insufficiency, there will be an increase in residual anions. It is possible to calculate the residual anions (anion gap). They represent the difference between the measured cations (mainly sodium) and the measured anions (mainly bicarbonate and chloride).

$$\text{Residual anions} = Na^+ - (HCO3^- + Cl^-)$$

In normal individuals:

$$\text{Residual anions} = 140 - (24 + 104) = 12 \text{ mEq/l}$$

Addition of organic acids to blood is expressed by residual anion values above 16 mEq/l. Situations that can lead to an increase in residual anions are diabetic acidosis, lactic acidosis and renal insufficiency (Table 2).

Table 2. Causes of acidosis with anion gap

Diabetic ketoacidosis	Methanol intoxication
Lactic acidosis	AAS intoxication
Renal acidosis	Paraldehyde intoxication
Uraemia	Glycol intoxication

Non-residual anions hyperchloraemic metabolic acidosis

Metabolic acidosis associated with normal values of residual anions means that the reduction of bicarbonate is necessarily associated with an increase in chloride ions. Hyperchloraemic metabolic acidosis occurs both by excessive chloride gain and by excessive loss of bicarbonate.

Hyperchloraemia may occur with chloride administration such as HCl or ammonium chloride, as well as administration of large quantities of saline solution (Na^+ = 154 mEq/l and Cl^- = 154 mEq/l) that can promote hyperchloraemic acidosis.

Patients with ureterosigmoidostomy frequently develop hyperchloraemic, hypokalaemic metabolic acidosis. Hyperchloraemic metabolic acidosis develops as a result of sodium secretion (in exchange for hydrogen) and bicarbonate (in exchange for chloride), as well as reabsorption of ammonia, ammonium, hydrogen ions and chloride when these segments are exposed to urine. The mechanism that appears to be most responsible for hyperchloraemic metabolic acidosis is excess absorption of chloride and ammonia, which maintains a chronic endogenous acid load. Hypokalaemia and total body depletion of potassium may occur in patients with urinary intestinal diversion. Potassium depletion is probably the result of renal potassium wasting as a consequence of renal damage, osmotic diuresis, and gut loss through intestinal secretion. The patient loses large quantities of potassium because, contrary to chloride, sodium and urea, the potassium ion is not reabsorbed by the intestinal mucosa. Furthermore, the patient with ureterosigmoidostomy frequently presents diarrhoea that can result in additional large losses of potassium.

Gastrointestinal alkali losses occur with fluid loss below the pylorus. Diarrhoea, and loss of biliary or pancreatic secretions can result in hyperchloraemic metabolic acidosis (by fistula, GI suction or vomits in the presence of intestinal obstruction). The loss of bicarbonate by the GI system is compensated by renal retention of chloride, which determines a normal value of residual anions (Table 3).

Table 3. Causes of acidosis without anion gap

GI loss of HCO_3^-	Infusion of NH_4Cl
Diamox	Hyperchloraemia (large saline infusions)
Tubular renal acidosis	Ureterosigmoidostomy

Alterations of potassium

Hypokalaemia is a prominent aspect that accompanies metabolic alkalosis. The cause of hypokalaemia has been attributed to two main mechanisms:

1. Changes across the cellular membrane. Although the cellular membrane is permeable to water and to electrolytes, the Na^+ and K^+ ions inside and outside of the cell have different concentrations. This occurs because the 'sodium pump' actively transports these ions across the cell membrane. The cellular membrane is permeable to hydrogen ions. In metabolic alkalosis the H^+ is reduced in blood and in extracellular fluid, so that H^+ migrates to the interstitial

space out of the cell. In order to maintain the electric balance across the cell membrane, potassium ions migrate from the interstitial space to within the cell, leading to a fall in extracellular potassium and, consequently, to hypokalaemia.

2. Changes in the distal convoluted tubule of the kidney. Under the effect of aldosterone, there is sodium reabsorption in the renal distal convoluted tubule. The reabsorption of sodium is almost complete, particularly in states of hyponatraemia. Each ion of reabsorbed sodium is exchanged by one ion of potassium or one ion of hydrogen.

The preferential elimination of potassium or of hydrogen depends on the acid–base balance and on the availability of these ions in the extracellular space. In cases of alkalosis, where the excess bicarbonate generates lack of H^+ in the extracellular space, the sodium ion is preferentially exchanged for the potassium ion, which is lost in the urine, leading to hypokalaemia. A reduced elimination of hydrogen ions reduces the acidity of the urine and in advanced cases may lead to alkaluria. In states of acidosis, the inverse mechanisms in the equilibrium between potassium and hydrogen lead to hyperkalaemia.

Clinical implications

As states of severe hypo- or hyperkalaemia may result in important clinical manifestations (central nervous system, arrhythmias), it is imperative not to neglect the potassium metabolism when handling acid–base deviations. It is important to remember that, independently of the cause, all states of acidosis are associated with hyperkalaemia and all states of alkalosis are associated with hypokalaemia.

Quick interpretation of arterial blood gases

First step

If the values of the parameters shown in Table 4 are within the minimum and maximum values, the blood gases are considered normal.

Table 4. Normal parameters of the arterial blood gases

	Variable	Normal value	Minimum	Maximum
Blood acidity	pH (units)	7.4	7.35	7.45
Oxygenation	PaO_2 (mmHg)	90	80	100
Ventilation	$PaCO_2$ (mmHg)	40	35	45
Metabolism	HCO_3 (mM/l)	24	22	26
Base excess	BE (mM/l)	0	−5	+5
Oxygenation	SaO_2 (%)	97	94	100

Second step

Verify the pH. If it is below 7.35, the blood is acidaemic. If it is above 7.45, the blood is alcalaemic.

Third step

If the pH is abnormal, identify whether the process is primarily metabolic or primarily respiratory. Verify $PaCO_2$. If it is outside the limits of normality, it will indicate a respiratory cause. If $PaCO_2$ is within the normal range, verify the plasma bicarbonate ($HCO3^-$) and base excess. These parameters will be altered in primarily metabolic disturbances.

1. If the pH is low (acidaemia): $PaCO_2$ will be elevated (defining a respiratory acidosis) or the bicarbonate will be low and base excess will be negative (defining a metabolic acidosis).
2. If the pH is high (alcalaemia): $PaCO_2$ will be low (defining a respiratory alcalosis) or the bicarbonate and base excess will be high (defining a metabolic alcalosis).

Fourth step

Respiratory acidosis (increase in $PaCO_2$) may result from acute or chronic respiratory insufficiency. When acute, it is called uncompensated. When chronic, it is called compensated, because after months or years of renal compensation there is retention and increase in plasma bicarbonate with increased base excess in blood. Variations of pH of the blood are attenuated and are much less intense than in uncompensated respiratory acidosis. To differentiate respiratory acidosis, follow this procedure: calculate the variation of the $PaCO_2$ regarding the normal as 40 mmHg.

Take the following example. Blood-gas analysis reveals a $PaCO_2$ of 50 mmHg. The variation will have been 10 mmHg. In acute respiratory acidosis, pH will vary by 0.08 unit for each 10 mmHg of variation in $PaCO_2$. Therefore, the pH will be 7.32. In chronic respiratory acidosis, for each 10 mmHg of $PaCO_2$ variation, the pH variation will be only 0.03 mmHg. Therefore, the expected pH will be 7.37. This occurs because of the above-mentioned renal compensation. Verify and confirm the eventual compensation, identifying in the arterial blood-gas analysis the elevated levels of bicarbonate and the increased base excess.

Non-invasive evaluation of blood gases

Pulse oximetry

Pulse oximetry (Table 5 (1)) displays in real time the arterial blood oxygen saturation (SpO_2). It may not be exactly the oxygen saturation that relates the arterial

oxygen content to the oxygen capacity, as originally described one century ago. However, is very close to haemo-oximetry measured by the light absorption of several light beams of different wave lengths traversing a blood sample. SpO_2 has become the fifth vital sign in the clinical arena, joining temperature, pulse, blood pressure and respiratory rate. As a matter of fact, it is easier to monitor a critically ill patient with SpO_2, a continuous variable, than with intermittent collections of blood for arterial PO_2. However, we must keep in mind that there are several limitations when we use SpO_2 instead of PaO_2. First, it will not detect cases of hyperoxia because after SpO_2 reaches 100%, arterial PO_2 may be somewhere between 200 and 600 mmHg. Oxygen intoxication may occur without perception, with potential harmful effects, particularly in neonates. Furthermore, pulse oximetry operates with only two wave lengths, is unable to identify carboxyhaemoglobin and cannot read saturations below 60 or in patients in shock. Despite these limitations, pulse oximetry is very helpful in patients with respiratory insufficiency and under mechanical ventilation. It may help expeditiously to adjust the mechanical ventilator during weaning and without the need for repeated arterial puncture.

Table 5. Invasive and non-invasive or minimally invasive variables for blood-gas monitoring

	Variable	Arterial blood	Surrogate	Central venous blood
Blood acidity	pH (units)_	7.4		(3) 7.35
Oxygenation	PaO_2 (mmHg)	90		
Metabolism	HCO_3 (mM/l)	24		(4) 26
Base excess	BE (mM/l)	Zero		(5) 0
Oxygenation	SaO_2 (%)	97	(1) $SpO_2 = 97$	(6) Sat 70%
Ventilation	$PaCO_2$ (mmHg)	40	(2) $PetCO_2 = 35$	(7) $PvCO_2 = 46$

Capnography

The measurement of CO_2 in the expired air directly indicates changes in the elimination of CO_2 from the lungs (Table 5 (2)). Indirectly, it indicates changes in the production of CO_2 at the tissue level and in the delivery of CO_2 to the lungs by the circulatory system. Therefore, capnography constitutes an important non-invasive technique that can monitor CO_2 production, pulmonary perfusion and alveolar ventilation, as well as respiratory patterns. The CO_2 concentration reaches a maximum at the end of exhalation. This maximum concentration is called end-tidal carbon dioxide concentration or tension, depending on whether it is expressed in fractional concentration ($FetCO_2$) or mmHg ($PetCO_2$). End-tidal carbon dioxide reflects CO_2 concentration of alveoli emptying last. The normal value of end-tidal CO_2 is around 5% or 35–37 mmHg. The gradient between the blood CO_2 ($PaCO_2$) and exhaled CO_2 ($PetCO_2$) is usually 5–6 mmHg. $PetCO_2$ can be used to estimate $PaCO_2$ in patients with essentially normal lungs.

In patients with lung disease, the end-tidal CO_2 pressure ($PetCO_2$) can differ from $PaCO_2$ because of ventilation–perfusion (VA/Q) mismatching, and changes

in $PetCO_2$ may be seen with corresponding increase, decrease, or no change in $PaCO_2$, depending on what happens to VA/Q mismatching. A large experimental pulmonary embolus immediately decreased VCO_2 per breath almost entirely due to an increase in alveolar dead space. Alveolar dead space can be estimated by a variable described by Rodger et al. [15]: the steady-state end-tidal alveolar dead space fraction = $(PaCO_2 - PetCO_2)/PaCO_2$.

Central venous blood

Normally, central venous blood is slightly more acid than arterial blood (Table 5 (3)). This is because venous CO_2 is around 46 mmHg (Table 5 (7)) instead of 40 mmHg as in arterial blood. It is true that bicarbonate will be increased as well, because, as previously seen, bicarbonate is transported in venous blood as $HCO3^-$ through the chloride-shift mechanism (Table 5 (4)). However, the increased bicarbonate is insufficient to maintain pH at 7.40. Normal individuals keep the arterial-to-venous differences within narrow limits. The venous-to-arterial gradient of PCO_2 varies from 5 to 10 mmHg. Delta-pH will be around 0.05 and the bicarbonate difference will be around 2 mM/l. No difference is expected between the arterial and the venous blood (Table 5 (5)). Increased differences of these variables will be markers of low perfusion states. The oxygen saturation of central venous blood (Table 5 (6)) is closely related to cardiac output, and it has been pointed out that central venous oxygen saturation below 70% should be corrected without delay in early septic shock.

In conclusion, in the clinical setting, non-invasive blood-gas monitoring has been preferred over arterial punctures. Technology has provided ways to measure both arterial haemoglobin saturation (SpO_2) and end-tidal carbon dioxide ($PetCO_2$). With the availability of non-invasive blood-gas monitoring, patient care and comfort are improved. Overall, non-invasive monitoring can aid in the diagnosis of some pulmonary diseases and monitor patients' progress.

References

1. Siggaard-Andersen O (1963) Blood acid-base alignment nomogram. Scales for pH, pCO2, base excess of whole blood of different hemoglobin concentrations, plasma bicarbonate, and plasma total-CO_2. Scand J Clin Lab Invest 15:211–217
2. Stewart PA (1983) Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 61:1444–1461
3. Siggaard-Andersen O, Fogh-Andersen N (1995) Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand 39(Suppl 106):123–128
4. Jorgensen K, Astrup P (1957) Standard bicarbonate, its clinical significance and a new method for its determination. Scand J Clin Lab Invest 9:122–123
5. Van Slyke DD, Cullen GE (1917) Studies of acidosis. I. The bicarbonate concentration of the blood plasma; its significance, and its determination as a measure of acidosis. J Biol Chem 30:289–346

6. Singer RB, Hastings AB (1948) An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine 27:223–242
7. Siggaard-Andersen O, Engel K, Jorgensen K et al (1960) A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. Scand J Clin Lab Invest 12:172–176
8. Siggaard-Andersen O, Engel K (1960) A new acid-base nomogram. An improved method for the calculation of the relevant acid-base data. Scand J Clin Lab Invest 12:177
9. Severinghaus JW, Bradley AF (1958) Electrodes for blood PO_2 and PCO_2 determination. J Appl Physiol 13:515
10. Mellemgaard K, Astrup P (1960) The quantitative determination of surplus amounts of acid or base in the human body. Scand J Clin Lab Invest 12:187
11. Mattar JA, Weil MH, Shubin H et al (1974) Cardiac arrest in the critically ill. II. Hyperosmolal states following cardiac arrest. Am J Med 56:162–168
12. Graf H, Arieff AI (1986) The use of bicarbonate in the therapy of organic acidosis. Intensive Care Med 12:285
13. Cerra FB (1988) The syndrome of multiple organ failure. In: Cerra FB, Bihari D (eds) New horizon III: cell injury and organ failure. Society of Critical Care Medicine, Fullerton
14. Anoymous (2000) Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.Part 6: Advanced cardiovascular life support. Section 6: Pharmacology II: Agents to optimise cardiac output and blood pressure. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. Circulation 102(Suppl.):I129–I135
15. Rodger MA, Jones G, Rasuli P et al (2001) Steady-state end-tidal alveolar dead space fraction and D-dimer. Chest 120:115–119

INFECTIONS, SEPSIS, MODS

Chapter 42

Epidemiology of infections in the PICU

I. Salvo, F. Izzo, A. Wolfler

Sepsis is a common cause of admission to the intensive care unit [1]. Although morbidity and mortality are significantly lower in paediatric patients than in adults, sepsis is a leading cause of death and disability among newborns and children [2]. A paediatric expert panel of the International Sepsis Forum (ISF) has recently reached a consensus on the definition of sepsis and the clinical approach to sepsis-related diagnoses in children [3]. The benefits of spending resources on sepsis, especially in children, are not in doubt and may improve outcome and quality of care [1].

In Italy, only data concerning diagnosis and mortality rates of patients in paediatric intensive care units (PICUs) have been published [4]. Currently, no data on sepsis-related diagnosis in Italian PICUs are available.

In this chapter, we present a prospective, observational, multicentre study (SISPE, Società Italiana Sepsi Pediatrica) in which a network comprising 26 Italian PICUs was developed. We describe the paediatric population treated in our PICUs and provide information on sepsis-related diagnoses. The data are preliminary and concern results obtained during the first 5 months of the study.

Methods

All of the Italian PICUs ($n = 22$) and most of the mixed adult/paediatric intensive care units that treat children continuously ($n = 4$), for a total of 26 units, were contacted and all accepted to participate in the study.

Seven units were subsequently excluded due to lack or incomplete data. Data were thus obtained from 19 units: 15 PICUs and four mixed adult/paediatric units. The characteristics of all the participating units are described in Table 1.

The study was conducted during 1 year, from March 1, 2004 to February 28, 2005, in all paediatric patients, from newborns (included premature babies up to 32 weeks gestational age and weight $\geq$ 1500 g) to children up to 16 years of age.

The data-collection form consisted of two parts. The first part was for all children admitted to the ICU, and recorded the following data: date of birth, gender, date of admission in ICU, diagnosis on admission, type of admission (medical, election or emergency surgery, trauma), immunocompetence, gravity score at admission (paediatric index of mortality, PIM2) (Table 2), date of discharge, diagnosis on discharge, outcome (survival/death). The second part of the form was

Table 1. Characteristics of the participating centres

	Number of beds	Newborns	Medical	Surgical		
				General	Cardiac	Neurosurgery
1	10		x	x	x	x
2	6	x	x	x		x
3	6	x	x	x		
4	4	x	x			
5	4	x	x	x		
6	2	x	x	x		
7	2		x	x		
8	6	x	x	x	x	x
9	3	x		x		
10	10	x	x	x	x	x
11	6	x	x	x		
12	5	x	x	x		x
13	9		x	x		
14	6	x	x	x		
15	6	x	x	x		
16	12		x	x		
17	8		x	x		
18	4	x			x	
19	2		x	x		

Table 2. Paediatric index of mortality (PIM2) score

1. Systolic blood pressure, mmHg (unknown = 120)
2. Pupillary reactions to bright light (3 mm and both fixed = 1, other or unknown = 0)
3. PaO_2, mmHg (unknown = 0); FIO_2 at the time of PaO_2 if oxygen via ETT or headbox (unknown = 0)
4. Base excess in arterial or capillary blood, mmol/l (unknown = 0)
5. Mechanical ventilation at any time during the first hour in ICU (no = 0, yes = 1)
6. Elective admission to ICU (no = 0, yes = 1)
7. Recovery from surgery or a procedure is the main reason for ICU admission (no = 0, yes = 1)
8. Admitted following cardiac bypass (no = 0, yes = 1)
9. High-risk diagnosis. Record the number in brackets. If in doubt, enter 0.
   [0] None
   [1] Cardiac arrest preceding ICU admission
   [2] Severe combined immune deficiency
   [3] Leukaemia or lymphoma after first induction
   [4] Spontaneous cerebral haemmorhage
   [5] Cardiomyopathy or myocarditis
   [6] Hypoplastic left-heart syndrome
   [7] HIV infection
   [8] Liver failure is the main reason for ICU admission
   [9] Neurodegenerative disorder
10. Low-risk diagnosis. Record the number in brackets. If in doubt, enter 0.
   [0] None
   [1] Asthma is the main reason for ICU admission
   [2] Bronchiolitis is the main reason for ICU admission
   [3] Croup is the main reason for ICU admission
   [4] Obstructive sleep apnoea is the main reason for ICU admission
   [5] Diabetic ketoacidosis is the main reason for ICU admission

completed only for patients who were admitted for sepsis or who developed sepsis during their stay in the ICU. It recorded:

- Sepsis-related diagnosis (sepsis, severe sepsis and septic shock) and multiple organ dysfunction (MODS), as defined according to the criteria published by Proulx et al. in 1996 [5] (Tables 3, 4)
- Nature of infection (certain/presumed): a 'certain diagnosis' needed to be supported by documented infection upon cultural examination, while 'presumed diagnosis' meant the presence of clinical, biochemical, or radiological signs of infection.
- Site of infection and aetiology of infection, if well-known
- Blood exams, specifying values at admission, discharge, and worst values for parameters such as WBC, platelets, PCR, temperature, PT, PTT, ATIII, protein C activity
- Enrolment date and evolution of infection and of sepsis-related diagnosis
- Antibiotic therapy and rationale of the therapy (prophylactic, empirical, or guided)

A Microsoft Access database was created and provided together with a detailed instruction manual to all ICUs. Use of the database was discussed in a meeting before the start of the study and involving all ICUs chiefs. A preliminary test-patient allowed the reliability of the collected data and the correct functioning of the system to be verified. Collected data were sent to the coordinating centre (Ospedale dei Bambini Buzzi, Milano) and acquired with a specific software. At the end of the study, all ICUs were visited by one of the study coordinators to confirm and complete data collection (especially for sepsis-related diagnosis).

Table 3. Proulx criteria for sepsis-related diagnosis in children

SIRS: Defined by the presence of at least two of the following criteria:

- Temperature more than 38°C rectal (37.8°C oral, 37.2°C axillary) or less than 36.0°C rectal (35.8°C oral, 35.2°C axillary)
- Heart rate more than 90th percentile for age
- Tachypnoea with a respiratory rate more than 90th percentile for age, or hyperventilation, as indicated by $PaCO_2$ less than 32 mmHg
- WBC count 12 000 cells per mm^3 or < 4000 cells per mm^3 or more than 10% immature (band) form

Sepsis: Characterised as a SIRS caused by an infection (any positive culture obtained immediately prior to or during admission to the paediatric ICU, showing bacterial, viral, or fungal pathogen and/or clinical evidence of infection, e.g. chickenpox or purpura fulminans)

Severe sepsis: Characterised by the occurrence of sepsis plus one of the following criteria:

- Decreased level of consciousness (Glasgow Coma Score < 15 without disease of the CNS)
- Arterial blood lactate level more than 1.6 mEq/l or venous blood lactate more than 2.2 mEq/l
- Urine output, measured with an urinary catheter, less than 1 ml/kg/h for 2 consecutive hours

Septic shock: In the presence of hypotension with two distinct measurements of blood pressure less than the third percentile for age, after administration of 20 ml/kg or more of crystalloid or colloid plus:

- The requirement of inotropic or vasopressor support (excluding dopamine < 5 μg/kg/min) or
- Any of the previously defined diagnostic criteria for severe sepsis

Table 4. Proulx's criteria for a diagnosis of multiple organ dysfunction (MODS) in children

MODS is defined as the simultaneous dysfunction of two organs.

1. Cardiovascular system
   - Systolic BP < 40 mmHg for patients younger than 12 months or < 50 mmHg for patients 12 months or older
   - Heart rate < 50 or more than 220 beats/min for patients younger than 12 months, or < 40 or > 200 beats/min for patients age 12 months or older
   - Cardiac arrest
   - Serum pH < 7.2 with a normal $PaCO_2$
   - Continuous IV infusion of inotropic agents to maintain blood pressure and/or cardiac output (dopamine < 5γ/kg/min was excluded)
2. Respiratory system
   - Respiratory rate > 90 breaths/min for patients younger than 12 months or > 70 breaths/min for patients 12 months or older
   - $PaCO_2$ more than 65 mmHg
   - PaO_2 less than 40 mmHg in the absence of cyanotic congenital heart disease
   - Mechanical ventilation (for > 24 h in a postoperative patient)
   - PaO_2/FiO_2 < 200 in the absence of cyanotic congenital heart disease
3. Neurologic system
   - Glasgow Coma Score < 5
   - Fixed dilated pupils
4. Haematologic system
   - Haemoglobin < 5 g/dl
   - WBC count < 3,000 cells per mm^3
   - Platelets count < 20,000 cells per mm^3
   - D-dimer more than 0.5 μg/ml with prothrombin time > 20 s or partial thromboplastin time > 60 s
4. Renal system:
   - Serum urea nitrogen value of 100 mg/dl, or more
   - Serum creatinine concentration of 2.0 mg/dl or more, in the absence of preexisting renal disease
   - Dialysis
5. Hepatic system:
   - Total bilirubin level more than 3 mg/dl, excluding icterus due to breast feeding
6. GI system: Gastroduodenal bleeding and one of the following criteria when believed by the treating physician to be the result of gastroduodenal bleeding:
   - Drop in the haemoglobin level of 2 g/dl or more over 24 h
   - Blood transfusion
   - Hypotension with blood pressure less than third percentile for ages
   - Gastric or duodenal surgery
   - Death

Results

The study consisted of 1415 patients, with a male/female ratio of 1:5. The average age in months was 37.4 (median 10), while the mean length of stay was 5 days (median 1.5). Table 5 list the characteristics of the patients at each centre.

Table 5. Patient characteristics

Centre	Number of admission	Age (month)s	Length of stay (days)	PIM2 (%)	Mortality (%)
1	118	49.58 (26.5)	3.36 (1)	2.8	0.8
2	95	37 (8)	5.69 (1)	12.6	9.4
3	47	24.7 (0)	7.14 (5)	8.1	12.7
4	143	0 (0)	7.6 (5)	2	0
5	110	30.75 (10)	2.8 (1)	2.3	0
6	30	49.97 (33.5)	6.2 (3)	4.3	3.3
7	20	42.39 (30)	5.5 (2)	2.6	0
8	112	17.25 (1)	8.9 (5)	5.5	5.3
9	46	20.93 (7.5)	3.68 (2)	1.4	6.5
10	152	32.21 (3.5)	5.68 (3)	8.8	4.67
11	88	35.83 (16)	7 (2)	4.7	4.55
12	91	47.38 (19)	2.4 (1)	3.9	4.49
13	58	39.94 (21)	3.65 (2)	14.9	7.69
14	89	38.18 (9)	5.87 (4)	7.2	9.78
15	102	65.96 (43)	2.63 (1.5)	6	2.97
16	61	54.18 (33.5)	9.36 (5.5)	7.7	13.56
17	30	37.7 (10)	8.3 (4)	13.2	27.59
18	11	7.3 (3)	5.53 (4)	4.1	9
19	12	60.48 (53)	3.81 (3)	8.9	0
Total	1415	37.4 (10)	5.1 (1.5)	6.1	5.16

Overall, surgical patients accounted for 42.4%, medical patients for 51.5%, and trauma patients for 5.6% of all patients. Surgical patients were further divided according to general, cardiac, neurosurgery, and transplant.

The PIM 2 score within the first hour of admission was 6.2%, with an observed mortality of 5.2% (70 children). Medical patients had a mean length of stay of 6.7 days and recorded the highest mean PIM 2 score (8.8%) as well as the highest mortality (58 children, 82.8% of all deaths).

The incidence of a sepsis-related diagnosis (sepsis, severe sepsis, septic shock) was 10.1%. In this group of patients, sepsis accounted for 6.9%; severe sepsis for 1.4%, and septic shock for 1.8%. The observed mortality was 2% for sepsis, 35% for severe sepsis, and 53.8% for septic shock. Table 6 shows the incidence of a sepsis-related diagnosis at each centre.

Of the 70 children who died, the largest group was represented by oncology patients (15 children, 21.4%). The second leading cause of death was infection, with an overall mortality rate of 14.3% (10 children).

Concerning septic patients, the most frequent site of infection was the lung, followed by bloodstream infection, and central nervous system infection. Lung infection was recorded in 65 patients (46.4%). Only two of these patients died, and both were immunodeficient. Bloodstream infection accounted for 29 children (20.7%) and nine deaths (including 3 immunodeficient patients). CNS infection was diagnosed in 21 patients (15%) with six deaths (none of these patients were immunodeficient). The site associated with the highest mortality rate site was the central nervous system. Meningitis was the cause of six of the ten deaths due to sepsis; these six children had no other disease.

Table 6. Incidence of sepsis categories per centre

Centre	Sepsis category (%)		
	Sepsis	Severe sepsis	Septic shock
1	9.3	1.7	0.8
2	0	0	3.15
3	4.2	2.1	8.5
4	0	0	0
5	9	2.7	0.9
6	36	3	3
7	20	0	0
8	8.2	4.5	
9	0	0	0
10	5.4	0.6	1.3
11	15.9	1.1	3.4
12	2.2	0	5.5
13	0	0	0
14	11.2	3.3	4.5
15	0.9	0	0.9
16	21.3	1.6	1.6
17	6.6	6.6	0
18	0	0	0
19	9	0	0

Discussion

This report represents the first Italian study on the incidence of sepsis-related diagnoses in the PICU. The patient characteristics are similar to those published in other studies with respect to age, number of postoperative paediatric patients, and length of stay in the PICU [6]. Severity score on admission, measured as the PIM 2 score, predicted a number of deaths comparable to the overall mortality observed. The PIM 2 score was previously tested in Australia and New Zealand, i.e. the two countries where the score was developed, and was found to be the most accurate severity score and the most suitable mortality prediction model [7]. Our results show that this score also performed well in our population. Moreover, the ease in collecting the necessary data and the small number of variables make it a good instrument to use in comparing different PICUs.

Our data show a lower incidence of sepsis diagnosis than that reported by other authors: 10.2% vs 23%, published by Leclerc et al. [8], and 29%, published by Proulx et al. [5], even with the same sepsis definitions and criteria. While these data are preliminary and cover only 5 months, from March to July, they show significant differences among units (see Table 1) regarding number of beds and number of admissions, even though the patient populations were homogeneous for age and length of stay in the PICU.

Mortality due to severe sepsis and septic shock appears to be similar to the rates reported in other European studies (35% for severe sepsis and 67% for septic shock in France) [8] but higher than in North American studies, which reported a decrease in mortality over the last 20 years. In fact, at selected centres, mortality in

previously healthy children was close to zero. This seems to confirm the need for a critical look at our treatment practices [1].

Finally, our data show that severe sepsis and septic shock caused by meningococcal infection represent is associated with a high risk of mortality and with a poor prognosis even in previously healthy patients.

SISPE Study Group

The SISPE Study Group consists of the following individuals:

P Vitale, A Conio (Ospedale Sant'Anna, Turin); G Ottonello (Ospedale Gaslini, Genua); C Gallini, S Mella (Ospedale Sant'Antonio e Biagio e Cesare Arrigo, Alessandria); E Lupa, F Ferrero (Ospedale Maggiore della Carità, Novara); E Zoia, A Mandelli (Ospedale Buzzi, Milan); L Napoletano, S Leoncino (Clinica De Marchi, Milan); E Galassini (Ospedale Fatebenefratelli, Milan); A Baraldi, S Molinaro (Spedali Civili, Brescia); P Santuz (Ospedale Civile Borgo Trento, Verona); P Cogo, A Pettenazzo (Ospedale Civile T.I. Pediatrica, Padua); L Meneghini, F Giusti (Ospedale Civile Anestesia, Padua); A Sarti (Ospedale Burlo, Trieste); E Iannella, S Baroncini (Ospedale Sant'Orsola Malpigli, Bologna); M Calamandrei, A Messeri (Ospedale Meyer, Florence); M Marano, C Tomasello (Ospedale Bambin Gesù DEA, Roma); A Onofri, M Ferrari (Ospedale Bambin Gesù Anestesia, Rome); M Piastra, E Caresta (Ospedale Gemelli, Rome); A Dolcini (Ospedale Santo Bono, Naples); C Rovella, A M Guddo (Ospedale G A Di Cristina, Palermo); M Astuto, N Disma (Ospedale Policlinico, Catania); D Salvo, D Buono (Ospedale San Vincenzo, Taormina)

References

1. Ruokonen E, Pettila V (2005) Surviving Sepsis campaign — outcome of severe sepsis can be improved by revising procedural standards. Acta Anaesthesiol Scand 49:597–598
2. Carcillo J (2005) Reducing the global burden of sepsis in infants and children: a clinical practice research agenda. Pediatr Crit Care Med 6(3): S157–S164
3. Randolph A (2005) The purpose of the 1st International Sepsis Forum on Sepsis in Infants and Children. Pediatr Crit Care Med 6(3):S1–S2
4. Bertolini G, Ripamonti D, Cattaneo A et al (1998) Pediatric risk of mortality: an assessment of its performance in a sample of 26 Italian intensive care units. Crit Care Med 26(8):1427–1432
5. Proulx F, Fayon M, Farrell CA et al (1996) Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest 109:1033–1037
6. Gemke R, Bonsel G (1995) Comparative assessment of pediatric intensive care: a national multicenter study. Crit Care Med 23:238–245
7. Slater A, Shann F, Pearson G (2003) PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 29:278–285
8. Leclerc F, Leteurtre S, Duhamel A et al (2005) Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. Am J Respir Crit Care Med 171: 348–353

Chapter 43

Strategy in the treatment of secondary peritonitis

R. Hahn, S. Stortecky, C. Spiss

Despite advances in diagnosis, surgery, antimicrobial therapy and intensive-care support, severe secondary peritonitis remains a potentially fatal affliction. Reported mortality rates range from 30 to 60%, which is due to the fact that different entities are summarised under the term peritonitis. Clearly, patients with an anastomotic disruption will face a different outcome from those with perforated peptic ulcer [1].

Different operative strategies such as planned re-laparotomies and laparotomies on demand have been introduced to improve the outcome. In the past decades these techniques have been evaluated in patients suffering from infected necrotising pancreatitis or from severe bacterial peritonitis following perforation or anastomotic disruption of the digestive tract. All surgical effort follows straight goals: primary source control, cleaning of the peritoneal cavity, prevention of persistent or recurring peritonitis.

In recent years there has been a well-accepted consensus on the treatment of severe sepsis [2]; the existing evidence for several problems, such as haemodynamic support or sedation and analgesia in sepsis has been compiled [3, 4].

Most patients suffering from secondary peritonitis can be treated successfully with a single operation. Others, with diffuse severe peritonitis, need further surgical interventions. The reported mortality rate for patients who need at least two laparotomies is about 15% (Krenzien and Lorenz 1990, 20–40%; Teichmann 2000, 10–15%; Reith 1997, 15–20%, Brügger 1999, 10%) [5–8].

Open-abdomen management is necessary in some of these patients, as it is not possible to close the abdomen or because it is the chosen strategy for a certain patient.

We will report our experiences in 58 patients suffering from severe secondary peritonitis with open-abdomen management. With all the restrictions of retrospective analyses, we were able to demonstrate that comparable groups of patients showed a different clinical outcome.

The purpose of this study was to compare different treatment regimens for open-abdomen management following severe secondary peritonitis from the viewpoint of the intensivist. As our data show that some treatment strategies are more favourable than others, we especially emphasise the role of open management with vacuum technique and abdominal dressing.

Pathophysiology

The abdominal cavity and the intra-abdominal organs are lined by a mesothelial membrane, the peritoneum. It covers the abdominal viscera and creates a potential space—the peritoneal cavity. The peritoneum measures about two square meters [1].

In healthy adults the peritoneal cavity contains less than 100 ml of peritoneal fluid, with a protein content of 30 g/l and a cell count of less than 300/µl, mainly scattered macrophages and lymphocytes.

During inflammation the peritoneal fluid content increases significantly, protein content can double, containing cytokines and after influx of inflammatory cells, particularly monocytes and neutrophils, the cell count can increase up to 1 000/µl [9].

The activation of the inflammatory response results in accelerated generation of fibrin, which polymerises to form adhesions and the capsule of abscesses [10, 11].

During peritonitis there is a high gradient of mediators and bacterial toxins between the peritoneal cavity and the systemic circulation due to the barrier function of the peritoneum.

Finally, the barrier function of the gut is reduced and bacterial translocation enhances or initiates further clinical problems.

The surgical therapy of peritonitis is based on three principles: (1) elimination of the source, (2) reduction of bacterial contamination and (3) prevention of persistent or recurrent intra-abdominal infection [12].

Classification and stratification

Peritonitis denotes inflammation of the peritoneum from any cause. It may be regarded as the localised equivalent of the systemic inflammatory response seen after any trigger of inflammation. Intra-abdominal infection denotes peritonitis caused by bacteria (e.g. a local inflammatory process initiated by bacteria and their toxins). Intra-abdominal abscess is an intra-abdominal infection that has been confined within the abdominal cavity [13].

Intra-abdominal infection is defined as an inflammatory response of the peritoneum to micro-organisms and their toxins, which results in purulent exudate in the abdominal cavity. Conditions without such peritoneal inflammatory response, in which contamination has occurred but infection is not established (e.g. early traumatic bowel perforation), or in which the infectious process remains contained within a diseased, but resectable, organ (e.g. gallbladder or appendix), represent 'simple' forms of peritonitis, easily cured by an operation and not requiring prolonged additional antibiotic therapy [14].

Many attempts have been made to classify peritonitis in general, and secondary peritonitis in particular, which include a large variety of different pathological conditions ranging in severity from a local problem such as gangrenous appendicitis to a devastating condition such as diffuse postoperative peritonitis due to a

dehiscence of a gastro-duodenal anastomosis. A simplified classification of peritonitis is presented in Table 1. It differentiates between the relatively rare forms of primary peritonitis, which usually respond to medical treatment; the commonly occurring secondary peritonitis that mandates surgical intervention; and tertiary peritonitis, which often does not respond to any treatment [14].

Monitoring of the clinical course: severity marker

One often faces the situation that patients starting with similar conditions experience different outcomes. It might be assumed that identification of those with a worse outcome could improve their clinical course. Several outcome markers have been tested for their importance in predicting an unfavourable outcome in patients with secondary peritonitis. We will discuss two scoring systems: the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sepsis-Related Organ Failure Assessment (SOFA) score. The first defines the reaction of the body to a certain stimulus; the second scores the degree of organ dysfunction in five organ systems. The Mannheimer Peritonitis Index (MPI) is an intraoperative macropathological scoring system, which also has been demonstrated to have a predictive value for patient outcome [15, 16]. Finally, the predictive value of acute-phase proteins in predicting patient outcome will be discussed [17].

Acute Physiology and Chronic Health Evaluation II

The multifaceted nature of abdominal surgical infections makes it difficult to define precisely the disease and to assess its severity and therapeutic progress. The mortality of intra-abdominal infection is related mainly to the severity of the patient's systemic response and his or her physiological reserves, best estimated using the APACHE II scoring system [18]. The APACHE II score has been validated prospectively in a large number of patients and has been adopted by the Surgical Infection Society as the best available method of risk stratification in intra-abdominal infection [19].

Twelve physiological variables, five chronic diseases, age and admission state of the patient are used for calculation. It reaches a sensitivity of 50–70% and a specificity of 90% to predict the outcome for a certain patient group. It has been approved among others by the second European consensus conference for intensive-care medicine [20].

Sepsis-Related Organ Failure Assessment score

In the SOFA score, failure of six organs (lung, coagulation system, liver, cardiovascular system, central nervous system and kidney) are coded from 0 (normal) to 4 (most abnormal). Therefore, the highest possible score is 24 (Table 2). We used the SOFA score besides APACHE II to define organ failure in our patients [21].

It has been shown that after surgery for postoperative peritonitis, the postoperative time course of the SOFA organ failure score was significantly different between patients with or without intra-abdominal persistent sepsis. The lack of improvement of SOFA scores after 48 hours and confirmed at day 3 or day 4 suggests persistent abdominal sepsis and may support the need for surgical re-exploration [22].

Mannheimer Peritonitis Index

The MPI was developed in Germany. It is a score that has proven to be a valuable outcome marker [23–25]. It consists of eight variables, including age, sex, duration of peritonitis before operation, organ dysfunction, and also quality of exudates (faecal, purulent) and source of infection (Table 3). The severity of peritonitis is graded into three classes: MPI < 21 (mortality approx. 2.5%), MPI 21–29 (mortality approx. 23%), MPI > 29 (mortality approx. 60%). An MPI of 26 and above is defined as severe peritonitis. In 2003 Billing reported a mortality of 41% in patients with an MPI above 29 [16].

Protein C

Karamarkovic carried out a prospective study enrolling 60 patients to evaluate the predictive value of protein C as a marker of outcome [17]. Protein C was of excellent predictive value and achieved a sensitivity of 80% and a specificity of 87.5% in discriminating survivors from non-survivors within the first 48 hours of the study (AUC –0.917; $p < 0.001$). However, evidence concerning protein C is very limited, as there are no further studies available.

Intra-abdominal pressure

Patients with severe peritonitis often face massive fluid substitution during the initial resuscitation due to third-space loss. The intra-abdominal oedema and the gut distension lead to a marked increase of the intra-abdominal pressure. Increased intra-abdominal pressure can cause increased inspiratory pressure in ventilated patients, renal failure and haemodynamic deterioration. The syndrome is well known as abdominal compartment syndrome and has gained interest in recent years. Decompressive laparotomy is the only effective treatment to treat this life-threatening condition.

In patients who are likely to have increased intra-abdominal pressure, the routine measurement of intra-abdominal pressure is of high importance. The standard method for assessing the intra-abdominal pressure is intravesical pressure measurement. It is a single time measurement with a high variation coefficient in repeated measurements [26].

In our institution we had good results with an intra-gastric probe (ACM; Spiegelberg-System, Spiegelberg, Hamburg, Germany) for online measurements.

We compared both methods in patients at risk for increased abdominal pressure and found a good correlation with an acceptable mean bias and a small variation coefficient using both systems and in repeated measurements [27].

Management

The initial management of the patient with intra-abdominal infection is resuscitation and physiological organ system support, combined with appropriate monitoring. A fast surgical evaluation and intervention are essential if possible.

Early fluid requirements may be substantial because of considerable third-space fluid loss into the peritoneal cavity, the retroperitoneum, and the lumen of the gastrointestinal tract. An adequate early goal-directed therapy leads to a pronounced reduction of mortality [28].

For patients with extensive intraperitoneal or retroperitoneal inflammation and significant early fluid requirements, monitoring of bladder pressures to detect an abdominal compartment syndrome should be performed.

Systemic antibiotics are administered based on knowledge of the probable composition of the infecting flora. For first-line treatment we follow local and international guidelines as published by the Infectious Diseases Society of America or the Paul Ehrlich Society of Chemotherapy in Germany. Coverage is directed against aerobic Gram-negative organisms and anaerobes when the source of contamination is unknown; however, if the infection is known to arise from the upper gastrointestinal tract (for example, as a result of a perforated ulcer), coverage directed against aerobes alone is adequate.

The selection of an empiric broad-spectrum antibiotic regimen is guided by considerations of patient-specific toxicity, cost, and local patterns of antimicrobial resistance; the many available regimens are of largely equivalent clinical efficacy. The optimal duration of therapy is unknown.

When source control has been effective, the role of antibiotics is a purely adjuvant one, and the course can be restricted to 5–7 days [14]. The key challenge is the surgical source control. If it is possible to contain the source in the first operation, patients face a favourable outcome (mortality 10–19%) [16].

All together the management of the patient with severe peritonitis follows the concepts presented in the Surviving Sepsis Campaign. In 2003 experts from 11 international organisations developed guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician [2]. Evidence-based recommendations were made regarding many aspects of the acute management of sepsis and septic shock.

The campaign points out the importance of source control and includes early goal-directed therapy [28].

Initial presentation

The patient with intra-abdominal infection presents with pain, abdominal tenderness, fever and gut paralysis and signs of general illness. Of note, only 50% of the patients have fever [9]. Most important is a timely evaluation through a surgeon. In this first period the principles of the early goal-directed therapy should be followed and be accompanied by an adequate analgesia.

An early surgical intervention in critically ill patients should not be delayed by extended diagnosis.

Sepsis

Intra-abdominal infection regularly leads to a systematic inflammatory response (Table 4), translocation of bacteria and endotoxins. As the reason for the systemic inflammatory response is an abdominal infection, the criteria for sepsis are fulfilled [29].

In our group of patients described below, 72.5% needed vasopressor support (55% noradrenaline above 0.1 µg/kg/min) on the first day of open management of the abdomen.

Surgical therapy

The surgical therapy of severe peritonitis is based on three major principles: (1) elimination of the source of infection, (2) reduction of bacterial contamination, and (3) prevention of persistent or recurrent intra-abdominal infection [12].

Source control

Traditionally, severe peritonitis has been approached by performing a midline laparotomy to identify and eliminate the source of peritonitis. It allows the surgeon to perform a complete cleansing of the peritoneal cavity in order to reduce the bacterial contamination. Ongoing contamination is controlled by closure, exclusion or resection of the infective focus. If source control is established during the first operation, the patient faces a favourable outcome [12, 16].

Controversy exists regarding the surgical management of the left colon. The general concept is that a primary anastomosis in a strongly contaminated peritoneal cavity is at high risk of dehiscence. So the perforated segment is resected, the proximal end exteriorised as an end-colostomy, and the distal part is simply closed (Hartmann's procedure) or transformed in a mucous fistula.

The question of which patients benefit from primary anastomosis, avoiding a second laparotomy, has been addressed in various trials, which show no clear results. Therefore, this decision is at the discretion of the individual surgeon.

Reduction of bacterial contamination

The second goal is reached by aspiration of all gross purulent exudates and removal of faecal debris or food particles. Pelvic regions, paracolic gutter and subphrenic spaces must be opened and debrided.

Intraoperative peritoneal lavage is performed by most surgeons; the addition of antibiotics to the lavage solution appears to be without clear benefit. Antiseptics are avoided because of possible toxic side-effects [30].

Prevention of persistent or recurrent infection

Postoperative peritoneal lavage, intra-abdominal drains and re-laparotomy have been used to prevent persistent or recurrent infection. The clinical value of these measures remains unclear.

The postoperative peritoneal lavage is extremely labour intensive and can lead to complications (vascular or visceral erosion, spread of infection).

As intra-abdominal infection often persists or recurs in severe peritonitis, the concept of re-laparotomy, on demand or planned, has been introduced. Re-laparotomy on demand indicates that the patient has to show clinical signs of persistent or recurrent intra-abdominal infection, a worsening of his clinical situation. The other concept is the re-laparotomy at fixed intervals or the open-abdomen treatment. Both allow inspection of the peritoneal cavity and anastomosis, debridement and abdominal lavage.

One major advantage of the recently introduced vacuum-assisted abdominal closure with abdominal dressing (VAC-AD) for open-abdomen treatment is the possibility of performing dressing changes in the intensive-care unit (ICU; technique is described later). Therefore there is no need for additional operating-theatre resources. Regular inspections may be done in the ICU without any delay. Furthermore, its use helps to avoid the deleterious effects of increased intra-abdominal pressure – intra-abdominal compartment syndrome.

Classically, open management of the abdomen involved leaving the abdominal wall open and packing the defect with saline-soaked gauzes. Many variations have been described (use of non-adsorbable meshes, transparent drapes, even saline bags) [12, 13].

In recent years we have had good experience with VAC-AD. We have reached a state that we nowadays have conscious, spontaneously breathing patients with VAC-AD-assisted open-abdomen management and peridural analgesia for changing the VAC-AD system.

Sedation and analgesia

Adequate analgesia and sedation are a basis of modern intensive-care medicine. The quality of analgesia is defined by the patient if he can be asked. Pain, agitation and anxiety may evoke a stress response leading to increased myocardial oxygen consumption, hypercoagulability, dys-synchronous mechanical ventilation, and

inadvertent removal of endotracheal tubes and other monitoring devices [3]. Pain hinders early mobilisation, breathing and coughing.

Pain is a major risk factor for reactive depression, which itself clearly alters the clinical course. Sedation is used to make the situation bearable for the patient. Recently, evidence-based management guidelines for analgesia, sedation and neuromuscular blocking for patients with sepsis have been presented [3, 4]. Recommendations are made for the use of sedation protocols, regular evaluation and daily interruption, awakening and re-titration. The regimen we use in our intensive-care ward is analgesia based. Following the World Health Organization guidelines, every patient has a non-steroidal pain medication, supported by opiates such as sufentanil or remifentanil. In special cases we combine both substances: sufentanil for basic requirements, remifentanil for situations with peak pain such as dressing changes. Ketamin-S is often used as a co-analgetic drug. Whenever possible, we try to base our analgesia on neuraxial methods. However, the use of epidural catheters in patients with sepsis is questioned even in our team. On the other hand, the quality of pain control that can be reached with neuraxial blocking is unique [31–33]. Other positive side-effects of epidural analgesia are improved tissue oxygenation [34, 35], reduced postoperative gut paralyses [36, 37], possible effects on cardiac events [38] and pulmonary outcome.

Long-term outcome

Although the management of the critically ill patient with peritonitis is commonly challenging, often frustrating, and invariably expensive, long-term quality of life in survivors is good [39].

Retrospective evaluation of 58 patients with open-abdomen management due to secondary peritonitis

Methods

In our retrospective study we identified 58 patients who underwent open management of the abdomen for severe peritonitis between 2001 and 2005. We compared 58 patients who were treated with either abdominal dressing-assisted VAC therapy (AD group, 51.7%) or alternative treatment procedures (AP group), such as saline-soaked gauzes and dressing with transparent drapes (48.3%).

The vacuum-assisted closure therapy (VAC-KCI) for open-abdomen management, extended with abdominal dressing, was introduced in our institution some years ago. The VAC abdominal dressing is indicated for the temporary bridging of abdominal wall openings where primary closure is not possible or repeated abdominal entries are necessary. After trying to attain primary source control as described above and thorough cleansing, the VAC abdominal dressing system is applied as described below. Each dressing assembly contains:

1. An internal non-adherent contact layer – polyurethane, film-covered (encap-

sulated) foam with surrounding meshed apron. The contact layer is placed over the omentum or exposed internal organs and the apron is tucked between the abdominal wall and viscera to stabilise the contact layer within the wound bed and reduce the formation of adhesions. The polyurethane film is perforated with small slits to allow active fluid removal when VAC therapy is applied.

2. Outer-layer polyurethane open-cell foam pieces with perforations for easier sizing. The polyurethane open-cell foam is applied over the internal non-adherent contact layer and assists with abdominal fluid removal.
3. VAC drapes to be placed over the cell foam and surrounding intact skin to create an airtight seal for the application of negative pressure therapy.
4. Therapeutic regulated accurate care (TRAC) pad with tubing – the TRAC pad tubing is connected to the VAC ATS pump. The TRAC technology accurately senses the amount of negative pressure being applied to the wound site. This feature helps ensure that the target therapy pressure is maintained. The VAC ATS device provides controlled negative pressure to the abdominal wound to hold the wound closed and for removal of fluid from the abdominal wound. The negative pressure draws the fluid up through the internal non-adherent contact layer and into the outer layer open-cell foam, where the TRAC pad tubing can remove the fluid into the VAC ATS collection canister (Fig. 1).

Due to the abdominal dressing layer, the suction reaches the retroperitoneum, avoiding abscess formation and adhesions of the gut with the abdominal wall.

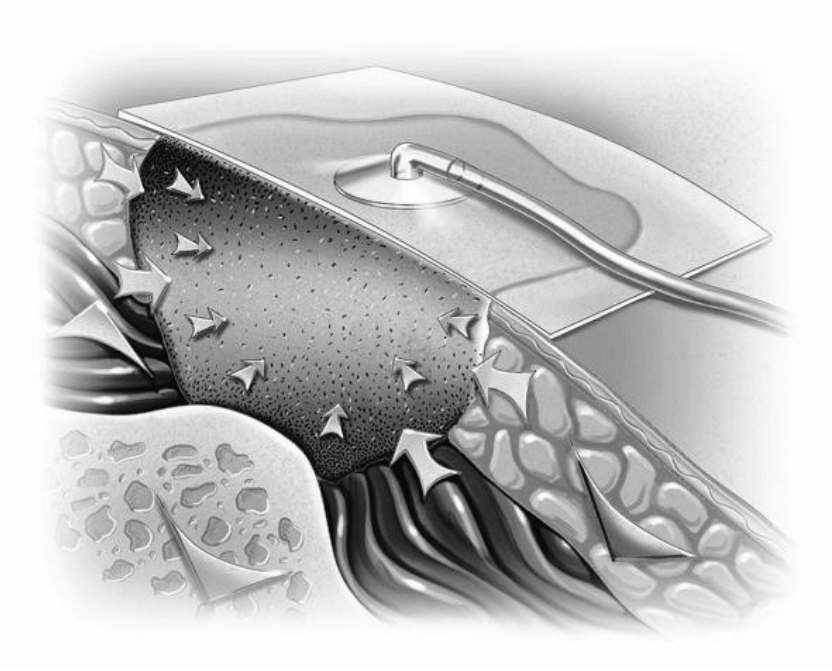


Fig. 1. Vacuum-assisted closure therapy with abdominal dressing for open-abdomen management

The first dressing change is planned 24 h after the operation. Afterwards the dressing is changed every 2–3 days. The changing is done in the ICU without the need for an operating theatre. In combination with epidural analgesia, early weaning from mechanical ventilation and even extubation is possible, followed by an early mobilisation. The later closure of the abdomen is eased [40].

We recorded the hospital mortality due to all causes, demographic data, intensive-care data such as days of ventilatory support, days with dialysis, days on ICU, vasopressor support, haemodynamic data as available, surgical and bacteriological data. We analysed the first 5 days after the start of the open management, then every fifth day until the patient left the ICU.

The APACHE II score and the SOFA score were assessed using the clinical data and laboratory values collected during the 24 hours before the start of open management of the abdomen. Repeated measurements of the SOFA score were done for 5 days. Peritonitis was classified using the MPI, which includes demographic details and macroscopic, intraoperative description.

Hospital morbidity included all local and systemic complications during and after open management of the abdomen. Hospital mortality included all in-hospital deaths.

Statistical analyses were performed using Statview 5.0 (SAS Institute Inc., Cary, NC, USA). Dichotomous variables were compared using chi square or Fisher's exact test where appropriate. Continuous variables were compared using Student's t-test. Significance is defined as $p \leq 0.05$. Data are expressed as mean ± standard deviation or number (percentage).

Table 1. Classification of intra-abdominal infections [41]

Primary peritonitis	(A) Spontaneous peritonitis in children
	(B) Spontaneous peritonitis in adults
	(C) Peritonitis in patients with CAPD
	(D) Tuberculous or other granulomatous peritonitis
Secondary peritonitis	(A) Acute perforations peritonitis
	1. Gastrointestinal perforation
	2. Intestinal ischaemia
	3. Pelviperitonitis and other forms
	(B) Postoperative peritonitis
	1. Anastomotic leak
	2. Accidental perforation and devascularisation
	(C) Post-traumatic peritonitis
	1. After blunt trauma
	2. After penetrating abdominal trauma
Tertiary peritonitis	
	(A) Peritonitis without evidence for pathogens
	(B) Peritonitis with fungi
	(C) Peritonitis with low-grade pathogenic bacteria

Table 2. Sepsis-related Organ Failure Assessment (SOFA) score. Five organ systems are scored according to their dysfunction. A system without dysfunction is scored with 0 [21]

SOFA score	1	2	3	4
Respiration (PaO_2/FiO_2)	< 400	< 300	< 200	< 100
Coagulation thrombocytes in 1 000/mm^3	< 150	< 100	< 50	< 20
Liver (bilirubin mg/dl)	1.2–1.9	2.0–5.9	6.0–11.9	> 12
Circulation	Mean arterial pressure < 70mmHg	Dopamine or dobutamine < 5*	Dopamine >5* or nor(adrenaline) < 0.1*	Dopamine 15* or nor(adrenaline) > 0.1*
Glasgow Coma Scale	13–14	10–12	6–9	< 6
Renal function creatinine mg/dl diureses in ml in 24 h	1.2–1.9	2.0–3.4	3.5–4.9 < 500	> 5 < 200

*Vasopressors for at least 1 h, µg/kg /min

Table 3. Mannheimer Peritonitis Index (MPI). If a criterion in the left column is fulfilled, the points in the right column are counted up for the MPI. It has proven to be a valuable outcome predictor [16, 24, 25, 42]

Age > 50 years	5
Female	5
Organ failure	7
Malignancy	4
Preoperative duration of peritonitis > 24 h	4
Other source than colon	4
Diffuse peritonitis	6
Exudate	
clear	0
cloudy, purulent	6
faecal exudate	12

Table 4. Systemic inflammatory response and sepsis (SIRS). Two of the following criteria denote a SIRS, sepsis is a SIRS of infectious origin. Severe sepsis: sepsis + organ dysfunction; septic shock: sepsis and vasopressor support [29]

Temperature	< 36° or > 38° Celsius
White platelet count	> 12 000/µl or < 4 000/µl or > 10% neutrophil granulocytes
Tachycardia	> 90/min
Tachypnoea	Respiratory frequency > 20/min or pCO_2 < 4.3 kPa
Sepsis	SIRS of infectious origin
Severe sepsis	Sepsis with organ dysfunction
Septic shock	Sepsis with hypotension after adequate fluid resuscitation

Details of patients

There were 37 men and 21 women (59.8 years, SD 16.6 years). Twenty-five patients (43.1%) had had at least one operation before the laparostomy. The anatomic origin of the peritonitis is presented in Table 5.

All patients had a sepsis syndrome and needed ventilatory support. Fifty-five per cent were in septic shock (55.2% of our patients needed adrenaline or noradrenaline above 0.1 µg/kg/min).

All patients received appropriate fluid resuscitation (mean fluid administration 92.4 ml/kg/day on the first day of laparostomy). The following parameters showed no significant difference between the treatment groups: age, sex, body mass index, APACHE II score, MPI, use of vasopressor and fluid administration in the first 24 h. All patients received antibiotics. Further patient details are given in Tables 6 and 7.

Table 5. Surgical details of patients in the study. Source, origin of secondary peritonitis. One patient could not be scored due to missing data

	AP	VAC-AD	Total
Stomach	2 (7.14%)	4 (13.79%)	6 (10.53%)
Small bowel	5 (17.86%)	10 (34.48%)	15 (26.32%)
Colon	14 (50.00%)	10 (34.48%)	24 (42.11%)
Pancreas	3 (10.71%)	0 (0.00%)	3 (5.26%)
Trauma	2 (7.14%)	2 (6.90%)	4 (7.02%)
Liver cirrhosis	1 (3.57%)	0 (0.00%)	1 (1.75%)
Acute abdomen	1 (3.57%)	3 (10.34%)	4 (7.02%)
	28 (100.00%)	29 (100.00%)	57 (100.00%)

Table 6. Details of patients. Data are expressed as number (percentage) or mean (standard deviation)

	AD	AP	Total	*p*
Number	30 patients	28 patients	58 patients	-
Age (years)	58.2 ± 17.0	61.5 ± 16.3	59.8 ± 16.6	ns
Sex (M:F)	19M:11F; 63% M	18M:10F; 64% M	37M:21F 64% M	ns
BMI (kg/m^2)	30.0 ± 9.4	27.0 ± 5.8	28.5 ± 8.0	ns
APACHE II Score	23.5 ± 6.7	23.2 ± 5.8	23.4 ± 6.2	ns
SOFA Score	9.8 ± 2.4	11.8 ± 2.7	11.2 ± 2.7	<0.0001
MPI	27.8 ± 6.5	28.2 ± 6.0	28.0 ± 6.2	ns
Survivors	21 (70%)	10 (35.7%)	31 (53.4%)	–
Non-survivors	9 (30%)	18 (64.3%)	27 (46.5%)	0.017

Results

Every patient needed ventilatory support for at least 2 days after the start of the open management of the abdomen. The mean duration of ventilatory support was 25 days (2–106 days). Ten of 58 patients (17.2%) had a renal failure. Thirty-two patients (55.2%) needed vasopressor support above 0.1 μg/kg/min. There was no significant difference in the duration of ventilatory support, vasopressor support or renal failure indicating haemodialyses between the treatment groups. Details of hospital morbidity and intensive-care stay are listed in Table 7.

In total, 27 patients died (46% of 58 patients), of whom 18 were in the alternative procedure group (64.3% of 28 patients) and nine in the abdominal dressing group (30% of 30 patients, $p < 0.05$).

Twenty-three patients died from multi-organ failure in the SICU, two of a myocardial infarction and two of a massive pulmonary embolism.

The mean APACHE II score in the survivors was 22.2 (SD 5.3) compared with 24.7 (SD 7) among those who died. The mean SOFA score on the first day with laparostoma in the survivors was 10.1 (SD 2.9) compared with 12.4 (SD 1.9) among those who died. Repeated measurements of the SOFA score were done for the first 5 days. A decrease in the first 72 hours was noted in 61.5% of the survivors, compared with 35.7% in the non-survivors. So the APACHE II score, the SOFA score and the MPI showed a significant difference between survivors and non-survivors. The mean duration of intensive-care stay was 49 days (5–193). Thirty-one patients (53.4%) were discharged from the hospital. In 32 patients (55%), the abdominal wall had been closed successfully during the initial hospital stay. One patient died after closure of the abdominal wall.

Table 7. Details of stay in ICU. Numbers are expressed as mean ± standard deviation (range)

	AP	AD	Total
Ventilatory support (days)	23.0 ± 21.2 (2–77)	26.7 ± 25.3 (2–106)	24.0 ± 22.2 (2–106)
Renal failure resulting in dialyses (days) in 10 patients Duration of hf	4/28 (14.3%) 9.2 ± 8.6 days (2–23)	6/30 (20%) 24.8 ± 25.3 days (5–60)	10/58 16.1 ± 18.5 days (2–60)
Vasopressor support (days)	11.9 ± 11.7 (1–47)	10.8 ± 11.8 (0–38)	11.4 ± 11.6 (0–47)
Duration of stay on ICU (days)	52.5 ± 48.4 (5–193)	46.1 ± 34.5 (11–131)	49.3 ± 41.2 (5–193)

Discussion

Severe peritonitis is a serious condition with a high mortality. We report our experiences in 58 patients with peritonitis who were treated with open-abdomen management. Our patients were in a very serious state: all needed ventilatory

support, 55% needed vasopressor support above 0.1 μg/kg/min, with a mean APACHE II score of 23.4 ± 6.2, a mean MPI of 28.7 ± 6.2 and a SOFA score of 11.1 ± 2.7. In our group of patients we found an overall mortality of 46%.

In our retrospective study we compared vacuum-assisted abdominal closure with abdominal dressing with alternative procedures. There was a marked reduction of the mortality in the VAC-AD group with an in hospital mortality of 30% (9/30), compared to 64.3% (18/28) in the AP group ($p < 0.05$).

The APACHE II score based on data collected during the last 24 h before the start of the open management and the MPI showed a significant difference between survivors and non-survivors, but not between the different treatment groups. The acute physiological score is well known to be predictive in severe peritonitis [16].

Only the SOFA score assessed on the first day of the laparostoma, indicating the degree of organ dysfunction, showed a significant difference between the treatment groups, with lower values in the abdominal dressing group. There were no differences of known risk factors such as diabetes, hypertension, body mass index or coronary artery disease between the groups.

Vacuum-assisted closure therapy is a standard tool for complex superficial wounds. The major mechanisms are reduction of the local oedema, stimulation of localised blood flow, promotion of granulation tissue formation, reduction of bacterial colonisation and wound contraction due to the negative pressure. Additionally, intensive-care procedures are not hindered (prone position, early weaning and mobilisation). As the changing of the dressing is done in the ICU, it is safer for the patient (no transport required) and efficient. The abdominal dressing prevents clogging of the gut with the peritoneum and provides efficient drainage up to the retroperitoneum. Both effects are preventive for abscess formation. And finally the closure of the abdominal wall is eased [40].

Patients with severe peritonitis and abdominal sepsis are a major challenge for everyone who is involved in the treatment of this very serious condition. The evidence presented in the Surviving Sepsis Campaign helps the intensivist in his decision finding. Early source control and optimal treatment of patients with an open abdomen are the cornerstones of surgical therapy. Vacuum-assisted closure therapy with abdominal dressing will be an important point in bridging the time of open abdomen management. However, further prospective studies are necessary to prove the positive effects of VAC therapy.

References

1. Marshall JC, Innes M (2003) Intensive care unit management of intra-abdominal infection. Crit Care Med 31(8):2228–2237
2. Dellinger RP, Carlet JM, Masur H et al; Surviving Sepsis Campaign Management Guidelines Committee (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32(3):858–873
3. Vender JS, Szokol JW, Murphy GS, Nitsun M (2004) Sedation, analgesia, and neuromuscular blockade in sepsis: an evidence-based review. Crit Care Med 32(11 Suppl):S554–561

4. Arroliga A, Frutos-Vivar F, Hall J et al; International Mechanical Ventilation Study Group (2005) Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest 128(2):496–506
5. Krenzien J, Lorenz W (1990) Scoring systems for severe intra-abdominal infections [German]. Zentralbl Chir 115(17):1065–1079
6. Teichmann W, Herbig B (2000) Therapy principles in diffuse peritonitis [German]. Chirurg 71(1):120–128
7. Reith HB (1997) Therapy of peritonitis today. Surgical management and adjuvant therapy strategies [German]. Langenbecks Arch Chir 382(4 Suppl 1):S14–S17
8. Brugger E, Seiler CA, Mittler M et al (1999) New approaches to the surgical treatment of diffuse peritonitis [German]. Zentralbl Chir 124(3):181–186
9. Van Aken HK, Reinhart Zimpfer M (2001) Intensivmedizin. In: Hendelmann G, Keier C, Schulte Am Esch J, (eds) Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie, vol. 2. Georg Thieme Verlag, Stuttgart, New York, p 647
10. McRitchie DI, Girotti MJ, Glynn MF et al (1991) Effect of systemic fibrinogen depletion on intraabdominal abscess formation. J Lab Clin Med 118(1):48–55
11. Hau T, Simmons RL (1978) Heparin in the treatment of experimental peritonitis. Ann Surg 187(3):294–298
12. Bosscha K, van Vroonhoven TJ, van der Werken C (1999) Surgical management of severe secondary peritonitis. Br J Surg 86(11):1371–1377
13. Wittmann DH, Schein M, Condon RE (1996) Management of secondary peritonitis. Ann Surg 224(1):10–18
14. Schein M, Wittmann DH, Lorenz W (1996) Duration of antibiotic treatment in surgical infections of the abdomen. Forum statement: a plea for selective and controlled postoperative antibiotic administration. Eur J Surg Suppl 576:66–69
15. Bosscha K, Reijnders K, Hulstaert PF et al (1997) Prognostic scoring systems to predict outcome in peritonitis and intra-abdominal sepsis. Br J Surg 84(11):1532–1534
16. Billing A, Frohlich D, Schildberg FW (1994) Prediction of outcome using the Mannheim peritonitis index in 2003 patients. Peritonitis Study Group. Br J Surg 81(2):209–213
17. Karamarkovic A, Radenkovic D, Milic N et al (2005) Protein C as an early marker of severe septic complications in diffuse secondary peritonitis. World J Surg 29(6):759–765
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13(10):818–829
19. Nystrom PO, Bax R, Dellinger EP et al (1990) Proposed definitions for diagnosis, severity scoring, stratification, and outcome for trials on intraabdominal infection. Joint Working Party of SIS North America and Europe. World J Surg 14(2):148–158
20. Anonymous (1994) Predicting outcome in ICU patients. 2nd European Consensus Conference in Intensive Care Medicine. Intensive Care Med 20(5):390–397
21. Vincent JL, Moreno R, Takala G et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22(7):707–710
22. Paugam-Burtz C, Dupont H, Marmuse JP et al (2002) Daily organ-system failure for diagnosis of persistent intra-abdominal sepsis after postoperative peritonitis. Intensive Care Med 28(5):594–598
23. Demmel N, Maag K, Osterholzer G (1994) The value of clinical parameters for determining the prognosis of peritonitis – validation of the Mannheim Peritonitis Index [German]. Langenbecks Arch Chir 379(3):152–158

24. Fugger R, Rogy M, Herbst F et al (1988) Validation study of the Mannheim Peritonitis Index [German]. Chirurg 59(9):598–601
25. Linder MM, Wacha H, Hermann U et al (1987) The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis [German]. Chirurg 58(2):84–92
26. Malbrain ML, Chiumello D, Pelosi P et al (2005) Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med 33(2):315–322
27. Hahn R, Spiss C (2005) Comparison of two methods for assessing the intraabdominal pressure. Abstract ESA Meeting, Wien
28. Rivers E, Nguyen B, Haystad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345(19):1368–1377
29. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 29(4):530–538
30. Hau T, Nishikawa R, Phuangsab A (1983) Irrigation of the peritoneal cavity and local antibiotics in the treatment of peritonitis. Surg Gynecol Obstet 156(1):25–30
31. Block BM, Liu SS, Rowlingson AJ et al (2003) Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 290(18):2455–2463
32. Flisberg P, Tornebrandt K, Walther B, Lundberg J (2001) Pain relief after esophagectomy: thoracic epidural analgesia is better than parenteral opioids. J Cardiothorac Vasc Anesth 15(3):282–287
33. Flisberg P, Rudin A, Linner R, Lundberg CJ (2003) Pain relief and safety after major surgery. A prospective study of epidural and intravenous analgesia in 2696 patients. Acta Anaesthesiol Scand 47(4):457–465
34. Kabon B, Fleischman E, Treschan T et al (2003) Thoracic epidural anesthesia increases tissue oxygenation during major abdominal surgery. Anesth Analg 97(6):1812–1817
35. Treschan TA, Taguchi A, Ali SZ et al (2003) The effects of epidural and general anesthesia on tissue oxygenation. Anesth Analg 96(6):1553–1557
36. Fotiadis RJ, Badvie S, Weston MD et al (2004) Epidural analgesia in gastrointestinal surgery. Br J Surg 91(7):828–841
37. Zugel N, Bruer C, Breitschaft K, Angster R (2002) Effect of thoracic epidural analgesia on the early postoperative phase after interventions on the gastrointestinal tract [German]. Chirurg 73(3):262–268
38. Beattie WS, Badner NH, Choi P (2001) Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 93(4):853–858
39. Scheingraber S, Kurz T, Dralle H (2002) Short- and long-term outcome and health-related quality of life after severe peritonitis. World J Surg 26(6):667–671
40. Garner GB, Ware DN, Cocanous CS et al (2001) Vacuum-assisted wound closure provides early fascial reapproximation in trauma patients with open abdomens. Am J Surg 182(6):630–638
41. Wittmann DH (1996) Duration of antibiotic treatment in surgical infections of the abdomen. Pharmacokinetic basis for short courses of antimicrobial therapy. Eur J Surg Suppl 576:19–23
42. Demmel N, Muth G, Maag K, Osterholzer G (1994) Prognostic scores in peritonitis: the Mannheim Peritonitis Index or APACHE II? [German]. Langenbecks Arch Chir 379(6):347–352

Chapter 44

Combination therapy for sepsis: the wave of the future or too complex to consider?

S.M. Opal, A.S. Cross

After a distressingly long series of failed clinical trials in the development of innovative therapies for sepsis, a number of interventions have recently been shown to improve the outcome in sepsis [1, 2]. The mortality rate in severe sepsis has improved over the past 20 years [1], and part of the explanation for this improved outlook for septic patients is the availability of better treatment strategies. Recent successful clinical trials have evolved from the experience gained in earlier failed clinical trials and advances in the understanding of the molecular pathogenesis of sepsis [3, 4]. The landmark report that recombinant human activated protein C (rhAPC, drotrecogin alpha activated) reduced the relative risk of mortality in septic shock over a control group by almost 20% represents the first large successful phase-3 trial in severe sepsis [5]. This study was followed in rapid session by reports of improved outcomes with early goal-directed therapy (aggressive resuscitation) for septic patients [6] and tight blood-sugar control to prevent sepsis in high-risk ICU patients [7]. After decades of study, stress-doses of glucocorticoids have finally been shown to provide survival benefit in selected patients with vasopressor-dependent septic shock [8, 9].

We now find ourselves in the enviable position of being able to choose between several different treatment options, each of which provides benefit to our patients by different mechanisms. When should these adjuvant interventions be used, and in what sequence or combination would they be most effective? How can we study new agents in a therapeutic environment where other sepsis treatments are already available? These questions will inevitably require careful study and will necessitate the application of multiple interventions at the same time.

Clinical investigations into improved therapies for sepsis are fraught with pitfalls and challenges, as evidenced by the recent meta-analysis of 21 clinical sepsis studies by Natanson et al [10]. They assessed the net efficacy of differing classes of anti-inflammatory mediator strategies from over 10 000 patients enrolled in recent sepsis studies. The results of their analyses clearly demonstrated that it is not possible to make accurate predictions of efficacy based upon outcomes in small phase-2 trials. Large confidence intervals surround the point estimates from these small trials (usually consisting of 100–500 randomised patients), making accurate predictions of reliable incremental treatment benefits difficult. For a number of reasons [i.e. highly selected patient populations, reporting artefacts (publishing only small positive trials rather that small negative trials), involvement of dedicated

investigators with detailed knowledge of the study drug] phase-2 trial results often look better than large phase-3 trial results.

This difference is strikingly evident in sepsis trials, in which large phase-3 studies with large numbers of randomised patients (usually 1000–3000 patients) have consistently demonstrated tight confidence intervals but marginal if any overall improvement in mortality when patients receiving treatment interventions were compared with a concomitant placebo control group. When the results of all these studies were pooled, there was a small, but significant improvement in survival with anti-mediator agents (odds ratio 1.17). The mediator therapies studied included tumour necrosis factor (TNF), interleukin-1 (IL-1) inhibitors, corticosteroids, and a variety of other anti-mediator therapies. The unfavourable 'signal-to-noise' ratio ('signal' being the intrinsic activity of the anti-sepsis therapy and 'noise' being the inherent heterogeneity and variable outcome in critically ill patients, independent of the treatment under investigation) makes it difficult to prove efficacy in a randomised, double-blind, controlled clinical trial. Indeed, one must carry out a very large study with a highly active compound in order to detect even a small yet statistically significant benefit in a phase-3 study. Perhaps the use of combination therapies with simultaneous interventions will provide proof of efficacy in situations in which the benefits accrued by single agents may be exceedingly difficult to detect [3, 4].

An example of this problem of proving efficacy of a single agent in a multi-centre clinical trial has been published recently concerning human recombinant bactericidal/permeability-increasing protein (BPI). As opposed to immunomodulator therapies directed against host response elements, BPI targets one of the critical microbial mediators, lipopolysaccharide (LPS), from gram-negative bacteria. This highly active anti-endotoxin protein was studied in a large, international, controlled trial in children with meningococcal sepsis [11]. Despite truly heroic efforts by investigators to optimise the clinical design and implement the study drug in a timely fashion, BPI-treated patients showed only a modest, yet statistically significant improvement in organ injury scores (neurological events, amputation rates, blood product requirements) with no significant reduction in overall mortality. This treatment strategy failed to meet the primary study endpoints and therefore was not approved for use in meningococcal sepsis.

Furthermore, in this study, as in other failed studies with anti-inflammatory agents, the problem was not due to a lack of biologic activity of the study drug. LPS is clearly an essential mediator of gram-negative sepsis and BPI is a highly active LPS inhibitor; yet, BPI failed to show convincing efficacy in the phase-3 sepsis trial [11]. Numerous anti-mediator agents have unambiguous evidence of activity in disrupting the target molecule. Indeed, many anti-TNF interventions and anti-IL-1 agents that failed in initial sepsis trials have subsequently become licensed products in other disease processes, such as inflammatory bowel disease and rheumatoid arthritis [4, 12]. This indicates that sepsis is a far more complex and multi-factorial process than many inflammatory diseases. The intrinsic heterogeneity and complexity of sepsis necessitates that we accommodate for this variability in future treatment interventions for severe sepsis and septic shock.

Sepsis can be thought of as a multi-stage process in which microbial pathogens progressively overwhelm host defences and initiate a potentially lethal, excessive and dysregulated host response [4, 13]. Microbial products collectively known as pathogen associated molecular patterns (PAMPs) are recognised via Toll-like receptors as well as other pattern-recognition receptors and stimulate cells of the innate immune system to produce inflammatory mediators (including cytokines, chemokines, proteases, oxidative radicals, and phospholipid mediators). They also activate acute-phase responses that include coagulation components, kinins and other vasoactive amines, and complement elements. By the time the clinical diagnosis of sepsis is made, the entire network of sepsis-induced inflammatory and coagulopathic processes is already widely activated. The multi-factorial nature of the septic process makes it unlikely that a single intervention aimed at one mediator, no matter how intrinsically active, will provide significant benefit across a broad spectrum of sepsis-related pathologies. Even though the use of recombinant form of the endogenous anticoagulant activated protein C was effective in large clinical trials, the rather modest impact on overall mortality (6% absolute reduction in 28-day all-cause mortality) leaves much room for improvement in the management of sepsis [5].

After the septic process is initiated, elements of the adaptive immune system and numerous cellular defence mechanisms are then activated in an effort to maintain viability of the host. Apoptotic pathways, cellular hibernation, cytopathic hypoxia, and bewildering arrays of counter-regulatory and anti-inflammatory systems are activated. Targeting some of these late mediators, such as reactive oxygen and nitrogen intermediates, apoptotic and necrotic pathways or late-acting cytokines, e.g. macrophage migration inhibitory factor (MIF) or high mobility group box-1 (HMG-1), may prove beneficial [13, 14]. Even here, it seems likely that significant improvements in survival rates will only become evident when combined with therapies directed at multiple stages of the sepsis process. A suggested approach for the future is outlined in Fig. 1. Selected treatments would be strategically designed to meet the inherent complexity manifest in the pathophysiology of human septic shock. There are multiple potential sites for intervention, including: (1) PAMPs; (2) early host-derived pro-inflammatory mediators; (3) coagulation activation; (4) late host-derived inflammatory mediators, and (5) cytopathic hypoxia, apoptosis, and necrosis.

As pointed out recently in a comprehensive review of preclinical and clinical trials in sepsis [15], anti-inflammatory agents are most likely to be proven efficacious when used in clinical situations in which there is a high risk of mortality. Carefully chosen combinations of anti-sepsis agents may prove to be beneficial in these most severely ill patients [4, 16]. It is anticipated that the likelihood of response to immunomodulatory agents will become more predictable through the use of genomics and proteomics. This may allow for specific interventions that are logically tailored to the patient's individual needs. Perhaps as important will be the facility, through gene-chip technology, to avoid treatments that may be toxic to specific patients and potentially worsen outcome.

Combination therapy directed at a single stage (e.g. inhibitors of both IL-1 and

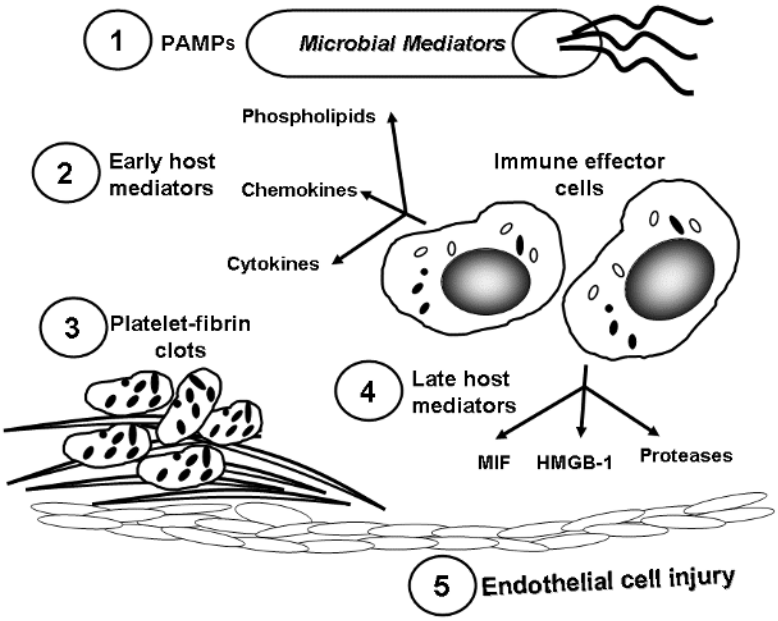


Fig. 1. Five potential sites for intervention with combination therapy for severe sepsis. *PAMPs*, Pathogen associated molecular patterns; *MIF*, macrophage migration inhibitory factor; *HMGB-1*, high mobility group box-1

TNF cytokine generation) may or may not be more effective than monotherapy in sepsis [17, 18]. Experimental evidence obtained from some sepsis models indicates that inhibition of IL-1 and TNF may actually increase the risk of immunosuppression and lead to excess mortality [19]. Combination agents should be chosen such that they complement each other, to the net benefit of the patient's underlying molecular pathology. This combination strategy is highly efficacious in animal models and may prove to be the optimal approach in the future for the management of human sepsis [20].

The clinical trial paradigm in the development of anti-sepsis agents has been the standard double-blind, placebo-controlled single-agent trial design. This model is based upon a traditional regulatory position that it is inappropriate to conduct a trial of combination therapy until all the individual components of the treatment regimen have shown independent efficacy and safety. Now that several large studies have demonstrated safety and modest effectiveness, combination studies are warranted to determine whether additive or even synergistic effects are achievable in sepsis studies. A trial of activated protein C in combination with tight glucose control, stress-dose steroids, and/or early goal-directed resuscitation strategies should be undertaken. Moreover, agents directed against microbial mediators (anti-LPS or other bacterial toxins, anti-lipoteichoic acid, or anti-peptidoglycan agents) may need to be studied in combination with therapies directed against

early host-derived mediators (e.g. cytokines, proteases, reactive oxygen intermediates, coagulation elements) and late-acting agents such as HMGB-1, MIF, and apoptosis inhibitors.

Many such combinations could be reasonable and the choice of the correct combination might be guided in the near future by the availability of rapid access to genomic and proteomic data. Small molecule inhibitors and immunomodulators will become available for clinical study as the intracellular pathways that underlie the septic process are better defined. Combination therapy has proven highly successful in the management of life-threatening viral diseases like hepatitis C and HIV infection, and it has become the standard of care for many neoplastic diseases [4].

The time has come to advance our therapeutic approach to management of severe sepsis with combination therapy [16, 21]. Recent studies have shown that multiple interventions provide small but significant improvements in outcome. There is little reason to believe that dramatic breakthroughs will occur in the future with continued adherence to a monotherapy approach. We must accept the complexity and dynamic nature of the signalling networks responsible for the molecular pathogenesis of sepsis and respond with a carefully chosen regimen of combination agents directed against the multiple pathways involved in sepsis. The emerging technology to provide real-time and accurate assessment of the immune status of each septic patient over the course of illness will greatly facilitate the optimal use of combination therapy in the future. Monumental recent advances in our understanding of the pathophysiology of sepsis should be matched by an intelligent set of combination approaches to sepsis therapies, if real progress is to be achieved in the care of patients with severe sepsis and septic shock.

References

1. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554
2. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving sepsis campaign guidelines for severe sepsis and septic shock. Crit Care Med 32:858–873
3. Micek ST, Kollef MH (2003) Management of severe sepsis: integration of multiple pharmacologic interventions. Pharmacotherapy 23(11):1486–1496
4. Cross AS, Opal SM (2003) A new paradigm for the sepsis: time to consider combination therapy? Ann Intern Med 138:502–505
5. Bernard GR, Vincent J-L, Laterre P-F et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
6. Rivers E, Nyguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
7. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critical ill patients. N Engl J Med 345:1359–1367
8. Annane D (2002) The resurrection of steroids for sepsis resuscitation. Minerva Anestesiol 68:127–131
9. Annane D, Sebille V, Charpentier C et al (2002) Effort of treatment with low doses of

hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
10. Natanson C, Esposito CJ, Banks SM (1998) The sirens' song of confirmatory sepsis trials: selection bias and sampling error. Crit Care Med 26:1927–1931
11. Levin M, Quint PA, Goldstein B et al (2000) Recombinant bactericidal/permeability-increasing protein as adjunctive treatment for children with severe meningococcal sepsis: a randomized trial. Lancet 356:961–967
12. Marshall JC (2003) Such stuff as dreams are made of: mediator-targeted therapy in sepsis. Nat Rev Drug Disc 2:391–405
13. Calandra T, Echtenacher B, LeRoy D et al (2000) Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nat Med 6:165–171
14. Wang H, Bloom O, Zhang M et al (1999) HMG-1 as a late mediator of endotoxin lethality in mice. Science 285: 248–251
15. Eichacker PQ, Parent C, Kalil A et al (2002) Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. Am J Respir Crit Care Med 166:1197–1205
16. Kumar A, Mann HJ (2004) Appraisal of four novel approaches to the prevention and management of sepsis. Am J Health Syst Pharm 61:765–774
17. Remick DG, Call DR Ebong SJ et al (2001) Combination therapy with soluble TNF receptors plus interleukin-1 receptor antagonist reduces sepsis mortality. Crit Care Med 29:473–481
18. Rijneveld AW, Florquin S, Branger J et al (2001) TNF-alpha compensates for the impaired host defense of IL-1 type I receptor-deficient mice during pneumococcal pneumonia. J Immunol 167:5240–5246
19. Opal SM, Cross AS, Jhung JW et al (1996) Potential hazards of combination immunotherapy in the treatment of experimental septic shock. J Infect Dis 173:1415–1421
20. Cross AS, Opal SM, Palardy JE et al (1993) The efficacy of combination immunotherapy in experimental Pseudomonas sepsis. J Infect Dis 176:112–118
21. Cariou A, Vinsonneau C, Dhainaut JF (2004) Adjunctive therapies in sepsis: an evidence-based review. Crit Care Med 32:S562-S570

Chapter 45

Implementation of the Surviving Sepsis Campaign guidelines

J.-L. Vincent

Guidelines are available and used in almost all walks of life to direct and advise, whether it be on how to design the most effective and visually attractive website or which route to take when travelling from A to B. Medicine is no different, and guidelines, published by official representative bodies or groups of opinion leaders, abound. Intensive care medicine has been relatively slow to jump on the guideline 'bandwagon' partly, as we will see later, because of the lack of convincing evidence on which to base such recommendations. However, guidelines are now widely available on subjects as diverse as nutritional support [1], weaning from mechanical ventilation [2], and end-of-life decision making and care [3]. Research in intensive care medicine moves at an incredibly fast pace, and with the ever increasing number of 'specialist' journals and widespread access to the web facilitating rapid dispersion of new results and publications, intensivists are bombarded almost daily with information about a potentially valuable new technique or therapy or a previously unknown risk of an old, well-accepted treatment. The difficulty lies in assimilating all this new 'knowledge' and determining exactly how and when it should be applied to patients. This is where guidelines come into their own, by providing a clear and complete analysis of all the available data and summarising the evidence in order to provide clear directions as to how each patient in that situation should be managed. Guidelines ensure that, if followed, patients will be treated according to the very latest standard of care. In addition to this traditional role, they are also increasingly being used to reduce variability in clinical practice and to standardise care, provide protection against medical litigation, and even to reduce costs [4].

However, guidelines have their drawbacks, and implementing them may not be as clear-cut as first appears. In this chapter, we will discuss the development, benefits, and limitations of the recently developed Surviving Sepsis Campaign guidelines for the management of the patient with severe sepsis or septic shock [5].

Surviving Sepsis Campaign guidelines: development

Severe sepsis affects some 30% of intensive care unit (ICU) admissions and is associated with ICU mortality rates of round 30%. Septic shock is associated with ICU mortality rates of round 50%. Despite many years of intense research, only one agent, drotrecogin alfa (activated), has so far been identified that specifically affects

the sepsis response and by so-doing improves survival [6]. However, many other aspects of general ICU patient management can influence outcomes—the challenge for the physician is to accumulate all the individual components into an effective package for each patient with severe sepsis or septic shock.

The Surviving Sepsis Campaign (www.survivingsepsis.org/) was established in 2002 as a collaborative project initiated by three major intensive/critical care organisations: the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF), and is funded by unrestricted educational grants from several leading industry companies. The Campaign has three phases:

I. The Barcelona Declaration of 2002: a six-point action plan to improve awareness, diagnosis, and treatment of sepsis, and to encourage improved education of physicians, politicians, and patients; the overall aim is to decrease the relative mortality of sepsis by 25% by 2009.
II. The development of guidelines for the management of patients with severe sepsis or septic shock.
III. The creation of methods to encourage application of the guidelines, and assessment of their effectiveness in improving outcomes.

Following the Barcelona Declaration, guidelines for the management of the patient with severe sepsis and septic shock were developed using a modified Delphi methodology by a group of about 50 international critical care and infectious disease experts in the diagnosis and management of infection and sepsis [5]. Recommendations were graded from A to E depending on the level of evidence then available:

A: Supported by at least two large, randomised trials with clear-cut results
B: Supported by one large, randomised trial with clear-cut results
C: Supported by small, randomised trial(s) with uncertain results
D: Supported by a study with non-randomised, contemporaneous controls
E: Studies with historical controls, uncontrolled studies, case series, expert opinion

All aspects of management of the patient with severe sepsis were covered, divided into 18 categories, from initial resuscitation to consideration of limitation of life support, and recommendations were developed for each category. Paediatric considerations were listed separately.

Clearly, this is an ambitious and worthy project. By providing an evidence-based summary of the vast amount of available literature, the Surviving Sepsis Campaign has provided a means of disseminating the available data in a reliable and concise manner that can be used by physicians to assist in their daily decisions regarding the management of patients with severe sepsis or septic shock.

Surviving Sepsis Campaign guidelines: application

Clearly published guidelines are of little value if they are not adopted into clinical practice. As clinicians tend to be conservative by nature, the Surviving Sepsis

Campaign has introduced the 'sepsis bundle,' which takes the guidelines and converts them into operationalisable packages that can be applied more easily at the bedside and, when implemented as a group, have a greater effect on outcome than the individual elements alone. This approach has been taken up in conjunction with the Institute for Healthcare Improvement (www.ihi.org) and two sepsis bundles have been developed (Table 1):

Table 1. The Surviving Sepsis Campaign Sepsis Bundles (adapted from www.ihi.org/IHI/Topics/CriticalCare/Sepsis/Changes)

Sepsis Resuscitation Bundle—within 6 h:
- Blood lactate concentrations measured
- Blood cultures prior to antibiotic administration
- Broad-spectrum antibiotics within 3 h
- Treat hypotension and/or elevated lactate with fluids
- Administer vasopressors for ongoing hypotension
- Maintain adequate central venous pressure (≥ 8 mmHg)
- Maintain adequate central venous oxygen saturation (≥ 70%)

Sepsis Management Bundle—within 24 h:
- Maintain blood glucose on average < 150 mg/dl
- Assess eligibility for the use of drotrecogin alpha (activated)
- Administer steroids in septic shock (unless normal ACTH test)
- If receiving mechanical ventilation, maintain inspiratory plateau pressure at < 30 cmH_2O

1. The Severe Sepsis Resuscitation Bundle describes seven tasks that should begin immediately, but must be accomplished within the first 6 h of presentation for patients with severe sepsis or septic shock. While some items may not be completed if the clinical conditions described in the bundle do not apply in a particular case, clinicians must assess for them.
2. The Sepsis Management Bundle lists four management goals. Efforts to accomplish these tasks should also begin immediately, but these items may be completed within 24 h of presentation for patients with severe sepsis or septic shock.

The following criteria were used to choose the specific guideline recommendations that should be included in the sepsis bundles: (a) evidence suggested that the use of the intervention was associated with decreased mortality; and (b) the recommendation could be converted into data elements that can be precisely defined and that can be audited [7]. The number of goals in the bundles was limited to ensure their implementation was feasible. Hospitals implementing the Sepsis Bundles are encouraged to develop 'Improvement' or 'Change Teams' who will be responsible for developing protocols around the Sepsis Bundles that will function well within their individual institution but, importantly, must include all of the bundle elements. It is recommended that the improvement team is multidisciplinary, comprising representatives from all departments involved in the change processes—doctors, nurses, pharmacists, respiratory therapists, clerks and technicians. A key focus of these sepsis bundles is ongoing data collection and audit to verify that the guidelines are indeed being implemented and to determine whether the changes are actually leading to improved outcomes. To achieve this, the bundle

goals are converted to quality indicators, each with an associated measure representing success or failure of that goal. Following measurement of baseline performance, the hospital or unit tries to improve their rate of achieving the pre-specified goals and measures. Feedback is then provided to all, with further education, training, and reinforcement such that further improvements can be realised. Ongoing studies suggest that implementation of these bundles is feasible and may indeed improve outcomes [8].

Surviving sepsis campaign guidelines: limitations

One of the problems with critical illness, and perhaps sepsis in particular, is the complexity of the process(es) involved and the lack of clear evidence for or against many of the established interventions used in the ICU [9–11] on which to base recommendations. Indeed, while the Surviving Sepsis Guidelines [5] certainly provide useful guidance for any physician regularly treating patients with severe sepsis or septic shock, a close look reveals some interesting data regarding the many uncertainties that remain in the field of sepsis and critical illness as a whole. Of the 52 recommendations, just five are grade A, i.e. supported by at least two randomised controlled trials with clear-cut results, and more than half the recommendations are only supported by grade E evidence (Fig. 1). The fact that only five recommendations are supported by at least two clear-cut randomised controlled trials in fact summarises the situation regarding intensive care medicine as a whole, in which randomised controlled trials are often difficult to conduct. The heterogeneous nature of the intensive care population is one reason why it is difficult to show the impact of short-term interventions on long-term outcomes. In addition, many treatment strategies are life-saving (use of mechanical ventilation in respiratory failure, blood transfusions in acute haemorrhage, administration of vasopressor agents in severe shock, etc.), and cannot ethically be studied in a randomised controlled trial [11]. In a survey of 46 candidates for the 1998 Belgian Intensive Care Board examination, 54% of those questioned were unable to provide an answer to the question: 'Which accepted therapeutic interventions in critical care medicine have been shown to reduce mortality in prospective, randomised, clinical trials?' Just over a third gave an answer, but all of these could be challenged [10]. In addition, many intensivists believe that interventions have been proved effective by randomised controlled clinical trial when in fact they have not [9]. Evidence-based medicine is notoriously difficult to apply in intensive care [11] if based predominantly on randomised controlled studies. As a result, other forms of evidence take on a relatively greater importance than is needed in many other medical specialties where the randomised controlled trial is more easily applicable. In sepsis, a key problem has been in defining and characterising septic patients to achieve a relatively homogeneous patient group. Attempts have been made recently to create better definitions for patients with sepsis in order to improve the quality and comparability of clinical trials [12, 13]. Genomics, proteomics, and microarray technology may also provide a means of classifying more

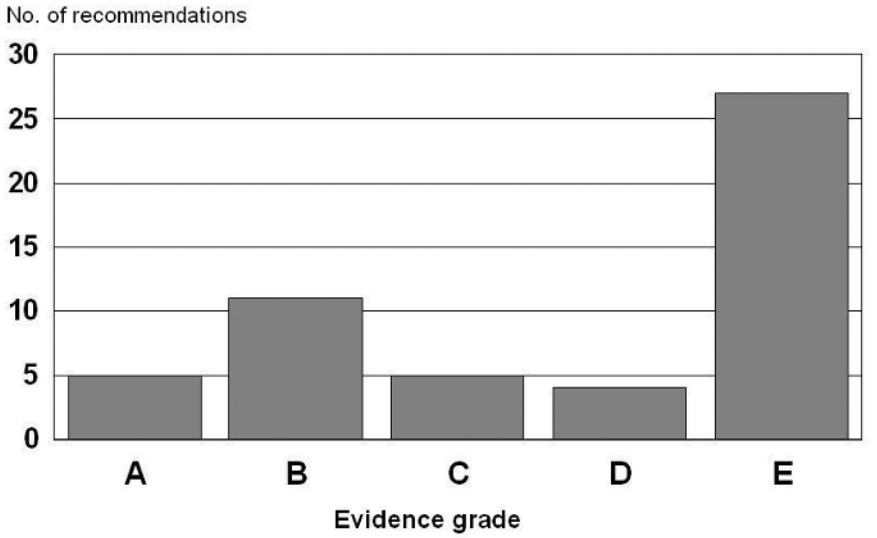


Fig. 1. Number of recommendations of each grade (see text) in the Surviving sepsis campaign guidelines

homogeneous patient populations and monitoring their response to treatments in the future [14].

A good example of the many uncertainties that remain is the case of steroid administration in septic shock. The pivotal study by Annane et al. [15] did show an increased survival rate in patients who received steroid therapy, but this became statistically significant only after a complex statistical analysis using adjusted hazard ratios. Hence, some people have argued that we do not have definitive evidence. This is why a European study called Corticus is currently evaluating the beneficial effects of steroid administration in septic shock, randomising patients to receive hydrocortisone or not, with Dr D Annane serving as a member of the steering committee. However, the Surviving Sepsis Campaign considered that there is enough evidence to recommend the use of stress doses of corticosteroids in septic shock. This raises an interesting issue, in that if the guidelines recommend corticosteroid use, is there still sufficient equipoise for the European study to continue, or should it, in fact, be stopped?

Likewise, what do we know about tight glucose control in sepsis? This intervention was reported to be effective in the surgical ICU of a single centre [16] and the results were extended to the medical ICU [17], but we do not know whether this strategy can be applied everywhere. We also do not know whether this approach is applicable to more unstable patients with severe sepsis and septic shock. The discontinuation of a recent multicentre study in Germany suggests we should be careful before implementing this strategy.

As clearly stated by the authors [5], the Surviving Sepsis Campaign Guidelines provide guidance for the clinician caring for a patient with severe sepsis or septic shock, but they are not necessarily applicable to all patients and cannot replace the clinician's

decision-making capability when he or she is provided with a patient's unique set of clinical variables. This highlights a potential limitation of all guidelines. If they are too weak or vague and too much flexibility is introduced, then the guidelines become ineffectual; if they are too strong, then the guidelines risk becoming too simplistic and dogmatic and physicians will find them impossible to apply to many patients. Some people argue that avoiding variability in clinical practice is a good thing. I do not believe this is true. If there is a superior treatment, of course we should all apply it, but where there is uncertainty, variability can in fact favour the development of new ideas and new strategies. This does not, of course, mean that each physician can do whatever he or she wants; every decision needs to be based on sound data and well-supported by evidence. The development of the sepsis bundles is an attempt to try and improve and standardise clinical implementation of the guidelines, allowing for a degree of flexibility in how the bundles are applied at a local level, while still stressing the importance of including each bundle element. However, who is going to 'apply' the sepsis bundle, to verify that it has been implemented in full, and to perform the required ongoing data collection and analysis? Will it require a specially employed assistant, and if so who will finance this? Or will it be added to the workload of the already overburdened clinician? These are issues that need to be carefully considered if this system is going to be effectively implemented.

Another limitation of the current sepsis bundles is the problem of haemodynamic management. The bundle includes a very crude assessment of fluid challenge, and the recommendation to give vasopressors when the patient is not responding adequately to fluid administration. It is highly likely that the sepsis bundles will be claimed as support by those who do not provide sufficient amounts of fluids and give excessive amounts of vasopressor agents, a situation that we are actually trying to avoid! I would suggest that we need to be more specific in terms of fluid challenge, giving it under strict control of cardiac filling pressures until no further clinical improvement, and simply avoiding hypotension (this obviously allows vasopressor agents to be used when required). This criticism may seem semantic, but it is not: avoidance of hypotension is essential, and vasopressor agents provide one means of achieving this, but it is not the use of vasopressors themselves that is beneficial.

Another limitation with the sepsis bundles is the time factor: Once time limits are created, one may feel one's management is optimal as long these relatively artificial limits are respected. As a crude example, if antibiotics must be given within 3 h, is it acceptable to slightly delay their administration in fulminant septic shock or in meningoccemia, as long as the 3-h limit is not exceeded? If drotrecogin alfa (activated) should be considered within 24 h, would it be acceptable to give it say after 14 h, when it could have been given 2 or 3 h earlier?

Finally, as mentioned above, intensive care research does not stop simply because a set of guidelines has been published and there is therefore no more to be said on the issue! Many uncertainties remain across the field of intensive care medicine, and in sepsis in particular, e.g. which intravenous fluids and how much fluid should be used during resuscitation? Which vasoactive drugs should be used and to which endpoints should they be titrated? Should corticosteroids be given in patients with severe sepsis as well as those with septic shock? As newer techniques

to monitor the microcirculation become available, should we adjust the dose of drotrecogin alfa (activated) or the duration of treatment according to microcirculatory parameters? Although we have made considerable progress in the management of the patient with severe sepsis and septic shock, these questions and many others require further study to provide us with the answers that will ensure that treatment is optimised and outcomes maximised. As the results of such trials become available, they will need to be incorporated into the guidelines (and bundles) as rapidly as possible to ensure that patients continue to be treated with the very latest best standard of care if the Surviving Sepsis Campaign targets are to be achieved.

Conclusions

The Surviving Sepsis Campaign guidelines have been described as 'landmark' (http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis/SepsisExpertHostMitchellLevy.htm), and they indeed represent an important advance in the management of patients with severe sepsis and septic shock. However, many of the recommendations are based on low-grade evidence and many uncertainties remain. Translating the guidelines into sepsis bundles may facilitate their implementation into clinical practice, but the logistics of this approach may make it difficult for some hospitals or units to do so, and a checklist approach may be preferable. Checklists are widely used outside medicine, e.g. by airline pilots to monitor safety measures. To improve team communication in the ICU and help prevent oversights in key areas of ICU patient management; we recently proposed the FAST HUG mnemonic (for feeding, analgesia, sedation, thromboembolic prophylaxis; head of bed elevation; ulcer prevention; and glucose control) [18]. For the management of the patient with severe sepsis, I propose rather a checklist of ten items, listed in Table 2, which, when treating a sepsis patient, should each be met as soon as possible, thereby avoiding any potential problems with artificially imposed time limits.

Table 2. Severe Sepsis Resuscitation Checklist. Each item should be accomplished as soon as possible

- Arterial blood gases with blood lactate concentrations measured
- Blood and other relevant cultures prior to antibiotic administration
- Broad-spectrum antibiotics likely to cover all pathogens
- Placement of a central venous catheter
- Fluid challenge based on central venous pressure (stop when an increase in CVP is not followed by any clinical improvement)
- Keep adequate blood pressure at all times (usually > 65 mmHg); place an arterial catheter in case of arterial hypotension
- Maintain central venous oxygen saturation or mixed venous oxygen saturation $\geq$ 70%
- Assess eligibility for the use of drotrecogin alfa (activated)
- Avoid hyperglycaemia (150 mg/dl may be an acceptable limit)
- Administer steroids in septic shock (unless normal ACTH test)
- If receiving mechanical ventilation, maintain inspiratory plateau pressure (if possible <30 cmH_2O)

The Surviving Sepsis Campaign represents the considerable progress we have made in recent years in the management of the patient with sepsis, and carries hope for the future, but further discussion and study are needed to help us interpret and implement the guidelines optimally.

References

1. Heyland DK, Dhaliwal R, Drover JW et al (2003) Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. J Parenter Enteral Nutr 27:355–373
2. MacIntyre NR, Cook DJ, Ely EW Jr et al (2001) Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 120:375S-395S
3. Truog RD, Cist AF, Brackett SE et al (2001) Recommendations for end-of-life care in the intensive care unit: The Ethics Committee of the Society of Critical Care Medicine. Crit Care Med 29:2332–2348
4. Bergman DA (1999) Evidence-based guidelines and critical pathways for quality improvement. Pediatrics 103:225–232
5. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32:858–873
6. Bernard GR, Vincent JL, Laterre PF et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
7. Levy MM, Pronovost PJ, Dellinger RP et al (2004) Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. Crit Care Med 32:S595-S597
8. Nguyen HB, Corbett SW, Cho T et al (2004) Improving the uniformity of care with the STOP sepsis bundle. Crit Care Med 32:A11-A44 (abs)
9. Ferreira F, Vincent JL, Brun-Buisson C et al (2001) Doctors' perceptions of the effects of interventions tested in prospective, randomised, controlled, clinical trials: results of a survey of ICU physicians. Intensive Care Med 27:548–554
10. Vincent JL (2000) Which therapeutic interventions in critical care medicine have been shown to reduce mortality in prospective, randomized, clinical trials? Crit Care Med 28:1616–1620
11. Vincent JL (2004) Evidence-based medicine in the ICU: important advances and limitations. Chest 126:592–600
12. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31:1250–1256
13. Calandra T, Cohen J (2005) The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 33:1538–1548
14. Hopf HW (2003) Molecular diagnostics of injury and repair responses in critical illness: what is the future of 'monitoring' in the intensive care unit? Crit Care Med 31:S518-S523
15. Annane D, Sebille V, Charpentier C et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
16. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in the critically ill patient. N Engl J Med 345:1359–1367

17. Krinsley JS (2004) Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 79:992–1000
18. Vincent JL (2005) Give your patient a fast hug (at least) once a day. Crit Care Med 33:1225–1229

PERIOPERATIVE MEDICINE

Chapter 46

Perioperative cardiac risk stratification

M. Brudniewski, A.P. Schmidt, J.O.C. Auler jr

Cardiovascular events are considered the main cause of death in the perioperative period. The most important events are acute myocardial infarction (AMI), unstable angina, cardiac failure, severe arrhythmias, and sudden death. In this scope, patients often need clinical consultation to stratify the perioperative cardiac risk.

The prevalence of cardiovascular disease increases with age, and it is estimated that the number of persons older than 65 years in the United States will increase 25–35% over the next 30 years [1]. Unfortunately, this is the same age group in which the largest number of surgical procedures is performed [2].

The purpose of preoperative evaluation is not to give medical clearance but rather to evaluate the patient's current medical status; make recommendations concerning the evaluation, management, and risk of cardiac problems over the entire perioperative period; and provide a clinical risk profile that the patient, primary physician, anaesthesiologist, and surgeon can use in making treatment decisions that may influence short-and long-term outcomes. No test should be performed unless it is likely to influence patient treatment [3]. The cost of risk stratification cannot be ignored. The need for better methods of objectively measuring cardiovascular risk has led to the development of multiple non-invasive techniques in addition to established invasive procedures [3].

If successful, cardiac risk stratification classifies patients into various risk categories so that their management can be tailored to their needs. Low-risk patients may be spared further testing, and postoperative management may be changed for patients at higher risk [4, 5]. The goal of risk stratification is to reduce overall mortality and morbidity. Clarification of risk status allows clinicians to provide better informed consent. From a societal perspective, reducing perioperative complications and avoiding unnecessary testing could result in substantial cost savings. The major harms of stratification arise from the use of potentially unnecessary preoperative exams and the consequent possibility of ineffective or harmful interventions. Harm may also result from delay of the planned noncardiac surgery [6]. Therefore, the goal of consultation is the rational use of testing in an era of cost containment and optimal care of the patient [3].

The consultant should also bear in mind that perioperative evaluation may be the ideal opportunity to affect long-term treatment of a patient with significant cardiac disease or risk of such disease. The referring physician and patient should be informed of the results of the evaluation and the implications for the patient's prognosis. The consultant can also assist in planning for follow-up [3].

Clinical predictors of risk

There are three clinical predictors groups of surgical risk: (1) type of surgery, (2) patient's functional status, and (3) cardiac risk factors, which are based on clinical data.

Type of surgery

The clinician should analyse whether emergency surgery is required, and the nature of the surgical procedure. Emergency surgery is associated with a major number of perioperative cardiac events. Mangano et al. [1] determined that cardiac complications are two to five times more likely to occur in emergency surgical procedures than in elective operations. This finding is not surprising because the necessity for immediate surgical intervention may makes it impossible to evaluate and treat such patients optimally [3]. For example, the mortality rate for repair of patients with ruptured abdominal aortic aneurysms is more than ten times higher than that for elective asymptomatic aneurysms [7]. For elective surgery, cardiac risk can be stratified according to a number of factors, including the magnitude of the surgical procedure. A large-scale study supported the low morbidity and mortality rates in superficial procedures performed on an ambulatory basis [8]. Several large surveys have demonstrated that perioperative cardiac morbidity is particularly concentrated among patients who undergo major thoracic, abdominal, or vascular surgery, especially when they are 70 years of age or older [1, 9–12]. Major surgery is related to procedure stress, which depends on anaesthetic-surgery time, loss of fluids and blood, and haemodynamic instability (Table 1) [3]. Patients who require vascular surgery appear to have an increased risk of cardiac complications, because many of the risk factors contributing to peripheral vascular disease are also risk factors for CAD. The usual symptomatic presentation for CAD in these patients may be obscured by exercise limitations imposed by advanced age and/or intermittent claudication, and major arterial operations are often time-consuming and may be associated with substantial fluctuations in intravascular fluid volumes, cardiac filling pressures, systemic blood pressure, heart rate, and thrombogenicity [1]. Some studies [13, 14] suggested that clinical evidence of CAD in a patient who has peripheral vascular disease appears to be a better predictor of subsequent cardiac events than the particular type of peripheral vascular operation to be performed. In addition, certain situations do not lend themselves to comprehensive cardiac evaluation, although surgical care may be qualified as semi-elective. In some patients, the impeding danger of the disease is greater than the anticipated perioperative risk. Examples include patients who require arterial bypass for limb salvage or mesenteric revascularisation to prevent intestinal gangrene. Patients with malignant neoplasm also pose a diagnostic and therapeutic dilemma with respect to preoperative cardiac risk evaluation [3]. Although CAD is the overwhelming risk factor for perioperative morbidity, procedures of different levels of stress are associated with different levels of morbidity and mortality. Superficial and ophthalmologic procedures represent the lowest risk and are rarely associated with

excess morbidity and mortality. Major vascular procedures represent the highest risk. Within the intermediate risk category, morbidity and mortality vary, depending on the surgical location and extent of the procedure. Some procedures may be short, with minimal fluid shifts, while others may be associated with prolonged duration, large fluid shifts, and greater potential for postoperative myocardial ischaemia and respiratory depression. Therefore, the physician must exercise judgment to correctly assess perioperative surgical risks and the need for further evaluation [3].

Table 1. AHA cardiac risk[a] stratification for noncardiac surgical procedures

Risk	Surgery
High (reported cardiac risk often > 5%)	• Emergent major operations, particularly in the elderly • Aortic and other major vascular surgery • Peripheral vascular surgery • Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate (reported cardiac risk generally < 5%)	• Carotid endarterectomy • Head and neck surgery • Intraperitoneal and intrathoracic surgery • Orthopaedic surgery • Prostate surgery
Low[b] (reported cardiac risk generally < 1%)	• Endoscopic procedures • Superficial procedure • Cataract surgery • Breast surgery

[a]Combined incidence of cardiac death and nonfatal myocardial infarction
[b]These patients do not generally require further preoperative cardiac testing

Patient's functional status

Functional status scales have demonstrated to be good predictors of future cardiac events in the general population. The most important scales are described in detail elsewhere; briefly, they are: Duke Activity Status Index [15], Canadian Cardiovascular Society's classification of angina [16], NYHA classification of CHF [17], and the Specific Activity Scale [18]. Those scales try to correlate clinical data with patients functional status, without realising supplemental tests. However, adequate studies showing that a patient's functional status may predict cardiovascular events in the perioperative period of noncardiac surgery do not exist. The Duke Activity Status Index was developed to assess functional capacity in a manner that correlates with oxygen uptake by weighting questions according to the known metabolic cost of each activity [15]. The clinician should also observe the limitations of the scales. The Duke Activity Status Index was not studied as a predictor of cardiac events in the perioperative period of noncardiac surgery [6], neither was the Specific Activity

Scale (whose application is very difficult). Furthermore, physician's and patient's subjectivity is difficult to control when applying the scales. The NYHA and CCS scales are adequate to assess a specific group of patients, but they cannot be generalised to all patients. Studies of patients undergoing major noncardiac surgery have shown that severe limitation of activity [19] or inability to reach a target heart rate on bicycle ergometry [20] predicts postoperative cardiac risk.

Cardiac risk factors

Advanced age (> 70 years), coronary artery disease (history of myocardial infarction, angina pectoris, ischaemic ST-segment changes on electrocardiogram), congestive heart failure (CHF) (presence of ventricular dysfunction is the better predictor), arterial hypertension, diabetes mellitus (> incidence of acute myocardial infarction and silent myocardial ischaemia), and peripheral vascular disease are well-recognised cardiac risk factors.

Cardiac risk indices and algorithms in noncardiac surgery

The American Society of Anesthesiologists (ASA) score was the first clinical index developed to predict risk [21]. Although it is subjective, it has been found to be a sensitive predictor of death in very large numbers of patients (>100 000) and of major nonfatal complications [22–24]. The ASA score performs less well than other clinical risk indices in predicting cardiac complications [20, 25].

In 1977, Goldman et al. developed the original Cardiac Risk Index (Table 2). It was the first validated multivariate model developed to predict cardiac complications in a general surgical population [25]. Scores were assigned to each variable according to its weight in the model, and a risk index for cardiac death and life-threatening complications was developed. The higher the score, the higher the predicted risk; scores range from class I (low risk) to class IV (high risk). Patients with angina were excluded from this index. This is a good index for low-and high-risk patients; however, it may fail in identifying intermediate-risk patients. Nine years later, Detsky et al. [26] (Table 2) modified the original Cardiac Risk Index, added the variables of significant angina and remote myocardial infarction, and simplified the scoring system into three classes of risk (Class I: 0–15 points, Class II: 20–30 points, Class III: 30 points). The modified version improved predictive accuracy among higher-risk patients. Class II and III predict a high risk of perioperative cardiac events (10–15%). Nonetheless, a low Cardiac Risk Index scores (class I) does not reliably identify patients who have a low risk of perioperative cardiac events, and information on 'low-risk' variables should be collected for these patients [16]. In summary, based on ACP guidelines, patients should initially be assessed by using the modified Cardiac Risk Index so that patients at high risk of postoperative cardiac events can be detected. For the remaining patients, obtaining information about 'low-risk' variables will allow further clinical classification into low-and intermediate-risk groups [6].

Table 2. Cardiac risk index and modified cardiac risk index. *MI*Myocardial infarction, *ECG*electrocardiogram, *CCS*Canadian Cardiovascular Society, *CHF*congestive heart failure, *PVCs*premature ventricular contractions

Multivariate cardiac risk indicator variables	Goldman index		Detsky index	
	Variable	Points (0–53)	Variable	Points (0–110)
Age	>70 years	5	>70 years	5
History of MI or Q-wave on ECG	Within 6 months	10	Within 6 months More than 6 months previously	10 5
History of angina	Not independently predictive		CCS class III CCS class IV	10 20
Left ventricular dysfunction or CHF	S3 or jugular venous distension	11 11	Pulmonary oedema within 1 week Any previous pulmonary oedema	10 5
Arrhythmia	Any rhythm other than sinus >5 PVCs	7	Any rhythm other than sinus >5 PVCs	5
Other heart disease	Important aortic stenosis	3	Critical aortic stenosis	20
Other medical problems	Any of the following: PO_2 <60 mmHg, PCO_2 > 50 mmHg, K^+ concentration <3 mmol/l, BUN level > 50 mmol/l, creatinine concentration> 260 µmol/l, bedridden	3	Any of the following: PO_2 <60 mmHg, PCO_2 > 50 mmHg, K^+ concentration <3 mmol/l, BUN level> 50 mmol/l, creatinine concentration > 260 µmol/l, bedridden	5
Findings for ischaemia on ECG	Not independently predictive		Not independently predictive	
Type of surgery	Emergency Intrathoracic or abdominal	4 3	Emergency	10
Scores	Class I Class II Class III Class IV	0–5 6–12 13–25 > 25	Class I Class II Class III	0–15 20–30 > 30

Algorithms are used in the assessment of cardiac risk in the perioperative period to aid in the decision whether the clinician should perform supplementary evaluation or not. The most commonly used algorithms are from the American College of Cardiology (ACC)/American Heart Association (AHA) and from the American College of Physicians (ACP). The ACP uses the modified Cardiac Risk

Index for the initial cardiac risk assessment, and then, in Detsky class I patients, increases the number of risk variables (Table 3) for greater precision (Figs. 1, 2). The ACC/AHA algorithm does not use the specific Cardiac Risk Index, but determines the risk of cardiac events through variables. It ranks low-, intermediate-, and high-risk for cardiac events patients, and uses non-invasive tests, based on metabolic equivalents and type of surgery, for the diagnosis of perioperative ischaemia (Fig. 3).

Table 3. Low-risk variables for ACP algorithm. *ECG*Electrocardiogram, *AMI*acute myocardial infarction. Adapted form ACP guidelines

> 70 years	Heart failure history
Angina history	Hypertension with severe left ventricular hypertrophy
Diabetes mellitus	Ischaemic ST abnormalities on resting ECG
Q-waves on ECG	Ventricular ectopy history
AMI history	

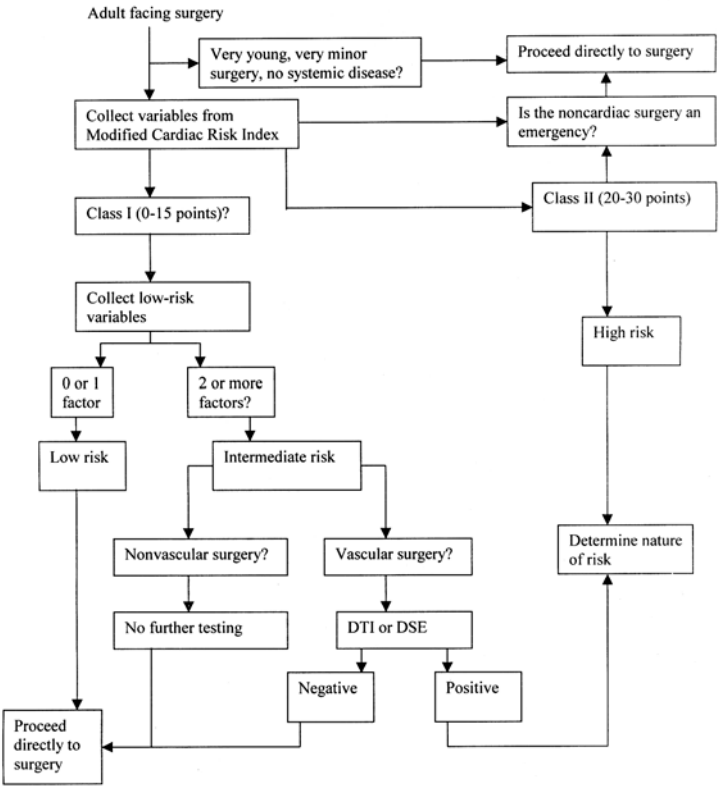


Fig. 1. Adapted from American College of Physicians Algorithm for the risk assessment and management of patients at low or intermediate risk for perioperative cardiac events. *DTI* Dipyridamole thallium imaging, *DES* dobutamine stress echocardiography

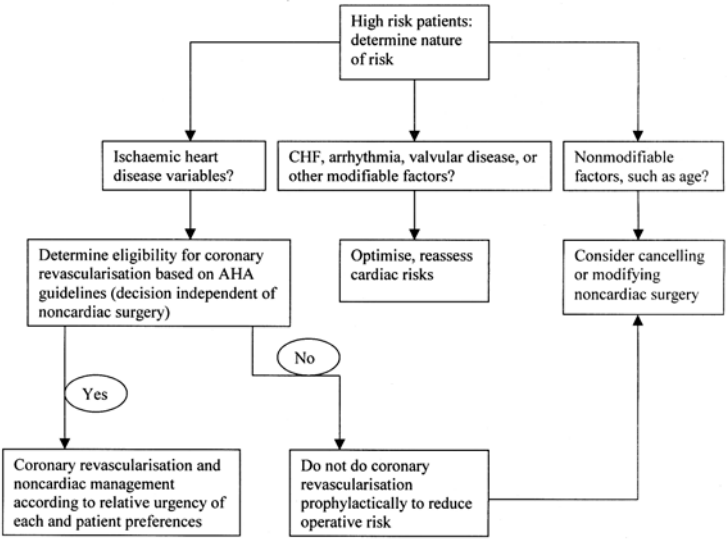


Fig. 2. Adapted from ACP Algorithm for the management of patients at high risk for perioperative cardiac events

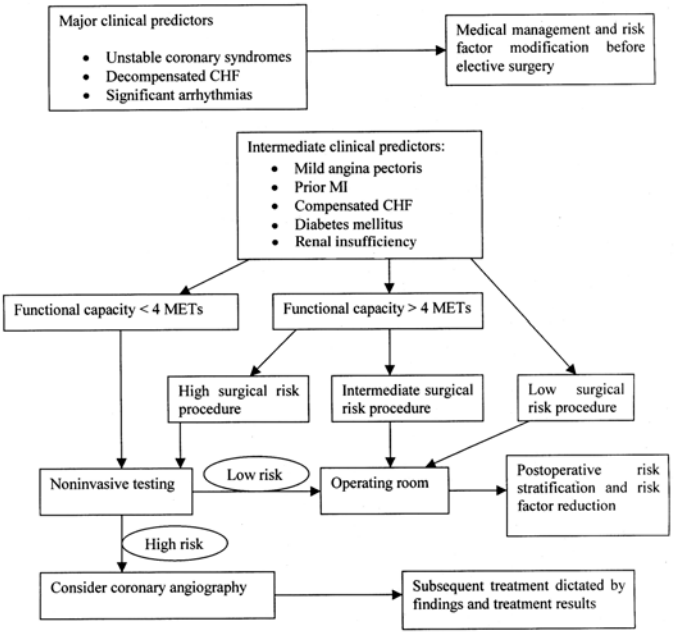


Fig. 3. Algorithm to preoperative cardiac assessment. *CHF*Congestive heart failure, *MI* myocardial infarction, *METs*metabolic equivalents, *ECG*electrocardiogram. (Adapted from ACC/AHA)

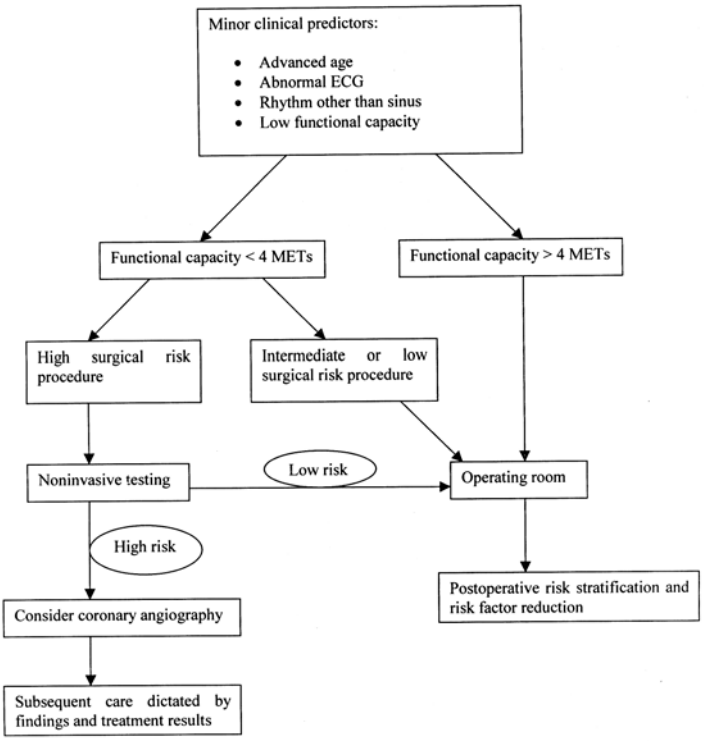


Fig. 4. Algorithm to preoperative cardiac assessment. *CHF* Congestive heart failure, *MI*myocardial infarction, *METs* metabolic equivalents, *ECG* electrocardiogram. (Adapted from ACC/AHA)

Supplemental preoperative evaluation

When assessing a patient's risk of major cardiac events during or after a noncardiac operation, the clinician uses clinical evaluation to determine the risk of fatal and nonfatal cardiac events and may refine the risk assessment of intermediate-risk patients through non-invasive testing [16].

Non-invasive tests available for further risk stratification include those that assess left ventricular function (radionuclide angiography, echocardiography, and contrast ventriculography), cardiac ischaemia (exercise or pharmacological stress testing and ambulatory electrocardiography monitoring), or both (dobutamine stress echocardiography) [16]. Identification of high-risk patients whose long-term outcome would be improved with medical therapy or coronary revascularisation procedures is a major goal of preoperative non-invasive testing [3].

Postoperative events probably have multifactorial causes; therefore, non-inva-

sive testing may never be able to stratify patients fully. Tests done before surgery cannot account for every intra-and postoperative factor. For example, the perioperative period is a time of hypercoagulability, catecholamine surges, pain, and operative stresses, all of which may influence oxygen demand, and of factors other than coronary stenosis that may influence oxygen supply, leading to myocardial ischaemia [6].

The perioperative guidelines from the ACC/AHA recommend testing before surgery when two of three factors are present that are intermediate clinical predictors (Canadian class 1 or 2 of angina, prior myocardial infarction, based on history or pathologic Q waves, compensated or prior heart failure, or diabetes), poor functional capacity (~4 metabolic equivalents, METs), and high surgical risk procedure (aortic repair or peripheral vascular surgery, prolonged surgical procedures with large fluid shifts or blood loss, and emergency major operations). Emergency major operations may require immediate proceeding to surgery without sufficient time for non-invasive testing or preoperative interventions [3].

Resting left ventricular function

Studies demonstrated a greater risk of complications in patients with a left ventricular ejection fraction (LVEF) < 35% [27–33]. Poor left ventricular systolic or diastolic function is mainly predictive of postoperative heart failure, and in critically ill patients, death. However, left ventricular function was not found to be a consistent predictor of perioperative ischaemic events [3]. Preoperative non-invasive evaluation of left ventricular function is recommended in patients with current or poorly controlled heart failure (HF), or with prior HF, and in patients with dyspnoea of unknown origin [3].

Assessment of risk for CAD and functional capacity

In recent episodes of chest pain or the ischaemic equivalent in clinically intermediate-or high-risk patients scheduled for an intermediate-or high-risk operative procedure, the 12-lead ECG is recommended for: asymptomatic persons with diabetes mellitus, patients with prior revascularisation, asymptomatic male more than 45 years old or females more than 55 years old with two or more atherosclerotic risk factors, or patients with prior hospital admission for cardiac causes [3].

The exercise or pharmacological stress testing is recommended if there is a diagnosis of patients with intermediate pre-test probability of CAD; prognostic assessment of patients undergoing initial evaluation for suspected or proven CAD; evaluation of subjects with significant change in clinical status; demonstration of proof of myocardial ischaemia before coronary revascularisation; evaluation of adequacy of medical therapy; prognostic assessment after an acute coronary syndrome; evaluation of exercise capacity when subjective assessment is unreliable; diagnosis of CAD patients with high or low pre-test probability; those with resting ST depression less than 1 mm, those undergoing digitalis therapy, and those with

ECG criteria for left ventricular hypertrophy; and detection of restenosis in high-risk asymptomatic subjects within the initial months after PCI [3].

Coronary angiography is recommended in the perioperative evaluation before noncardiac surgery for patients with suspected or known CAD with evidence for high risk of adverse outcome based on non-invasive test results, angina unresponsive to adequate medical therapy, unstable angina, equivocal non-invasive test results in patients at high-risk undergoing high-risk surgery; multiple markers of intermediate clinical risk and planned vascular surgery; moderate to large region of ischaemia on non-invasive testing but without high-risk features and without lower LVEF; non-diagnostic noninvasive test result in patients of intermediate clinical risk undergoing high-risk noncardiac surgery; urgent noncardiac surgery while convalescing from acute MI; perioperative MI; medically stabilised class III or IV angina and planned low-risk or minor surgery [34].

Risk stratification in cardiac surgery

In cardiac surgery, it has long been accepted that operative or hospital mortality is an indicator of quality of care. This is true to a large extent: death following heart surgery is often due to failure to achieve a satisfactory cardiac outcome, itself the cause of major early morbidity and poor long-term results. Crude operative mortality fails as a measure of quality only when there are major variations in case mix. For operative mortality to remain a valid measure of quality of care, it must be related to the risk profile of the patients receiving surgery, hence the need for a reliable risk stratification model [35]. Another reason for the regular use of risk stratification in the assessment of cardiac surgical results is to avoid the impression that some surgeons and hospitals seem to have worse results than others, whereas in fact this is due to their treating a large proportion of high-risk patients [35].

Currently, there are two scales for risk stratification in cardiac surgery: the EuroSCORE [35] and the Bedside Estimation of Risk (Bernstein and Parsonnet) [36].

The EuroSCORE has three groups of risk factors with respective weights:

1. Patient-related factors: age over 60 (one point per 5 years or part thereof), female (1), chronic pulmonary disease (1), extracardiac arteriopathy (2), neurological dysfunction (2), previous cardiac surgery (3), serum creatinine 200mmol/l (2), active endocarditis (3), and critical preoperative state (3).
2. Cardiac factors: unstable angina on intravenous nitrates (2), reduced left ventricular ejection fraction (30–50%: 1, 30%: 3), recent (< 90 days) myocardial infarction (2), and pulmonary systolic pressure 60mmHg (2); and
3. Operation-related factors: emergency (2), other than isolated coronary surgery (2), thoracic aorta surgery (3), and surgery for post-infarct septal rupture (4).

In a study of 14 799 patients, the mortality rates per group were: low-risk group (EuroSCORE 1–2): 0.8%, medium-risk group (EuroSCORE 3–5): 3%, and high-risk group (EuroSCORE 6 plus): 11.2% [35]. This is a simple, objective, and up-to-date system for assessing heart surgery.

In 2000, Bernstein and Parsonnet reported the Bedside Estimation of Risk in cardiac surgery through a logistic regression model in which 47 potential risk factors were considered. A method requiring only simple addition and graphic interpretation was designed for approximating the estimated risk easily and quickly.

The risk factors and respective points analysed by this score system are: female gender (6), age (70–75: 2.5, 76–79: 7, > 80: 11), congestive heart failure (2.5), severe chronic obstructive pulmonary disease (6), diabetes (3), ejection fraction (30–49%: 6.5, < 30%: 8), hypertension (3), left-mainstem stenosis > 50% (2.5), morbid obesity (1), preoperative intraaortic balloon pump (4), first operation (10), second or subsequent reoperation (20), aortic valve procedure (0), mitral valve procedure (4.5), combination valve procedure and aortocoronary bypass (6). The graph provided by the model allows determination of the estimated risk from the total score obtained by summing the individual scores for the risk factors present. It allows the risk of surgical mortality faced by an individual patient to be estimated, which provides an informative aid to patients and physicians contemplating cardiac surgery [36].

References

1. Mangano DT (1990) Perioperative cardiac morbidity. Anesthesiology 73:153–184
2. Fleisher LA, Eagle KA (2001) Lowering cardiac risk in noncardiac surgery. N Engl J Med 345:1677–1682
3. Eagle KA, Berger PB, Calkins H, et al (2002) ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 105:1257–1267
4. Wong T, Detsky AS (1992) Preoperative cardiac risk assessment for patients having peripheral vascular surgery. Ann Intern Med 116:743–753
5. Wenger NK (1990) A 50-year-old useful report on coronary risk for noncardiac surgery [Editorial]. Am J Cardiol 66:1375–1376
6. Palda VA, Detsky AS (1997) Perioperative assessment and management of risk from coronary artery disease. Ann Intern Med 127:313–328
7. Taylor LM Jr, Porter JM (1987) Basic data related to clinical decision-making in abdominal aortic aneurysms. Ann Vasc Surg 1:502–504
8. Warner MA, Shields SE, Chute CG (1993) Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437–1441
9. Backer CL, Tinker JH, Robertson DM et al (1980) Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257–262
10. Greenburg AG, Saik RP, Pridham D (1985) Influence of age on mortality of colon surgery. Am J Surg 150:65–70
11. Plecha FR, Bertin VJ, Plecha EJ et al (1985) The early results of vascular surgery in patients 75 years of age and older: an analysis of 3259 cases. J Vasc Surg 2:769–774
12. Goldman L (1983) Cardiac risks and complications of noncardiac surgery. Ann Intern Med 98:504–513
13. Roger VL, Ballard DJ, Hallett JW Jr et al (1989) Influence of coronary artery disease on

morbidity and mortality after abdominal aortic aneurysmectomy: a population-based study. Am Coll Cardiol 14:1245–1252
14. L'Italien GJ, Cambria RP, Cutler BS et al (1995) Comparative early and late cardiac morbidity among patients requiring different vascular surgery procedures. J Vasc Surg 21:935–944
15. Hlatky MA, Boineau RE, Higginbotham MB et al (1989) A brief self administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 64:651–654
16. Palda VA, Detsky AS (1997) Guidelines for assessing and managing the perioperative risk from coronary artery disease associates with major noncardiac surgery. Report of the American College of Physicians. Ann Intern Med 127:309–328
17. Eagle KA, Brundage BH, Chaitman BR et al (1996) Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/ American Heart Association Task Force on Guidelines (Committee) on perioperative cardiovascular evaluation for noncardiac surgery). Circulation 93:1280–1316
18. Goldman L, Hashimoto B, Cook F, et al (1981) Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation 64(6):1227–1234
19. Browner WS, Li J, Mangano DT (1992) In-hospital and long-term mortality in male veterans following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 268:228–232
20. Gerson MC, Ilurst JM, Ilertzberg VS et al (1985) Cardiac prognosis in noncardiac geriatric surgery. Ann Intern Med 103:832–837
21. Drips RD, Lamont A, Eckenhoff JE (1961) The role of anesthesia on surgical mortality. JAMA 178:261–266
22. Cohen MM, Duncan PG (1988) Physical status score and trends in anesthetic complications. J Clin Epidemiol 41:83–90
23. Owend WD, Dykes MI, Gilbert JP et al (1975) Development of two indices of postoperative morbidity. Surgery 77:586–592
24. Menke IL, Klein A, John KD et al (1993) Predictive value of ASA classification for the assessment of perioperative risk. Int Surg 78:266–270
25. Goldman L, Caldera DL, Nussbaum SR et al (1977) Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845–850
26. Detsky AS, Abrams HB, McLaughlin JR et al (1986) Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1:211–219
27. Fletcher JP, Antico VF, Gruenewald S et al (1989) Risk of aortic aneurysm surgery as assessed by preoperative gated heart pool scan. Br J Surg 76:26–28
28. Pedersen T, Kelbaek H, Munck O (1990) Cardiopulmonary complications in high-risk surgical patients: the value of preoperative radionuclide cardiography. Acta Anaesthesiol Scand 34:183–189
29. Lazor L, Russel JC, DaSilva J et al (1988) Use of the multiple uptake gated acquisition scan for the preoperative assessment of cardiac risk. Surg Gynecol Obstet 167:234–238
30. Pasternack PF, Imparato AM, Bear G et al (1984) The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysms resection. J Vasc Surg 1:320–325
31. Mosley JG, larke JM, Ell PJ et al (1985) Assessment of myocardial function before aortic surgery by radionuclide angiocardiography. Br J Surg 72:886–887
32. Fiser WP, Thompson BW, Thompson AR et al (1983) Nuclear cardiac ejection fraction and cardiac index in abdominal aortic surgery. Surgery 94:736–739

33. Halm EA, Browner WS, Tubau JF et al (1996) Echocardiography for assessing cardiac risk in patients having noncardiac surgery. Ann Intern Med 125:433–441
34. Scanlon PJ, Faxon DP, Audet AM, et al (1999) ACC/AHA guidelines for coronary angiography: a report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 33:1756–1824
35. Nashef SAM, Roques F, Michel P et al (1999) European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardio-Thorac Surg 16:9–13
36. Bernstein AD, Parsonnet V (2000) Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg 69:823–828

Chapter 47

Risk evaluation and anaesthetic strategy in perioperative myocardial ischaemia

B. Drenger

The patient with coronary artery disease (CAD) presents a special challenge to the anaesthesiologist. The combination of an increased surgical stress response with limited coronary reserve exposes the patient to a particularly vulnerable situation during the perioperative period. Typically, patients with CAD are older, with a higher rate of co-morbidities and thus more sensitive to the development of haemodynamic instability and organ dysfunction. The current trend of more aggressive surgical intervention in sicker patients, in whom the prevalence of CAD is higher, creates a requirement for the development of more comprehensive approach to the perioperative management of these patients.

Today, the continual search for defining new standards of patient care is of particular relevance for cardiovascular anaesthesiologists. The development of new monitoring modalities and new anaesthetic strategies are creating processes that make it possible for patients to survive complex operations and that may change patient outcome.

Current trends in anaesthesia education

In recent years, we have witnessed dramatic changes in patient management, with extensive involvement of the anaesthesiologist in clinical decision-making in the patient with heart disease. Advancements in monitoring technology and pharmacological management and support have promoted new educational opportunities for the anaesthesiologist-in-training. An important aspect of education is the implementation of patient safety practices in the daily routine. Patient safety practice is defined as a process whose application reduces the probability of adverse events resulting from medical action or procedure. Not all interventions, no matter how much they are supported by common sense or how physiologically sound they are, will stand the scrutiny of evidence-based medicine and fulfil standards of safety and effectiveness. Thus, particularly in the face of limited resources, we have to prioritise interventions and treatment strategies that promote quality improvement and patient safety. We also have to promote practice methods that emphasise the prevention of adverse events and not only, although important, the prevention of errors. For example, transoesophageal echocardiography (TEE) is one of the methods developed for intraoperative decision-making and instant evaluation of quality of surgical practice [1].

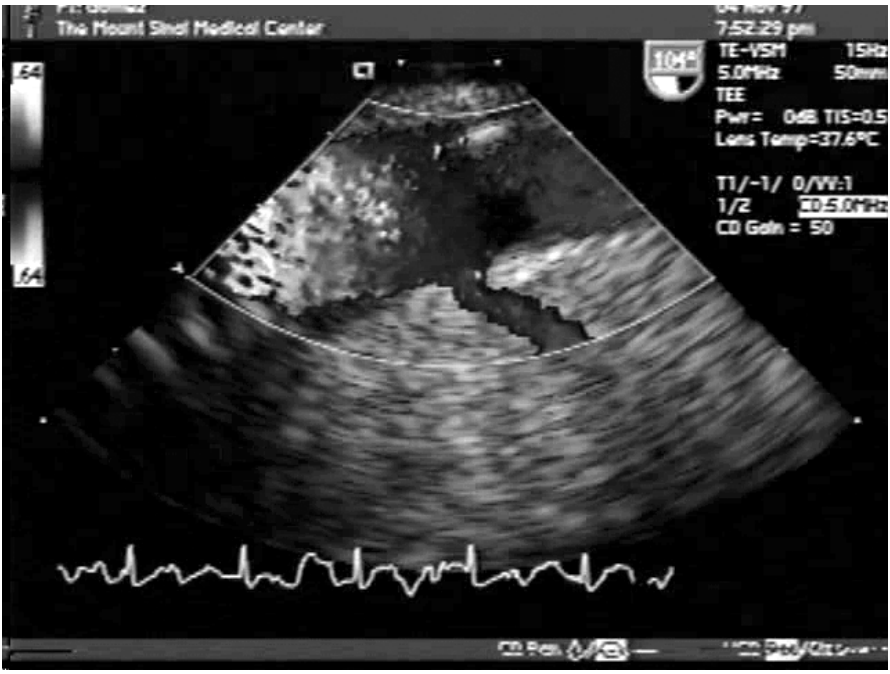


Fig. 1. Transoesophageal echocardiography (TEE) guidance in endovascular aortic repair: Demonstration of type II retrograde non-graft related endoleak

TEE has introduced a new dimension for real-time elaborated evaluation of cardiac chambers and valves, haemodynamic assessment of ventricular function, therapeutic interventions, and guidance of instrumentation insertion during percutaneous approach for minimally invasive direct-vision CABG procedures and aortic endovascular repair.

Of similar importance are the new non-invasive methods for cardiac output measurement, which may also provide information on aortic blood flow or estimates of stroke volume. All of these methods are of particular importance in reducing medical errors, thus promoting quality improvement and patient satisfaction.

An integral part of the progress in education in anaesthesia is the involvement of the anaesthesiologist-in-training in clinical research. Whatever we achieve in basic research is only applicable in our patients after testing in humans. This task becomes more difficult every day, with increasingly strict regulations, but it does not rule out our ability to perform hypothesis-driven original research, in addition to multi-centre and industry-supported studies. Only original research will promote the in-depth involvement and specific interest of our residents and fellows in cardiovascular medicine.

Physiological perturbations in the perioperative period are related to the increased effect of the stress response on the coronary circulation during surgery and anaesthesia. The result of the imbalance between myocardial oxygen supply (in-

creased contractile force per unit of time) and demand (shortening of the diastolic time) is only one component contributing to the phenomenon of intraoperative myocardial ischaemia. Activation of peripheral and central neural responses has a major impact on the coronary circulation, which promotes peripheral release of local inflammatory mediators, such as cytokines and prostaglandins, and central activation of the hypothalamic-pituitary-adrenal axis. The latter stimulates the release of catecholamines, cortisol and other stress hormones from the adrenals, which cause tachycardia, hypertension, and inflammatory responses, such as hypercoagulability and leukocyte activation [2]. Cardiovascular morbidity is therefore related to the sustained burst in the body's inflammatory response and immune function. The continuation of the stress response in these CAD patients into the postoperative period, and the surgical pain promote coronary and peripheral vasoconstriction, increased afterload, and hypercoagulability and thus, an increased risk for myocardial ischaemia. At this time it remains unclear whether specific anaesthetic techniques offer any benefit in terms of improved patient outcome, patient satisfaction, or reduced use of medical resources. Moreover, it may be the anaesthetic strategy rather than the anaesthetic technique that changes patient outcome. Among those strategies, special emphasis should be given to systematic preoperative evaluation, intraoperative patient monitoring, medical control of heart rate, prevention of blood prothrombotic state, preservation of normothermia, and continuation of strict patient monitoring in the postoperative period.

General vs regional anaesthesia

The anaesthetic technique may affect the stress response differentially. While general anaesthesia (GA) usually does not attenuate the release of stress hormones, regional anaesthesia (RA) may modulate afferent neural stimulation pathways. However, adrenergic tone, as assessed by plasma concentrations of catecholamines and cortisol, are not consistently diminished in RA patients [3]. Nevertheless, Yeager et al. [3] demonstrated that, even with similar plasma cortisol concentrations, a significantly higher incidence of cardiac and respiratory complications was shown in the GA group than in RA patients.

The pivotal question is whether epidural anaesthesia produces better outcomes than a well-balanced general anaesthetic technique. Second, and no less important, is the question whether, independently of the type of anaesthesia, the postoperative analgesic regimen changes cardiac morbidity. The low incidence of short-term cardiac events curtails researchers' ability to detect significant differences between the two types of anaesthesia. Thus, a subpopulation of high-risk patients who are particularly prone to developing haemodynamic instability may have a higher incidence of adverse cardiac morbidity, and those results might be reflected on the general population. Indeed, two groups who studied vascular patient population have shown higher cardiac morbidity in GA than in RA patients [3, 4]. In a prospective randomised study, Bode et al. [5] examined 423 lower-risk vascular

patients; they did not find any differences between the RA and the GA group. However, inadequate RA converted to GA was associated with a higher death rate than successful RA or GA (9.4% vs 1.6%). Christopherson et al. [6] investigated 100 low-risk patients who underwent lower-extremity vascular surgery under GA or RA. The incidence of cardiac morbidity and other complications was similar. However, the study had to be terminated prematurely because of the significant re-operation rate in the GA patients due to graft occlusion in the presence of comparable rates of risk factors, a fact that was attributed to a higher tendency for hypercoagulation.

Hypercoagulable state

Hypercoagulability after surgery is a phenomenon of unclear aetiology that is manifested by increased platelets activity, high fibrinogen and factor VIII concentrations, and low levels of antithrombin III; all of which may lead to an increased risk of postoperative coronary thrombosis, unstable angina, and acute myocardial infarction. The surgical stress is associated with increased release of catecholamines and angiotensin, which promote platelet aggregation, and the metabolic response is manifested by accelerated hepatic synthesis of acute-phase reactant proteins, including fibrinogen and a decrease in antithrombin III synthesis [4]. The use of epidural anaesthesia and postoperative epidural analgesia may reduce the tendency for the patient to develop a high coagulable state by reducing the stress response, thus lowering production of plasminogen activator inhibitor (improved fibrinolysis) [7].

Medical control of the stress response

Avoiding perioperative myocardial ischaemia in high-risk cardiac patients is based on preventing tachycardia, maintaining normothermia and haematocrit, and by dedicated pain management [8]. While the relationship between intraoperative tachycardia and ischaemia is not certain, and the correlation between intraoperative ischaemia and postoperative cardiac morbidity is poor, prolonged episodes of postoperative ischaemia are associated with a higher incidence of myocardial morbidity [9].

The perioperative use of β-blockade is associated with a reduction in the sympathetic stress response and ischaemic episodes. Mangano and Poldermans demonstrated a significant decrease in mortality and postoperative myocardial infarction (PMI) days and months after surgery [10, 11]. Both agreed that vascular patients are an intrinsically high-risk subgroup of patients that will benefit from a multimodal treatment approach. However, because of the inherent methodological limitations of these two studies and the absence of an obvious explanation for the improved remote patient outcome, months after the procedure, the results continue to generate substantial discussion between researchers. Recent publications,

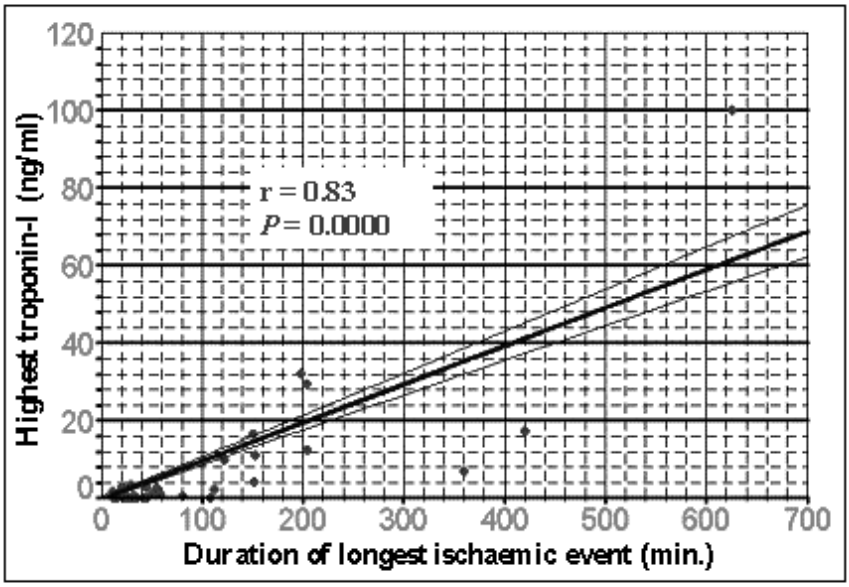


Fig. 2. Peak cTn-I is strongly correlated with the longest, as well as cumulative, ischaemia duration, and is associated with the majority of cardiac complications after vascular surgery. (Adapted from [9])

some of them still in Abstract form [12, 13], could not identify obvious differences between patients medically treated with β-blockade or placebo. The Danish Diabetic Postoperative Mortality and Morbidity (DIPOM) trial [12] showed equal composite outcome of mortality, PMI, unstable angina, and congestive heart failure (CHF) (20–21%) at 18 months follow-up, indicating that diabetes alone is not a sufficient indication to initiate β-blockade therapy and that other risk factors have a significant contribution as well. The MAVS study reported that perioperative metoprolol administration (vs placebo) also resulted in a similar primary outcome between groups [13].

Perioperative medicine is a multi-disciplinary venture and anaesthesiologists are not the only players. Surgeons, family physicians, internists, and cardiologists each have an opinion, and may not appreciate or accept what someone else recommends. As there are no formal guidelines for perioperative β-blockade, a practical approach would seem to be to initiate BB therapy in high-risk cardiac patients with no contraindications a week prior to surgery, or at least start β-blockade during surgery or soon after. It is more controversial to target the medical treatment to a certain low heart-rate threshold, but it is definitely strongly recommended not to stop current β-blockade treatment, or other anti-ischaemic therapy prior to surgery, an act that will result in a definitely worse outcome.

With regards to the controversy regarding the need for preoperative myocardial

revascularisation compared to initiating or increasing medical therapy, the debate has not yet been put to rest. Again, many variables have to be considered, i.e. the urgency of the surgical intervention, the patient's willingness, the severity of the coronary disease and the clinical symptoms, and the planned surgical procedure. Recently, McFalls et al. [14], in the VA Cooperative Study 'Coronary Artery Revascularization Prophylaxis' (CARP) trial, demonstrated, in patients scheduled for vascular surgery, a similar short- and long-term mortality rate in the PCI/CABG group vs the medical therapy group, as well as similar secondary endpoints, such as MI or stroke. Although this study emphasised the importance of aggressive perioperative therapy in vascular high-risk patients, it did not assess low-risk patients, those undergoing non-vascular surgery, or those urgently in need of surgery, who have indications for PCI/CABG prior to operation. An unanswered dilemma is the complex considerations regarding the timing of operation of PCI patients in whom drug-eluting stents were inserted. In those patients, premature cessation of antithrombotic therapy might be a grave risk for stent occlusion and MI due to the slow epithelialisation of the inner surface of the stent.

Table 1. Anaesthesia perioperative commitment

Preoperative evaluation
Continuity of medical treatment
Intraoperative monitoring and ischaemia prevention
Postoperative follow-up and monitoring
Postoperative multimodal analgesia
Multimodal strategy to enhance recovery

Perioperative comprehensive pain management

In 1979, Behar and Magora introduced the first clinical use of epidural narcotic analgesia with the first human use of epidural morphine [15]. As an evolution of this pioneering work, the current emphasis is on providing comprehensive pain management from the moment a patient arrives at hospital. Already in 1986, we showed the advantage of giving epidural methadone to relieve the pain caused by hip fracture in patients soon after their admission to the emergency room. Such patients often have severe underlying illnesses and frequently need to be stabilised prior to surgery [16]. The choice of methadone for use as an epidural narcotic was based on its high lipid solubility, which accounts for its rapid onset of action and rapid elimination, but with a prolonged duration of action (4 h). Its epidural administration is not accompanied by drug accumulation in the body nor by significant rostral spread, and thus by a low rate of urinary retention or respiratory depression. These properties are especially advantageous in elderly patients and in patients with urological problems [17].

The pre-emptive approach of early administration of regional analgesia to patients with traumatic injury, early in their hospitalisation course, continues to lead our practice, particularly in the elderly population and in those suffering from

heart disease. Recently, Matot et. al. [18] showed that the early institution of epidural analgesia to hip fracture patients who also suffered from heart disease significantly reduced the incidence of adverse cardiac events. Lower rates of fatal and non-fatal MI, CHF, new-onset atrial fibrillation, and the incidence of intra- and postoperative cardiac events were observed in comparison to a control group who received a conventional intramuscular analgesic regimen.

Understanding the pharmacokinetics of opioid administration via the spinal route (epidural or intrathecal) is a key issue for the anaesthetic management of the patient. With lipophilic drugs administered in the epidural space, the mode of administration determines the pattern of the analgesic effect, i.e. a bolus dose of fentanyl will have mainly a regional effect on spinal neural tissue, while continuous infusion will have a systemic effect, similar to I.V. administration [19]. Addition of non-opioid drugs may enhance the analgesic effect, such as with α-2 agonists (clonidine) or neostigmine, but their side effects should be taken into consideration.

Another approach to the anaesthetic care of emergent lower-extremity orthopaedic surgery patients with severe underlying illnesses (ASA 3E-4E) is based on early intervention with 3-in-1 femoral block performed immediately upon the patient's arrival at the hospital, or on admission to the ward. This approach relieves pain, permitting better nursing, reduces the amount of opioid medications and their side effects, and prevents tachycardia and secondary cardiac ischaemia. In the operating theatre, a 3-in-1 block might be performed first to allow painless positioning of the patient for sciatic nerve block or intrathecal anaesthesia. Thus, the intraoperative anaesthetic approach in this subgroup of patients who are too sick for conventional neuroaxial blockade is based on integration of peripheral nerve blocks (sciatic and femoral blocks), with or without mini-dose neuroaxial blockade at time of operation. This complex management is relevant, as in a certain percentage of patients (about 25%) peripheral blocks will not cover all nerve branches, such as the lateral femoral cutaneous nerve, the obturator nerve which innervates the hip joint capsule. This approach is also appropriate to overcome the positioning-related significant pressure feeling that remains in the perineum area.

The similarity in postoperative outcome with various types of perioperative anaesthetic strategies leads us to recognise the importance of factors such as patient satisfaction and patient comfort. Adequate pain control, avoiding nausea and vomiting, and maintaining normothermia are pivotal in reducing perioperative ischaemia. Continuation of cardiac medications and early initiation of antithrombotic agents are essential in preventing further cardiac complications.

References

1. Kolev N, Brase R, Swanevelder J; the European Perioperative TOE Research Group (1998) The influence of transoesophageal echocardiography on intra-operative decision making. A European Multicenter study. Anaesthesia 53:767–773
2. Liu SS, Carpenter RL, Neal JM (1995) Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology 82:1474–1506
3. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T (1987) Epidural anesthesia and analgesia in high-risk patients. Anesthesiology 66:729–736
4. Tuman KJ, McCarthy RJ, March RJ (1991) Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 73:696–704
5. Bode RH, Lewis KP, Zarich SW (1996) Cardiac outcome after peripheral vascular surgery: comparison of general and regional anesthesia. Anesthesiology 84:3–13
6. Christopherson R, Beattie C, Frank SM et al (1993) Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 79:422–434
7. Rosenfeld BA, Beattie C, Christopherson R et al (1993) The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 79:435–443
8. Fleisher LA (1998) Anesthetic management and perioperative surveillance. Prog Cardiovasc Dis 40:441–452
F9. Landesberg G, Luria MH, Cotev S et al (1993) Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 341:715–719
10. Mangano DT, Layug EL, Wallace A et al (1996) Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. New Engl J Med 335:1713–1720
11. Poldermans D, Boersma E, Bax JJ et al (1999) The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. New Engl J Med 341:1789–1794
12. Juul AB, Wetterslev J, Kofoed-Enevoldsen A et al (2004) The Diabetic Postoperative Mortality and Morbidity (DIPOM) trial: rationale and design of a multicenter, randomized, placebo-controlled, clinical trial of metoprolol for patients with diabetes mellitus who are undergoing major noncardiac surgery. Am Heart J. 147:677–683
13. Yang H, Raymer K, Butler R et al (2004) Metoprolol after vascular surgery. Can J Anaesth 51:A7
14. McFalls EO, Ward HB, Moritz TE (2004) Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 351:2795–2804
15. Behar M, Magora F, Olshwang D, Davidson JT (1979) Epidural morphine in treatment of pain. Lancet 1(8115):527–529
16. Nyska M, Klin B, Shapira Y et al (1986) Epidural methadone for preoperative analgesic management of patients with proximal femoral fracture. Br Med J 293:1347–1348
17. Drenger B, Magora F, Evron S, Caine M (1986) The action of intrathecal morphine and methadone on the lower urinary tract in the dog. J Urol 135: 852–855
18. Matot I, Oppenheim-Eden A, Ratrot R et al (2003) Preoperative cardiac events in elderly patients with hip fracture randomized to epidural or conventional analgesia. Anesthesiology 98:156–163
19. Ginosar Y, Riley ET, Angst MS (2003) The site of action of epidural fentanyl in humans: the difference between infusion and bolus administration. Anesth Analg 97:1428–1438

Chapter 48

Practice recommendations guidelines for pulmonary artery catheter

M. Brudniewski, A. P. Schmidt, J.O.C. Auler jr

In 1945, Dexter et al. performed the first venous catheterisation of the right atrium and ventricle (under X-ray) and, 2 years later, discovered the measuring technique of pulmonary capillary wedge pressure (PCWP) [1]. In 1970, Swan developed a new technique of catheterisation of the pulmonary artery catheter (PAC) that used a flow-directed balloon-tipped catheter, without the use of X-ray. This approach allowed PAC to be done at the bedside in the coronary or intensive care unit [1], so that intracardiac pressures, cardiac output, mixed venous oxygen saturation, and derived haemodynamic parameters can be readily determined [2].

It is estimated that nearly 1.5 million PACs are sold annually in the United States and that approximately 25% of them are used in the management of high-risk surgical and trauma patients [3]. Since its introduction, PAC has become part of the everyday management of cardiology, anaesthesiology, and intensive care patients, but its use remains controversial [4]. Connors et al. questioned the advantages of the additional information and effectiveness derived from this device [5], which provoked considerable discussion and controversy about the use of PAC. However, it must be emphasised that PAC is a diagnostic intervention, and that demonstration of a relationship between a diagnostic intervention upon patient admission to the intensive care unit (ICU) and patient outcome is especially difficult. In order for PAC to influence outcome, the information provided by the catheter must modify the treatment of the patient [2]. Since it is used in more severely ill patients, misinterpretation of results may lead to erroneous consequences, further discrediting the use of PAC [6].

Indications, adverse effects, and complications

General indications for use include obtaining information to make a diagnosis, observing the response to interventions and therapy, and providing continuous monitoring of the patient's condition.

Cardiac indications for use of PAC in critically ill patients include: acute heart failure, cardiac tamponade, cardiac output measurement, left ventricular function determination, major surgery in patients with a cardiac history, cardiogenic shock, intra-aortic balloon counterpulsation therapy, pharmacological therapy, and haemodynamic instability [1]. Other indications include trauma, sepsis, acute respira-

tory distress syndrome, pulmonary hypertension, and abdominal compartment syndrome (Table 1).

Table 1. Common indications for pulmonary artery catheter (PAC)

–Acute heart failure	–Haemodynamic instability
–Cardiac tamponade	–Trauma
–Cardiac output measurement	–Sepsis
–Left ventricular function determination	–Acute respiratory distress syndrome
–Major surgery in patients with a cardiac history	–Pulmonary hypertension
–Abdominal compartment syndrome	–Cardiogenic shock
–Pharmacological therapy	–Intra-aortic balloon counterpulsation
–Cardiac surgery	–Orthotopic liver transplantation

Complication from pulmonary artery (PA) catheterisation can occur with the establishment of central venous access, the catheterisation procedure, and catheter residence [7]. Malpositioning, unintentional puncture of nearby arteries, bleeding, neuropathy, air embolism, and pneumothorax are complications of establishing central venous access [7]. Dysrhythmias (premature ventricular and atrial contractions, ventricular tachycardia or fibrillation) are the primary and most frequently observed complications of the catheterisation procedure. Catheter advancement can produce right bundle-branch block, and in patients with left bundle-branch block it can precipitate a complete heart block [7].

Venous thrombosis, thrombophlebitis, balloon rupture, pulmonary embolism and infarction, sepsis, mural thrombus, endocardial vegetations or endocarditis, pulmonary artery rupture, and death are complications related to catheter residence [1, 7]. The incidence of venous thrombosis can be reduced with heparin. In general, the incidence of infection is related to the duration of placement, and it increases significantly when catheters are in place for more than 72–96 h. Poor technique at the time of insertion can introduce contamination from the skin flora. Pulmonary artery rupture occurs in an estimated 0.03 – 0.2% of patients. Mortality from this complication has been estimated to be 41–70% [7].

Continuous cardiac output × bolus method

Simultaneous cardiac output determination by both bolus and the continuous method is not possible because of system design, which prevents direct and instantaneous comparison between the two measurements [8].

The bolus thermodilution technique gives intermittent measurements, leading to a sequential and erratic evaluation of the patient's haemodynamic profile. It is time-consuming for physicians and nurses, subject to user-induced error due to improper injection technique, may place the patient at risk of fluid overload (e.g. hourly determinations of cardiac output for 24 h would entail giving the patient 720 ml fluid), and provides an additional site of introduction of bacteria into the blood stream. The reproducibility of cardiac output is also affected by respiration

such that there may be a 30% difference between determinations at peak inspiration versus peak expiration during mechanical ventilation [8]. Thus, bolus thermodilution is inherently less attractive as a monitoring tool than continuous measures, which average flow over time, allow haemodynamic calculations, and do not require volume administration [8]. However, the continuous technique does not provide instantaneous cardiac output measurements. The cardiac output value displayed reflects averaged data over a 3-min period.

Mihaljevic et al. [9], using an in vitro flow model, reported that both bolus and continuous cardiac output (CCO) methods possess a systematic error that causes overestimation of the real blood flow values. The degree of overestimation was significantly lower in the group of CCO measurements, especially at low flow rates. The CCO measurement provided higher accuracy and greater resistance to thermal noise than standard bolus thermodilution measurements. Lower reproducibility of the continuous method was the sole disadvantage suggested in this in vitro study.

Yelderman et al. [10] and Lichtental and Gordan [11] showed, in animal models, that the filament pulmonary artery catheter associated with the monitor could be used safely over the wide range of flow conditions encountered in the clinical environment, with no additional risk compared to standard catheters. Studies demonstrated that the continuous thermodilution method using a filament pulmonary artery catheter (IntelliCath) and a computer algorithm (Vigilance) is as accurate and precise as the reference bolus thermodilution (Edwards 9520A, Baxter) method to calculate cardiac output [12].

Compared with the intermittent cardiac output determination, the CCO system has negligible bias when patients are haemodynamically stable but this bias increases in unstable critically ill patients [13, 14]. The better reproducibility of the continuous method allows the detection of smaller variations in cardiac output, suggesting that this technique is better than the bolus technique [13–15].

Although Boldt et al. [16] demonstrated that CCO measurement agreed closely with bolus cardiac output measurement in low as well as high cardiac output conditions, Bottiger et al. [17] found a lack of agreement between the two methods when compared immediately following cardiopulmonary bypass, presumably due to the post-bypass effects of the hypothermic regimen. A decrease in the accuracy of CCO measures is observed in rapid infusion of fluid administration [18], use of an upper-body warming blanket [19], practice of veno-venous extracorporeal membrane oxygenation [20], and during liver transplantation [21]. Thus, rapid changes of temperature rather than the absolute temperature value itself probably interfere in the precision of continuous method [8].

The computerised analysis of these continuous thermodilution cardiac output devices uses a cross-correlation technique, which assumes stability of cardiac output. Consequently, a rapid change in cardiac output may lead to clinically important delays in the response of the CCO monitor [8]. The presence of intracardiac cardiac shunts in vitro (right-to-left and left-to-right) markedly affects the accuracy of thermodilution measurements, and mean systematic error is greater for continuous than for bolus measurements [9].

Haemoglobin saturation of mixed venous blood

A non-specific indicator of the total body balance between oxygen delivery and oxygen consumption of perfused tissues is provided by the haemoglobin saturation of mixed venous blood (SvO2) [8]. SvO_2 can be measured intermittently, through sample gas analysis, or continuously, using the principle of the spectrophotometry method. Major changes in SvO_2 are due to changes in oxygen transport, haemoglobin content, cardiac output, or whole-body oxygen consumption [22]. Oxygen consumption is directly proportional to the difference between arterial and mixed venous oxygen saturation, which, in turn, reflects the balance of arterial oxygen contents, global oxygen delivery (cardiac output × arterial oxygen content), and tissue oxygen extraction [8]. Mixed venous oxygenation does not reflect tissue oxygenation, only global oxygen extraction. Consequently, a normal or high SvO_2 cannot exclude tissue hypoxia in individual organs, especially in special circumstances such as sepsis or major burns, in which maldistribution of oxygenated blood is known to occur [8].

Taking into account the risks and costs of PAC, some authors examined to what extent PAC measurement of central venous oxygen saturation could replace that of SvO_2. It resulted in conflicting data, mostly depending on the patients' underlying diseases [23–25]. Furthermore, comparison of central venous oxygen saturation with that of true mixed venous blood has demonstrated a correlation between these measurements, but the absolute level of agreement of the measurements has generally been insufficient to commend central venous saturation as a useful surrogate measurement of SvO_2. Consequently, these two types of venous oxygen monitoring appear to be not interchangeable in critically ill patients [8].

Several factors, such as blood flow velocity, distance of the catheter tip from the vessel wall, haemoglobin concentration, blood coagulability, refractive index of the plasma, erythrocyte shape and position in the flowing blood stream, and degree of 'rouleaux' formation have been reported to influence the accuracy of continuous SvO_2 monitoring using fiber-optic PAC [8].

Although maintenance of the SvO_2 higher than 60% was initially suggested as an important therapeutic end-point based on one small study [26], it seems impossible to establish in the absolute a 'normal' value of SvO_2. Furthermore, SvO_2 variations appear to be more informative than the absolute value [8]. End-organ response rather than arbitrary numeric goals should ideally guide resuscitation therapy. In the setting of distribution shock states, such as sepsis, SvO_2 may be pathologically high or normal, and a fall in SvO_2 may reflect recovery rather than deterioration [8]. However, altered SvO_2 should be interpreted cautiously. Each of the four determinants of SvO_2 is independent from the others, a feature that is rarely seen in clinical practice. As the mathematical relationship between SvO_2 and its determinants is linear (SaO_2 and oxygen consumption), or hyperbolic (cardiac output and haemoglobin), the weight of SaO_2 or oxygen consumption is independent from their absolute value [8].

Heiselman et al. [27] studied the prognostic value of SvO_2 in 20 patients with septic shock, and found that if the initial SvO_2 was less than 65%, the mortality rate

was 100%. In contrast, Giunta et al. [28] reported no correlation between SvO_2 and mortality in a study of 15 septic shock patients. Jugan et al., examining the usefulness and significance of SvO_2 monitoring in orthotopic liver transplantation, concluded that continuous monitoring of SvO_2 may be useful, but cannot substitute for intermittent determinations of other haemodynamic or oxygenation parameters [29]. No benefit from SvO_2 monitoring was observed in two prospective, well-designed studies that blinded the medical management team to the SvO_2 data [30, 31].

Thus, in the absence of convincing data that continuous venous oximetry has any effect on ICU stay, morbidity, or mortality in critically ill patients, it is difficult to recommend the use of this expensive technology in all patients requiring PAC [8].

Volumetric catheter

Assessment of the patient's preload status during the resuscitation of critically ill patients is vital. Traditionally, preload has been assessed through the use of right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP), which are often referred to as the 'filling pressures.' The use of these filling pressures is based upon the assumption that ventricular compliance does not change [32]. However, in critically ill patients, ventricular compliance is dynamic, causing a variable relationship between pressure and volume [33]. The volumetric parameters include stroke volume, right ventricle end-diastolic volume (RVEDV), right ventricle end-systolic volume (RVESV), and right ventricular ejection fraction (RVEF).

Patients with a variety of clinical indications benefit from the incorporation of the volumetric catheter, including those with trauma, sepsis, acute respiratory distress syndrome, cardiac surgery, pulmonary hypertension, abdominal compartment syndrome, and therapy with PEEP [32]. Use of the volumetric PAC requires ensuring optimal catheter position for the purpose of maximal accuracy and reproducibility of measurements.

Measurements using thermal dilution technology can be disrupted by conditions causing unsteady temperature of the blood in the pulmonary artery. Examples include conditions causing large changes in venous return, such as shivering, coughing, or changes in intrathoracic pressure. The administration of large volumes of fluid over a short period of time can result in erroneous measurements. Rapid changes in the baseline temperature of the body can contribute to variations in measurements. Full-length sequential compression devices applied to the legs with a cooling device, upon inflation, may cause a large increase in venous return to the right heart consisting of blood that has been cooled, contributing to thermal 'noise.' Another situation that may contribute to unreliable measurements is the presence of tachycardia (rates greater than 150 bpm), which interferes with accurate measurements of the patient's R–R interval [32].

In a prospective clinical trial with 13 patients, Yu et al. [34] noticed that the information derived from right ventricular end-diastolic volume index does not

lead to a change in treatment in most instances. However, patients with increased intra-abdominal pressures may show misleadingly high PAOP despite low preload. These patients will clearly benefit from the additional information derived from ventricular volume measurements.

Use of end diastolic volume index (EDVI) as an end-point for resuscitation does not carry a specific value as a resuscitation target. Instead, for every patient one must ask, 'At what EDVI is the SVI the highest given the patient's RVEF?' There will be variation from patient to patient [55].The addition of continuous volumetric parameters in conjunction with CCO and SvO_2 provides a continuous assessment of preload, afterload, and contractility along with oxygen delivery and consumption [35, 36].

ASA guidelines

In 2003, the American Society of Anesthesiologists (ASA) published guidelines on the role of the PAC in the perioperative setting [7]. The ASA Task Force argued that it was difficult to determine the safety and efficacy of PAC based on scientific evidence. Three variables should be considered when determining the risks and benefits of PAC monitoring:

1. Patient factors: Patients should be evaluated for preexisting medical conditions that may increase the risk of haemodynamic instability (i.e. cardiovascular, pulmonary, or renal disease).
2. Procedure factors: Major surgical procedures may be associated with significant haemodynamic fluctuations, which may damage organ systems.
3. Practice setting factors: Complications from haemodynamic disturbances may be increased if the technical and cognitive skills of the physicians and nurses caring for the patient are poor.

Scientific evidence of effectiveness

Effects on treatment decisions

Studies in postoperative and intensive care patients have demonstrated that PAC data provide new information or seem to change therapy in 30–62% of cases (Table 2) [37–44]. However, there was no association with mortality among patients whose therapy was altered based on PAC data, but the quality of this evidence is poor [41–43].

Table 2. Studies and results of PAC on mortality rates. *ICU* Intensive care unit, *SvO_2* haemoglobin venous oxygen saturation, *GDT* goal-directed therapy, *PO* perioperative

Authors	Setting	Mortality
Connors et al. [5]	ICU	Increased
Boutros and Lee [30]	SvO_2, ICU	No benefit
Connors et al. [37]	ICU	No benefit
Eisenberg, Jaffe, Schuster [38]	ICU	No benefit
Quinn and Quebberman [39]	ICU	No benefit
Rekik et al. [40]	ICU	No benefit
Tuchschmidt and Sharma [41]	ICU	No benefit
Steingrub et al. [42]	ICU	No benefit
Mimoz et al. [43]	ICU	No benefit
Staudinger et al. [44]	ICU	No benefit
Boyd, Gounds, Bennett [45]	GDT	Decreased
Tuchschmidt et al. [46]	GDT, Sepsis	Decreased
Gattinoni et al. [47]	GDT	No benefit
Sandham et al. [48]	GDT, PO	No benefit
Berlauk et al. [49]	Vascular surgery	No benefit
Joyce et al. [50]	Aortic reconstruction	No benefit
Isaacson et al. [51]	Aortic reconstruction	No benefit
Schiller et al. [52]	Trauma	Decreased
Chang et al. [53]	Trauma	Decreased
Bishop et al. [54]	Trauma	No benefit
Chittock et al. [58]	ICU severely ill	Decreased
Chittock et al. [58]	ICU low severity illness	Increased

Preoperative catheterisation

No high-quality evidence exists to infer that routine, or even selective, preoperative catheterisation improves outcome regarding haemodynamic optimisation [7].

Perioperative monitoring

- Goal-directed therapy: The use of pre- and postoperative protocols to achieve high oxygen delivery rates was associated with significantly lower 28-day mortality rates [45]. A smaller trial also reported that a higher cardiac index was associated with lower mortality in patients with septic shock [46], although other randomised trials of goal-directed therapy have been less encouraging (increased or no difference in mortality rates). A larger trial involved 762 high-risk patients and reported no difference in mortality, organ dysfunction, or length of stay when the goals of normal cardiac index, supranormal cardiac index, and normal mixed oxygen saturation were compared [47]. Recently, Sandham et al. [48] carried out a randomised trial with 1994 high-risk (ASA physical status III or IV), elderly (60 years) patients submitted to elective or urgent major abdominal, thoracic, vascular, or hip-fracture surgery, and a minimum ICU stay of 24 h. They concluded that goal-directed therapy with PAC did not decrease mortality or postoperative morbidity compared to standard therapy without PAC.
- Haemodynamic monitoring:

1. Cardiac surgery: There is conflicting evidence from controlled studies regarding the benefit that cardiac surgery patients receive from PAC.
2. Peripheral vascular surgery: A randomised controlled trial (RCT), limited by discrepancies in data reporting and by uncertain methods of group assignment, found that patients were less likely to experience intraoperative disorders if PAC were placed preoperatively and if haemodynamic status was optimised. The postoperative complications seemed to be lower in the catheter group too. Otherwise, postoperative morbidity and mortality did not differ between groups [49].
3. Abdominal aortic reconstruction: There are only two RCTs that compared PAC and central venous catheter. No differences in outcomes were found [50, 51].
4. Neurosurgery: Studies only addressed the ability of PAC to detect air embolism and did not measure clinical outcomes.
5. Trauma: Some studies (retrospective analyses and RCT) of limited quality have suggested that haemodynamic monitoring of trauma patients, often including PAC, improves outcome [52, 53]. Another trial, involving 58 patients, reported no significant benefit from PAC and goal-directed therapy, but it also suffered from design limitations [54].
6. Obstetric-gynaecologic procedures: Evidence regarding the effectiveness of PAC is lacking.
7. Paediatric catheterisation: The effect of PAC on clinical outcomes is poorly studied.
8. Meta-analyses: A meta-analysis of 16 RCTs, between 1970 and 1996, involving PAC, yielded a relative risk ratio (RRR) of 0.81 (95% CI, 0.60–1.10) for mortality in patients treated with PAC, and in the surgical series the RRR was 0.58 (95% CI, 0.36–0.94) [55]. The same research team, with 12 of the 16 trials, calculated a RRR of 0.78 (0.65–0.94) for the incidence of organ failure [56]. However, the validity of these results is arguable given the disparate patient population and protocols and the numerous designs of the different studies. Another meta-analysis of PAC, which examined results from four homogenous controlled trials involving vascular surgery patients, yielded an odds ratio of 1.198 ($P = 0.60$; CI was not reported) [57]. Chittock et al. [58] carried out an observational cohort study of 7310 critically ill adult patients in whom PAC was used. They reported that hospital mortality rate, analysed by multivariable logistic regression, may decrease in the most severely ill patients while increasing in a population with lower severity illness.

Expert opinion of effectiveness

Due to deficiencies in the evidence, it is difficult to draw meaningful conclusions about the effectiveness and safety of PAC based on currently available data. In general, the evidence suggests that routine use of PA catheters in low-risk patients does not reduce mortality, length of stay, or other surrogate markers for severity of illness. The evidence does not exclude the possibility that PAC improves outcome in select clinical circumstances.

Clinical experiences suggest that PA catheter monitoring of selected surgical

patients can reduce the incidence of perioperative complications. The expert opinion is that access to these data for selected indications and settings, coupled with accurate interpretation and appropriate treatment tailored to haemodynamic status, can reduce perioperative mortality and morbidity through reduced cardiac and pulmonary complications.

Reliance on clinical assessment or alternative devices is inadequate; trans-oesophageal echocardiogram, which can provide similar and important additional information, may be unavailable or impractical. Numerous studies have shown that PAC data are more accurate than clinical assessment in evaluating the haemodynamic status of complicated patients.

Experience and understanding are major determinants of PAC effectiveness. Experienced PAC users can achieve better outcomes and encounter fewer complications because of their enhanced skill in the interpretation of PAC data, in the prompt design of rational treatment strategies, and in the use of safe techniques of catheter insertion and management.

The risk of PAC is both appropriate and necessary in selected surgical patients undergoing procedures associated with complications from haemodynamic changes (e.g. cardiac surgery, aortic reconstruction) or entering surgery with preexisting risk factors for haemodynamic disturbances (e.g. advanced cardiopulmonary disease). The level of haemodynamic risk should be assessed as a function of the three interrelated variables cited above.

The cost-effectiveness of the PAC cannot be properly ascertained without establishing its clinical effectiveness, and until the latter occurs, estimations of cost effectiveness can be based only on speculative assumptions.

Conclusions

Currently available evidence from published research provides incomplete information about the effectiveness of PAC monitoring and the incidence of complications. Gaps in the evidence occur at several levels: surgical procedures that have been examined represent only a subset of clinical settings; poor design and lack of statistical power to demonstrate benefit in some studies; and studies without randomised designs, which generally do not control for differences in case mix and practitioner skill).

The evidence reviewed does not support the routine use of PAC when there is a low risk of haemodynamic complications. The appropriateness of routine PAC depends on the combination of risks associated with the patient, surgery, and practice setting. Routine catheterisation is generally inappropriate for low- or moderate-risk patients.

Expert opinion suggests that PAC may benefit patients who are at high risk of complications related to haemodynamic instability during the intraoperative and postoperative periods. Reductions in morbidity and mortality will not be observed if physicians and nurses using PACs lack competence in basic technical and cognitive skills [4].

The incorporation of continuous measurements provides the caregiver with the opportunity to identify problems earlier, intervene sooner, and have information about the effects of the intervention quickly. As a result, there is an opportunity to improve patient survival and potentially reduce ICU and/or hospital length of stay, thereby containing costs [32].

References

1. Bakker R (2004) The evidence-based character of the pulmonary artery catheter (in cardiac patients). Eur J Cardiovasc Nursing 3:165–171
2. Murphy GS, Vender JS (2004) Do pulmonary artery catheters influence outcome in noncardiac surgery? In Fleisher R. Evidence-based practice of anesthesiology. Philadelphia, Saunders, pp 331–335
3. Bernard GR, Sopko G, Cerra F et al (2000) Pulmonary artery catheterization and clinical outcomes: National heart, lung, and blood institute and Food and Drug Administration workshop report. JAMA 283(19):2568–2572
4. Gómez CMH, Palazo MGA (1998) Pulmonary artery catheterization in anaesthesia and intensive care. Br J Anaesth 81:945–956
5. Connors AFJ, Speroff T, Dawson NV et al (1996) The effectiveness of right heart catheterization in the initial care of critical ill patients. JAMA 276:889–897
6. Steltzer H, Krenn CG, Krafft P et al (1997) The pulmonary artery catheter: Current status in clinical practice. Acta Anaesth Scand 41(1):84–87
7. Roizen MF, Berger DL, Gabel RA et al (2003) Practice guidelines for pulmonary artery catheterization. Anesthesiology 99:998–1014
8. Cariou A, Monchi M, Dhainaut JF (1998) Continuous cardiac output and mixed venous oxygen saturation monitoring. J Crit Care 13(4):198–213
9. Mihaljevic T, von Segesser L, Tonz M et al (1995) Continuous versus bolus thermodilution cardiac output measurements — A comparative study. Crit Care Med 23:944–949
10. Yelderman M, Quinn MD, McKown RC et al (1992) Continuous thermodilution cardiac output measurement in sheep. J Thoracic Cardiovasc Surg 104:315–320
11. Lichtental PR, Gordan D (1996) Testing the safety of Baxter continuous cardiac output monitoring system. J Clin Monit 13:243–249
12. Schmid ER, Tornic R (1994) Accuracy of continuous cardiac output by thermodilution. Anesthesiology 81:A519
13. Haller M, Zollner C, Briegel J et al (1995) Evaluation of a new continuous thermodilution cardiac output monitor in critically ill patients. Crit Care Med 23:860–966
14. Le Tulzo, Belghith M, Seguin P et al (1996) Reproducibility of thermodilution cardiac output determination in critically ill patients: Comparison between bolus and continuous method. J Clin Monitor 12:379–385
15. Lichtental PR, Wade LD (1993) Accuracy of the Vigilance/Intellicath continuous cardiac output system during and after cardiac surgery. Anesthesiology 79:A474 (abs)
16. Boldt J, Menges T, Wollbruck M, et al (1994) Is continuous cardiac output measurement using thermodilution method reliable in the critically ill patient? Crit Care Med 22:1913–1918
17. Bottiger BW, Raunch H, Bohrer H et al (1995) Continuous versus intermittent cardiac output measurement in cardiac surgical patients undergoing hypothermic cardiopulmonary bypass. J Cardiothorac Vasc Anesth 9:405–411

18. Greim C, Roewer N, Laux G et al (1996) Accuracy, of continuous cardiac output determination with the heat filament catheter varies with infusion rates. Anesthesiology 85:A398 (abs)
19. Spackman ER, Abenstein JF (1993) Continuous cardiac output may be more accurate than bolus thermodilution output during the use of an upper-body warming-blanket. Anesthesiology 79:A473 (abs)
20. Haller M, Zollner C, Manert W et al (1995) Thermodilution cardiac output may be incorrect in patients on venovenous extracorporeal lung assist. Am J Respir Crit Care Med 152:1812–1817
21. Bottiger BW, Sinner B, Motsch J et al (1997) Continuous versus intermittent thermodilution cardiac output measurement during orthotopic liver transplantation. Anaesthesia 52:207–214
22. Reinhart K (1991) Fiberoptic SvO2 monitoring as indicator of changes in whole body oxygen supply/demand relationship. In: Dhainaut JF, Payen D (eds) Strategy in bedside haemodynamic monitoring (update in intensive care and emergency medicine). Springer, Berlin Heidelberg New York Tokyo, 72–85
23. Berridge JC (1992) Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. Br J Anaesth 69:409–410
24. Dahn MS, Lange MP, Jacobs LA (1988) Central mixed and splanchnic venous oxygen saturation monitoring. Intensive Care Med 14:373–377
25. Martin C, Auffray JP, Badetti C et al (1992) Monitoring of central venous oxygen saturation in critically ill patients. Intensive Care Med 18:101–104
26. Martin WE, Cheung PW, Johnson CC et al (1973) Continuous monitoring of mixed venous oxygen saturation in man. Anesth Analg 52:784–793
27. Heiselman D, Jones J, Cannon L (1986) Continuous monitoring of mixed venous oxygen saturation in septic shock. J Clin Monit 2:237–245
28. Giunta F, Brandi LS, Mazzanti T et al (1992) The relationships between oxygen delivery and consumption and continuous mixed venous oximetry are predictive parameters in septic shock. Adv Exp Med Biol 317:813–823
29. Jugan E, Albaladejo P, Jayais P et al (1992) Continuous monitoring of mixed venous oxygen saturation during orthotopic liver transplantation. J Cardiothorac Vasc Anesth 6:283–286
30. Boutros AR, Lee C (1986) Value of continuous monitoring of mixed venous blood oxygen saturation in the management of critically ill patients. Crit Care Med 14:132–134
31. Jastremski MS, Chelluri L, Benney KM et al (1989) Analysis of the effects of continuous on-line monitoring of mixed venous oxygen saturation on patient outcome and cost-effectiveness. Crit Care Med 17:148–153
32. Leeper B (2003) Monitoring right ventricular volumes. AACN Clin Issues 14(2):208–219.
33. Cheatham ML (2000) Right ventricular end-diastolic volume measurements in the resuscitation of trauma victims. Int J Crit Care 7(3):165–176
34. Yu M, Takiguchi SRN, Takanishi D, et al (1995) Evaluation of the clinical usefulness of thermodilution volumetric catheters. Crit Care Med 23:681–686
35. Nelson LD (1996) The new pulmonary arterial catheters: Right ventricular ejection fraction and continuous cardiac output. Crit C Clin 12(4):795–818
36. Chang MC (1999) Monitoring of the critically injured patient. New Horizons 7(1):35–45
37. Connors AF Jr, Dawson NV, McCaffree DR et al (1987) Assessing haemodynamic status in critically ill patients: Do physicians use clinical information optimally? J Crit Care 2:174–180
38. Eisenberg PR, Jaffe AS, Schuster DP (1984) Clinical evaluation compared to pulmonary

artery catheterization in the haemodynamic assessment of critically ill patients. Crit Care Med 12:549–553
39. Quinn K, Quebberman EJ (1981) Pulmonary artery pressure monitoring in the surgical intensive care unit: Benefits vs. difficulties. Arch Surg 116:872–876
40. Rekik N, Brochard L, Rauss A et al (1989) Prospective assessment of the benefit and risk of Swan Ganz catheter in critically ill patients. Am Rev Resp Dis 139:A17 (abs)
41. Tuchschmidt J, Sharma OP (1987) Impact of haemodynamic monitoring in a medical intensive care unit. Crit Care Med 15:840–843
42. Steingrub JS, Celoria G, Vickers-Lahti M et al (1991) Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. Chest 99:1451–1455
43. Mimoz O, Rauss A, Rekik N et al (1994) Pulmonary artery catheterization in critically ill patients: A prospective analysis of outcome changes associated with catheter-prompted changes in therapy. Crit Care Med 22:573–579
44. Staudinger T, Locker GJ, Laczika K et al (1998) Diagnostic validity of pulmonary artery catheterization for residents at an intensive care unit. J Trauma 44:902–906
45. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270:2699–2707
46. Tuchschmidt J, Fried J, Astiz M et al (1992) Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 102:216–220
47. Gattinoni L, Brazzi L, Pelosi P et al (1995) A trial of goal-oriented haemodynamic therapy in critically ill patients: SvO2 Collaborative Group. N Engl J Med 333:1025–1032
48. Sandham JD, Hull RD, Brant RF et al (2004) A randomized, controlled trial of the use of pulmonary-artery catheter in high risk surgical patients. N Engl J Med 348:5–14
49. Berlauk JF, Abrams JH, Gilmour IJ et al (1991) Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: A prospective, randomized clinical trial. Ann Surg 214:289–299
50. Joyce WP, Provan JL, Ameli FM et al (1990) The role of central haemodynamic monitoring in abdominal aortic surgery: A prospective randomized study. Eur J Vasc Surg 4:633–636
51. Isaacson IJ, Lowdon JD, Berry AJ et al (1990) The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: A comparative study of two selected, randomized groups. J Vasc Surg 12:754–760
52. Schiller WR, Bay RC, Garren RL et al (1997) Hyperdynamic resuscitation improves survival in patients with life-threatening burns. J Burn Care Rehabil 18:10–16
53. Chang MC, Meredith JW, Kincaid EH et al (2000) Maintaining survivors values of left ventricular power output during shock resuscitation: A prospective pilot study. J Trauma 49:26–33
54. Bishop MH, Shoemaker WC, Appel PL et al (1995) Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma 38:780–787
55. Ivanov RI, Allen J, Sandham JD et al (1997) Pulmonary artery catheterization: A narrative and systematic critique of randomized controlled trials and recommendations for the future. New Horiz 5:268–276
56. Ivanov RI, Allen J, Calvin JE et al (2000) The incidence of major morbidity in critically ill patients managed with pulmonary artery catheters: A meta-analysis. Crit Care Med 28:615–619
57. Barone JE, Tucker JB, Rassias D et al (2001) Routine perioperative pulmonary artery

catheterization has no effect on rate of complications in vascular surgery. Am Surg 67:674–679

58. Chittock DE, Dhingra VK, Ronco JJ et al (2004) Severity of illness and risk of death associated with pulmonary artery catheter use. Crit Care Med 32:911–925

Chapter 49

Perioperative neuroprotection: is it possible to prevent brain injury in high risk patients?

A.P. Schmidt, M. Brudniewski, J.O.C. Auler jr

The brain is a very complex organ that interacts with the numerous physiological functions of the body. The anaesthesiologist and/or intensivist can alter the cerebral physiology and improve the physiological reserve of the brain with the purpose of providing cerebral protection. Protecting the brain from ischaemia and other perioperative insults is an important concern for anaesthesiologists. However, a lack of understanding of the pathophysiological reactions and biochemical events involved in brain injury and a lack of evidence of physiological and pharmacological measures for cerebral protection account for development of secondary brain injuries with additional morbidity. Given the decline in mortality of high-risk patients and improvement of surgical and anaesthesia techniques, attention has focused on morbidity and, in particular, neurological morbidity.

Perioperative brain protection refers to prophylactic measures instituted during the perioperative period to prevent or reduce ischaemic damage and to improve neurological outcomes. Brain protection may be passive and involve the avoidance of deleterious interventions, or active and refer to the application of beneficial strategies [1]. The aim of this review is to focus on selected aspects of brain physiology and their potential impact on cerebral protection and to discuss potential neuroprotective measures in the management of high-risk patients, emphasising results of clinical trials.

Brain physiology and mechanisms of brain injury

The brain requires large amounts of energy to maintain cellular integrity and support neurotransmission; however, the brain has virtually no glucose reserve. Glucose is stored as glycogen and enters glial cells (astrocytes) using a facilitated ATP Na–K transport system. Through this system, the amount of glucose transported into astrocytes decreases when plasma glucose increases [2]. When hyperglycaemia occurs, this transport system may be altered in the injured brain, leading to secondary brain injury. Glycaemia plays a key role in determining outcome following an ischaemic event and is an independent predictor of mortality [3, 4]. In critically ill patients, morbidity and mortality have been reduced by insulin therapy set up to maintain blood glucose concentrations less than 110 mmol l^{-1} [5]. Hyperglycaemia is deleterious to the injured brain and even moderately elevated

serum glucose levels may worsen outcome, emphasising the need for perioperative glycaemic control.

The brain is the organ with the highest rate of oxygen consumption, with the exception of the glomic cells of the carotid body [6]. Most of the brain oxygen consumption is used to maintain cellular integrity and electrogenesis as well as to sustain cellular-transport metabolism through hydrolysis of ATP [7, 8]. If hypoxia occurs, electrogenesis is quickly impaired, potentially jeopardising cerebral autoregulation, cerebrovascular reactivity, and neuronal integrity. Neuronal viability and integrity deteriorate if hypoxia persists, and neuronal damage becomes irreversible at normothermia [7, 8]. Taken together, these findings suggest that tight control of oxygenation is pivotal to prevent perioperative neurological complications.

Regarding arterial pressure control, the increased morbidity and mortality related to severe trauma to an extracranial organ system are primarily attributable to hypotension. Hypotension is a major determinant of outcome from severe head injury. Resuscitation protocols for brain-injured patients should assiduously avoid hypovolaemic shock and hypotension [9]. Intraoperative hypotension presents also an adverse effect on the outcome of subarachnoid haemorrhage, being related to more frequent and severe manifestations of vasospasm. A long-lasting effect of brain retraction is possibly the cause of this phenomenon [10]. Drug therapy for hypertension has not been validated as being of benefit for improving outcome in patients suffering from a cerebral vasospasm after subarachnoid haemorrhage [1].

Regarding mechanisms of cerebral injury, primary brain injury causes cellular disruption or death through terminal depolarisation of neurons and failure of ionic pumps. As a result, ionic homeostasis of neurons is lost, membranes and organelles are damaged, and toxic molecules leak into the interstitium [11]. Secondary brain injury is caused by excitotoxic neurotransmitters, calcium, expression of immediate early genes, nitric oxide, metabolites of anaerobic metabolism (lactate and hydrogen ions), and oxygen free radicals. Primary and secondary brain injury provoke an inflammatory response that leads to programmed cell death (apoptosis) and glial scarring in areas of neuronal death [11].

Incidence and risk factors for perioperative neurological complications

Cerebral injury may occur during anaesthesia and surgery, particularly during cardiac surgery and neurosurgery [12].

The neurological complications after major surgery or in critically ill patients are associated with significantly increased mortality, morbidity, and resource utilisation [13]. These complications result in a longer duration of hospitalisation or stay in the intensive care unit and increased costs [14]. The type of surgery, presence of symptomatic cerebrovascular disease, advanced age, diabetes mellitus, and probably aortic atheroma represent the most important risk factors for neurological complications after major surgery, such as cardiac surgery [15].

Several studies have investigated the risk factors for neurological complications after cardiac surgery [16–19]. Proximal aortic atherosclerosis, history of preopera-

tive neurological disease, use of intra-aortic balloon pump, diabetes mellitus, history of hypertension, history of pulmonary disease, history of unstable angina, and age were significantly related to central nervous system complications after cardiac surgery [20]. The aetiology of neuropsychological dysfunction after cardiac surgery with cardiopulmonary bypass remains unresolved and is probably multifactorial. Demographic predictors of cognitive decline include age and years of education. Perioperative factors including number of cerebral emboli, temperature, mean arterial pressure, and jugular bulb oxygen saturation have varying predictive power. Recent data suggest a genetic predisposition for cognitive decline after cardiac surgery in patients possessing the apolipoprotein E4 allele. Regarding noncardiac procedures, postoperative cognitive dysfunction is strongly associated with increasing age in elderly patients [21]. Type of surgery and hospitalisation may be important prognostic factors. However, studies addressing risk factors for adverse neurological outcomes after noncardiac procedures are still lacking [22–25].

After preoperative consideration of the individual risk of each patient, neuroprotective physiological measures and/or pharmacological neuroprotection may offer an improved outcome to some high-risk patients [15]. Predicting patients at risk of postoperative cognitive decline allows the possibility of many important interventions. Predictive therapies to reduce cellular injury associated with neurological insults lend hope of a future ability to markedly decrease the impact of major surgery on short-term and long-term neurological, cognitive, and quality-of-life outcomes in high-risk patients.

Markers of brain injury

The diagnosis of cerebral injury currently relies on clinical neurological examination, computed tomography, and magnetic resonance imaging. However, these methods may be not suitable for some situations, such as the postoperative period in high-risk patients. Therefore, identification of potential peripheral serum markers of brain injury would be useful [26].

Recently, several potential serum markers of brain injury have been investigated, such as neuron-specific enolase (marker of neuronal injury) and S100B protein (marker of glial injury). However, results regarding the correlation between these serum markers and neurological outcome are still preliminary and controversial. New studies are needed to further investigate the role of these substances as markers of brain injury and neurological outcome [26, 27].

More recently, new data suggest a genetic predisposition towards cognitive decline after cardiac surgery [28, 29]. Apolipoprotein E (ApoE) is a glycosylated protein and the ApoE gene is polymorphic, presenting three major alleles: ε2, ε3, and ε4. Genes such as ApoE might also play a role in postoperative cognitive dysfunction. The mechanism by which the ApoE4 allele could contribute to the neurocognitive dysfunction commonly seen after cardiac surgery still remains uncertain. It may be that it magnifies the detrimental effects of CPB, perhaps by

altering neuronal repair, by affecting neuronal susceptibility to injury, or by increasing atherosclerotic embolic load. However, additional studies are needed to clarify genetic predisposition to postoperative cognitive dysfunction.

Measures for neuroprotection

Brain protection may be defined as the prevention or attenuation of neuronal damage related to abnormalities in cerebral metabolism, histopathology, or neurological function occurring after a hypoxic or an ischaemic event [30].

Although the major focus of recent cerebral protection research has been the development of receptor-specific drugs, this effort has resulted in few improvements in patient outcome. Until advances in pharmacology translate into improvements in humans, the clinician and his or her patients will be well-served by using more traditional techniques to prevent and treat cerebral ischaemic events. This approach will involve interventions to identify patients who are experiencing or at risk of developing cerebral ischaemia, and to alter systemic physiology in an attempt to lessen the duration and severity of any ischaemic insult [31].

Agents used for cerebral protection can exert their effects through: (1) reduction in oxygen demand, (2) increase in oxygen delivery, (3) arresting deleterious pathological intracellular processes [30]. Initial therapy should include interventions to improve cerebral perfusion and the oxygen-carrying capacity of the blood. Once this is accomplished, measures should be taken to control blood glucose concentrations and treat hyperthermia. In otherwise stable surgical patients, mild reductions in patient temperature also may be of benefit, provided the temperature reductions do not introduce problems in systemic physiology and the patient is rewarmed prior to awakening from general anaesthesia [31].

Physiological measures

Perioperative physiological neuroprotection involves a strict control of temperature, glycaemia, oxygen consumption, and arterial blood pressure [32].

In regard to temperature control, hypothermia is common during anaesthesia and surgery owing to anaesthetic-induced inhibition of body thermoregulation [32]. Perioperative hypothermia is associated with several complications, including metabolic, cardiovascular, immunological, and haemostatic undesirable side effects [33]. However, cooling the body below the normal physiologic temperature has been used as a therapeutic tool and acknowledged to offer some degree of brain protection. Hypothermia is used most often during cardiac surgery with cardiopulmonary bypass, as a means of protecting the brain from ischaemic injury. Hypothermia is also used during some neurosurgical procedures and is being investigated as a treatment for ischaemic stroke and traumatic brain injury. Under specific patient and clinical conditions, it can provide substantial benefits since even mild hypothermia may reduce cell injury by suppressing excitotoxins and oxygen radicals, stabilising cell membranes, and reducing the number of abnormal

electrical depolarisations [34]. Numerous animal studies have emerged addressing the potential benefits of mild hypothermia as a neuroprotection measure since it impairs neuronal death after cerebral ischaemia [35–37].

Mild hypothermia has also been investigated in several human studies. It has been reported to improve outcome in survivors of cardiac arrest without an increased incidence of complications [35], and is associated with less neurological dysfunction and better outcome in patients undergoing cerebral aneurysm surgery [38]. However, it has failed to improve outcome in head-injured patients [36] and no controlled trials have been performed addressing hypothermia in stroke patients. It therefore remains unclear whether hypothermia improves neurological outcome in postoperative high-risk patients.

Pharmacological and anaesthetic measures

While several compounds have proven to provide brain protection in animal models [1, 30, 39], clinical results of these compounds have been disappointing in humans. The reasons are not well clarified to date, but may be related to a lack of knowledge of brain chemistry and normal neuronal function and to the lack of specificity of available neuroprotective drugs to areas of brain injury, since these compounds significantly affect normal brain, causing neurological side effects [1, 30, 32, 39].

Pharmacological cerebral protection includes therapy directed at prevention of cerebral ischaemia and resuscitation of ischaemic tissue [30]. Agents used for neuroprotection in anaesthesia or perioperative care include: barbiturates, volatile anaesthetics (isoflurane), lidocaine, propofol, benzodiazepines, calcium channel blockers (nimodipine), NMDA antagonists, phenytoin, steroids, free radical scavengers, prostaglandin inhibitors and other less investigated pharmacological measures [30, 39] (Table 1). Most of the anaesthetic agents share potential mechanisms of brain protection and have been shown to present neuroprotective effects in animal models of ischaemia. However, they remain to be validated in prospective clinical trials [1]. The main pharmacological approaches for cerebral protection are briefly discussed below, but are described in detail elsewhere [1, 6, 30, 39].

Table 1. Pharmacological agents used for neuroprotection in anaesthesia and/or perioperative care

Barbiturates	NMDA antagonists (ketamine, remacemide)
Phenytoin	Volatile anesthetics (isoflurane, sevoflurane)
Lidocaine	Corticosteroids
Propofol	Magnesium
Benzodiazepines	Free radical scavengers
Calcium channel blockers (nimodipine)	Prostaglandin inhibitors
Iron chelators	α_2-agonists (dexmedetomidine)
Tirilazad mesylate	Modulators of arachidonic acid metabolism
Cyclosporin A	Substance P antagonists
Estrogen derivatives	Dexanabinol

Barbiturates

The primary mechanism by which barbiturates protect the central nervous system (CNS) is their ability to decrease the cerebral metabolic rate, thus improving the ratio of oxygen supply to demand and reducing the energy expenditure required for synaptic transmission, while maintaining the energy required for basic cellular functions [40]. Other potential mechanisms against CNS ischaemia are described in Table 2.

Table 2. Other potential mechanisms against CNS ischaemia of barbiturates and other anaesthetic agents

Reduction in synaptic transmission
Redistribution of cerebral blood flow
Suppression of seizure activity
Membrane stabilisation
Reduction of cerebral oedema
Scavenging of free radicals
Alteration of fatty acid metabolism
Reduction in cerebrospinal fluid secretion

Barbiturates protected against focal cerebral ischaemia in animals, but did not improve outcome in stroke patients [41] and their neuroprotective effects in human clinical trials remain to be determined, since even their capacity to reduce postoperative cognitive dysfunction after cardiopulmonary bypass is disputed [42, 43].

Volatile anaesthetics

Isoflurane, like many other anaesthetics, has the ability to reduce cortical electrical activity and reduce central oxygen consumption and has been extensively studied as a potential neuroprotector agent [44]. Volatile anaesthetics provide protection against focal ischaemia in animals [45–47], inhibit delayed neuronal death after ischaemia in vitro [48], and exert antiapoptotic properties in animal models of ischaemia [49]. Recently, the gaseous anaesthetic xenon has been investigated for its potential neuroprotective effects in models of neuronal injury [50], perhaps related to antagonism of NMDA receptors. However, clinical trials implicating volatile anaesthetics and xenon in neuroprotection are still needed.

Although there is still a lack of clinical data regarding anaesthesia and volatile anaesthetics as neuroprotective agents in humans, it can be stated that accumulating experimental evidence favours anaesthesia compared to being awake in situations at risk of causing cerebral ischaemia. The best anaesthetic agent to be used for neuroprotection remains controversial [1].

Calcium channel blockers (nimodipine)

Nimodipine has been extensively investigated as a neuroprotector since it improves outcome after subarachnoid haemorrhage by protecting brain against vasospasm [51]. Some benefit has also been demonstrated in patients with head trauma complicated by subarachnoid haemorrhage [52].

NMDA antagonists

Toxic effects in brain injury are strictly related to an overstimulation of the glutamatergic system (excitotoxicity), mainly through activation of NMDA receptors [53]. Since excitotoxicity is related to neuronal suffering and death, agents able to reduce glutamatergic activity during ischaemia or brain injury are of potential interest for the development of new neuroprotective pharmacological approaches in humans.

However, the clinical effects of NMDA receptor antagonists are variable and in some cases are associated with negative side effects and even neuronal toxicity [53]. The S(+)-enantiomer of ketamine appears to be a suitable neuroprotective drug in animal models of cerebral ischaemia [54]; however, clinical trials in humans remain to be performed.

Free radical scavengers

The production of free radicals is an inevitable step along ischaemia and leads to neuronal damage and death [32]. Although several agents known to be free radical scavengers (vitamins C and E, mannitol, methiamine, glutathione-SH) or to promote free radical metabolism (superoxide dismutase, catalase) may theoretically present neuroprotective effects, clinical trials in humans are still awaited [30, 32, 39].

Corticosteroids

Corticosteroids are well-known for their anti-inflammatory properties and have been proposed to play neuroprotective effects at several different levels of ischaemia, including the onset of the inflammatory response [30]. Steroids may also inhibit lipid peroxidation and lipolysis, reverse intracellular calcium accumulation, but maintain normal cerebral blood flow and energy metabolism [39].

Despite the existence of a few positive studies regarding neuroprotective effects of steroids, the results of several other laboratory studies of focal cerebral ischaemia have demonstrated that corticosteroid treatment of ischaemic brain infarction and oedema in experimental animals and humans has, in most instances, shown no benefits [30].

Preconditioning

Preconditioning relies on the fact that prior exposure of the brain to minor insults will induce an increased tolerance to further injurious events. The underlying mechanisms mediating neuroprotection remain unclear but activation of mitochondrial ATP-dependent potassium channels appears to be a pivotal feature of preconditioning [30]. Many factors (ischaemia, hypoxia, hyperoxia, seizures, hypothermia, heat shock, hypo- or hyperglycaemia) and several drugs (volatile anaesthetics, morphine, the potassium channel opener diazoxide, and erythromycin) that may be associated with preconditioning are currently under investigation regarding their use as neuroproctective measures [55–58].

Taken together, these data indicate that preconditioning is a potential alternative for neuroprotection and clinical trials are needed to further investigate this promising therapy.

Conclusions

Recent improvements in understanding the mechanisms of cerebral ischaemia and cell death have led to the development of new neuroprotective strategies, which were shown to be efficacious in animal models. Unfortunately, most of these promising agents have proved disappointing in human clinical trials. Therefore, to date, evidence-based medicine for perioperative neuroprotection consists mainly in avoiding deleterious interventions rather than beneficial strategies or pharmacological interventions. Clinical trials are needed to identify effective pharmacological measures, such as neuroprotectors, by focusing on specific subgroups of patients, more homogenous patient samples, careful statistical power analysis, and randomisation and accurate evaluation of sustained neurological improvement.

References

1. Hans P, Bonhomme V (2004) The rationale for perioperative brain protection. Eur J Anesthesiol 21:1–5
2. Feinendegen LE, Herzog H, Thompson KH (2001) Cerebral glucose transport implies individualized glial cell function. J Cereb Blood Flow Metab 21(10):1160–1170
3. Weir CJ, Murray GD, Dyker AG et al (1997) Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long-term follow up study. BMJ 314(7090):1303–1306
4. Szczudlik A, Slowik A, Turaj W et al (2001) Transient hyperglycemia in ischemic stroke patients. J Neurol Sci 189(1–2):105–111
5. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345(19):1359–1367
6. Bissonnette B (2004) Cerebral protection. Paediatr Anaesth 14:403–406
7. Siesjo BK (1984) Cerebral circulation and metabolism. J Neurosurg 60:883–908
8. Raichle ME (1983) The pathophysiology of brain ischemia. Ann Neurol 13:2–10

9. Chesnut RM, Marshall LF, Klauber MR et al (1993) The role of secondary brain injury in determining outcome from severe head injury. J Trauma 34(2):216–222
10. Chang HS, Hongo K, Nakagawa H (2000) Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. J Neurosurg 92(6):971–975
11. Wheeler DW (2002) Secondary neuronal injury mechanisms. Anaesth Intensive Care Med 3:120–123
12. Henriksen L (1984) Evidence suggestive of diffuse brain damage following cardiac operations. Lancet 1:816–820
13. Arrowsmith JE, Grocott HP, Reves JG et al (2000) Central nervous system complications of cardiac surgery. Br J Anaesth 84(3):378–393
14. Hogue CW Jr, Sundt TM 3rd, Goldberg M et al (1999) Neurological complications of cardiac surgery: the need for new paradigms in prevention and treatment. Semin Thorac Cardiovasc Surg 11(2):105–115
15. Boeken U, Litmathe J, Feindt P et al (2005) Neurological complications after cardiac surgery: risk factors and correlation to the surgical procedure. Thorac Cardiovasc Surg 53(1):33–36
16. Breuer AC, Furlan AJ, Hanson MR et al (1983) Central nervous system complications of coronary artery bypass graft surgery: prospective analysis of 421 patients. Stroke 14(5):682–687
17. Hammeke TA, Hastings JE (1988) Neuropsychologic alterations after cardiac operation. J Thorac Cardiovasc Surg 96(2):326–331
18. Kuroda Y, Uchimoto R, Kaieda R et al (1993) Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. Anesth Analg 76(2):222–227
19. Newman MF, Croughwell ND, Blumenthal JA et al (1995) Predictors of cognitive decline after cardiac operation. Ann Thorac Surg 59(5):1326–1330
20. Roach GW, Kanchuger M, Mangano CM et al (1996) Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 335(25):1857–1863
21. Johnson T, Monk T, Rasmussen LS et al (2002) Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 96(6):1351–1357
22. Dodds C, Allison J (1988) Postoperative cognitive deficit in the elderly surgical patient. Br J Anaesth 81(3):449–462
23. Abildstrom H, Rasmussen LS, Rentowl P et al (2000) Cognitive dysfunction 1–2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. Acta Anaesthesiol Scand 44(10):1246–1251
24. Abildstrom H, Christiansen M, Siersma VD et al (2004) Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. Anesthesiology 101(4):855–861
25. Rasmussen LS, Johnson T, Kuipers HM et al (2003) Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 47(3):260–266
26. Ali MS, Harmer M, Vaughan R (2000) Serum S100 protein as a marker of cerebral damage during cardiac surgery. Br J Anaesth 85(2):287–298
27. Rasmussen LS, Christiansen M, Eliasen K et al (2002) Biochemical markers for brain damage after cardiac surgery – time profile and correlation with cognitive dysfunction. Acta Anesthesiol Scand 46:547–551
28. Tardiff BE, Newman MF, Saunders AM et al (1997) Preliminary report of a genetic basis

for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. Ann Thorac Surg 64:715–720
29. Steed L, Kong R, Stygall J et al (2001) The role of apolipoprotein E in cognitive decline after cardiac operation. Ann Thorac Surg 71:823–826
30. Hall R, Murdoch J (1990) Brain protection: physiological and pharmacological considerations. Part II: The pharmacology of brain protection. Can J Anaesth 37:762–777
31. Lanier WL (1999) The prevention and treatment of cerebral ischemia. Can J Anaesth 46:R46-R56
32. Murdoch J, Hall R (1990) Brain protection: physiological and pharmacological considerations. Part I: The physiology of brain injury. Can J Anaesth 37:663–671
33. Polderman KH (2004) Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality – Part 2: Practical aspects and side effects. Intensive Care Med 30(5):757–769
34. Kabon B, Bacher A, Spiss CK (2003) Therapeutic hypothermia. Best Pract Res Clin Anaesthesiol 17(4):551–568
35. Anonymous (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The hypothermia after cardiac arrest study group. New Engl J Med 346:549–556
36. Clifton GL, Miller ER, Choi SC et al (2001) Lack of effect of induction of hypothermia after acute brain injury. New Engl J Med 344:556–563
37. Schwab S, Schwarzs S, Spranger M et al (1998) Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 29:2461–2466
38. Hindman BJ, Todd MM, Gelb AW et al (1999) Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. Neurosurgery 44:23–32
39. Sutcliffe AJ (2003) Cerebral protection during anaesthesia. In: Gullo A (ed) Anaesthesia, Pain, Intensive Care and Emergency Medicine. Springer, Milan, pp 725–737
40. Steen PA, Michenfelder JD (1980) Mechanisms of barbiturate protection. Anesthesiology 53:183–185
41. Schwab S, Spranger M, Schwarz S et al (1997) Barbiturate coma in severe hemispheric stroke: useful or obsolete? Neurology 48:1608–1613
42. Nussmeier NA, Arlund C, Slogoff S (1986) Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by barbiturate. Anesthesiology 64:165–170
43. Zaidan JR, Klochany A, Martin WM et al (1991) Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology 74:406–411
44. Newberg LA, Michenfelder JD (1983) Cerebral protection by isoflurane during hypoxemia or ischemia. Anesthesiology 59:29–35
45. Warner DS, McFarlane C, Todd MM et al (1993) Sevoflurane and halothane reduce focal ischemic brain damage in the rat. Possible influence on thermoregulation. Anesthesiology 79(5):985–992
46. Werner C, Mollenberg O, Kochs E et al (1995) Sevoflurane improves neurological outcome after incomplete cerebral ischaemia in rats. Br J Anaesth 75(6):756–760
47. Engelhard K, Werner C, Reeker W et al (1999) Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. Br J Anaesth 83(3):415–421
48. Sullivan BL, Leu D, Taylor DM et al (2002) Isoflurane prevents delayed cell death in an organotypic slice culture model of cerebral ischemia. Anesthesiology 96(1):189–195
49. Kawaguchi M, Drummond JC, Cole DJ et al (2004) Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. Anesth Analg 98(3):798–805

50. Wilhelm S, Ma D, Maze M et al (2002) Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology 96(6):1485–1491
51. Pickard JD, Murray GD, Illingworth R et al (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 298(6674):636–642
52. Harders A, Kakarieka A, Braakman R (1996) Traumatic subarachnoid hemorrhage and its treatment with nimodipine. German tSAH Study Group. J Neurosurg 85(1):82–89
53. Hoyte L, Barber PA, Buchan AM et al (2004) The rise and fall of NMDA antagonists for ischemic stroke. Curr Mol Med 4(2):131–136
54. Proescholdt M, Heimann A, Kempski O (2001) Neuroprotection of S(+) ketamine isomer in global forebrain ischemia. Brain Res 904(2):245–251
55. Nishio S, Yunoki M, Chen ZF et al (2000) Ischemic tolerance in the rat neocortex following hypothermic preconditioning. J Neurosurg 93(5):845–851
56. Moncayo J, de Freitas GR, Bogousslavsky J et al (2000) Do transient ischemic attacks have a neuroprotective effect? Neurology 54(11):2089–2094
57. Zaugg M, Lucchinetti E, Spahn DR et al (2002) Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. Anesthesiology 97(1):4–14
58. Bhardwaj A, Castro III AF, Alkayed NJ et al (2001) Anesthetic choice of halothane versus propofol: impact on experimental perioperative stroke. Stroke 32(8):1920–1925

Chapter 50

Drug interactions in anaesthetic practice

V. Fodale, L.B. Santamaria

Drugs administered during general anaesthesia act synergistically to produce amnesic, analgesic, hypnotic, and paralytic effects while minimising adverse effects. The interaction of anaesthetics is unique to each patient since the absorption, distribution, and clearance of drugs varies in individuals [1]. These interactions are well-known by anaesthesiologists and are even purposely used to obtain optimal anaesthetic effects [2].

Interactions between anaesthetic drugs and long-term medications are more complicated in clinical practice. Anaesthetists encounter many patients who, due to their surgical condition or medical illnesses, are on concurrent medication that may potentially interact with the drugs of anaesthesia [3]. This kind of interaction may be harmful for the patient during anaesthesia [2, 4].

In this survey, the most common interactions between anaesthetics and popular drugs or alternative medicines taken prior to surgery are discussed.

Consequences and mechanisms of drug interactions

Traditionally, the consequences of an interaction may be classified as additive, synergistic, potentiation, or antagonism, whereas the mechanisms involved in drug interactions may be one of three types: pharmaceutical, pharmacokinetic, or pharmacodynamic [4].

Pharmaceutical interactions

Pharmaceutical interactions refer to direct chemical combinations between drugs or their absorption into the material of their containers.

Particular attention should be given to the administration of fluids in patients coming from the ward, as fluids may contain drugs that potentially interact with anaesthetics. Patients from intensive care units are at increased risk, due to the high number of drugs and substances commonly co-administered with fluids (drugs, parenteral nutrition, sedatives, neuromuscular blocking drugs). For instance, sodium thiopentone and either vecuronium or pancuronium, when administered in combination or rapid succession, form a white precipitate that is extremely insoluble in plasma [4], resulting in patient awareness, with or without muscle relaxa-

tion. Moreover, there is the possibility that this precipitate will occlude narrow blood vessels or even cause pulmonary infarction [5].

Pharmacokinetic interactions

Pharmacokinetic interactions occur when one drug changes the disposition or the concentration of another drug at the receptor site, leading to altered plasma concentration and altered drug response. These changes in drug concentration at the receptor site may be produced by alteration of: (a) drug absorption and uptake in the body, (b) drug distribution, (c) drug metabolism, and (d) drug elimination or excretion by non-metabolic routes [3]. Interactions affecting distribution and metabolism are the most important for anaesthesiologists and are a source of adverse reactions associated with anaesthesia [3, 6].

Distribution

The extent of the distribution of a drug within the body depends on several factors, including tissue blood flow, lipid solubility, and protein binding. Inhalational and intravenous anaesthetics often produce significant haemodynamic changes that may profoundly affect peripheral blood flow and perfusion [4]. Specifically, effective drug absorption can be inhibited, hepatic blood flow reduced, renal excretion reduced, metabolism inhibited or accelerated, and drug displacement from albumin can occur.

Metabolism and elimination

Drugs are eliminated from the body by several processes, of which by far the most important for intravenous drugs is biotransformation in the liver [4]. Phase 1 metabolism comprises oxidation, reduction, or hydrolysis, of which the former is usually catalysed by cytochrome P450 enzymes located predominantly in the liver. This family of enzymes is classified as CYP1, CYP2, and CYP3, each of which is further classified based on substrate selectivity. Of the 60 isoforms identified, CYP 3A4 is probably the most important cytochrome P450 isoform for drug metabolism. It is involved in the metabolism of intravenous anaesthetic agents [5], midazolam [7], and alfentanil [8], whereas CYP 2E1 catalyses metabolism of halogenated anaesthetic agents [5].

Potentially significant drug interactions can occur when a drug that is a potent inducer or inhibitor of a specific CYP isoenzyme is administered with a drug that is a substrate of (and therefore metabolised by) that same isoenzyme. The concern is greatest when the substrate drug has a narrow therapeutic index, since a small change in plasma concentration could result in toxicity or reduced efficacy, depending on whether the precipitant drug inhibits the metabolism of the substrate drug (resulting in a higher plasma concentration) or induces the metabolism of the substrate drug (resulting in a lower plasma concentration) (Table 1).

Table 1. Inducers and inhibitors of cytochrome P450 enzymes [4–6]

Inducers
Alcohol
Barbiturates
Carbamezapine
Isoniazid
Phenytoin
Primidone
Rifampicin
Tobacco smoke
Inhibitors
Cimetidine
Diltiazem
Erythromycin
Fluconazole
Fluoxetine
Fluvoxamine
Grapefruit Juice
Indinavir
Itraconazole
Ketoconazole
Nelfinavir
Omeprazole
Paroxetine
Propofol
Ritonavir
Saquinavir
Sertraline
Troleandromycin
Verapamil

Enzyme induction most commonly occurs when drugs are given at relatively high doses, although in humans a number of drugs at therapeutic doses, such as rifampicin, barbiturates, phenytoin, and carbamazepine, can induce P450 enzymes. In contrast to enzyme inhibition, enzyme induction is responsible for fewer adverse reactions in anaesthesia.

Antibiotics and antifungal drugs. A number of antibiotics, most notably the macrolides and azole antifungal drugs, have been implicated in significant enzyme inhibition, resulting in adverse interactions with anaesthetic-related drugs.

Drug interactions can arise with virtually any antifungal therapy since phase 1 oxidative reactions are an important mechanism for biotransformation of azole antifungals [9]. All azoles are also reversible inhibitors of CYP enzymes in humans [9]; this inhibition is probably a collateral effect of their antifungal mechanism, namely inhibition of 14-alpha-demethylase, a CYP P450 enzyme in fungi involved in the biosynthesis of ergosterol.

In vitro, ketoconazole and itraconazole are potent inhibitors of midazolam hydroxylation [10]. Pre-treatment of volunteers with these antimycotics for 4 days increased the triazolam elimination half-life six- to seven-fold [11].

Calcium-channel blockers. The calcium-channel blockers diltiazem and verapamil interact with benzodiazepines, significantly increasing the bioavailability of midazolam and triazolam and prolonging the elimination half-life [12, 13]. These medications therefore have potentially profound and prolonged sedative effects.

Ethanol and cigarette smoke. Ethanol and cigarette smoke cause relatively selective induction of the cytochrome P450 isoenzymes CYP 2E1 and CYP 1A, respectively [4, 14].

Proton-pump inhibitors. The proton-pump inhibitors omeprazole, lansoprazole, and pantoprazole are used for the treatment of peptic ulcers and other hypersecretory conditions. They undergo extensive metabolism in the liver, mediated by the polymorphically expressed enzyme CYP 2C19 [15], and this accounts for a pronounced interindividual variability in their pharmacokinetics. Other substrates for CYP 2C19 include S-mephenytoin, propranolol, diazepam, and a number of tricyclic antidepressants. In poor metabolisers of S-mephenytoin, diazepam is more slowly metabolised than in subjects who are extensive metabolisers [4, 16, 17].

H2-receptor antagonists. The H2-receptor antagonist cimetidine binds to cytochrome P450 enzymes, inhibiting their activity and thus impairing hepatic metabolism of a large number of drugs, including opioids, benzodiazepines, lidocaine, and warfarin. The result is a greater than expected plasma drug concentration of the drug and thus a more pronounced clinical effect, which may also be prolonged [3, 4]. Ranitidine does not inhibit P450; nevertheless, it does form a complex with hepatic cytochrome P450, but more weakly than cimetidine. Famotidine and nizatidine do not inhibit P450 enzymes [4].

Monoamine oxidase inhibitors. Monoamine oxidase catalyses the oxidative deamination of important neurotransmitters and neuromodulators, such as adrenaline, noradrenaline, dopamine, and serotonin. During treatment with monoamine oxidase inhibitors, large amounts of noradrenaline accumulate in the brain and in the sympathetic terminals, and administration of an indirectly acting sympathomimetic may cause an exaggerated release of noradrenaline, with a potentially fatal hypertensive response [4].

Volatile anaesthetics. As mentioned above, CYP 2E1 is probably the major enzyme responsible for metabolism of the fluorinated volatile anaesthetics. Biotransformation of these drugs results in the formation of products that can cause either renal or hepatic toxicity.

Halothane undergoes oxidative metabolism to form trifluoroacetyl halide (TFA), by a pathway mainly involving CYP 2E1 [18]. Most TFA is excreted by the kidneys, but a small percentage binds covalently to lipoproteins and proteins, including P450 enzymes, to form a TFA-hapten, which, in susceptible individuals, is thought to be responsible for halothane hepatitis. This pathway is enhanced by

induction of P450, and it is therefore advisable to avoid using halothane in patients taking potent enzyme inducers.

Chronic isoniazid therapy induces the metabolism of enflurane and isoflurane, markedly increasing peak fluoride concentrations [19, 20], whereas cimetidine, an inhibitor of cytochrome P450 enzymes, decreases the incidence and severity of liver damage in animal models of halothane hepatitis [4, 21].

Pharmacodynamic interactions

A pharmacodynamic drug interaction occurs when one drug alters the responsiveness of the target tissue or receptor of another drug. This type of interaction is more limited than pharmaceutical or pharmacokinetic interactions.

Antidepressants. Tricyclic and tetracyclic antidepressants act by specifically blocking the reuptake of endogenous catecholamines and serotonin into nerve terminals. In patients receiving these drugs, the circulatory effects of adrenaline and noradrenaline are potentiated [22].

Electrolyte disturbances. Hypokalaemia caused by diuretics may potentiate the activity of nondepolarising muscle relaxants, leading to prolonged paralysis [4].

Neuromuscular blocking drugs. Prophylactic administration of antimicrobial agents to surgical patients has become standard practice to minimise the risk of postsurgical infections [23]. For the great majority (93%), the first antibiotic dose is administered at the time of induction of anaesthesia [24]. Nevertheless, clinically important interactions are found between antimicrobials and drugs of anaesthesia. Several classes of antibiotics possess neuromuscular blocking actions, including aminoglycosides, tetracyclines, polymixins, and linocosamides [4, 25]. Potentiation of neuromuscular block by aminoglycosides can occur with relatively small doses of drugs, and enough can be absorbed from irrigation of the intrapleural space, peritoneal cavity, or even a wound to give rise to clinical problems [4]. Since this procedure is still a debated question involving medical, ethical, economic, and legal issues, a targeted, non-standardised, antibiotic prophylaxis aimed at reducing potential risks for surgical patients is suggested [26].

Long-term therapy with antiepileptic drugs, phenytoin, carbamazepine, or sodium valproate has been associated with resistance to the nondepolarising muscle relaxants [27, 28, 29]. There is an increase in the dose of muscle relaxant required to achieve a given degree of block and a reduction in the duration of action, related to a decrease in the sensitivity of the post-junctional membrane to acetylcholine [4].

Consumption of herbs, homeopathics, and alternative drugs by surgical patients increases the risk of drug interactions during anaesthesia

There has been a significant increase in the proliferation and use of dietary supplements known as neutraceuticals [30]. In the Unites States, a survey found that 51% of surgical patients took preoperative alternative supplements (herbs, vitamins, dietary supplements, or homeopathic products) [31]. Consumption of herbs by surgical patients may increase the risk of botanical–drug interactions, since botanical products may exacerbate cardiovascular, neuromuscular, or sedative effects of anaesthetics, or may result in increased surgical bleeding [30]. Classification by potential adverse effects revealed that 27% of surgical patients consume alternative medicines that may inhibit coagulation, affect blood pressure (12%), cause sedation (9%), have cardiac effects (5%), or alter electrolytes (4%) [31]. To allow for clearance of botanical medicines, the American Society of Anaesthesiologists (ASA) recommends the discontinuation of herbs at least 2 weeks prior to surgery [32]. Nevertheless, 70% of patients who consumed botanical medicines did not disclose their use during interviews with anaesthetists [33].

Garlic inhibits platelet aggregation, reduces thromboxane, increases fibrinolytic activity, and increases streptokinase-activated plasminogen activator [34, 35]. It may augment the effects of warfarin, heparin, and nonsteroidal anti-inflammatory drugs, resulting in an abnormal bleeding time, with increased risk of intraoperative or postoperative bleeding, also during neuraxial block [30].

Ginger has been found to be a potent inhibitor of thromboxane synthetase, which can prolong bleeding time [36]; therefore, its use should be avoided in patients taking anticoagulants, such as warfarin, heparin, or aspirin, and the caveat about neuraxial blocks should also be applied [30].

Ginkgo biloba has been associated with spontaneous and increased bleeding when combined with anticoagulants and would be expected to increase the risk of operative haemorrhage, since it inhibits platelet-activating factor, decreases fibrinogen levels, and decreases plasma viscosity, possibly due to flavonoids and ginkgolide B [37]. In addition, concomitant use with anticonvulsants drugs (e.g. carbamazepine, phenytoin, phenobarbital) should also be avoided as the latter may decrease the effectiveness of these highly useful drugs [38]. It has also been suggested that ginkgo should be avoided in patients taking tricyclic antidepressant agents as it may lower the efficacy of these agents [30].

The use of ginseng should be avoided with concomitant use of anticoagulants. Ginseng, with its potential hypoglycaemic effects, should be avoided, or at least used cautiously, in patients taking insulin or oral hypoglycaemic medications. Also, blood glucose levels should be monitored perioperatively in patients at risk, as well as neurosurgical patients receiving steroids, and patients with diabetic or renal failure [30].

Long-term use of *liquorice (Glycyrrhiza glabra)* may cause hypokalaemia, pseudo-aldosteronism, hypertension, or arrhythmias [39]. Hypokalaemia can potentiate anaesthetic muscle relaxants and cause adverse cardiovascular effects [1, 40].

Long-term consumption of the illicit herb *marijuana* (*Cannabis sativa*) greatly

increases anaesthetic requirements due to extensive hepatic drug metabolism [41].

Piper methysticum *(Kava kava)* has anaesthetic, analgesic, anticonvulsive, antifungal, sleep-inducing, and spasmolytic properties [30]. Antinociceptive effects produced by kava kava may be similar to local anaesthetic responses [42, 43]. The herb can potentiate the effects of barbiturates and benzodiazepines, causing excessive sedation [44].

The herb *Ephedra sinica* (ma huang) is the botanical precursor of ephedrine, a drug used as a vasopressor during anaesthesia. It is a cardiovascular stimulant (acts as an α- or β-adrenergic agonist) and is a potent bronchodilator [45]. Obviously, the preoperative use of the herb ephedra could be problematic since it could interact with the cardiovascular effects of volatile anaesthetic agents [31]. Patients taking ephedra under general anaesthesia may experience severe hypotension, which can be controlled with phenylephrine instead of ephedrine [30]. Concomitant use with oxytocin may cause hypertension [46].

The sedative herb *Valeriana officinalis* may interact with anaesthetic barbiturates, hypnotics, benzodiazepines, or narcotics [31]. It also increases the effectiveness of anti-seizure medications and prolongs the actions of other sedatives [30].

Conclusions

Patients scheduled for anaesthesia are likely to receive multiple pre-operative drug therapy and also many peri-operative medications. Greater communication, knowledge, and scientific research are needed to safely integrate complementary and alternative medicines in the management of the surgical patient [31]. Unfortunately, anaesthetists tend not to report drug interactions that occur during anaesthesia, especially those of a minor nature; therefore, the true number of drug interactions is unknown [47].

Adverse drug reactions and drug interactions can occur more often in geriatric patients than in younger patients. In addition, elderly patients may experience unusual sensitivity to a single drug, compared with younger patients. Despite these considerations, medications in the aged population are almost often continued up to, and including, the day of surgery (especially medications for cardiovascular conditions), since complications are more likely to occur when these medications are interrupted. For these reasons, the benefits and risks of multiple medications and the administration of certain types of drugs must be carefully considered in these patients. When taking drug interactions into account, the anaesthetist must also consider whether potential effects are deleterious or not, before choosing the drugs and doses to be administered.

References

1. Vuyk J (1999) Drug interactions in anaesthesia. In: Bovill JG, Howie MB (eds) Clinical Pharmacology for Anaesthetists. WB Saunders, London, pp 377–387
2. Kubler A (2000) Drug interactions in anaesthesiology. Pol Merkuriusz Lek 9:598–599
3. Wood M (1991) Pharmacokinetic drug interactions in anaesthetic practice. Clin Pharmacokinet 21:285–307
4. Bovill JG (1997) Adverse drug interactions in anaesthesia. J Clin Anaesth 9(6 Suppl):3S-13S
5. Shorten G (2000) Deleterious drug interactions in anaesthetic practice. Proceeding Annual Scientific Meeting SIVA, Belfast, pp S3
6. Kuchta A, Golembiewski J (2004) Medication use in the elderly patient: focus on the perioperative/perianesthesia setting. J Perianesth Nurs 19:415–424
7. Wandel C, Bocker R, Bohrer H et al (1994) Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth 73:658–661
8. Kharasch ED, Thummel KE (1993) Human alfentanil metabolism by cytochrome P450 3A3/4. An explanation for the interindividual variability in alfentanil clearance? Anesth Analg 76:1033–1039
9. Gubbins PO, McConnell SA, Penzak SR (2001) Antifungal agents. In: Piscitelli S, Rodvold KA (eds) Drug interactions in infectious diseases. Human, Totowa, pp 185–217
10. Gascon MP, Dayer P (1991) In vitro forecasting of drugs which may interfere with the biotransformation of midazolam. Eur J Clin Pharmacol 41:573–578
11. Varhe A, Olkkola KT, Neuvonen PJ (1994) Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. Clin Pharmacol Ther 56:601–607
12. Backman JT, Olkkola KT, Aranko K et al (1994) Dose of midazolam should be reduced during diltiazem and verapamil treatments. Br J Clin Pharmacol 37:221–225
13. Varhe A, Olkkola KT, Neuvonen PJ (1996) Diltiazem enhances the effects of triazolam by inhibiting its metabolism. Clin Pharmacol Ther 59:369–375
14. Gonzalez FJ (1988) The molecular biology of cytochrome P450s. Pharmacol Rev 40:243–288
15. Andersson T (1996) Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet 31:9–28
16. Caraco Y, Tateishi T, Wood AJ (1995) Interethnic difference in omeprazole's inhibition of diazepam metabolism. Clin Pharmacol Ther 58:62–72
17. Ishizaki T, Chiba K, Manabe K (1995) Comparison of the interaction potential of a new proton pump inhibitor, E3810, versus omeprazole with diazepam in extensive and poor metabolizers of S-mephenytoin 4'-hydroxylation. Clin Pharmacol Ther 58:155–164
18. Gut J, Christen U, Huwyler J (1993) Mechanisms of halothane toxicity: novel insights. Pharmacol Ther 58:133–155
19. Mazze RI, Woodruff RE, Heerdt ME (1982) Isoniazid-induced defluorination in humans. Anesthesiology 57:5–8
20. Gauntlett IS, Koblin DD, Fahey MR et al (1989) Metabolism of isoflurane in patients receiving isoniazid. Anesth Analg 69:245–249
21. Plummer JL, Wanwimolruk S, Jenner MA et al (1984) Effects of cimetidine and ranitidine on halothane metabolism and hepatotoxicity in an animal model. Drug Metab Dispos 12:106–110
22. Svedmyr N (1968) The influence of a tricyclic antidepressive agent (protriptyline) on

some of the circulatory effects of noradrenaline and adrenaline in man. Life Sci 7:77–84
23. Markantonis SL, Kostopanagiotou G, Panidis D et al (2004) Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. Clin Ther 26:271–281
24. Martin C, Pourriat JL (1998) Quality of perioperative antibiotic administration by French anaesthetists. J Hosp Infect 40:47–53
25. Cammu G (2001) Interactions of neuromuscular blocking drugs. Acta Anaesthesiol Belg 52:357–363
26. Fodale V, Praticò C, Lucanto T et al (2004) Is prophylactic administration of antimicrobial agents to surgical patients a safe procedure? The anaesthesiologist's point of view. Proceedings of World Conference on Dosing of Anti-infectives (WCDA). Nürnberg, Germany, pp 157
27. Hickey DR, Sangwan S, Bevan JC (1988) Phenytoin-induced resistance to pancuronium. Use of atracurium infusion in management of a neurosurgical patient. Anaesthesia 43:757–759
28. Ornstein E, Matteo RS, Schwartz AE et al (1987) The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. Anesthesiology 67:191–196
29. Blanc-Bimar MC, Jadot G, Bruguerolle B et al (1979) Modification of curarization of two short-acting curare-like agents after the administration of two antiepileptic agents. Ann Anesth Fr 20:685–690
30. Sabar R, Kaye A, Frost E (2001) Perioperative considerations for the patient taking herbal medicines. Heart Disease 3:87–96
31. Norred CL, Zamudio S, Palmer SK (2000) Use of complementary and alternative medicines by surgical patients. AANA J 68:13–18
32. Weintraub PS (1999) New and old media used to distribute ASA's patient safety message about herbal medications. ASA Newsletter 63:23–35
33. Kaye AD, Clarke RC, Sabar R et al (2000) Herbal medicines: current trends in anaesthesiology practice—a hospital survey. J Clin Anaesth 12:468–471
34. Bordia A, Verma SK, Srivastava KC (1998) Effect of garlic *(Allium sativum)* on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostglandins Leukot Essent Fatty Acids 58:257–263
35. Legnani C, Frascaro M, Guazzaloca G et al (1993) Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. Arzneimittelforschung 43:119–122
36. Backon J (1986) Ginger: inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry. Med Hypotheses 20:271–278
37. Chavez ML, Chavez PI (1998) Ginkgo (part 1): History, use, and pharmacologic properties. Hosp Pharm 33:658–672
38. Miller LG (1998) Herbal medicinals. Arch Intern Med158:2200–2211
39. Shintani S, Murase H, Tsukagoshi H et al (1992) Glycyrrhizin (licorice)-induced hypokalemic myopathy. Eur Neurol 32:44–52
40. Stedwell RE, Allen KM, Binder LS (1992) Hypokalemic paralysis: A review of the etiologies, pathophysiology, presentation, and therapy. Am J Emerg Med 10:143–148
41. Ashton CH (1999) Adverse effects of cannabis and cannabinoids. Br J Anaesth 83:637–649
42. Jamieson DD, Duffield PH (1990) The antinociceptive actions of kava components in mice. Clin Exp Pharmacol Physiol 17:495–507

43. Singh YN (1983) Effects of kava on neuromuscular transmission and muscular contractility. J Ethnopharmacol 7:267–276
44. Anonymous (1998) Piper methysticum (kava kava). Altern Med Rev 3:458–460
45. Tinkelman DG, Avner SE (1977) Ephedrine therapy in asthmatic children. Clinical tolerance and absence of side effects. JAMA 237:553–557
46. Gruenwald J, Brendler T, Jaenicke C (1998) PDR for herbal medicines. Medical Economics Co 826–827
47. Dawson J, Karalliedde L (1998) Drug interactions and the clinical anaesthetist. Eur J Anaesthesiol 15:172–189

Chapter 51

Perioperative myocardial ischaemia

P. Foëx

The effects of myocardial ischaemia on cardiac function have been studied for many years. This is not surprising, as myocardial ischaemia and its consequences are among the leading causes of morbidity and mortality.

Ever since the introduction of ambulatory ischaemia monitoring [1], it has become clear that many episodes of myocardial ischaemia are not associated with anginal pain [2]. The absence of pain may relate to increased levels of beta-endorphins [3]; to the presence of autonomic neuropathy, especially in diabetic patients [4]; or to other reasons. However, silent myocardial ischaemia is a predictor of adverse outcome in medical patients [5].

Perioperative myocardial ischaemia occurs in a high proportion of adult patients, especially those undergoing vascular surgery and those with uncontrolled hypertension [6]. The adverse effect of perioperative myocardial ischaemia on cardiac outcome was emphasised by Slogoff and Keats in 1985 [7], in a study that showed a high proportion of postoperative myocardial infarction in patients who had myocardial ischaemia during surgery. Later, a strong relationship between preoperative myocardial ischaemia and postoperative adverse cardiac outcome was demonstrated [8–10]. The relationship is even stronger when postoperative myocardial ischaemia is also present [11]. This is most likely due to the fact that there are usually more episodes of ischaemia after than before surgery, and their duration is also longer; as a result, the total ischaemic load (ischaemic burden) is larger [12]. Adverse cardiac events occur in patients with prolonged ischaemia, and ischaemia of more than 2 h is likely to be associated with a cardiac event [13]. The reasons for the increased severity of ischaemia include postoperative hypoxaemia, especially nocturnal [15], altered coagulation status, and haemodynamic abnormalities such as tachycardia, hypo- and hypertension. Regional anaesthesia does not seem to reduce the risk of myocardial ischaemia [16, 17] because most of the ischaemic burden does not occur during anaesthesia and surgery. In the long-term, patients who have suffered episodes of perioperative myocardial ischaemia are more at risk for cardiac events than patients who have not experienced perioperative ischaemia. The long-term prognosis is particularly poor in patients who have suffered perioperative unstable angina or myocardial infarction, both of which are related to myocardial ischaemia [18].

Effects of acute myocardial ischaemia

The time-course of the effects of ischaemia on the cardiac tissue is well-known. A few seconds after the onset of ischaemia, there is a marked reduction of contractile function resulting from decreased ATP production. Leakage of potassium ions is responsible for the alterations of ST-segments. Within minutes, an intracellular acidosis develops associated with an increase in myoplasmic calcium and the beginning of cell swelling. Later, cellular lesions become irreversible; the ultrastructure of the cells is altered, and macromolecules such as CK-MB and troponins are released. The increased myoplasmic Ca^{2+} concentration plays a central role in the damage to the cells and their membranes.

The mechanical effects of acute coronary occlusion or progressive coronary constriction include reductions of systolic shortening and thickening. Both are abolished when flow is interrupted [19]. Together with the reduction of systolic function, ischaemic segments demonstrate paradoxical wall motion, namely, post-systolic shortening or thickening. These phenomena develop as a function of the severity of the reduction of coronary blood flow.

Acute or progressive ischaemia of the left ventricle causes an increase in chamber stiffness not only in the ischaemic segment but also in remote non-ischaemic segments [19]. This generalised effect likely results from the release of metabolic mediators and contributes to an elevation of left ventricular end-diastolic pressure, especially in the presence of volume loading [19]. This increase, in turn, leads to a vicious cycle, as coronary blood flow is further impaired by increasing diastolic wall tension.

Causes of myocardial ischaemia

Myocardial ischaemia occurs in the presence of fixed or dynamic coronary artery stenoses. In the right ventricle, ischaemia may result purely from afterload mismatch, which is the term used to describe the effect of acute, or of acute on chronic pulmonary hypertension.

The main causes of ischaemia with fixed coronary stenoses include tachycardia, excessive left ventricular filling, anaemia, hypoxaemia, and hypotension. These changes decrease the oxygen supply whereas tachycardia, systolic hypertension, and beta-adrenergic stimulation increase the oxygen requirements. Tachycardia is especially harmful because it decreases supply, owing to the reduced duration of diastole, but increases demand [7]. Postoperatively, the heart rate is generally faster than preoperatively [20]. This contributes to myocardial ischaemia and adverse outcome, similar to the situation in patients with critical illnesses [21]. Conversely, close control of the heart rate decreases the risk of ischaemia [22].

The causes of ischaemia with dynamic stenoses include those described above. In addition, activation of the autonomic nervous system plays an important role, as part of the vessel wall is still responsive to vasoconstrictors such as noradrenaline. Autonomic imbalance has been reported after anaesthesia and surgery and

can last for several days [23]. This may promote inappropriate vasoconstriction and contribute to postoperative ischaemia. Endothelium-derived mediators (endothelins, thomboxane) can cause vasoconstriction, facilitate the development of microcoagulation, reduce lysis, and increase the risk of plaque disruption.

The reasons for perioperative ischaemia relate to the physiological stress represented by surgery. Increases in adrenaline, noradrenaline, cortisol, and free fatty acids increase myocardial oxygen demand and may impair its supply. The imbalance between demand and supply is responsible for myocardial ischaemia, calcium overload, and, eventually, cellular lesions. Myocardial ischaemia, in turn, causes instability in atheromatous plaques. This facilitates haemorrhages and fissures in the plaques and thus local thrombosis. In addition, plaque disruption may occur as a result of the release of inflammatory mediators during and after major surgery [24] or trauma, or in response to acute illnesses.

Endothelial dysfunction is a feature of coronary heart disease. It causes an accentuation of coronary vasoconstriction in response to adrenergic stimulation and may convert acetylcholine-induced vasodilatation into vasoconstriction. In addition the effects of endothelins are increased.

Prevention of perioperative myocardial ischaemia

An important goal is to ensure cardiovascular stability and to avoid the often unrecognised risk of nocturnal hypoxaemia. Prophylactic drug therapy is less successful than could be anticipated. Currently, calcium channel blockers [25], clonidine [26], beta-blockers [25], nicorandil (a K^+_{ATP} channel opener), and statins [27] have shown some efficacy. Statins may be beneficial because of their effects on inflammatory mediators.

Myocardial ischaemia: paradoxes

While the adverse effects of myocardial ischaemia are well known, paradoxically, ischaemia may play a protective role. This is the case with ischaemic pre- and post-conditioning.

Myocardial pre-conditioning was described by Reimer et al. [28] and Murry et al. [29] in 1986. These authors demonstrated that short periods of ischaemia, lasting about 5 min, decreased the rate of ATP depletion during a more prolonged period of ischaemia and reduced the extent of tissue infarction. Ischaemic pre-conditioning is the most powerful mechanism for myocardial protection. It can result from short periods of myocardial ischaemia or from remote ischaemia, e.g. from the limb [30] or viscera [31]. Pre-conditioning has two windows: an acute memory phase lasting 1–3 h, and a late memory phase starting 12–24 h after ischaemia and lasting from 2–4 days.

Central to ischaemic and pharmacological pre-conditioning are the mitochondrial K^+_{ATP} channels. Many sarcolemmal receptors, such as those for adenosine,

bradykinin, and angiotensin, play a triggering role in the activation of intracellular pathways. Alpha-adrenoceptors and delta-opioid receptors are also involved in pre-conditioning. A number of intracellular mediators, such as G-proteins, phospholipase C, protein kinase C, free radicals, and calcium, act as signal transducers in early pre-conditioning [32–34], whereas nitric oxide, lipopolysaccharides, heat stress, and monophosphoryl lipid A are signal transducers in late pre-conditioning [32]. There is little doubt that ischaemic pre-conditioning is clinically relevant, as patients with angina shortly before infarction have a better prognosis than those without angina [35].

Pre-conditioning can also be induced pharmacologically by K^{+}_{ATP} channel openers (nicorandil), inhalation anaesthetics, and opioids. Inhalation anaesthetics have been shown to pre-condition the myocardium, resulting in cardioprotection against experimental myocardial infarction. Protection by isoflurane, desflurane, or sevoflurane is very similar to ischaemic pre-conditioning and shows the same pattern of signal transduction [32, 33, 36, 37]. Recently, several studies in cardiac surgical patients have suggested that pharmacological pre-conditioning with sevoflurane minimises cardiac damage [38–39] and may improve the long-term prognosis [38–40].

Myocardial post-conditioning

Recently, Zhao et al. [36] showed that reperfusion injury is minimised by short sequences of ischaemia–reperfusion. It has been established that, after a period of ischaemia, reperfusion can cause myocardial damage, leading to increased cell death or prolonged dysfunction (myocardial stunning). The main mechanism of reperfusion injury is the increase in blood flow. This causes proton (H^{+}) washout and increased entry of sodium into the cell. The increased sodium concentration allows sodium to be exchanged for calcium, resulting in myoplasmic calcium overload. Experimentally, pharmacological post-conditioning by isoflurane has been described [41].

Conclusions

Perioperative myocardial ischaemia is common and associated with adverse cardiac events. Its prophylaxis with cardiac drugs is only of limited value. By contrast, ischaemic myocardial pre- and post-conditioning appear to be protective. Inhalation anaesthetics and opioids are known to induce pharmacological pre-conditioning and possibly post-conditioning, thereby conferring protection. Thus ischaemia is both beneficial and harmful, but this paradox is not fully understood

References

1. Holter NJ (1961) Methods for heart studies. Science 134:1214–1220
2. Deanfield JE, Maseri A, Selwyn AP et al (1983) Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 2:753–758
3. Droste C, Roskamm H (1989) Silent myocardial ischemia. Am Heart J 118:1087–1092
4. O'Sullivan JJ, Conroy RM, MacDonald K et al (1991) Silent ischaemia in diabetic men with autonomic neuropathy. Brit Heart J 66:313–315
5. Raby KE, Barry J, Treasure CB et al (1993) Usefulness of Holter monitoring for detecting myocardial ischemia in patients with nondiagnostic exercise treadmill test. Am J Cardiol 72:889–893
6. Allman KG, Muir A, Howell SJ et al (1994) Resistant hypertension and preoperative silent myocardial ischaemia in surgical patients. Brit J Anaesth 73:574–578
7. Slogoff S, Keats AS (1985) Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107–114
8. Raby KE, Goldman L, Creager MA et al (1989) Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. New Engl J Med 321:1296–1300
9. Mangano DT, Browner WS, Hollenberg M et al (1990) Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. New Eng J Med 323:1781–1788
10. Pasternack PF, Grossi EA, Baumann FG et al (1992) Silent myocardial ischemia monitoring predicts late as well as perioperative cardiac events in patients undergoing vascular surgery. J Vasc Surg 16:171–179
11. Raby KE, Barry J, Creager MA et al (1992) Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. J Am Med Assoc 268:222–227
12. Mangano DT, Wong MG, London MJ et al (1991) Perioperative myocardial ischemia in patients undergoing noncardiac surgery—II: Incidence and severity during the 1st week after surgery. J Am Coll Cardiol 17:851–857
13. Landesberg G, Luria MH, Cotev S et al (1993) Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 341:715–719
14. Reeder MK, Muir AD, Foex P et al (1991) Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia. Brit J Anaesth 67:626–631
15. Reeder MK, Goldman MD, Loh L et al (1992) Postoperative hypoxaemia after major abdominal vascular surgery. Brit J Anaesth 68:23–26
16. Windsor A, French GW, Sear JW et al (1996) Silent myocardial ischaemia in patients undergoing transurethral prostatectomy. A study to evaluate risk scoring and anaesthetic technique with outcome. Anaesthesia 51:728–732
17. Marsch SC, Schaefer HG, Skarvan K et al (1992) Perioperative myocardial ischemia in patients undergoing elective hip arthroplasty during lumbar regional anesthesia. Anesthesiology 76:518–527
18. Mangano DT, Browner WS, Hollenberg M et al (1992) Long-term cardiac prognosis following noncardiac surgery. J Am Med Assoc 268:233–239
19. Marsch SC, Wanigasekera VA, Ryder WA et al (1993) Graded myocardial ischemia is associated with a decrease in diastolic distensibility of the remote nonischemic myocardium in the anesthetized dog. J Am Coll Cardiol 22:899–906

20. Knight AA, Hollenberg M, London MJ et al (1988) Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. Anesthesiology 68:681–688
21. Sander O, Welters ID, Foëx P et al (2005) Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications. Critic Care Med 33:81–88
22. Raby KE, Brull SJ, Timimi F et al (1999) The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. Anesth Analg 88:477–482
23. Marsch SC, Skarvan K, Schaefer HG et al (1994) Prolonged decrease in heart rate variability after elective hip arthroplasty. Br J Anaesth 72:643–649
24. Baigrie RJ, Lamont PM, Kwiatkowski D et al (1992) Systemic cytokine response after major surgery. Brit J Surg 79:757–760
25. Stevens RD, Burri H, Tramer MR (2003) Pharmacologic myocardial protection in patients undergoing noncardiac surgery: a quantitative systematic review. Anesth Analg 97:623–633
26. Wallace AW, Galindez D, Salahieh A et al (2004) Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology 101:284–293
27. Kertai MD, Boersma E, Westerhout CM et al (2004) Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. Am J Med 116:96–103
28. Reimer KA, Murry CE, Yamasawa I et al (1986) Four brief periods of myocardial ischemia cause no cumulative ATP loss or necrosis. Am J Physiol 251:H1306-H1315
29. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136
30. Oxman T, Arad M, Klein R et al (1997) Limb ischemia preconditions the heart against reperfusion tachyarrhythmia. Am J Physiol 273:H1707-H1712
31. Clavien PA, Yadav S, Sindram D et al (2000) Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. Ann Surg 232:155–162
32. Zaugg M, Schaub MC, Foëx P (2004) Myocardial injury and its prevention in the perioperative setting. Brit J Anaesth 93:21–33
33. Zaugg M, Lucchinetti E, Spahn DR (2002) Differential effects of anesthetics on mitochondrial K(ATP) channel activity and cardiomyocyte protection. Anesthesiology 97:15–23
34. Zaugg M, Lucchinetti E, Spahn DR et al (2002) Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. Anesthesiology 97:4–14
35. Kloner RA, Shook T, Przyklenk K et al (1995) Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? Circulation 91:37–45
36. Zhao ZQ, Corvera JS, Halkos ME et al (2003) Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol 285:H579-H588
37. Warltier DC, Kersten JR, Pagel PS et al (2002) Editorial view: anesthetic preconditioning: serendipity and science. Anesthesiology 97:1–3
38. Julier K, da Silva R, Garcia C et al (2003) Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. Anesthesiology 98:1315–1327
39. De Hert SG, Van der Linden PJ, Cromheecke S et al (2004) Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 101:299–310

40. Garcia C, Julier K, Bestmann L et al (2005) Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. Brit J Anaesth 94:159–165
41. Chiari PC, Bienengraeber MW, Pagel PS et al (2005) Isoflurane protects against myocardial infarction during early reperfusion by activation of phosphatidylinositol-3-kinase signal transduction: evidence for anesthetic-induced postconditioning in rabbits. Anesthesiology 102:102–109

Chapter 52

Left ventricular systolic and diastolic dysfunction

P. Foëx

In the United States, there are 4.9 million people with heart failure and 400 000 new cases are reported annually [1]. A similar prevalence of heart failure exists in northern Europe, while the prevalence of heart disease, particularly coronary heart disease, is lower in southern Europe. As coronary heart disease is a major cause of cardiac failure, it can be assumed that heart failure and ventricular dysfunction are also somewhat less common in southern Europe than in northern Europe and in North America. However, because of the prevalence of heart failure, a large number of patients present for surgery with impaired cardiac function. These patients are at risk for major complications of anaesthesia and surgery.

Heart failure is a process in which the venous return to the heart is normal but the heart is unable to pump sufficient blood to meet the body's metabolic needs at normal filling pressures. Heart failure may result from systolic dysfunction, diastolic dysfunction, or both.

Systolic dysfunction

Ventricular systolic dysfunction is characterised by a loss of contractile strength of the myocardium accompanied by compensatory ventricular remodelling, consisting of hypertrophy and/or dilatation. Pump failure may result primarily from work overload; mechanical abnormalities (valvular heart disease); myocardial abnormalities (cardiomyopathies); abnormal cardiac rhythm or conduction; or myocardial ischaemia/infarction. Heart failure may also result from viral myocarditis and from the administration of drugs used in the treatment of cancer (toxic heart failure).

The development of ventricular systolic dysfunction is associated with activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAS). Sympathetic activation increases contractility, heart rate, and vascular tone, while activation of RAS causes sodium and water retention and contributes to peripheral vasoconstriction, as angiotensin is a very potent vasoconstrictor. In the presence of increased preload and afterload, there is necessarily a decrease in ventricular emptying. An ejection fraction less than 45%, is usually associated with an increase in diastolic volume, constituting a dilated cardiomyopathy.

In the early stages, overall pump function may be maintained at rest but the exercise capacity is impaired. At more advanced stages, cardiac output is reduced

even at rest and systemic vascular resistance is unable to decrease when metabolic demands increase.

Systolic dysfunction may be present if some myocardium is hibernating [2, 3]. This condition of down-regulated function in response to decreased myocardial blood flow or successive episodes of ischaemia (repetitive myocardial stunning) can resolve after myocardial revascularisation. The presence of hibernating myocardium can be detected by dobutamine echocardiography and other techniques of myocardial imaging. Coronary revascularisation may be beneficial.

The factors that precipitate heart failure include uncontrolled hypertension, atrial fibrillation, non-compliance with medication, myocardial ischaemia, anaemia, renal failure, non-steroidal anti-inflammatory drugs, and excess sodium.

A recent UK study of patients with stable heart failure has shown that the 5-year mortality was 41.5% in those with systolic dysfunction (ejection fraction less than 50%) and 25.2% in those with diastolic dysfunction alone (ejection fraction more than 50%) [4].

Diastolic dysfunction

Ventricular diastolic dysfunction is characterised by altered relaxation of the cardiac fibres, resulting in slower pressure decline, reduced rapid filling, and increased myocardial stiffness. In many patients, diastolic dysfunction may exist while systolic function remains essentially normal. Approximately 30–50% of patients with heart failure have normal or near-normal left ventricular systolic function, as evidenced by the ejection fraction [5]; symptoms of failure may be absent [6]. Gandhi et al. found that, left ventricular ejection fraction and the extent of regional motion were similar during and after resolution of acute episodes of hypertensive pulmonary oedema. This further supports the role of diastolic dysfunction [7].

Diastolic dysfunction may result from a thickened ventricular wall, as in restrictive or infiltrative cardiomyopathies, and/or tachycardia, as the latter decreases the filling time resulting in elevated diastolic ventricular pressure. Indeed, pacing-induced tachycardia is used to create experimental models of heart failure.

Advancing age, hypertension, diabetes, left ventricular hypertrophy, and coronary artery disease are the main risk factors for diastolic dysfunction. Diastolic heart failure affects women particularly frequently [5]. This may be due to an increased remodelling in response to pressure overload [8].

The annual mortality from diastolic heart failure is estimated to be between 5% and 8% [6]. It is four times higher than the mortality of persons without heart failure but half that of patients with systolic heart failure [9].

The presence of significant diastolic dysfunction has several major implications for patients with acute illnesses or presenting for major surgery during which fluid shifts are an issue: as diastolic distensibility is reduced, inadequate fluid replacement causes an exaggerated reduction in cardiac output. Conversely, fluid overload causes exaggerated increases in end-diastolic left ventricular pressure and pulmo-

nary artery occlusion pressure. This may result in acute pulmonary oedema with volume loads that would be well-tolerated in the absence of diastolic dysfunction. The onset of atrial fibrillation is poorly tolerated as it decreases the atrial contribution to filling.

Diagnosis of diastolic dysfunction and diastolic heart failure

The diagnosis of diastolic heart failure requires symptoms and signs of heart failure with a normal left ventricular ejection fraction, and absence of valvular abnormalities on echocardiography. Doppler echocardiography measures the velocity of intracardiac blood flow and is very useful to document early and late diastolic filling (E and A waves, respectively). The E-wave velocity is influenced by early diastolic relaxation and left atrial pressure. It is altered by diastolic dysfunction.

Management of diastolic heart failure

The initial aim is to reduce pulmonary venous congestion. Diuretics, nitroglycerin, supplemented by morphine, and additional oxygen are needed. However, aggressive diuresis may cause severe hypotension because of excessive reduction of atrial pressure. Nitroglycerin is particularly indicated if there is myocardial ischaemia, as acute ischaemia has a profound effect on early relaxation and on myocardial stiffness [10].

While there have been many large studies of the pharmacological treatment of systolic heart failure, there is little data on that of diastolic heart failure [11]. The controlled studies Candesartan in Heart Failure [12] and Perindopril for Elderly People with Chronic Heart Failure [13] are addressing this issue. However, until gene therapy is introduced, some time in the future [14], the treatment of left ventricular diastolic dysfunction remains empirical, with avoidance of excessive sodium intake, cautious use of diuretics (lest reduced preload reduces cardiac output), restoration and maintenance of sinus rhythm at a heart rate that optimises ventricular filling, and the correction of precipitating factors such as myocardial ischaemia and arterial hypertension. Calcium channel blockers, ACE inhibitors, or angiotensin receptor antagonists are used for their effect mostly on surrogate outcomes.

Because treatment of diastolic dysfunction is difficult, it is very important to prevent its development. As arterial hypertension is a major cause of diastolic dysfunction, early detection and treatment of hypertension is critical. However, stage 3 hypertension (180 mmHg/ 110 mmHg) remains common and is very frequently poorly controlled. Note that recent studies have shown that the beta-blocker atenolol, often used in the management of hypertension in association with a thiazide diuretic, is effective in controlling blood pressure but is ineffective in preventing cardiac and cerebrovascular complications of arterial hypertension [15, 16]. While widely prescribed in the management of arterial hypertension, beta-blockers may be less effective than other agents [17].

New therapeutic avenues for severe heart failure

Over the past few years, prostaglandin E_1 has been studied as a bridge to heart transplantation due to its potential benefits resulting from systemic and pulmonary vasodilatation [18]. Triiodothyronine has been advocated because patients with heart failure have low triiodothyronine levels and its administration after cardiac surgery has been shown to be beneficial [19]. Nesiritide, a human recombinant brain natriuretic peptide (BNP), has shown promising results in some patients when compared with dobutamine [20]. Levosimendan, a calcium sensitiser, increases inotropy without an increase in cytosolic calcium; therefore it does not require energy to extrude calcium from the myocytes. It is also a vasodilator. Recent results seem very favourable [21]. As heart failure can be caused by lack of synchrony of cardiac contraction, cardiac resynchronisation by insertion of a biventricular pacemaker is now recommended in the management of drug-refractory cardiac failure [22]. Implanted cardiac defibrillators are also used very successfully to prevent death due to severe arrhythmias in patients with heart failure [23].

Cardiac failure and perioperative risk

All the studies of risk factors for perioperative cardiac complications of anaesthesia and surgery include heart failure, even in its incipient forms, often as the most important factor [24, 25].

A clear association exists between low ejection fraction and postoperative acute left ventricular failure [26–28]. In addition, patients with poor cardiac function may tolerate anaesthesia poorly. This is not surprising as inhalation anaesthetics exhibit strong negative inotropic properties because they reduce both transmembrane calcium flux and activated calcium release from the sarcoplasmic reticulum of cardiac cells [29–31]. Even nitrous oxide exhibits negative inotropic properties [32]. Intravenous induction agents, such as thiopentone and propofol [33], have strong negative inotropic properties. Of the drugs in the current anaesthetic armamentarium, only etomidate is devoid of negative inotropy. Similarly, benzodiazepines and opioids do not depress contractility. This may be advantageous as, in the face of an already depressed myocardium, further negative inotropy is poorly tolerated. At variance with other agents, xenon does not cause myocardial depression [34] but its high cost precludes widespread use.

Postoperatively, other factors contribute to worsening of cardiac function: silent ischaemia, especially in hypertensive patients [35], and nocturnal hypoxaemia [36] are frequently observed. In addition, fluid overload may precipitate acute left ventricular failure.

Conclusions

Cardiac failure may result from systolic or diastolic dysfunction. The latter is not always recognised and yet, in the long-term, it has serious implications, especially in hypertensive patients. Both systolic and diastolic dysfunction can be exaggerated by anaesthesia and by events in the perioperative period. Optimal treatment of systolic and diastolic dysfunction before anaesthesia and surgery is essential to minimise the risk of adverse perioperative cardiac outcome.

References

1. Rich MW, Nease RF (1999) Cost-effectiveness analysis in clinical practice: the case of heart failure. Arch Intern Med 159:1690–1700
2. Wijns W, Vatner SF, Camici PG (1998) Hibernating myocardium. New Engl J Med 339:173–181
3. Camici PG, Wijns W, Borgers M et al (1997) Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation 96:3205–3214
4. MacCarthy PA, Kearney MT, Nolan J et al (2003) Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. Brit Med J 327:78–79
5. Vasan RS, Benjamin EJ, Levy D (1995) Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 26:1565–1574
6. Aurigemma GP, Gaasch WH (2004) Clinical practice. Diastolic heart failure. New Engl J Med 351:1097–1105
7. Gandhi SK, Powers JC, Nomeir AM et al (2001) The pathogenesis of acute pulmonary edema associated with hypertension. New Engl J Med 344:17–22
8. Weinberg EO, Thienelt CD, Katz SE et al (1999) Gender differences in molecular remodeling in pressure overload hypertrophy. J Am Coll Cardiol 34:264–273
9. Vasan RS, Larson MG, Benjamin EJ et al (1999) Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 33:1948–1955
10. Marsch SC, Wanigasekera VA, Ryder WA et al (1993) Graded myocardial ischemia is associated with a decrease in diastolic distensibility of the remote nonischemic myocardium in the anesthetized dog. J Am Coll Cardiol 22:899–906
11. Vasan RS, Benjamin EJ (2001) Diastolic heart failure - no time to relax. New Engl J Med 344:56–59
12. Yusuf S, Pfeffer MA, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 362:777–781
13. Cleland JG, Tendera M, Adamus J et al (1999) Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. Eur J Heart Fail 1:211–217
14. Webster KA, Bishopric NH (2000) Molecular aspects and gene therapy prospects for diastolic failure. Card Clin 18:621–635
15. Carlberg B, Samuelsson O, Lindholm LH (2004) Atenolol in hypertension: is it a wise choice? Lancet 364:1684–1689
16. www.ascotstudy.org

17. Messerli FH, Beevers DG, Franklin SS et al (2003) Beta-Blockers in hypertension-the emperor has no clothes: an open letter to present and prospective drafters of new guidelines for the treatment of hypertension. Am J Hypertens 16:870–873
18. Stanek B, Sturm B, Frey B et al (1999) Bridging to heart transplantation: prostaglandin E1 versus prostacyclin versus dobutamine. J Heart Lung Transplant 18:358–366
19. Carrel T, Eckstein F, Englberger L et al (2002) Thyronin treatment in adult and pediatric heart surgery: clinical experience and review of the literature. Eur J Heart Fail 4:577–582
20. Silver MA, Horton DP, Ghali JK et al (2002) Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol 39:798–803
21. Follath F, Cleland JG, Just H et al (2002) Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 360:196–202
22. Gregoratos G, Abrams J, Epstein AE et al (2002) ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. Circulation 106:2145–2161
23. Moss AJ, Zareba W, Hall WJ et al (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. New Engl J Med 346:877–883
24. Goldman L, Caldera DL, Nussbaum SR et al (1977) Multifactorial index of cardiac risk in noncardiac surgical procedures. New Engl J Med 297(16):845–850
25. Lee TH, Marcantonio ER, Mangione CM et al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100(10):1043–1049
26. Lazor L, Russell JC, DaSilva J et al (1988) Use of the multiple uptake gated acquisition scan for the preoperative assessment of cardiac risk. Surg Gynecol Obstet 167:234–238
27. Baron JF, Mundler O, Bertrand M et al (1994) Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. New Engl J Med 330:663–669
28. Godet G, Riou B, Bertrand M et al (2005) Does preoperative coronary angioplasty improve perioperative cardiac outcome? Anesthesiology 102:739–746
29. Huneke R, Fassl J, Rossaint R et al (2004) Effects of volatile anesthetics on cardiac ion channels. Acta Anaesthesiol Scand 48:547–561
30. Housmans PR, Bartunek AE (2001) Effects of volatile anesthetics on ryanodine-treated ferret cardiac muscle. J Cardiovasc Pharmacol 38:211–218
31. Lee DL, Zhang J, Blanck TJ (1994) The effects of halothane on voltage-dependent calcium channels in isolated Langendorff-perfused rat heart. Anesthesiology 81:1212–1219
32. Messina AG, Yao FS, Canning H et al (1993) The effect of nitrous oxide on left ventricular pump performance and contractility in patients with coronary artery disease: effect of preoperative ejection fraction. Anesth Analg 77:954–962
33. Hamilton DL, Boyett MR, Harrison SM et al (2000) The concentration-dependent effects of propofol on rat ventricular myocytes. Anesth Analg 91:276–282
34. Goto T, Hanne P, Ishiguro Y et al (2004) Cardiovascular effects of xenon and nitrous oxide in patients during fentanyl-midazolam anaesthesia. Anaesthesia 59:1178–1183
35. Allman KG, Muir A, Howell SJ et al (1994) Resistant hypertension and preoperative silent myocardial ischaemia in surgical patients. Brit J Anaesth 73:574–578
36. Reeder MK, Goldman MD, Loh L et al (1992) Postoperative hypoxaemia after major abdominal vascular surgery. Brit J Anaesth 68:23–26

Chapter 53

Challenges in perioperative medicine: positioning

M. Klimek, F. Grüne

When performing a Medline search with the term 'patient positioning,' one will be surprised: There are many recent papers on patient positioning for all kinds of radiodiagnostic and radiotherapeutic procedures, and there are no fewer, but much older papers on positioning for surgical procedures. However, when reading these papers, only a small number of them can be considered to describe prospective randomised double-blind trials. For this reason, a lot of the information presented here is based on (personal) clinical experience. Another surprising result of a search in the literature is that, even in the most important textbooks on clinical anaesthesia, there are relatively few pages dedicated to patient positioning, compared with the amount of space devoted to discussing pharmacological and pathophysiological topics. Nonetheless, there are some very well-written books on this topic, and they must be strongly recommended [1, 2]. This article will therefore only highlight some of the medical and legal aspects of patient positioning. These should be considered as the minimum knowledge expected of every anaesthetist.

General aspects

Positioning a patient for a surgical procedure is challenging and the difficulty is often underestimated. Like much else in anaesthesia, positioning is expected to be always perfect, and many complications that arise as a result of it are met with surprise and concern [3]. Optimal positioning means a compromise between surgical and anaesthesiological demands:

The surgical demands include easy access to the surgical field, which improves the surgical results, shortens the duration of the procedure, and might lead to less blood loss and fewer complications. The anaesthesiological demands include safe positioning in a physiological posture, access to the airway, lines and monitoring devices, and no cardiorespiratory depression. Even if these major aspects are taken into consideration, serious patient instability during the procedure may arise, together with the problem of intraoperatively unnoticed skin and nerve damage, which can lead to serious, sometimes irreversible disability and functional impairment after the surgical procedure. Furthermore, beside the comfort, security, and stability of the patient, his or her dignity plays an important role in positioning, especially if locoregional anaesthesia is used.

Epidemiology

In general, the incidence of damage due to positioning is about 5/1000 cases [4]. According to the list of adverse outcomes in the ASA Closed Claims Study database, nerve injury represents the second largest class (16%)—behind death but before brain damage [5]. However, in the subgroup of patients undergoing cardiac surgery, the incidence of ulnaric nerve neuropathy as high as 38% was reported. In this group, a number of contributing factors other than positioning must be assumed [6, 7]. In 2000, the ASA published a 'practice advisory' for the prevention of perioperative peripheral neuropathies. This paper was not viewed as a 'standard' or 'guideline' due to the lack of scientific evidence in the field of patient positioning [8].

In addition to peripheral nerve injuries, also pressure sores, spinal injuries, cardiorespiratory complications, diathermy burns, and tourniquet sores must be taken into consideration when attempting to prevent complications of positioning [1, 3].

(Patho-)physiology

Global cardiovascular effects

Especially during procedures with greater volume shifts and in patients with concomitant cardiovascular disease, knowledge of the physiologic effects and the possible pathologic consequences of patient positioning is crucial for the anaesthetist.

Maintenance of blood pressure during and after changes in position is a result of different mechanisms, e.g. transmural vascular pressure, hydrostatic effects, muscular tone, venous valves, atrial reflexes, and autonomic responses to baroceptors.

In the neutral supine position, the influence of gravity on the vascular system is low. Intravascular pressures from head to toe vary slightly from mean pressures at the level of the heart. Furthermore, venous gradients from the periphery to the right atrium consist principally of the cyclic intrathoracic pressure changes that occur with respiration. Simply lying down, from a standing to neutral supine position, increases venous return from the lower body back to the heart, stretches the ventricular wall, and increases the stroke volume. Cardiac output shows a tendency to increase, too. If contractility and arteriovascular tone remain constant, arterial pressure increases. Baroceptor impulses are conducted from the heart, aorta, and carotid sinus via vagal fibres to the medulla oblongata. Increased efferent parasympathetic and efferent sympathetic activity change the parasympathetic/sympathetic balance, which decreases heart rate, stroke volume, and contractility and thereby results in little change in blood pressure [3].

The Trendelenburg manoeuvre to treat hypotension has been shown to be counterproductive. In the first reaction, cardiac output rises due to the increasing central blood volume by recovering pooled blood from caudal parts of the body. This again leads to activation of baroceptors of the great vessels of the chest and neck [9, 10]. The consequences are a rapid peripheral vasodilatation, unchanged

or reduced cardiac output, and decreased organ perfusion. Furthermore, myocardial O_2 consumption may be increased in the Trendelenburg position [11, 12]. Of course, the reduction of functional residual capacity, especially in obese patients, is another problem of this position [13].

Local effects

Any kind of positioning can induce severe stretch, ischaemia, and/or compression of any type of tissue, which finally will result in damage. Skin, nerves, muscles, and the eyes are most frequently damaged. Relevant risk-factors for damage due to positioning are different types of neuropathy (e.g. diabetic, uraemic, vitamin-deficiency, paraneoplastic, chemotherapy-induced), alcoholism, anatomic variants, pressure by cables and lines, a blood-pressure cuff placed too low at the elbow, pronation of the arms in supine position, too tight tapes, i.v. lines at uncomfortable places, scoliosis and kyphosis, but also members of the surgical team lying on the patient [1, 2]. The duration of the procedure plays another important role. The longer the procedure is expected to run, the more careful must be the measures taken to avoid positioning injury. For the anaesthesiologist, it is important to be aware of the fact that hypotension and hypothermia are predisposing factors for skin injury, but also the use of warming blankets can promote the occurrence of skin damage [14]. The severity of the injury varies from superficial skin erosions up to death due to positioning-induced compartment syndrome with rhabdomyolysis and multi-organ failure [15].

Pre-anaesthetic visit

During the pre-anaesthetic visit, the potential risks and dangers should be anticipated and measures to avoid their realisation should be planned. This includes damage due to positioning, which can be anticipated based on clinical findings, X-rays, and anamnesis. Anatomic variants and pathological deviations, e.g. preexisting neuronal damage, cervical ribs, 'shunt-arms,' and prostheses, should be documented. Neurological consult should be asked liberally [16]. The planned intraoperative position (e.g. knee–elbow, sitting position) must be taken into consideration, too. The risk of damage due to patient positioning should be addressed, if indicated, when asking for written informed consent to anaesthesia.

Intraoperative positioning

Nerves

The most important structures to protect are the peripheral nerves of the upper and lower extremities and the brachial plexus. An extended elbow and a supinated

forearm are recommended to protect the ulnar nerve [17]. Pronation, flexion of the elbow, and overly tight abduction of the arm should be avoided. The radial nerve is at special risk at the humerus, where it might be compressed by the edge of the table. The n. medianus is at particular risk at the elbow, where it might be damaged by paravascular injections and compression by blood-pressure cuffs that are placed too low. The brachial plexus in total is also at higher risk, if the cervical spine is hyperextended and the head rotated to the contralateral side. Additionally, an overextension in the shoulder region might lead to entrapment of the nerve between the clavicula and the first rib [18]. In accordance with the anatomic situation, falling backwards of the shoulder, abduction of the arms by more than 90°, strong exorotation of the arm, dorsal extension and too strong distal traction on the arm must be avoided [16]. At the lower extremity, the sciatic nerve must be protected by avoiding overly strong flexion and exorotation of the hip joint. Careful attention must also be paid to the peroneal nerve, which due to its superficial position is at greater risk for direct pressure.

Vessels

The use of tourniquets should be restricted to a maximum pressure of 100–150 mmHg above systolic blood pressure for not more than 2 h [19]. In all positions in which perfusion might be restricted, one should be alert of the fact that a reperfusion oedema with the risk of compartment syndrome can develop in the first hours after re-positioning. Serious complications can be avoided only if detected and treated in time. In the prone position, a poorly positioned pillow at the pelvis might lead to compression of the inferior vena cava (pillow too cranial) or compression of the femoral arteries (pillow too caudal). If the anaesthesiologist is in doubt of the state of perfusion of a certain extremity, placing the pulse-oximeter there might be a simple test for the integrity of perfusion.

Skin

The use of mattresses and pads has turned out to be useful to protect the skin. However, there are strong differences in the available materials. In general, air-mattresses have turned out to induce lower tissue-interface pressures (which means: smaller risk of decubitus) than mattresses made of jelly-polymers [20]. To reduce the pressure on the skin and the underlying tissue, padding is especially important at the following places: occiput (supine position), ear and eye (lateral and prone position), elbow and cubital tunnel, perineum and genitals (extension table, prone position), knees (knee–elbow position), underlying extremities (lateral position), heels (supine position).

Joints and ligaments

One should be aware of the fact that a relaxed patient (this might also be due to spinal anaesthesia!) has no muscle power to stabilise his or her spine. Especially in a patient with pre-existing degenerative disease and strong lordosis, a table that is too flat might lead to impressive shear forces at the spinal ligaments, which afterwards will cause severe lower back pain. Liberal use of extra pillows under the knees and in the back might be helpful to reduce the extremely high incidence (30%) of patients suffering from lower back pain postoperatively [16]. Furthermore, all joints are at high risk during intraoperative position changes. To avoid falls from the table, extremities should be secured with belts and tapes.

Eyes

Compression of the bulbi with resulting blindness is the severest form of damage due to intraoperative positioning, while erosion of the cornea due to direct mechanical trauma is the most common. The patient's eyes should be actively closed and protected against desinfection fluids, mechanical damage (e.g. during mask ventilation), and drying out. In case of postoperative blindness, an embolism in the retinal artery must be ruled out [21].

Other aspects

Some other important principles of good positioning should be highlighted :

Whenever the patient is placed head-down (Trendelenburg, prone position) there is a risk of swelling of the soft tissues of the face and the airway that might lead to difficulties postoperatively and can make early detubation impossible. Also, the venous drainage from the brain might be compromised, especially if these positions are used together with high-PEEP ventilation.

Whenever the surgical field is exposed at a level that is higher than the heart of the patient, there is a theoretical (and frequently enough practical) risk of venous air embolism. There even is a report of a severe venous air embolism during laparoscopic prostatectomy in extreme Trendelenburg position [22]. The anaesthesiologist should be aware of this risk and seriously think about extra monitoring devices, such as precordial Doppler or transoesophageal echocardiography.

Severe haemodynamic consequences can result if a patient is brought into lithotomy position too quickly. In this position, the peroneal nerve must also be protected against direct pressure. Flexion in the hip can stress the sciatic nerve and compromise perfusion of the lower extremities.

Special problems and limitations in positioning the patient can be anticipated by doing so while the patient is awake, i.e. before induction of anaesthesia.

Legal aspects

Anaesthetists and surgeons should cooperate in patient positioning for surgery according to interdisciplinary agreements. If not available, a written protocol is strongly recommended for every hospital. Next to mutual confidence between surgeon and anaesthetist, mutual information and coordination are mandatory prerequisites for safe patient positioning. The anaesthetist should take responsibility for the induction period, the intraoperative positioning of the head and the arm with i.v. lines, and the recovery period. The surgeon should take responsibility for intraoperative positioning of the whole rest of the body. If the anaesthetist notices possible dangers, he or she should inform the surgeon, who might modify the patient's position.

Before discharge from the recovery room, a short neurological examination should be performed routinely. A postoperative visit within 24 h is strongly recommended to detect neurological deficits actively. Frequently, patients complain about the fact that nobody talked to them after the procedure. At that moment, with the patient still in the hospital, neurological consultation can be done immediately, pathological findings can be documented, and therapy can be started. When talking to patients about the prognosis of nerve damage, one should be aware of the fact that in the worst case restitution of a severely damaged nerve takes place at a rate of 1 mm/day.

Conclusions

In accordance with the study of Martin and Warner [2], safe positioning relies on the following:

Knowledge: Everyone involved in patient positioning should have sufficient theoretical and practical knowledge of the general, unavoidable preconditions of correct positioning and the pathophysiological impact of all measures taken.

Anticipation: It is the art of anaesthesiology to anticipate the problems of each patient undergoing a certain procedure in a certain position, to try and find means to prevent these problems, and—if those means should fail—to have a 'plan B' to deal with and solve these problems. One should be aware of the fact that sometimes bringing back the patient to a normal supine position is unavoidable for solving certain problems.

Teamwork: For good positioning, there must be a sufficient number of people, and they must know how to position the patient. Coordination of the entire crew is mandatory. It is good clinical practice, that the anaesthetist who cares for the airway and stands at the head of the patient gives the commands when changing the patient's position.

Material: Before starting positioning, all of the needed devices should be collected and checked for usability. The surgical table must work without any defects and be suitable for the planned position.

With these four precautions in mind, positioning a patient still remains challenging, but it can be done in a safe, efficient, and successful manner.

References

1. Servant C, Purkiss S (eds) (2002) Positioning patients for surgery, University Press, Cambridge
2. Martin JT, Warner MA (eds) (1997) Positioning in anesthesia and surgery. WB Saunders, Philadelphia
3. Faust RJ, Cucchiara RF, Bechtle PS (2005) Patient positioning. In: Miller RD (ed) Anesthesia 6th ed, Elsevier, Philadelphia, pp 1151–1168
4. Cohen MM, Duncan PG, Pope EDB et al (1986) A survey of 112 000 anaesthetics at one teaching hospital (1975–1983). Canad Anaesth Soc J 33:22–31
5. Cheney FW, Domino KB, Caplan RA et al (1999) Nerve injury associated with anesthesia: A closed claims analysis. Anesthesiology 90:1062–1069
6. Hickey C (1993) Intraoperative somatosensory evoked potential monitoring predicts peripheral nerve injury during cardiac surgery. Anesthesiology 78:29–35
7. Haupt WF (1989) Intraoperative Lagerungsschäden des N. ulnaris bei anatomischen Varianten. Dtsch med Wschr 114:1789–1792
8. ASA Task Force on Prevention of Perioperative Peripheral Neuropathies (2000) Practice advisory for the prevention of perioperative peripheral neuropathies. Anesthesiology 92:1168–1182
9. Sibbald WJ, Paterson NA, Holliday RL (1979) The Trendelenburg position: hemodynamic effects in hypotensive and normotensive patients. Crit Care Med 7:218–224
10. Reich DL, Konstadt SN, Raissi S et al (1989) Trendelenberg position and passive leg raising do not significantly improve cardiopulmonary performance in the anesthetized patient with coronary artery disease. Crit Care Med 17:313–317
11. Sing RF, O'Hara D, Sawyer MA et al (1994) Trendelenburg position and oxygen transport in hypovolemic adults. Ann Emerg Med 23:564–567
12. Vretzakis G, Ferdi E, Papaziogas B et al (2004) Coronary sinus venoarterial CO_2 difference in different hemodynamic states. Acta Anaesthesiol Belg 55:221–227
13. Fahy BG, Barnas GM, Nagle SE et al (1996) Effects of Trendelenburg and reverse Trendelenburg postures on lung and chest wall mechanics. J Clin Anesth 8:236–244
14. Grous CA, Reilly NJ, Gift AG (1997) Skin integrity in patients undergoing prolonged operations. J Wound Ostomy Continence Nurs 24:86–91
15. Martin JT (1992) Compartment syndromes: Concepts and perspectives for the anesthesiologist. Anesth Analg 75:275–283
16. Bund M, Heine J, Jaeger K (2005) Lagerungsschäden aus der Sicht des Anästhesisten. Anästhesiol Intensivmed Notfallmed Schmerzther 40:329–339
17. Ekerot L (1977) Postanaesthetic ulnar neuropathy at the elbow. Scand J Plast Reconstr Surg 11:225–229
18. Britt BA, Gordon RA (1964) Peripheral nerve injuries associated with anaesthesia. Can Anaesth Soc J 11:514–536
19. Wilgis EF (1971) Observations on the effect of tourniquet ischemia. J Bone Joint Surg 53A:1343–1346
20. Westrate J (2005) The value of interface pressure measurements and pressure ulcer risk assessment in patients. PhD Thesis
21. Williams EL, Hart WM, Tempelhoff R (1995) Postoperative ischemic optic neuropathy. Anesth Analg 80:1018–1029
22. Memtsoudis SG, Malhotra V (2003) Catastrophic venous air embolus during prostatectomy in the Trendelenburg position. Can J Anaesth 50:1084–1085

Chapter 54

The neurotoxicity of commonly used general anaesthetics: is it possible?

V. Jevtovic-Todorovic[1]

Over the last 50–60 years there has been an exponential increase in the number of anaesthetic interventions in all age groups—from very young children to ageing adults. These interventions are increasingly complex and therefore require aggressive and highly-skilled anaesthetic management. Anaesthesia professionals are frequently involved in providing anaesthesia care on a repetitive and/or long-term basis (e.g. multiple surgical interventions, prolonged sedation in the intensive care units), in very early stages of human development (e.g. very premature babies—as young as 20 weeks post-conception) [1] as well as in the very late stages of human life.

Despite the widespread use and the utmost importance of general anaesthesia in modern medicine and dentistry, the mechanism(s) of action of commonly used general anaesthetics remains poorly understood. However, based on the numerous studies published over the last few decades, it is becoming increasingly evident that there are specific cellular targets through which general anaesthetics act [2]. These most often involve the enhancement of inhibitory synaptic transmission [3, 4] and/or the inhibition of excitatory synaptic transmission [4, 5]. In particular, it is also clear that many intravenous (e.g. barbiturates, benzodiazepines, propofol, etomidate) [2, 6, 7] and inhalational volatile (e.g. isoflurane, sevoflurane, desflurane, halothane) [8] anaesthetics promote inhibitory neurotransmission by enhancing γ-amino-butyric acid ($GABA_A$)-induced currents in neuronal tissue; these are often referred to as GABAergic agents. In addition, a small number of intravenous anaesthetics (e.g. phencyclidine and its derivative, ketamine) [9, 10] and inhalational anaesthetics (e.g. nitrous oxide, xenon) [11, 12] are known to inhibit excitatory neurotransmission by blocking *N*-methyl-d-aspartate (NMDA) receptors, a subtype of glutamate receptors.

Both GABA and glutamate, the major inhibitory and excitatory neurotransmitters, respectively, play important roles in normal functioning of the mammalian central nervous system (CNS). It has long been recognised that an imbalance in their

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functioning, as seen in various types of acute or chronic brain injury syndromes, may trigger massive and widespread neuronal cell death. Hence, general anaesthetics have been considered potentially beneficial in protecting the brain, especially against acute injury (e.g. status epilepticus, trauma, stroke), and numerous animal studies have suggested their effectiveness as neuroprotective agents [13–17].

However, recent animal investigations have revealed that clinically relevant concentrations and combinations of general anaesthetics can also injure neuronal cells in the adult brain as well as in the immature brain, suggesting that these agents could be potentially deleterious [18–21]. Is it possible that commonly used general anaesthetics are neurotoxic? This review will discuss presently recognised issues regarding the neurotoxic potential of general anaesthesia.

The psychotomimetic action of the NMDA-antagonist class of general anaesthetics in humans

About 50 years ago, the intravenous anaesthetic phencyclidine (PCP) was introduced into clinical medicine as a general anaesthetic, but was soon withdrawn because of its severe and sometimes long-lasting psychotomimetic effects, described as a schizophrenia-like psychosis [22]. Ketamine, a shorter-acting derivative of PCP, was soon after introduced in anaesthesia practice because the psychotomimetic reactions associated with ketamine anaesthesia, referred to as 'emergence' reactions, were less pronounced and not as long-lasting. In addition, it was observed in daily clinical practice that these troublesome side effects could be attenuated by co-administration of GABAergic general anaesthetics (e.g. barbiturates, benzodiazepines, propofol), making the adverse side effects of ketamine manageable [23]. The clinical observation that adults are more susceptible than children to ketamine-induced emergence reactions has resulted in a tendency for ketamine to be used more frequently in paediatric than in adult anaesthetic practice. Because of its psychotomimetic potential, ketamine is also a popular drug of abuse and is often called 'Special K.'

Although the psychotomimetic effects of nitrous oxide (N_2O) are not considered to be as profound, it has long been known that this anaesthetic gas causes psychotic symptoms that are usually considered pleasurable and exhilarating [24]. Thus, the itinerant early showmen introduced a term 'laughing gas' well over a century ago to describe the frolicking, drunken-like behaviour of a person inhaling N_2O. N_2O, like ketamine, is commonly abused, especially among health care professionals.

The cerebrocortical neurotoxicity of general anaesthetics in the adult mammalian brain

In the course of testing the neuroprotective potential of NMDA-antagonist drugs, including ketamine and N_2O, it was discovered that, when given systemically to

adult rats, these agents have acute neurotoxic effects on cerebrocortical neurons [18–21, 25, 26]. Extensive studies over the past two decades have determined that the mechanism of this neurotoxic action involves a polysynaptic neuronal network disturbance in which blockade of NMDA receptors disinhibits excitatory pathways, both glutamatergic and cholinergic, leaving them in a state of hyperactivity and resulting in overstimulation and injury of cerebrocortical neurons [27]. Thus, what begins as a potentially neuroprotective blocking action of ketamine and N_2O on certain types of neurons in specific brain regions culminates in hyperactivation and injury of certain other neurons in other brain regions. This neurotoxic reaction is mainly confined to specific neurons in the posterior cingulate/retrosplenial cortex (PC/RSC), was initially described as reversible, and consisted of prominent swelling of endoplasmic reticulum (ER) and mitochondria, giving the affected cell a striking vacuolated appearance. The vacuoles became evident within an hour after the initiation of N_2O or ketamine administration and gradually disappeared after discontinuation of the drug (within the next several hours) [20, 28]. It was subsequently found that, at higher doses/concentrations or after repeated administration, these anaesthetics caused irreversible neurodegeneration of neurons in a more disseminated pattern, involving several cortico-limbic brain regions in addition to the PC/RSC [28, 29]. These findings signify that the severity of this pathological reaction and its reversibility depend on the duration of NMDA receptor blockade. Of additional interest is a recent finding that N_2O and ketamine, when administered in low, individually nontoxic doses to adult rats, augment one another's reversible neurotoxic effect by an apparently synergistic mechanism. For example, when a low, nontoxic dose (20 mg/kg, i.p.) of ketamine (equivalent to 3 mg/kg, i.m. in humans; the anaesthetic dose of ketamine in humans is 5–10 mg/kg, i.m.) was supplemented with a low, nontoxic concentration (50 vol%) of N_2O (equivalent to 35 vol% N_2O in humans) it caused a more severe neurotoxic reaction than was produced by any dose of ketamine alone [20].

Many classes of pharmacological agents have been shown to protect against the neurotoxic effects of NMDA antagonists. Of special interest for the field of anaesthesiology is the finding that GABAergic anaesthetic agents (e.g. barbiturates, benzodiazepines, volatile anaesthetics, propofol) are very effective in protecting against this type of neuronal injury. It has been proposed that glutamate regulates inhibitory tone by tonically stimulating NMDA receptors located on inhibitory neurons, most notably GABAergic neurons. By acting at these NMDA receptors, glutamate maintains tonic inhibition over major excitatory input to PC/RSC neurons. When the NMDA receptors are blocked, tonic inhibition by glutamate is removed, resulting in disinhibition of the excitatory pathways that in turn leads to excessive stimulation and injury of PC/RSC neurons. Consistent with this disinhibition hypothesis, GABAergic anaesthetics that restore GABA tone suppress the neurotoxic effects of the NMDA antagonists ketamine and N_2O [26, 28, 30].

The cerebrocortical neurotoxic action of NMDA-antagonist anaesthetics has been shown to be an age-dependent phenomenon to which adult animals are highly sensitive and pre-adult animals are insensitive [19, 21, 31]. Experiments focusing on the reversible vacuole reaction induced in PC/RSC neurons revealed that N_2O and

ketamine do not induce a significant vacuole reaction in immature rats less than 30 days of age. At this age the reaction is very mild, while with increasing age it becomes more severe, but does not reach peak severity until full adulthood at 180 days of age [19].

An interesting proposal suggested a causal relationship between pathomorphological changes in the adult mammalian brain (i.e. acute swelling of PC/RSC neurons), as observed in animal studies, and the psychotomimetic disturbances observed in human and veterinary medicine after the administration of ketamine or N_2O. Is it possible that the clinically observed emergence reaction (schizophrenia-like reaction) after ketamine administration or the exhilarating behaviour observed during N_2O administration is due to an acute swelling of this subpopulation of cortical neurons? Interestingly, in 1938, Courville reported a vacuolar reaction in cortical neurons obtained from patients who died following N_2O administration [32]. In the late 1980s, the hypothesis was introduced that NMDA receptor hypofunction played a role in schizophrenia-like illnesses [27, 33]. To test this hypothesis, several researchers administered ketamine to human subjects in very low doses (approximately one tenth the dose required for surgical anaesthesia) and found that it transiently and reversibly triggered mild schizophrenia-like symptoms, including hallucinations, delusions, and related cognitive disturbances [34, 35]. It was also demonstrated that these psychotic symptoms could be successfully blocked by the GABAergic class of general anaesthetics, a pharmacological strategy that anaesthesiologists had been aware of and had successfully used for several decades to treat ketamine-induced emergence reactions. Evidence that the psychotomimetic effects of ketamine are blocked by benzodiazepines, barbiturates, or propofol, all of which block the neurotoxic effect of ketamine in the adult rat brain, suggests that similar receptor mechanisms underlie the psychotomimetic actions of ketamine in adult humans and the neurotoxic action of ketamine in adult rats. An additional basis for suggesting that similar receptor mechanisms are the cause of these two phenomena is the similar age-dependency profile for ketamine-induced psychotic reaction in humans and ketamine-induced neurotoxic reaction in rats. Clinical experience with ketamine as a general anaesthetic has revealed that it frequently exerts psychotomimetic actions in adults, and less frequently, if at all, in prepubertal children.

The cerebrocortical neurotoxicity of general anaesthetics in the ageing mammalian brain

Due to the high incidence of medical problems that require surgical intervention, geriatric patients are frequently subjected to anaesthesia. However, because of their general frailty and multiple concomitant diseases, elderly patients are particularly susceptible to anaesthesia-related complications. It has been recognised in daily clinical practice that elderly patients are more prone than younger adults to psychological disturbances caused by general anaesthesia, often referred to as 'toxic psychosis' (delirium, confusion, disorientation, memory impairment, agita-

tion) [36, 37]. It was traditionally believed that toxic psychosis in geriatric patients is a result of sudden disturbances of their already fragile homeostasis that are common with any surgical intervention (e.g. blood loss, fluid and nutritional imbalance, post-operative pain, fever, separation from the familiar environment). However, recent evidence suggests a link between some types of general anaesthesia and postoperative mental impairments, implying that the choice of anaesthesia plays an important role in the incidence of this debilitating complication [38–40].

N_2O and ketamine are occasionally used in geriatric anaesthesia. Since these are sympathomimetic drugs that cause minimal respiratory and cardiovascular depression, N_2O and ketamine are especially useful for frail elderly patients who cannot tolerate even the minimal depression of vital functions induced by other general anaesthetics. N_2O is occasionally given in combination with ketamine to elderly patients in order to achieve a stable condition during anaesthesia. It has been assumed that by combining these two agents a wider margin of safety is being achieved.

However, we have recently reported that ketamine, either individually or in combination with N_2O, induced a neurotoxic reaction in the PC/RSC of aged rats that is significantly more severe and longer-lasting than in young adult rats, suggesting that the ageing brain is more sensitive to NMDA receptor blockade and consequently more sensitive to the NMDA-antagonist class of general anaesthetics [41].

Although an exact explanation for the increase in neuronal vulnerability during the normal ageing process is not currently available, there are some possible explanations. For instance, based on presently published data, it appears that ageing significantly alters neuronal NMDA receptors. One group of studies showed that the ageing process contributes to an overall reduction in NMDA receptor density and/or NMDA-receptor-bearing neurons of the mammalian brain [42, 43]. However, other studies have shown that the actual NMDA receptor density is unchanged, but their function declines and their subunit composition changes with age [44, 45]. These findings suggest that aged neurons could be exquisitely sensitive to a further decrease in NMDA receptor function, such as caused by pharmacological blockade with NMDA antagonists. Our data found this to be the case: relatively small doses of ketamine alone or the addition of a small dose of ketamine to a nontoxic concentration of N_2O resulted in a severe and prolonged neurotoxic reaction in the aged brain that was significantly more profound than that observed in the young adult brain.

Furthermore, it has been shown that mitochondrial and ER functions and morphology are impaired during ageing, that their size and heterogeneity are increased, and that their membrane function declines (e.g. decline in membrane potential, increase in peroxide production, disturbances of metabolites and water transport, inhibition of protein and DNA synthesis/repair), resulting in serious vulnerability of these organelles within intact ageing neurons [46–48]. These findings confirm the observation that it takes an insult of very small magnitude and of short duration to disturb the delicate balance within a frail ageing neuron.

Whether the neuropsychotic properties of the NMDA-antagonist anaesthetics, N_2O and ketamine contribute to postoperative toxic psychosis in elderly patients

is not well-established. However, there is increasing evidence that the pathomorphological reaction in cerebrocortical neurons of rats and the psychotomimetic reaction caused by these anaesthetics in humans are mediated by a common mechanism involving disinhibition of excitatory neuronal pathways that innervate cerebrocortical neurons [26, 33]. If this is indeed the case, the extreme vulnerability of the aged human brain to occult pathomorphological changes in cerebrocortical neurons may be, at least in part, clinically detectable as a higher incidence of toxic psychosis in elderly patients.

The cerebrocortical neurotoxicity of general anaesthetics in the immature mammalian brain

A series of recent studies have documented that general anaesthetics from the NMDA-antagonist class (e.g. ketamine, N_2O) and/or the GABAmimetic class (e.g. benzodiazepines, barbiturate, isoflurane), commonly used in obstetric and paediatric anaesthesia, trigger widespread apoptotic neurodegeneration in the developing rat brain [49–51]. It is important to note that this neurotoxic phenomenon is mechanistically and pathomorphologically completely different from the neurotoxic phenomenon observed in the adult rat brain. Namely, as mentioned earlier, the immature brain is not sensitive to the adult neurotoxic mechanism (e.g. swelling of PC/RSC neurons) but is exceedingly sensitive to the apoptogenic action of these agents during brain development (e.g. synaptogenesis). Brain development occurs in different species at different times relative to birth. In rats and mice, it is mainly a postnatal phenomenon; in guinea pigs, it is exclusively a postnatal phenomenon; but in humans it extends from the sixth month of gestation to several years after birth [52]. It appears that the apoptotic type of cell death, which is a natural process (referred to as physiological cell death) occurring during synaptogenesis by which very small percentage of neurons that were unsuccessful in making their connection commit suicide, may be significantly augmented by the administration of general anaesthetics. It is believed that disturbance of the fine balance between GABA and glutamate neurotransmission, leading to excessive depression of neuronal activity and nonphysiological changes in the synaptic environment, during a crucial stage of brain development, may constitute a generic signal for a developing neuron to commit suicide. Since the goal of surgical anaesthesia is to render the patient unconscious and insentient to pain, this implies use of general anaesthetics at doses that ensure substantial receptor occupancy and profound depression of neuronal activity. What is the potential risk of this practice? It has been recently reported that clinically relevant doses of barbiturates, benzodiazepines, volatile anaesthetics (e.g. isoflurane), or ketamine trigger massive and widespread apoptotic neurodegeneration during synaptogenesis in the immature rat and mice brains [49–51]. In addition, a clinically relevant combination of anaesthetic agents (midazolam, N_2O and isoflurane) administered to immature rats over a 6-h period resulted in a robust apoptotic neurodegenerative reaction affecting several major brain regions (e.g. thalamus, hypothalamus, amygdala, parietal, temporal, occipi-

tal, cingulate cortices). More importantly, adolescent anaesthesia-treated animals showed behavioural disturbances, as demonstrated by significant learning/memory deficits compared to controls [49]. These deficits appeared to be permanent, in that they were still present during re-testing of the animals at young-adult age. Although research aimed at clarifying the underlying mechanism of anaesthesia-induced apoptotic neurodegeneration is still in an early stage, based on presently available data, it appears that activation of the two main apoptotic pathways, i.e. the intrinsic and extrinsic pathways, plays an important role. The intrinsic pathway is activated in the early phase of anaesthesia exposure (within the first 2 h), and the extrinsic pathway in the later phase (after 4–6 h of anaesthesia exposure) [53].

References

1. Rose VL (1999) Update on rate of pre-term singleton births. Am Fam Physician 59:2925
2. Franks NP, Lieb WR (1978) Where do general anesthetics act? Nature 274:339
3. Franks NP, Lieb WR (1994) Molecular and cellular mechanisms of general anaesthesia. Nature 367:607–614
4. Antkowiak B, Helfrich-Forster C (1998) Effects of small concentrations of volatile anesthetics on action potential firing of neocortical neurons in vitro. Anesthesiology 88:1592–1605
5. Pocock G, Richards CD (1993) Excitatory and inhibitory synaptic mechanisms in anaesthesia. Br J Anaesth 71:134–147
6. Zhang ZX, Lu H, Dong XP et al (2002) Kinetics of etomidate actions on GABA(A) receptors in the rat spinal dorsal horn neurons. Brain Res 953:93–100
7. Bali M, Akabas MH (2004) Defining the propofol binding site location on the $GABA_A$ receptor. Mol Pharmacol 65:68–76
8. Pearce RA (2000) Effects of volatile anesthetics on $GABA_A$ receptors: Electrophysiological studies. In Moody EJ, Skolnick P (eds): Molecular basis of anesthesia. CRC Press, Boca Raton
9. Lodge D, Anis NA, Burton NR (1982) Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. Neurosci Lett 29:281–286
10. Lodge D, Anis NA (1982) Effects of phencyclidine on excitatory amino acid activation of spinal interneurones in the cat. Eur J Pharmacol 77:203–204
11. Jevtovic-Todorovic V, Todorovic SM, Mennerick S et al (1998) Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 4:460–463
12. Franks NP, Dickinson R, de Sousa SL et al (1998) How does xenon produce anaesthesia? Nature 396:324
13. Haelewyn B, Yvon A, Hanouz JL et al (2003) Desflurane affords greater protection than halothane against focal cerebral ischaemia in the rat. Br J Anaesth 91:390–396
14. Loepke AW, Priestley MA, Schultz SE et al (2002) Desflurane improves neurologic outcome after low-flow cardiopulmonary bypass in newborn pigs. Anesthesiology 97:1521–1527
15. Kapinya KJ, Lowl D, Futterer C et al (2002) Tolerance against ischemic neuronal injury can be induced by volatile anesthetics and is inducible NO synthase dependent. Stroke 33:1889–1898
16. Mortier E, Struys M, Herregods L (2000) Therapeutic coma or neuroprotection by anaesthetics. Acta Neurol Belg 100:225–228

17. Nellgard B, Mackensen GB, Massey G et al (2000) The effects of anesthetics on stress responses to forebrain ischemia and reperfusion in the rat. Anesth Analg 91(1):145–151
18. Olney JW, Labruyere J, Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 244:1360–1362
19. Jevtovic-Todorovic V, Wozniak DF, Benshoff ND et al (2001) A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Res 895:264–267
20. Jevtovic-Todorovic V, Benshoff N, Olney JW (2000) Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. Br J Pharmacol 130:1692–1698
21. Jevtovic-Todorovic V, Todorovic SM, Mennerick S et al (1998) Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 4:460–463
22. Luby ED, Gottlieb JS, Cohen BD et al (1962) Model psychoses and schizophrenia. Am J Psychiatry 119:61–67
23. Reich DL, Silvay G (1989) Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 36:186–197
24. Frost EAM (1985) A history of nitrous oxide. In: Eger EI (ed) Nitrous Oxide. Elsevier, New York, pp 1–22
25. Fix AS, Horn JW, Wightman KA et al (1993) Neuronal vacuolization and necrosis induced by the noncompetitive N-methyl-D-aspartate (NMDA) antagonist MK(+)801 (dizocilpine maleate): a light and electron microscopic evaluation of the rat retrosplenial cortex. Exp Neurol 123:204–215
26. Olney JW, Labruyere J, Wang G et al (1991) NMDA antagonist neurotoxicity: mechanism and prevention. Science 254:1515–1518
27. Olney JW, Farber NB (1995) NMDA antagonists as neurotherapeutic drugs, psychotogens, neurotoxins, and research tools for studying schizophrenia. Neuropsychopharmacology 13:335–345
28. Jevtovic-Todorovic V, Beals J, Benshoff N et al (2003) Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain. Neuroscience 122:609–616
29. Corso TD, Sesma MA, Tenkova TI et al (1997) Multifocal brain damage induced by phencyclidine is augmented by pilocarpine. Brain Res 752:1–14
30. Jevtovic-Todorovic V, Wozniak DF, Powell S et al (2001) Propofol and sodium thiopental protect against MK-801-induced neuronal necrosis in the posterior cingulate/retrosplenial cortex. Brain Res 913:185–189
31. Farber NB, Wozniak DF, Price MT et al (1995) Age-specific neurotoxicity in the rat associated with NMDA receptor blockade: potential relevance to schizophrenia? Biol Psychiatry 38:788–796
32. Courville CD (1938) The pathogenesis of necrosis of the cerebral gray matter following nitrous oxide anesthesia. Ann Surg 107:371
33. Farber NB, Kim SH, Dikranian K et al (2002) Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. Mol Psychiatry 7:32–43
34. Newcomer JW, Farber NB, Jevtovic-Todorovic V et al (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 20:106–118
35. Krystal JH, Karper LP, Seibyl JP et al (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214
36. Bekker AY, Weeks EJ (2003) Cognitive function after anaesthesia in the elderly. Best Pract Res Clin Anaesthesiol 17:259–272
37. Chung FF, Chung A, Meier RH et al (1989) Comparison of perioperative mental function

after general anaesthesia and spinal anaesthesia with intravenous sedation. Can J Anaesth 36:382–387
38. Beliveau MM, Multach M (2003) Perioperative care for the elderly patient. Med Clin North Am 87:273–289
39. Berggren D, Gustafson Y, Eriksson B et al (1987) Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg 66:497–504
40. Lipowski ZJ (1989) Delirium in the elderly patient. N Engl J Med 320:578–582
41. Jevtovic-Todorovic V, Carter LB (2005) The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain. Neurobiology of Aging 26:947–956
42. Magnusson KR, Cotman CW (1993) Effects of aging on NMDA and MK801 binding sites in mice. Brain Res 604:334–337
43. Wenk GL, Walker LC, Price DL et al (1991) Loss of NMDA, but not GABA-A, binding in the brains of aged rats and monkeys. Neurobiol Aging 12:93–98
44. Gonzales RA, Brown LM, Jones TW et al (1991) N-methyl-D-aspartate mediated responses decrease with age in Fischer 344 rat brain. Neurobiol Aging 12:219–225
45. Magnusson KR (2000) Declines in mRNA expression of different subunits may account for differential effects of aging on agonist and antagonist binding to the NMDA receptor. J Neurosci 20:1666–1674
46. Mecocci P, MacGarvey U, Kaufman AE et al (1993) Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. Ann Neurol 34:609–616
47. Sastre J, Pallardo FV, Vina J (2003) The role of mitochondrial oxidative stress in aging. Free Radic Biol Med 35:1–8
48. Wei YH, Lee HC (2002) Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. Exp Biol Med 227:671–682
49. Jevtovic-Todorovic V, Hartman RE, Izumi Y et al (2003) Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23:876
50. Ikonomidou C, Bosch F, Miksa M et al (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283:70–74
51. Ikonomidou C, Bittigau P, Ishimaru MJ et al (2000) Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science 287:1056–1060
52. Dobbing J, Sands J (1979) Comparative aspects of the brain growth spurt. Early Hum Dev 3:79–83
53. Yon, JH, Daniel-Johnson J, Carter LB et al (2005) Anesthesia induces suicide in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Neuroscience (in press)

Chapter 55

Neuroprotection by *N*-methyl-D-aspartate antagonists

S. Himmelseher, E.F. Kochs

Introduction

Clinical neuroprotection: the challenge

Despite years of intense research efforts, the treatment and prevention of brain injury with *N*-methyl-D-aspartate (NMDA) antagonists remains a medical challenge. Numerous clinical trials seeking chemical neuroprotection with prolonged blockade of NMDA receptors (NMDAR) in the setting of cardiac surgery, head trauma, brain ischaemia, subarachnoid haemorrhage, and other acute brain insults failed to show improved patient outcome [1–3]. In view of this experience and a more comprehensive understanding of recent pathophysiological findings, two fundamental questions must therefore be raised: Is a treatment strategy of profound NMDAR blockade for neuroprotection still valid in acute brain insults? And, if the principle of reducing unbalanced NMDAR overactivation in order to achieve neuroprotection is applicable, what do improved therapeutic approaches to treating brain injury with NMDAR antagonists look like?

Neuronal networks, plasticity, and *N*-methyl-D-aspartate receptors

The basics: developing a broader understanding of pathophysiological changes

Glutamate has long been known as the major excitatory neurotransmitter in the vertebrate central nervous system (CNS), with intracellular concentrations ranging from 50 μM in astrocytes to 10 mM in glutamatergic neurons [4]. Extracellular glutamate is maintained at 1–3 μM, which provides a high synaptic signal-to-noise ratio. Transduction via glutamate activation of NMDARs induces receptor channel opening, and is mediated via calcium and sodium influx into cells. Regarding the use of NMDAR antagonists, moderate increases in intracellular calcium (Ca^{2+}) produced by NMDAR activity have been shown to be a physiological process and a prerequisite both for the expression of cell survival pathways and for a multitude of cerebral functions [5–8]. When these signals were reduced directly, by administration of high-dose NMDAR antagonists, apoptosis and cognitive deficits occurred in developing animals [9], and vacuolisation was observed in cerebral regions of adult rats without brain injury [10]. Although the changes could be prevented

by coadministration of γ-aminobutyric acid (GABA) receptor agonists [11], the mechanisms that underlie these phenomena are as yet unclear. However, as a conceptual framework, the involvement of disinhibition of excitatory pathways that heavily innervate the cerebrocortical network appears likely [12]. Taken together, the evidence accumulated may help explain why blocking virtually all NMDAR activity after brain injury is counterproductive. However, evaluation of the injured brain has indicated that the cascades of processes induced by cerebral insults lead to pathological conditions that are profoundly different from the physiological state of intact, uninjured brain tissue [13–15].

In brain trauma and ischaemia, the massive release of excitatory neurotransmitters into the extracellular compartment and the resultant overstimulation of excitatory membrane receptors and downstream pathways have been established as pivotal events in the evolution of irreversible brain damage [16, 17]. Nevertheless, the specificity of excitotoxic signalling, the recruitment of excitotoxic NMDAR activity, and the adaptive cellular defence in the brain, including rescue mechanisms mediated via NMDAR activity, remain poorly understood [17, 18]. For improved use schedules of NMDAR antagonists, three recent insights deserve brief mention: (1) Although Ca^{2+} ions have been considered as key regulators of excitotoxicity, new data suggest that specific second messenger pathways acting in concert with Ca^{2+} load mediate neurodegeneration [17]. At brain synapses, postsynaptic density proteins (PSD) bind and cluster NDMARs to the cytoskeleton and to intracellular signalling proteins. Increased NMDAR input facilitates assembly of the signalling molecules with the PDS proteins via kinase cascades. This leads to further kinase activation, NMDAR phosphorylation, and up-regulation. In the vicious circle that is generated, increased downstream transduction enhances NMDAR currents, and finally induces cell injury [17, 19–22]. NMDA antagonists that target these harmful protein-protein interactions, such as ketamine [19, 20], may therefore have more significant implications for neuroprotection than those reducing intracellular Ca^{2+} levels, only. (2) A key advance has been the discovery that NMDAR undergo activity-dependent alterations, with dynamic changes in availability and responsiveness in healthy and injured brain [7, 23–26]. While homeostatic plasticity appears as a feedback loop to maintain synaptic strength and plasticity within a functional dynamic network, injury-induced plasticity aims at initiating death, survival, and rescue mechanisms. NMDAR stimulation is linked to rapid forms of plasticity. The hypothesis that injury-induced NMDAR overactivation is followed within a short time by desensitisation and functional NMDAR loss is therefore appealing. It challenges the long-held belief that NMDAR must continuously be blocked to stop neuronal damage after brain injury. Interestingly, a recent report in a mouse brain trauma model confirmed that hyperactivation of glutamate NMDAR after injury was short-lived (< 1 h) and followed by a profound and long-lasting (> 7 days) functional NMDAR loss [26]. Far beyond, stimulation of NMDARs at 24 and 48 h after injury improved neurological recovery. Therapeutic protocols in which NMDA antagonists are continuously administered over prolonged post-injury time periods may therefore be useless or even harmful. (3) Recent work on traumatic brain injury and the ischaemic penumbra shows that

late cell death is exacerbated by metabolic stress after generation of delayed spontaneous depolarisations (DSD) in peri-lesional boundary zones [27–30]. DSD expand infarcted and contused tissue into the adjacent penumbra of reversible injury by excitotoxic processes throughout secondary insults and infarct maturation. Blocking the spread of DSD with one delayed administration of an NMDA antagonists proved to be neuroprotective in a rat model [29]. Together with recent evidence from direct monitoring of late depolarisation-like events in human brain tissue [31–34], this supports the concept that NMDA antagonists should be used at least once at a delayed time point in the course of neuroprotective therapy.

Translating concepts to the clinical scenario

Glutamate excitotoxicity and central nervous system monitors

Converting the pathophysiological data into meaningful therapeutic advances, NMDA antagonists should, in theory, be used immediately during or upon supraphysiological NMDAR activation. However, the extent and duration of NMDAR activation in animal and human brain tissue have not been reported to date, and NMDAR stimulation may vary from patient to patient and according to type and stage of disease. CNS monitoring could therefore help to gauge a better approach for the use of NMDA antagonists. However, in rodents, monitoring glutamate levels has shown that post-injury-related increases are short-lived (less than 1 h) [35, 36]. In contrast, microdialysis (MD) studies of the human brain in individuals who have suffered trauma, stroke, neurovascular procedures, or subarachnoid haemorrhage have suggested that glutamate levels rise for hours to days after primary injury, and may re-increase with severe secondary insults [35]. But, while this pattern may have contributed to the decision to use NMDA antagonists over days in previous, unsuccessful trials, investigators have been frustrated in trying to ascribe a single relative MD-glutamate increase as a marker for a deleterious neurochemical event. In MD samples, interstitial glutamate increases were in most cases not sustained enough to cause tissue damage and often accompanied by inhibitory transmitter rises. MD-glutamate levels may also poorly correlate with concentrations at the synaptic cleft [35]. Additionally, glutamate is an important substrate in intermediary cell metabolism and, due to extensive exchange between astrocytes, neurons, and vesicular compartments, may readily increase in the interstitial brain compartment [36, 37]. The interpretation of moderate brain MD-glutamate fluctuations thus appears to require relating size and architectural changes of the interstitial space to blood–brain barrier function and analytical imprecision. The discrimination between metabolic crises without brain ischaemia and brain ischaemia requires combined functional measures, such as MD and electrophysiology or MD and brain imaging studies with multiparameter monitors [38, 39].

Concluding remarks

A clinical trial for treating head injury and lessons for research proposals

The outline presented above leaves little doubt that overstimulation of NMDAR is a major contributor to irreversible brain damage. However, it is too soon to conclude that NMDA antagonists fail to provide clinical neuroprotection. Furthermore, a recent prospective, randomised, placebo-controlled, double-blind, multicentre pilot trial demonstrated improved patient outcome after use of a non-competitive NMDA receptor antagonist following traumatic brain injury [40]. Similar to ketamine, the drug had a lower binding affinity to the phencyclidine site in the NMDAR channel than dizocilpine. It was first administered within 2 h after the trauma, and a second time 4 h later. Future clinical work should therefore examine the effects of non-competitive NMDA antagonists. Agents that completely block all NMDAR functions should no longer be used. Compounds with NMDAR-channel-modifying properties may have meaningful impact. Initial drug injections should be performed within the shortest post-injury time interval possible. At a delayed time point, an additional injection may be needed. Continuous high-dose infusion of NMDA antagonists must not be used. Laboratory studies should analyse the effects of NMDAR stimulation in the subacute post-injury phase on long-term outcome. Sufficiently sophisticated trial designs that orientate NMDA antagonist administration at multimodal brain monitoring data may provide meaningful advances in meeting individual patient needs.

References

1. Birmingham K (2002) Future of neuroprotective drugs in doubt. Nat Med 8:5
2. Muir KW, Lees KR (2003) Excitatory amino acid antagonists for acute stroke. Cochrane Database Syst Rev 3:CD001244
3. Nagels W, Demeyere R, van Hemelrijck J et al (2004) Evaluation of the neuroprotective effects of S(+)-ketamine during open-heart surgery. Anesth Analg 98:1595–1603
4. Hansson E, Muyderman H, Leonova J et al (2000) Astroglia and glutamate in physiology and pathology: aspects on glutamate transport, glutamate-induced cell swelling, and gap-junction communication. Neurochem Int 37:317–329
5. Hardingham GE, Fukunaga Y, Bading H (2002) Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci 5:405–414
6. Hardingham GE, Bading H (2003) The Yin and Yang of NMDA receptor signalling. Trend Neurosci 26:81–89
7. Perez-Otano I, Ehlers MD (2005) Homeostatic plasticity and NMDA receptor trafficking. Trends Neurosci 28:229–238
8. Jiang X, Tian F, Mearow K et al (2005) The excitoprotective effect of N-methyl-D-aspartate receptors is mediated by a brain-derived neurotrophic factor autocrine loop in cultured hippocampal neurons. J Neurochem 94:713–722
9. Jevtovic-Todorovic V, Hartman RE, Izumi Y et al (2003) Early exposure to common anaesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 23:876–882

10. Nakao S, Miyamoto E, Masuzawa M et al (2002) Ketamine-induced c-fos expression in the mouse posterior cingulate and retrosplenial cortices is mediated not only via NMDA receptors but also sigma receptors. Brain Res 926:191–196
11. Jevtovic-Todorovic V, Benshoff N, Olney JW (2002) Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. Br J Pharmacol 130:1692–1688
12. Himmelseher S, Durieux M (2005) Revising a dogma: ketamine for patients with neurological injury. Anesth Analg 101: 524–534
13. Obrenovitch TP, Urenjak J, Zilkha E et al (2000) Excitotoxity in neurological disorders. Int J Dev Neurosci 18:281–287
14. Arundine M, Thymianski M (2004) Molecular mechanisms of glutamate-dependent neurodegeneration in ischemia and traumatic brain injury. Cell Mol Life Sci 61:657–668
15. Wang Y, Ju W, Liu L et al (2004) Amino-3-hydroxy-5-methylisoxazole-4-propionic acid subtype glutamate receptor (AMPAR) endocytosis is essential for N-methyl-D-aspartate-induced neuronal apoptosis. J Biol Chem 279:41267–41270
16. Glass TF, Reeves B, Sharp FR (2004) The impact of excitotoxic blockade on the evolution of injury following combined mechanical and hypoxic insults in primary rat neuronal cultures. Neurobiol Dis 17:378–384
17. Aarts MM, Thymianski M (2004) Molecular mechanisms underlying specificity of excitotoxic signaling in neurons. Curr Mol Med 4:137–147
18. Xin WK, Zhao XH, Xu J et al (2005) The removal of extracellular calcium: A novel mechanism underlying the recruitment of N-methyl-D-aspartate (NMDA) receptors in neurotoxicity. Eur J Neurosci 21:622–636
19. Liu Y, Zhang G, Gao C, Hou X (2001) NMDA receptor activation results in tyrosine phosphorylation of NMDA receptor subunit 2A (NR2A) and interaction of Pyk2 with NR2A after transient cerebral ischemia and reperfusion. Brain Res 909:51–58
20. Hou XY, Zhang GY, Yan JZ et al (2002) Activation of NMDA receptors and L-type voltage-gated calcium channels mediates enhanced formation of Fyn-PSD95-NR2A complex after transient cerebral ischemia. Brain Res 955:123–132
21. Li H, Zhang Q, Zhang G (2003) Signal transducer and activator of transcription-3 factor is mediated by N-methyl-D-aspartate receptor and L-type voltage gated Ca2+ channel during ischemia in rat hippocampus. Neurosci Lett 345:61–64
22. Shen WH, Zhang CY, Zhang GY (2003) Modulation of IkB kinase autophosphorylation and activity following brain ischemia. Acta Pharmacol Sin 24:311–315
23. Chen WG, West AE, Tao X et al (2003) Upstream stimulatory factors are mediators of Ca2+-response transcription in neurons. J Neurosci 23:2572–2581
24. Hawkins LM, Ptybylowski K, Chang K et al (2004) Export from the endoplasmatic reticulum of assembled N-methyl-D-aspartic acid receptors is controlled by a motif in the C terminus of the NR2 subunit. J Biol Chem 279:28903–28910
25. Bendel O, Prunell G, Stenquist A et al (2005) Exprimental subarachnoid hemorrhage induces changes in the levels of hippocampal NMDA receptor subunit mRNA: Brain Res Mol Brain Res 137:119–125
26. Biegon A, Fry PA, Paden CM et al (2004) Dynamic changes in N-methyl-D-aspartate receptors after closed head injury in mice: implications for treatment of neurological and cognitive deficits. Proc Natl Acad Sci 101:5117–5122
27. Somjen GG (2001) Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 81:1065–1096
28. Petzold GC, Windmüller O, Haack S et al (2005) Increased extracellular K+ concentration reduces the efficacy of N-methyl-D-aspartate receptor antagonists to block spread-

ing depression-like depolarizations and spreading ischemia. Stroke 36:1270–1277
29. Hartings JA, Rolli ML, Lu XCM et al (2003) Delayed secondary phase of peri-infarct depolarizations after focal cerebral ischemia: Relation to infarct growth and neuroprotection. J Neurosci 23:11602–11610
30. Rogatsky GG, Sonn J, Kamenir Y et al (2003) Relationship between intracranial pressure and cortical spreading depression following fluid percussion brain injury. J Neurotrauma 12:1315–1325
31. Strong AJ, Fabricius M, Boutelle MG (2002) Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke 33:2738–2743
32. Parkin M, Hopwood S, Jones DA et al (2005) Dynamic changes in brain glucose and lactate in pericontusional areas of the human cerebral cortex, monitored with rapid sampling on-line microdialysis: relationship with depolarisation-like events. J Cereb Blood Flow Metab 25:402–413
33. Hopwood SE, Parkin MC, Bezzina El et al (2005) Transient changes in cortical glucose and lactate levels associated with peri-infarct depolarisations, studied with rapid-sampling microdialysis. J Cereb Blood Flow Metab 25:391–401
34. Hillered L, Vespa PM, Hovda DA (2005) Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma 22:3–41
35. Schuhmann MU, Stiller D, Skarddelly M et al (2003) Metabolic changes in the vicinity of brain contusions: a proton magnetic resonance spectroscopy and histology study. J Neurotrauma 20:725–743
36. Chih CP, Roberts EL (2003) Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. J Cereb Blood Flow Metab 23:1263–1281
37. Magistretti PJ (2000) Cellular basis of functional brain imaging: insights from neuron-glia metabolic coupling. Brain Res 886:108–112
38. Vespa P, Bergsneider M, Hattori N et al (2005) Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab 25:763–765
39. Alves OL, Bullock R, Clausen T et al (2005) Concurrent monitoring of cerebral electrophysiology and metabolism after traumatic brain injury: an experimental and clinical study. J Neurotrauma 22:733–749
40. Lepeintre JF, Arbigny PD, Mathe JF et al (2004) Neuroprotective effect of gacyclidine. A multicenter double-blind pilot trial in patients with acute traumatic brain injury. Neurochirurgie 50:83–95

Chapter 56

Neuroprotection by dexmedetomidine

S. Himmelseher, E.F. Kochs

Introduction: neuroprotective dexmedetomidine

An anaesthetic/sedative agent will proceed to evaluation of neuroprotective efficacy in a clinical trial when two major prerequisites are fulfilled: first, a body of preclinical evidence for its neuroprotective effects is necessary, second, circumstantial information from human use must be available. While testing of many promising drugs does not proceed past the stage of demonstrating neuroprotection in the physiology laboratory, in 1999, the FDA approved the α2-adrenoceptor agonist dexmedetomidine (DEX) for use in humans for analgesia and sedation [1]. However, although DEX is increasingly being used in the care of neurosurgical patients [1–3], its neuroprotective effects were not evaluated in a patient trial. In the present article, we will therefore outline the current understanding of DEX-mediated neuroprotection, and compare this state of knowledge with key criteria for the design of a clinical trial by experts in the field of anaesthetic neuroprotection [4, 5].

Cerebral pharmacology of dexmedetomidine

Molecular effects

The imidazoline DEX is a non-subtype-selective α_2-adrenoceptor (α_2AR) agonist with an α_2:α_1 selectivity of 1600:1 [1–3]. Located in the central (CNS) and peripheral nervous system (PNS) at pre- and postsynaptic autonomic ganglia, α_2ARs are G-protein-coupled transmembrane receptors that react to DEX binding with an inhibition of calcium entry and hyperpolarisation due to increased potassium conductance. In sympathetic and noradrenergic neurons, activated presynaptic α_2ARs inhibit norepinephrine release. In the CNS, activated postsynaptic α_2ARs decrease sympathetic activity, which leads to hypotension, bradycardia, and sedation. At higher doses, however, α_2AR binding induces hypertension via activation of receptors at resistance vessels [1–3]. There are three α_2AR subtypes, α_{2A}, α_{2B}, and α_{2C} [6]. Although a role for α_{2C}ARs in brain monoamine release and hypothermia has been suggested [7], most investigators relate DEX's neuroprotective effects to the α_{2A} subtype [8, 9]. Neuroprotection by DEX appears, in part, to be mediated by imidazoline receptors. In the cerebral cortex, imidazoline-2 receptors (I2R) are predominantly located at astrocytes [3].

Effects in cell and animal models

Evidence from in-vitro and animal investigations demonstrated that DEX shows relevant cerebroprotective effects against injury from hypoxia, ischaemia, reperfusion, and seizure [10–24]. Most examiners related the neuroprotective action to a suppression of injury-induced supraphysiological sympathetic activity. Cerebral ischaemia is well-known to be associated with an increase in circulating and extracellular brain catecholamine concentrations [25, 26]. Treatment with DEX in different animal models reduces this increased sympathetic tone with the result of improved neurologic outcome [11–20]. This is consistent with the notion that suppression of enhanced catecholamine concentrations may be neuroprotective by balancing the ratio of cerebral oxygen demand to oxygen supply [27], by reducing excitotoxicity [10, 11, 28–30] and toxic catecholamine actions [31], and by improving penumbral perfusion [13, 32]. However, there seems to be controversial evidence regarding the final effects of central hyperadrenergic responses on tissue damage after brain ischaemia [33, 34] and of DEX's action on ischaemic brain catecholamine levels [14, 19]: While one study reported a decrease in striatal norepinephrine concentrations after DEX administration [14], another found a decrease in plasma rather than brain dopaminergic catecholamines [19]. To come to a standpoint in this issue, it appears reasonable to state that these data caution against singular, straight-forward one-line mechanistic interpretation of DEX's action. It is more appropriate to postulate that central catecholamines will act in concert with multiple overlapping mechanisms that eventually determine outcome after brain ischaemia. Consistent with this notion, DEX was reported to modify the expression of apoptosis-regulating proteins [21] and survival-promoting genes in the setting of cerebral ischaemia [22]. Interestingly, a recent report also showed that DEX attenuated cardiac dysfunction in an animal model of intracranial hypertension [35]. However, after analysing the use schedules of DEX in the animal research presented here, a major limitation of the work becomes evident: DEX was almost always administered before and during cerebral insults, and not after the acute period of brain injury. Thus, any predictive, theoretical interpretation of DEX's neuroprotective efficacy in situations conceivable for real brain trauma and cerebral ischaemia becomes difficult or impossible. Not surprisingly, DEX—when administered after the onset of cerebral ischaemia in a rat study—was not found to ameliorate brain damage [36].

Effects on cerebral haemodynamics

Although DEX is clinically used in the neurosurgical setting [1, 2], there is a paucity of information on its effects on intracranial haemodynamics and the cerebral vasculature. There is also a lack of investigation of the drug's interaction with brain metabolism. The net balance of a variety of brain and systemic effects will finally determine DEX's global action on cerebral haemodynamic and metabolic variables. These are influenced by the preexisting vessel tone and the effects of other anaesthetics and analgesics. In a dog model, systemic DEX caused arteriolar constriction

[37] and inhibited volatile anaesthetic-related cerebral vasodilatation [38]. In normothermic rabbits, topical DEX produced vasoconstriction, which was altered by hypothermia in a concentration-dependent manner [39]. In human volunteers, DEX infusion, at doses used for sedation, decreased cerebral blood flow (CBF) [40, 41]. Although this reduction in CBF may readily be explained by the cerebral vasoconstricting properties of α_2AR agonists [3], its clinical relevance for neurosurgical patients is complex and requires more detailed evaluation. Because DEX may be used in brain-injured patients, it has also to be noted that in the same study the drug decreased cardiac output and heart rate during its infusion and for a period of 30 min after drug discontinuation [41]. This observation extends our understanding of the time frames underlying α_2AR-agonist-induced molecular changes, and adds value to the therapeutic principles that preservation of haemodynamic stability and sufficient cerebral perfusion pressures must have priority in the treatment of brain-injured patients. Future studies of DEX's cerebral haemodynamic effects are urgently warranted.

The clinical reality

Deliberate and cautious dexmedetomidine use

In recent years, clinical experience with DEX has especially been gained during its intraoperative use in major vascular procedures [42], during sedation and analgesia in the intensive care unit [43], and in special neurosurgical settings, such as awake craniotomy [1–3, 44, 45]. The list of benefits of α_2AR agonists observed in this scenario includes anxiolysis, blood pressure stabilisation, analgesia, anaesthetic sparing effects, reduction of shivering, and sedation without significant respiratory depression or major cognitive impairment. However, fear of inadvertent hypotension, bradycardia, cardiac arrest, and postoperative sedation, as well as the variability of patient haemodynamic response to DEX, have so far prevented its universal acceptance. Since DEX induces an exceptional state of sedation with clear sensorium upon stimulation, analgesia, minimal respiratory depression, and the possibility for a quick return to a sleep-like state, most clinical experience with the drug has been gathered in the ICU [1, 43]. Here, very cautious administration schedules that avoid quick or high bolus loading doses are applied to prevent deleterious haemodynamic effects. In hypovolaemia, hypotension, severe pre-existent bradycardia, cardiac conduction problems, or severely reduced ventricular function, the use of DEX is therefore considered very critically [1]. This practice has also been applied in patients with (suspected) raised intracranial pressure, especially because it is not yet clear whether DEX uncouples CBF and cerebral metabolic oxygen requirements. However, when the principles of haemodynamic stability by blood pressure maintenance and volume replacement were adhered to, experienced clinicians reported unrecognised advantages from the use of DEX in neurosurgical patients [1, 2]. DEX is thus currently breaking ground in awake craniotomy procedures [44, 45].

Concluding remarks

Dexmedetomidine—Ready for a clinical trial on neuroprotection?

Taken together, from the standpoint of a clinical-trial designer, major limitations have been revealed by assessment of the information available on DEX [4, 5]: (1) DEX obviously exerts neuroprotective effects, but the underlying mechanisms remain elusive; (2) DEX must be applied within a time frame that would only allow for a study in the perioperative setting; and (3) DEX has unclear cerebral haemodynamic effects with harmful potential in humans. As additional caveats, it must be enumerated that all studies on DEX were carried out in small animal models, but there have been a series of failures in clinical trials of drugs that were highly effective in those small animals. Furthermore, there are no long-term outcome data demonstrating the persistent neuroprotective efficacy of DEX. This is very important, since it has recently been reported that neuroprotection provided by isoflurane in a rat ischaemia model dissipated 3 months after injury [46]. Does further laboratory study appear to be justified? If one throws the scales towards the knowledge gained in experiments with DEX, only, supportive arguments for future experiments may easily be found. But, what if such a decision would be forced to incorporate the fact that we are still waiting for prospective outcome data from studies on head-injured patients applying the 'Lund Principle' of normovolaemic vasoconstriction, in which the α_2AR agonist clonidine is used to reduce intracerebral blood volume [47]?

References

1. Robicsek SA, Rogers RJ, Hemmings HC (2004) Pharmacotherapy in the neurosurgical intensive care unit. In: Layon AJ, Gabrielli A, Friedman WA (eds) Textbook of neurointensive care. Saunders, Philadelphia, PA, pp 649–681
2. Cormack J, Orme R, Costello T (2005) The role of α2-agonists in neurosurgery. J Clin Neurosci 12:375–378
3. Khan ZP, Ferguson CN, Jones RM (1999) Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia 54:146–165
4. Warner DS (2004) Anesthetic provide limited but real protection against acute brain injury. J Neurosurg Anesthesiol 16:303–307
5. Traystman RJ (2004) Anesthetic mediated neuroprotection. Established fact or fancy. J Neurosurg Anesthesiol 16:308–312
6. MacMillan LB, Hein L, Smith MS et al (1996) Central hypotensive effects of the alpha2A-adrenergic receptor subtype. Science 273:801–803
7. Bucheler MM, Hadamek K, Hein L (2002) Two α2-adrenergic receptor subtypes, α2A and α2C, inhibit the transmitter release in the brain of gene-targeted mice. Neuroscience 109:819–826
8. Lahdesmaki J, Sallinen J, MacDonald E et al (2003) Alpha2-adrenergic drug effects on brain monoamines, locomotion, and body temperature are largely abolished in mice lacking the alpha2A-adrenoceptor subtype. Neuropharmacology 44:882–892
9. Ma D, Hossain M, Rajakumaraswamy N et al (2004) Dexmedetomidine produces its

neuroprotective effect via the alpha 2A-adrenoceptor subtype. Eur J Pharrmacol 502:87–97
10. Huang R, Chen Y, Yu ACH et al (2000) Dexmedetomidine-induced stimulation of glutamine oxidation in astrocytes: a possible mechanism for its neuroprotective activity. J Cereb Blood Flow Metab 20:895–898
11. Talke P, Bickler PE (1996) Effects of dexmedetomidine on hypoxia-evoked glutamate release and glutamate receptor activity in hippocampal slices. Anesthesiology 85:551–557
12. Hoffman WE, Kochs E, Werner C et al (1991) Dexmedetomidine improves neurologic outcome from incomplete ischemia in rats. Reversal by the α2-adrenergic antagonist atipamezole. Anesthesiology 75:328–332
13. Maier C, Steinberg GK, Sun GH et al (1993) Neuroprotection by the α2-adrenergic agonist dexmedetomidine in a focal model of cerebral ischemia. Anesthesiology 79:306–312
14. Matsumoto M, Zornow MH, Rabin BC et al (1993) The α2-adrenergic agonist, dexmedetomidine selectively attenuates ischemia-induced increases in striatal norepinephrine concentrations. Brain Res 627:325–329
15. Kim HK, Zornow M, Strnat MAP et al (1996) Dexmedetomidine does not attenuate increases in excitatory amino acids after transient global ischemia in the rabbit. J Neurosurg Anesthesiol 8:230–235
16. Kuhmonen J, Pokorny J, Miettinen R et al (1997) Neuroprotective effects of dexmedetomidine in the gerbil hippocampus after transient global ischemia. Anesthesiology 87:371–377
17. Jolkkonen J, Puurunen K, Koistinaho J et al (1999) Neuroprotection by the alpha2-adreoceptor agonist, dexmedetomidine, in rat focal cerebal ischemia. Eur J Pharmacol 372:31–36
18. Kuhmonen J, Haapalinna A, Sivenius J (2001) Effects of dexmedetomidine after transient and permanent occlusion of the middle cerebral artery in the rat. J Neural Transm 108:261–271
19. Engelhard K, Werner C, Kaspar S et al (2002) Effect of the α2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. Anesthesiology 96:450–457
20. Laudenbach V, Mantz Lagercrantz H et al (2002) Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. Anesthesiology 96 :134–141
21. Engelhard K, Werner C, Eberspächer E et al (2003) The effect of the α2-agonist dexmedetomidine and the N-methyl-D-aspartate S(+)-ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemia and reperfusion. Anesth Analg 96:524–531
22. Wittner M, Sivenius J, Koistinaho J (1997) Alpha2-adrenoceptor agonist, dexmedetomidine, alters acute gene expression after global ischemia in gerbils. 232:75–78
23. Halonen T, Kotti T, Tuunanen T et al (1995) α2-Adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convusions and neuronal damage. Brain Res 693:217–224
24. Tanaka K, Oda Y, Funao T et al (2005) Dexmedetomidine decreases the convulsive potency of bupivaciane and levobupivacaine in rats: involvement of α2-adrenoceptor for controlling convulsions. Anesth Analg 100:687–696
25. Globus MY, Busto R, Dietrich WD et al (1989) Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. J Cereb Blood Flow Metab 9:892–896

26. Perego C, Gatti S, Vetrugno GC et al (1992) Correlation between electroencephalogram isoelectric time and hippocampal norepinephrine levels, measured by microdialysis, during ischemia in rats. J Neurochem 59:1257–1262
27. Nemoto EM, Klementavicius R, Melick JA et al (1996) Norepinephrine activation of basal cerebral metabolic rate for oxygen (CMRO2) during hypothermia in rats. Anesth Analg 83:1262–1267
28. Madison DV, Nicoll RA (1986) Actions of noradrenaline recorded intracellularly in rat hippocampal pyramidal neurones in vitro. J Physiol 372:221–244
29. Vizi ES (2000) Role of high-affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. Pharmacol Rev 52:63–68
30. Milusheva EA, Baranyi M (2003) Implications of ionotropic glutamate receptors in the release of noradrenaline in hippocampal CA1 and CA3 subregions under oxygen and glucose deprivation. Neurochem Int 43:543–550
31. Stein SC, Cracco RQ (1982) Cortical injury without ischemia produced by topical monoamines. Stroke 13:74–83
32. Busija DW (1984) Sympathetic nerves reduce cerebral blood flow during hypoxia in awake rabbits. Am J Phys 247:H446–451
33. Blomquist P, Lindvall O, Wieloch T (1985) Lesions of the locus coeruleus system aggravate ischemic damage in the rat brain. Neurosci Lett 38:353–358
34. Gustafson I, Miyauchi Y, Wieloch TW (1989) Postischemic administration of idazoxan, an adrenergic receptor antagonist, decreases neuronal damage in the rat brain. J Cereb Blood Flow Metab 9:171–174
35. Hall SRR, Wang L, Milne B et al (2004) Central dexmedetomidine attenuates cardiac dysfunction in a rodent model of intracranial hypertension. Can J Anaesth 51:1025–1033
36. Karlsson BR, Loberg EM, Steen PA (1995) Dexmedetomidine, a potent alpha 2-agonist, does not affect neuronal damage following severe forebrain ischemia in the rat. Eur J Anaesthesiol 12:281–285
37. Iida H, Ohata H, Iida M et al (1999) Direct effects of alpha1- and alpha2-adrenergic agonists on spinal and cerebral pial vessels in dogs. Anesthesiology 91:479–485
38. Ohata H, Iida H, Dohi S et al (1999) Intravenous dexmedetomidine inhibits cerebrovascular dilation induced by isoflurane and sevoflurane in dogs. Anesth Analg 89:370–377
39. Iida H, Iida M, Ohata H et al (2004) Hypothermia attenuates the vasodilator effects of dexmedetomidine on pial vessels in rabbits in vivo. Anesth Analg 98:477–482
40. Zornow MH, Maze M, Dyck JB et al (1993) Dexmedetomidine decreases cerebral blood flow velocity in humans. J Cereb Blood Metab 13:350–353
41. Prielepp RC, Wall MH, Tobin JR et al (2002) Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg 95:1052–1059
42. Wijeysundera DN, Naik JS, Beattie C (2003) Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med 1114:742–752
43. Shehabi Y, Ruettimann U, Adamson H et al (2004) Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. Intensive Care Med 30:2188–2196
44. Bekker AY, Basile J, Gold M et al (2004) Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects. J Neurosurg Anesthesiol 63:114–117
45. Ard JL, Bekker AY, Doyle W et al (2005) Dexmedetomidine in awake craniotomy: a technical note. Surg Neurol 63:114–117

46. Elsersy H, Sheng H, Lynch JR et al (2004) Effects of isoflurane versus fentanyl-nitrous oxide anesthesia in long-term outcome from severe forebrain ischemia in the rat. Anesthesiology 100:1160–1166
47. Eker C, Asgeirsson B, Grande P et al (1998) Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 26:1881–1886

Chapter 57

Choice of anaesthetics for neurosurgical anaesthesia

P.M. Patel

The anaesthetic management of neurosurgical patients is, by necessity, based upon our understanding of the physiology and pathophysiology of the central nervous system (CNS) and the effect of anaesthetic agents on the CNS. Consequently, a great deal of investigative effort has been expended to elucidate the influence of anaesthetics on CNS physiology and pathophysiology. The current practice of neuroanaesthesia is based upon findings of these investigations. However, it should be noted that most studies in this field have been conducted in laboratory animals and the applicability of the findings to the human patient is debatable at best. A great deal of emphasis has been placed on the minor differences in anaesthetic-induced changes in cerebral blood flow (CBF), cerebral metabolic rate (CMR) and intracranial pressure (ICP) that have been consistently demonstrated in a variety of studies. Is this emphasis justified? It is not surprising that, in the absence of controlled studies demonstrating the superiority of one technique over another, interpretations of the available data differ and that opinions on the optimal approach to the neurosurgical patient also differ. A more important question to the practising anaesthesiologist is not whether the minor differences in CNS physiology induced by anaesthetics are relevant to *all* neurosurgical patients, but the *identification of clinical situations in which anaesthetic effects might be significant.*

In the present discussion, a brief review of the cerebrovascular effects of anaesthetic agents will be presented. Thereafter, situations in which the anaesthetic selection has been suggested to be relevant will be addressed:

1. Moderate to severe intracranial hypertension
2. Inadequate brain relaxation during surgery
3. Evoked potential (EP) monitoring
4. Intraoperative electrocorticography
5. Cerebral protection.

CNS effects of anaesthetic agents

It is now generally accepted that N_2O is a cerebral vasodilator and can increase CBF when administered alone. This vasodilation can result in an increase in ICP. In addition, N2O can also increase CMR to a small extent. The simultaneous administration of intravenous anaesthetics (barbiturates, propofol, benzodiazepines, narcotics) can substantially reduce this increase in CBF and CMR. The behaviour of a combina-

tion of volatile agents and N_2O is quite different. When administered in low doses, volatile agents can reduce CBF and CMR. The addition of N_2O to low-dose volatile agent anaesthesia increases both CBF and CMR. This N_2O-mediated vasodilation can be greater when higher doses of volatile agents are administered.

Volatile agents uniformly suppress CMR. At doses of 1.5–2.0 minimal alveolar concentration (MAC), the commonly used agents isoflurane, desflurane and sevoflurane all produce burst suppression of the electroencephalograph (EEG). At burst suppression, CMR is reduced by 50–60%. Volatile agents are also vasodilators. Their effect on CBF is biphasic. At doses of about 0.5 MAC, the suppression in CMR balances the vasodilatory effects and CBF does not change significantly. In doses greater than 1.0 MAC, the vasodilatory effect predominates and CBF increases. The addition of N_2O to volatile anaesthetic agents will increase CBF and CMR. This increase in CBF may not necessarily result in an increase in ICP. The effect of volatile agents on cerebral blood volume (CBV) parallel the CBF changes but are of a significantly lesser magnitude.

Intravenous hypnotic agents, with the exception of ketamine, all decrease CMR and CBF substantially. In appropriate doses, barbiturates, propofol and etomidate produce burst suppression of the EEG. Ketamine's effect on CBF and CMR are regionally specific; in the limbic structures, CBF and CMR increase whereas within the cortex, reductions in CBF and CMR occur.

Moderate to severe intracranial hypertension

Patients with intracranial hypertension (ICH) have symptoms of headache, nausea, vomiting and visual disturbance. Patients with severe ICH also have a reduced level of consciousness. Computed tomography scans demonstrate mass lesions, ventricular effacement, midline shifts of the brain and full basal cisterns. The brain's capacity to accommodate increases in CBV is exhausted and even slight increases in intracranial volume can result in dramatic increases in ICP. In patients with acute increases in ICP (for example, with traumatic brain injury, epidural and subdural haematomas), the effect of an increase in CBV on ICP is even greater. It is in these patients that the choice of anaesthetic agents must be considered carefully.

Agents that produce vasodilation can increase CBF and more importantly, CBV. The potential for a further increase in ICP is therefore apparent. Minor increases in ICP can be readily treated by modest hyperventilation and the use of diuretics. Consequently, for the majority of patients, it is unlikely that anaesthetic-induced increases in ICP will be substantial enough to compromise the brain. For example, in patients with intracranial tumours, there were no differences in outcome in patients anaesthetised with propofol–fentanyl, isoflurane–nitrous oxide or fentanyl–nitrous oxide [1]. Nonetheless, other studies have shown that dural tension is higher with isoflurane–fentanyl and sevoflurane–fentanyl anaesthesia in comparison to propofol–fentanyl anaesthesia [2]. In patients in whom the ability of the brain to compensate for further increases in CBV is exhausted, a technique that reduces CMR, CBV and ICP *may* be preferable. In such patients, it is the author's practice

to avoid nitrous oxide and volatile agents until such time as the dura is opened. An anaesthetic technique based on the infusion of propofol and narcotics may be a more prudent approach in so far as the reserve of the brain to compensate for increases in CBV is not encroached upon and may in fact be increased (reduction in CBV). Volatile agents may be introduced once the cranium has been opened and the dura has been reflected; observation of the brain and the surgical conditions can then dictate the anaesthetic regimen.

A similar logic may apply to the management of the patient with an acute head injury. Compensatory mechanisms are inadequate to offset the rapid increase in intracranial volume and ICP. In such patients, brain distortion and herniation can compromise regional brain perfusion, rendering the brain ischaemic. Moreover, experimental data have shown that hyperventilation, which is often employed to minimise or counteract volatile agent-induced vasodilation, can be ineffective in doing so with acute head injury [3]. A cogent argument can therefore be made that one should avoid nitrous oxide and volatile agents in the anaesthetic management.

'Tight brain' during surgery

Adequate brain relaxation facilitates neurosurgery and reduces the need for excessive brain retraction. Although uncommon, brain swelling can occur intraoperatively during surgery. This is most commonly seen during surgery for arterio-venous malformations, but it can occur during tumour surgery as well. The aetiology of brain swelling is not clear. Clearly, engorgement of the brain with blood plays a significant role. When brain swelling does occur, the brain is placed at risk for ischaemic injury. In addition, brain swelling interferes with surgery and on occasion, can prevent closure of the dura. This represents an urgent problem that demands the attention of the anaesthesiologist and the neurosurgeon. The approach to this difficult problem is reasonably well established and the following manoeuvres may be instituted:

- Check ventilation. Moderate hypocapnia (target $PaCO_2$ 25–30 mmHg) will produce cerebral vasoconstriction and the consequent reduction in brain bulk. Measurement of end-tidal CO_2 tension is occasionally misleading. Arterial blood gas analysis should be utilised judiciously to confirm hypocarbia
- Ensure normal oxygenation
- Control blood pressure. Target is normotension (within 10% of baseline blood pressure)
- Ensure adequate venous drainage from the brain. Neck torsion or the placement of endotracheal tube ties around the neck can impede venous drainage from the brain
- Head elevation (30° optimum)
- Check intrathoracic pressure. Rule out pneumothorax (especially if central line has been placed)
- Maintain adequate neuromuscular relaxation
- Administer mannitol.

If these measures are not adequate, consideration should be given to the potential deleterious effect of anaesthetic agents. In particular, attention should be focused on those agents that can increase brain bulk by producing cerebral vasodilation. The manipulation of anaesthetic administration can effect dramatic reductions in brain bulk:

- Make sure that the concentration of volatile agent is less than 0.5 MAC
- Discontinue the administration of N_2O
- Discontinue the administration of volatile anaesthetics
- Switch to an intravenous anaesthetic technique. A combination of propofol and narcotic infusion is ideal
- If the brain swelling does not abate, there is a high probability that the patient will have protracted ICH in the postoperative period. In that event, barbiturates (pentobarbital) may be administered until either the swelling is reduced or burst suppression of the EEG is attained. On rare occasions, the surgeons may elect to amputate brain or to close the scalp without replacing the bone flap.

Inadequate signal quality during evoked potential monitoring

Somatosensory evoked potentials

All volatile agents attenuate EPs in a dose-related manner (see an excellent review by Banoub et al. [4]). Somatosensory evoked potential (SSEP) amplitude can be attenuated at 1.0 MAC concentrations and can be abolished with higher concentrations. Simultaneously, a dose-dependent increase in latency is also observed. The newer volatile agents sevoflurane and desflurane appear to depress the amplitude of the SSEP to a lesser extent and their use may permit the delivery of a higher concentration (~1–1.5 MAC) [5]. Auditory EPs are relatively robust but even their waveforms will be affected at volatile anaesthetic concentrations that exceed 1.5 MAC. N_2O can also reduce the amplitude of the SSEP [6]. Intravenous agents, on the other hand, have a modest impact on EPs; in fact, EPs can be detected even with doses of barbiturates that produce burst suppression of the EEG.

Given that anaesthetic agents suppress EPs, the choice of anaesthetic agents for the maintenance of anaesthesia becomes an important consideration. Although volatile agents and N_2O suppress EPs, stable and robust recording of EPs can be obtained provided the concentration of the volatile agent is kept to 0.5 MAC or less and the nitrous oxide concentration is maintained in the 50–60% range. Without N_2O, the volatile anaesthetic concentration can be increased to about 1 MAC. Opiate infusion in addition will provide, in most circumstances, stable anaesthetic conditions that permit EP monitoring. If the quality of the signals is not adequate, the anaesthetic technique has to be modified. The technique that results in a very good signal is a total intravenous anaesthetic technique. The combination of propofol and a narcotic infusion results in excellent signals in most patients [7]. In addition, the variability in the amplitude of the EP is reduced by this technique in comparison to a N_2O-volatile agent–narcotic technique. This is an important consideration in

those patients with CNS abnormalities in whom the EP is already compromised by the primary disease. If the signal does not improve, it is highly unlikely that the cause of the problem is the anaesthetic.

Etomidate is unique among anaesthetic agents in that it actually increases the amplitude of SSEPs. Clinicians often administer etomidate by infusion to improve the quality of the recording. However, it is difficult to determine what exactly an improvement in the signal that is induced by etomidate means to the transmission of the signal from the peripheral nerve to the brain. In addition, the usual criteria for determining a change in the EP (amplitude reduction by 50% and latency delay by 10%) may not apply when etomidate is administered. Nonetheless, in patients with significant sensory abnormalities, an anaesthetic technique based on an etomidate infusion may be considered. Such a technique may allow reasonable EP recording, which otherwise may not be possible [8].

Motor evoked potentials

Motor evoked potential (MEP) monitoring is a relatively new technique that is being increasingly employed during spine surgery that entails a significant risk of injury to the motor tracts. In many instances, the ability to monitor reliably the motor tracts has replaced the intraoperative wake-up test. In the operating room, transcranial electrical rather than magnetic stimulation, applied to the scalp, is used to depolarise cortical pyramidal tracts and to evoke a motor response in the upper and lower extremities. MEPs are exquisitely sensitive to anaesthetic agents. Volatile agents (in concentrations as low as 0.2–0.3 MAC), barbiturates, propofol and midazolam all significantly suppress MEP [9, 10]. It is therefore apparent that the anaesthetic technique for MEP monitoring has to be substantially modified. In addition, the administration of muscle relaxants has to be strictly titrated to ensure that muscle contraction in the monitored limb is possible [11]. Etomidate, nitrous oxide, narcotics and ketamine are all reasonable agents to use. In the author's institution, the following technique has been successful:

- Premedication: Diazepam, 0.1 mg/kg 30–60 min prior to anaesthesia induction
- Induction: Sufentanil 1 μg/kg, etomidate 0.3 mg/kg
- Muscle relaxation: Vecuronium or rocuronium, administered by a servo-controlled loop mechanism that maintains the T1 twitch height at 35% of baseline twitch height
- Maintenance: 65% N_2O in oxygen, sufentanil infusion at 0.4–0.5 μg/kg/h
- Maintenance: Etomidate infusion 5–10 μg/kg/min after load of 0.1 mg/kg. Consider if additional anaesthetic is deemed necessary or if use of N_2O is not feasible (i.e. one-lung ventilation).

The recent introduction of a multiple stimulation device has simplified to some extent the anaesthetic management. Multiple stimuli, from two to five, with about a 75-ms interval between the stimuli, significantly improves the amplitude of the MEP. Moreover, this MEP is less susceptible to anaesthetic-induced suppression [12]. Accordingly, low doses of volatile agent (~0.3 MAC), propofol–N_2O, propofol–remifentanil [13] and isoflurane–N_2O–opioid [14] techniques may be compatible

with adequate MEP monitoring. However, it should be noted that the administration of isoflurane reduces the percentage of patients in whom reliable MEP recording is possible and it increases the variability in the amplitude of the MEP. Accordingly, it may be prudent to establish robust MEP monitoring before volatile agents are added to the anaesthetic regimen.

Intraoperative electrocorticography

In patients undergoing craniotomy for resection of seizure-producing foci, intraoperative electrocorticography (ECoG) is often employed. ECoG is used to identify precisely the location of the lesion and the margins of safe brain resection. Seizure foci are identified by characteristic spike waves that are elicited by electrical stimulation of the surrounding brain region. Once the foci are identified, they are removed. ECoG is then used to confirm the removal of the relevant focus – a lack of spike waves will confirm this.

Epilepsy surgery can be performed in an awake or anaesthetised patient. Awake craniotomy is usually reserved for cooperative adult patients. Uncooperative patients or paediatric patients are generally anaesthetised for the procedure.

During awake craniotomy, patients are usually sedated with an infusion of propofol during the craniotomy. Thereafter, the propofol infusion is discontinued and the patient is allowed to awaken. Upon resumption of consciousness, ECoG mapping is started. Propofol is an ideal agent to use because its pharmacokinetic properties permit rapid emergence from a state of anaesthesia. However, it should be remembered that propofol can have a profound effect on the ECoG. Residual propofol in the brain can result in EEG activation in the 18-Hz range [15]. This activation can obscure spike waves from the seizure foci, thereby making precise localisation of the foci difficult. The EEG activation can occur even when the patient appears to be fully awake! EEG activation is generally short lived and lasts about 20 min. It is therefore important to discontinue the administration of propofol at least 30 min before the start of ECoG. More recently, the addition of remifentanil to a propofol infusion has permitted a reduction in the dose of propofol; a more rapid emergence (within 10 min) is therefore possible. Anaesthetics that suppress seizure foci (benzodiazepine, volatile agents) should, in general, be avoided.

Electrocorticography during general anaesthesia is more challenging. Volatile anaesthetics, intravenous hypnotics and benzodiazepines can suppress spike waves. Therefore, during ECoG, the use of these agents must be minimised or avoided altogether. An anaesthetic technique that is commonly used for this procedure is a combination of N_2O, low-dose volatile agent and a narcotic infusion. Shortly before ECoG, the volatile agent is discontinued and the concentration of N_2O is increased to at least 65%. Once the volatile agent is eliminated, ECoG can be performed. During this time, the patient will be lightly anaesthetised and there is a significant risk of movement or coughing. It is therefore very important to ensure that the patient is paralysed. If the spike waves are not detectable, spike activity can be induced by the administration of one of the following:

- Methohexital, 0.3–0.5 mg/kg [16]. Methohexital results in spike-wave activity that emanates primarily from the seizure focus
- Etomidate, 0.1–0.2 mg/kg [17]. The resulting spike wave activity is more generalised than with methohexital
- Alfentanil, 50 μg/kg [18].

Brain protection

There is a considerable risk of cerebral ischaemia during neurosurgical procedures and a substantial investigative effort has focused upon the identification of agents that might reduce ischaemic brain injury. Given their propensity to reduce CMR, anaesthetics appear to be logical candidates. Volatile agents, barbiturates, propofol and ketamine have all shown neuroprotective efficacy in the laboratory. Unfortunately, this neuroprotection is short lived and is not sustained beyond a period of 2 weeks [19]. Neurons continue to die for a long time after the initial ischaemic insult and anaesthetics mitigate ongoing neuronal loss. In the circumstance of extremely mild ischaemic insults, such as those that are likely to occur with brain retraction, anaesthetics might produce sustained neuroprotection. However, with such mild insults, it is highly unlikely that differences in the neuroprotective efficacy for individual anaesthetics will be manifest. Accordingly, the available data do not support the selection of any given agent for purposes of neuroprotection. Adequate anaesthesia, regardless of how it is produced, will increase the tolerance of the brain to ischaemia in comparison to the awake state. Barbiturates may be used for purposes of neuroprotection in rare situations (such as prolonged temporary clipping during aneurysm surgery).

Among intravenous hypnotics, the only agent whose use might be considered controversial is etomidate. Etomidate can reduce CMR, CBF and ICP. These effects are similar to those produced by barbiturates and propofol. Unlike the latter agents, etomidate does not produce hypotension. Given this favourable pharmacological profile, the use of etomidate during neurosurgical procedures that entail a risk of cerebral ischaemia has been advocated. Unfortunately, it is quite clear from laboratory studies and studies in patients [20] that etomidate does not possess neuroprotective efficacy. In fact, it can *increase* ischaemic neuronal injury. The administration of etomidate for the purposes of neuroprotection therefore cannot be advocated. Single doses of etomidate for purposes of anaesthetic induction are unlikely to adversely affect neurons and its use in this manner is entirely appropriate.

Conclusions

In the vast majority of neurosurgical patients, the choice of anaesthetic agent is not relevant; it is unlikely to affect either the surgical field or the patient outcome. The best results are often obtained by the use of a technique with which the anaesthesia

care provider is familiar. In certain situations, however, the choice of the anaesthetic agent can directly impact the surgical field and may have an impact on patient outcome. It is during these situations that a solid command of physiology and the pathophysiology of the CNS and the impact that anaesthetic agents have on the brain is essential.

References

1. Todd MM, Warner DS, Sokoll MD et al (1993) A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy: propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology 78:1005–1020
2. Petersen KD, Landsfeldt U, Cold GE et al (2003) Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors. Anesthesiology 98:329–336
3. Scheller MS, Todd MM, Drummond JC (1987) A comparison of the ICP effects of isoflurane and halothane after cryogenic brain injury in rabbits. Anesthesiology 67:507–512
4. Banoub M, Tetzlaff JE, Schubert A (2003) Pharmacologic and physiologic influences affecting sensory evoked potentials: implications for perioperative monitoring. Anesthesiology 99:716–737
5. Bernard JM, Pereon Y, Fayet G, Guiheneuc P (1996) Effects of isoflurane and desflurane on neurogenic motor- and somatosensory-evoked potential monitoring for scoliosis surgery. Anesthesiology 85:1013–1019
6. Wolfe DE, Drummond JC (1988) Differential effects of isoflurane/nitrous oxide on posterior tibial somatosensory evoked responses of cortical and subcortical origin. Anesth Analg 67:852–859
7. Kalkman CJ, Traast H, Zuurmond WW, Bovill JG (1991) Differential effects of propofol and nitrous oxide on posterior tibial nerve somatosensory cortical evoked potentials during alfentanil anaesthesia. Br J Anaesth 66:483–489
8. Sloan TB, Ronai AK, Toleikis JR, Koht A (1988) Improvement of intraoperative somatosensory evoked potentials by etomidate. Anesth Analg 67:582–585
9. Kalkman CJ, Drummond JC, Ribberink AA (1991) Low concentrations of isoflurane abolish motor evoked responses to transcranial electrical stimulation during nitrous oxide/opioid anesthesia in humans. Anesth Analg 73:410–415
10. Kalkman CJ, Drummond JC, Ribberink AA et al (2005) The effect of propofol, etomidate, midazolam and fentanyl on motor evoked responses to transcranial electrical or magnetic stimulation in humans. Anesthesiology (in press)
11. Kalkman CJ, Drummond JC, Kennelly NA et al (1992) Intraoperative monitoring of tibialis anterior muscle motor evoked responses to transcranial electrical stimulation during partial neuromuscular blockade. Anesth Analg 75:584–589
12. Ubags LH, Kalkman CJ, Been HD (1998) Influence of isoflurane on myogenic motor evoked potentials to single and multiple transcranial stimuli during nitrous oxide/opioid anesthesia. Neurosurgery 43:90–94; discussion 94–95
13. Nathan N, Tabaraud F, Lacroix F et al (2003) Influence of propofol concentrations on multipulse transcranial motor evoked potentials. Br J Anaesth 91:493–497
14. Pelosi L, Stevenson M, Hobbs GJ et al (2001) Intraoperative motor evoked potentials to transcranial electrical stimulation during two anesthetic regimens. Clin Neurophysiol 112:1076–1187

15. Drummond JC, Iragui VJ, Alksne JF, Kalkman CJ (2005) Masking of epileptoid activity by propofol during seizure surgery. Anesthesiology (in press)
16. Wyler AR, Richey ET, Atkinson RA, Hermann BP (1987) Methohexital activation of epileptogenic foci during acute electrocorticography. Epilepsia 28:490–494
17. Gancher S, Laxer KD, Krieger W (1984) Activation of epileptogenic activity by etomidate. Anesthesiology 61:616–618
18. Keene DL, Roberts D, Splinter WM et al (1997) Alfentanil mediated activation of epileptiform activity in the electrocorticogram during resection of epileptogenic foci. Can J Neurol Sci 24:37–39
19. Kawaguchi M, Kimbro JR, Drummond JC et al (2000) Isoflurane delays but does not prevent cerebral infarction in rats subjected to focal ischemia. Anesthesiology 92:1335–1342
20. Hoffman WE, Charbel FT, Edelman G et al (1998) Comparison of the effect of etomidate and desflurane on brain tissue gases and pH during prolonged middle cerebral artery occlusion. Anesthesiology 88:1188–1194

Chapter 58

Brain protection – the clinical reality

P.M. Patel

One of the most feared complications of anaesthesia and surgery is the occurrence of cerebral ischaemia and neuronal injury. Although the incidence of stroke during surgery is quite low, during certain procedures the risk of stroke can be high. For example, the incidence of neurological complications during cardiac surgery has been reported to be approximately 2–6% [1]. The majority of these complications occur during the intraoperative period [2]. The risk of perioperative stroke in patients undergoing carotid endarterectomy (CEA) ranges from a high of about 15% to the more recently reported risk of 2.1% [3]. Neurosurgical procedures, particularly aneurysm and arterio-venous malformation (AVM) surgery, entail a significant risk of ischaemia. Given the large number of patients who undergo these procedures, the 'at-risk' population is substantial. This has fostered a considerable amount of interest in not only evaluating measures designed to prevent cerebral ischaemia but also in identifying anaesthetic agents that might decrease the brain's vulnerability to ischaemia.

In the present discussion, the pathophysiology of cerebral ischaemia is presented briefly. This is then followed by a summary of the available information regarding the cerebral protective efficacy of anaesthetic agents. Finally, the influence of physiological parameters on ischaemic brain injury and the management of the injured brain are discussed.

Pathophysiology

The brain is metabolically very active and its oxygen consumption is about 3.5–4.0 ml/100 g/min. Electrical activity of neurons (transient depolarisation and repolarisation with their attendant ionic shifts) consumes about 50% of the total energy production of neurons. Thus, energy consumption can be reduced significantly by agents that can render the electroencephalogram (EEG) isoelectric (e.g. barbiturates). The remaining 50% is used to maintain basal cellular homeostasis. Although this portion of the total energy consumption is not amenable to reduction by anaesthetic agents, hypothermia can reduce it substantially.

The normal cerebral blood flow (CBF) in humans is about 50 ml/100 g/min. The response of the brain to ischaemia has been well characterised [4]. With a moderate reduction of CBF, slowing of the EEG is observed. When CBF reaches about 20 ml/100 g/min, EEG isoelectricity occurs. At a flow of about 15 ml/100 g/min, evoked

responses can no longer be obtained. Although neurons do not immediately die at this flow rate, death will eventually occur if flow is not restored. Below a flow of 10 ml/100 g/min, ATP levels decline rapidly (within 5 min) and the neuron is unable to maintain ionic homeostasis. At this point, the neuron undergoes depolarisation (anoxic depolarisation) and neuronal terminals release massive quantities of neurotransmitters [5]. These neurotransmitters (such as glutamate) activate postsynaptic receptors, which results in the neuron being flooded with calcium [6]. By activating several biochemical cascades in a haphazard manner, calcium ultimately leads to neuronal death.

Cerebral ischaemia is broadly classified into two categories: global ischaemia and focal ischaemia. Global ischaemia is characterised by a complete cessation of CBF (e.g. cardiac arrest). In this situation, neuronal depolarisation occurs within 5 minutes. Selectively vulnerable neurons within the hippocampus and cerebral cortex are the first to die. The window of opportunity for the restoration of flow is very small because death of neurons is rapid. Focal ischaemia is characterised by a region of dense ischaemia (the so-called 'core') that is surrounded by a larger variable zone that is less ischaemic (the penumbra). Within the core, flow reduction is severe enough to result in relatively rapid neuronal death. Flow reduction in the penumbra is sufficient to render the EEG isoelectric but not severe enough to kill neurons rapidly. If, however, the flow is not restored, death and infarction will also occur in the penumbra, albeit at a much slower rate. Because of this slow rate of neuronal death, the window of opportunity for therapeutic intervention that is designed to salvage neurons is considerably longer in the setting of focal ischaemia. Most episodes of ischaemia in the operating room are focal in nature.

Influence of anaesthetics on the ischaemic brain

Barbiturates

The approach to the problem of cerebral ischaemia was initially focused on reducing the brain's requirement for energy. The rationale was that by reducing ATP requirements, the brain would be able to tolerate ischaemia for a longer time. Such a supply–demand concept had already been proven to be relevant in the case of cardiac ischaemia. Therefore, the agents investigated first were those that could render the EEG isoelectric (such agents would be capable of reducing ATP requirements by 50%).

Barbiturates can produce isoelectricity of the EEG and they have been studied extensively. In the setting of global ischaemia, barbiturates in EEG burst-suppression doses do not reduce ischaemia injury [7]. This is not particularly surprising because the EEG is rendered isoelectric rapidly after the occurrence of global ischaemia. In this situation, barbiturates would not be expected to provide much benefit. Barbiturates have been found to be efficacious in the treatment of focal ischaemia. A number of investigators have shown that barbiturates can reduce the extent of cerebral injury produced by occlusion of the middle cerebral artery [8].

In humans, thiopental loading has been demonstrated to reduce post-cardiopulmonary bypass neurological deficits. As a result, barbiturates have been considered to be the 'gold standard' cerebral protectants among anaesthetics. The protective efficacy ascribed to the barbiturates has recently been questioned on the basis that reduction in injury produced by barbiturate anaesthesia might have been a function of anaesthesia-induced hypothermia rather than barbiturates per se [9]. Although more recent studies, in which brain temperature was rigidly controlled, have confirmed the protective efficacy of barbiturates [8], it should be noted that the magnitude of the protective efficacy is modest. In addition, doses that produce burst suppression of the EEG may not be necessary to achieve protection; Warner and colleagues have shown that a dose of barbiturate that is approximately a third of the dose required to achieve EEG suppression can yield a reduction in injury that is of similar magnitude to that achieved with much larger doses [10].

The decision to administer barbiturates for the purposes of cerebral protection should be made after due consideration of the haemodynamic effects of barbiturates, the potential need for prolonged postoperative mechanical ventilation of a patient in whom emergence from anaesthesia is significantly delayed, and the relatively modest degree of protection that will be achieved.

Volatile anaesthetics

Like barbiturates, the volatile agents isoflurane, sevoflurane and desflurane can produce EEG burst suppression in high doses ($\approx$ 2 minimal alveolar concentration, MAC). Their effects on ischaemic neuronal injury have therefore received considerable attention. Isoflurane has been shown to be neuroprotective in models of hemispheric [11], focal [12] and near complete ischaemia [13]. Similarly, the available data suggest that both sevoflurane [14, 15] and desflurane [16] can reduce ischaemic cerebral injury. There does not appear to be a substantial difference among the volatile agents with regard to neuroprotective efficacy.

In most of the studies cited above, injury was evaluated a few days after the ischaemic insult. Data from Du and colleagues indicate that post-ischaemic neuronal injury is a dynamic process in which neurons continue to die for a long time after the initial ischaemic insult [17]. These investigators suggested that therapeutic strategies that are neuroprotective after short recovery periods may not produce long-lasting neuroprotection because of the continual loss of neurons in the post-ischaemic period. Volatile anaesthetics do produce neuroprotection after short recovery periods. However, Kawaguchi et al. recently demonstrated that isoflurane's neuroprotective efficacy was not sustained when the recovery period was extended to 2 weeks [18]. This suggests that volatile anaesthetics delay but do not prevent neuronal death. It should be noted that, by delaying neuronal death, volatile agents might increase the duration of the therapeutic window for the administration of other agents that have neuroprotective efficacy.

More recent work by Werner et al. has shown that, under some circumstances, sustained neuroprotection with volatile agents can be achieved. In a model of hemispheric ischaemia combined with hypotension, sevoflurane [19] produced

neuroprotection that was apparent even 4 weeks after ischaemia. In this study, it should be emphasised that the anaesthetised animals did not manifest any injury at all; in fact, not a single neuron was found to be injured. By contrast, a modest amount of injury was observed in the control animals. These data suggest that volatile agents can produce long-term neuroprotection *provided that the severity of injury is very mild*. Once even a small amount of neuronal injury does occur, infarct expansion will preclude long-term neuroprotection.

Propofol

Propofol shares a number of properties with barbiturates. In particular, propofol can also produce burst suppression of the EEG, thereby reducing the cerebral metabolic rate of oxygen ($CMRO_2$) by 50%. In a model of focal ischaemia, propofol significantly reduced the extent of cerebral infarction [20]. In fact, the ability of propofol to reduce injury is similar to that achieved with pentobarbital [21]. In a follow-up study, these investigators demonstrated that propofol protection was not sustained when injury was evaluated 3 weeks after ischaemia [22]. On the other hand, Engelhard et al. have shown that propofol neuroprotection is sustained 4 weeks post-ischaemia [23]. Note that in the study of Engelhard, the severity of ischaemic injury was relatively mild. Therefore, like the case with volatile agents, it appears that propofol does reduce injury provided the severity of the ischaemic insult is mild.

Etomidate

On paper, etomidate appears to be the ideal neuroprotective agent. It can reduce $CMRO_2$ by up to 50% by producing EEG burst suppression. Furthermore, unlike the barbiturates, etomidate is cleared rapidly and it does not cause myocardial depression or hypotension. Initial studies in the setting of global ischaemia demonstrated that etomidate can reduce ischaemic injury [24]. However, this reduction in injury was relatively small and it was confined to a single structure (the hippocampus). Subsequent studies in models of focal ischaemia revealed, surprisingly, that etomidate actually increased the volume of brain infarction (Drummond, in press). This injury-enhancing effect of etomidate has been attributed to its ability to reduce nitric oxide levels in ischaemic brain tissue (either by inhibiting nitric oxide synthase or by directly scavenging nitric oxide). Since nitric oxide is thought to be important in the maintenance of blood flow during ischaemia, it is conceivable that etomidate might increase the severity of ischaemia. The available data therefore do not support the use of etomidate as a neuroprotective agent.

Summary

Collectively, the available data indicate that barbiturates can protect the brain and that doses required to achieve this protection may well be less than those that

produce EEG burst suppression. This has considerable clinical relevance because neuroprotection might be achieved with doses that do not render the patient unconscious for a prolonged period of time. Similarly, protection may also be achieved with clinically relevant concentrations of volatile anaesthetics (≈ 1 MAC) and with propofol. The relative equivalence of protection that might be achieved with agents that have a different effect on $CMRO_2$ suggests that the ability of anaesthetic agents to reduce ischaemic neuronal injury may have less to do with $CMRO_2$ reduction per se but with modulation of pathophysiological cascades that are initiated by ischaemia.

Cerebral ischaemia – influence of physiological parameters

Physiological parameters, such as MAP, $PaCO_2$, blood glucose and body temperature, have a significant influence on the outcome after cerebral ischaemia. In this section, information regarding the effect of these parameters on the ischaemic brain is summarised. Where possible, specific management recommendations have been suggested.

Body temperature

The effect of deep and moderate hypothermia on the brain's tolerance is well known. For example, while the normothermic brain undergoes injury after 5 min of ischaemia, the brain made hypothermic to a temperature of 16°C can tolerate ischaemia for up to 30 min (and longer in certain situations). Similarly, cardiopulmonary bypass (CPB) is usually conducted at a temperature of 28°C in part to reduce the potential of ischaemic brain injury. Therefore, induction of deep and moderate hypothermia for cardiac surgery has been well established.

What has only recently been appreciated is that temperature reduction of only a few degrees (≈ 33–34°C) can also reduce the brain's vulnerability to ischaemic injury. In animal models of global cerebral ischaemia, intra-ischaemic mild hypothermia (temperature of 33°C) has been shown to reduce dramatically neuronal injury [25, 26]. In addition, the application of mild hypothermia after the ischaemic insult has also been shown to reduce injury provided the temperature is reduced within 30 min of the insult and duration of the hypothermia is extended to several hours. Similarly, intra- and post-ischaemic mild hypothermia can reduce cerebral injury after focal ischaemia [27]. This protective effect of hypothermia is greater in situations in which flow is restored after ischaemia and is less evident in situations where ischaemia is permanent (e.g. permanent occlusion of a cerebral vessel that is not recanalised) [28, 29].

In light of this dramatic protective effect of mild hypothermia, its use in the operating room setting has been advocated. Proponents of its use argue that hypothermia is readily achieved and it is not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can be readily rewarmed in the operating room after the risk of ischaemia has subsided. The efficacy of mild

hypothermia in reducing cerebral injury in humans who have sustained subarachnoid haemorrhage and who present in the operating room for aneurysm clipping has been evaluated in a randomised clinical trial [30]. Induction of mild hypothermia *did not* reduce the incidence of new neurological abnormalities in the postoperative period. These data, which have yet to be published, do not support the use of routine intraoperative hypothermia for aneurysm clipping.

By contrast, increases in brain temperature during and after ischaemia aggravate injury [31]. An increase of as little as 1°C can dramatically increase injury. Ischaemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. It therefore seems prudent to avoid hyperthermia in patients who have suffered an ischaemic insult or those who are at risk of cerebral ischaemia. In the operating room, hyperthermia is seldom a problem (witness our efforts to prevent hypothermia). One situation in which body temperature is often allowed to increase is during rewarming after hypothermic CPB. In that situation, hyperthermia (core body temperature in excess of 38°C) is not uncommon. The suggestion that increases in temperature in excess of 37–38°C should be avoided has some merit given the recent information regarding the deleterious effect of hyperthermia.

Cerebral perfusion pressure

Cerebral blood flow is normally autoregulated over a cerebral perfusion pressure (CPP) range of 50–150 mmHg. In hypertensive patients, the lower limit of autoregulation is shifted to the right. In most patients, maintenance of CBF can be assured with a CPP in excess of 50 mmHg. The question is whether this CPP is adequate to maintain perfusion in a brain that has undergone ischaemic injury. The ideal CPP in such patients has not been adequately studied. In head-injured patients, however, a higher than normal CPP is required to maintain normal CBF. Chan and colleagues have shown that a CPP of about 70 mmHg is adequate in head-injured patients [32]. A CPP of 70 mmHg is therefore a reasonable goal in patients who have undergone an ischaemic insult, provided the results of Chan et al. can be applied to such patients. In animal models of cerebral ischaemia, an increase in MAP produced by phenylephrine infusion is associated with a reduction in ischaemic brain injury [33].

By contrast, hypotension has been shown to be quite deleterious to the injured (ischaemic or traumatic) brain. Hypotension can increase cerebral infarct volumes significantly and should be avoided in patients who have suffered a stroke. Similarly, hypotension has been demonstrated to be one of the most important contributors to a poor outcome in patients who have sustained head injury. Maintenance of an adequate MAP and CPP is therefore critical. Elevation of MAP by alpha agonists such as phenylephrine is appropriate (with the assumption that the patient's intravascular volume is normal). There is a concern that these vasoconstrictors might produce cerebral vasoconstriction, thereby obviating the beneficial effect of an increased MAP. However, cerebral vessels do not have a high concentration of alpha receptors and therefore alpha agonists do not reduce CBF [34].

Blood glucose

In the normal brain that is adequately perfused, glucose is metabolised aerobically. The end products of aerobic glucose metabolism are water, CO_2 and ATP. When the brain is rendered ischaemic, oxygen is no longer available and aerobic metabolism of glucose is inhibited. Glucose is then metabolised anaerobically via the glycolysis pathway. The end products of this pathway are lactic acid and ATP. The lactic acid produced contributes to the acidosis that occurs in many ischaemic tissues.

Because the brain does not have glucose stores, the extent of lactic acidosis is limited. However, during hyperglycaemia, the supply of glucose to the brain is increased. Indeed, with hyperglycaemia, neuronal stores of glucose may be increased. In this situation, the amount of lactic acid produced is considerable and the cerebral pH decreases. This acidosis contributes significantly to neuronal necrosis [35]. In many laboratory and human studies, pre-existing hyperglycaemia has been shown to be associated with increased neurological injury [36]. As a corollary, treatment of hyperglycaemia with insulin has been shown to reduce neurological injury [37]. Consequently, it has been suggested that hyperglycaemia be treated in patients at risk of cerebral ischaemia and in those who have suffered an ischaemic insult. What is not certain is the threshold level of glucose beyond which treatment is indicated. The author's own treatment threshold is a blood glucose level that is greater than 200 mg/dl. This threshold is, however, rather arbitrary.

Seizure prophylaxis

Seizures commonly occur in patients with intracranial pathology. Seizure activity is associated with increased neuronal activity, increased CBF and cerebral blood volumes (consequently increased intracranial pressure) and cerebral acidosis. Untreated seizures can actually produce neuronal necrosis even with normal cerebral perfusion. Prevention and rapid treatment of seizures is therefore an important goal. Seizures can be rapidly treated with benzodiazepines, barbiturates, etomidate and propofol. For more long-lasting anti-epileptic activity, phenytoin and pentobarbital are often used.

Conclusions

Based on the above discussion, our approach to 'brain protection' is outlined below:

- The anaesthetised brain is less vulnerable to ischaemic injury than the awake brain. Although data regarding the relative merits of individual anaesthetics in humans are lacking, the available information is consistent with the premise that volatile anaesthetics do provide some, albeit transient, protection.
- Barbiturates, although long considered to be the gold standard, are not used routinely. In situations in which the risk of ischaemic injury is high (i.e. aneurysm and AVM surgery), barbiturates are administered. This practice is

largely empirical. Barbiturates are not administered during CEA. If, upon carotid cross-clamping, EEG changes suggestive of severe ischaemia are present, a shunt is inserted.

- Patients undergoing aneurysm and AVM surgery are routinely made hypothermic to a core body temperature of 33–34°C. This practice will be re-evaluated given the negative results of the recently completed IHAST trial. CEA patients are not made hypothermic because the risk of myocardial ischaemia in these patients upon rewarming is significant. Hyperthermia should be avoided.
- Cerebral perfusion pressure is maintained in the 'normal range' for the individual patient. In CEA patients, the MAP (in the absence of a shunt) may be increased by up to 10%.
- In diabetic patients, insulin is administered if glucose values exceed 250 mg/dl. Close monitoring of blood glucose is strongly advised to ensure that hypoglycaemia does not develop.

References

1. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD (1992) Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. J Thorac Cardiovasc Surg 104:1510–1517
2. Reed GD, Singer DE, Picard EH, DeSanctis RW (1988) Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits. N Engl J Med 319:1246–1250
3. Anonymous (1991) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 325:445–453
4. Siesjo BK (1981) Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab 1:155–185
5. Benveniste H, Drejer J, Schousboe A, Diemer NH (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43:1369–1374
6. Choi DW (1988) Calcium-mediated neurotoxicity: relationship to specific channel types and role in ischemic damage. Trends Neurosci 11:465–469
7. Todd MM, Chadwick HS, Shapiro HM et al (1982) The neurologic effects of thiopental therapy following experimental cardiac arrest in cats. Anesthesiology 57:76–86
8. Warner DS, Zhou J, Ramani R, Todd MM (1991) Reversible focal ischemia in the rat: effects of halothane, isoflurane, and methohexital anesthesia. J Cereb Blood Flow Metab 11:794–802
9. Drummond JC (1993) Do barbiturates really protect the brain? Anesthesiology 78:611–613
10. Warner DS, Takaoka S, Wu B et al (1996) Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. Anesthesiology 84:1475–1484
11. Baughman VL, Hoffman WE, Thomas C et al (1990) Comparison of methohexital and isoflurane on neurologic outcome and histopathology following incomplete ischemia in rats. Anesthesiology 72:85–94

12. Soonthon-Brant V, Patel PM, Drummond JC et al (1999) Fentanyl does not increase brain injury after focal cerebral ischemia in rats. Anesth Analg 88:49–55
13. Nellgard B, Mackensen GB, Pineda J et al (2000) Anesthetic effects on cerebral metabolic rate predict histologic outcome from near-complete forebrain ischemia in the rat. Anesthesiology 93:431–436
14. Warner DS, McFarlane C, Todd MM et al (1993) Sevoflurane and halothane reduce focal ischemic brain damage in the rat. Anesthesiology 79:985–992
15. Werner C, Mollenberg O, Kochs E, Schulte am Esch J (1995) Sevoflurane improves neurological outcome after incomplete cerebral ischaemia in rats. Br J Anaesth 75:756–760
16. Engelhard K, Werner C, Reeker W et al (1999) Desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats. Br J Anaesth 83:415–421
17. Du C, Hu R, Csernansky C et al (1996) Very delayed infarction after mild focal cerebral ischemia: a role for apoptosis? J Cereb Blood Flow Metab 16:195–201
18. Kawaguchi M, Kimbro JR, Drummond JC et al (2000) Isoflurane delays but does not prevent cerebral infarction in rats subjected to focal ischemia. Anesthesiology 92:1335–1342
19. Engelhard K, Werner C, Eberspacher E et al (2004) Sevoflurane and propofol influence the expression of apoptosis-regulating proteins after cerebral ischaemia and reperfusion in rats. Eur J Anaesthesiol 21:530–537
20. Gelb AW, Bayona NA, Wilson JX, Cechetto DF (2002) Propofol anesthesia compared to awake reduces infarct size in rats. Anesthesiology 96:1183–1190
21. Pittman JE, Sheng H, Pearlstein RD et al (1997) Comparison of the effects of propofol and pentobarbital on neurologic outcome and cerebral infarction size after temporary focal ischemia in the rat. Anesthesiology 87:1139–1144
22. Bayona NA, Gelb AW, Jiang Z et al (2004) Propofol neuroprotection in cerebral ischemia and its effects on low-molecular-weight antioxidants and skilled motor tasks. Anesthesiology 100:1151–1159
23. Engelhard K, Werner C, Eberspacher E et al (2004) Influence of propofol on neuronal damage and apoptotic factors after incomplete cerebral ischemia and reperfusion in rats: a long-term observation. Anesthesiology 101:912–917
24. Sano T, Patel PM, Drummond JC, Cole DJ (1993) A comparison of the cerebral protective effects of etomidate, thiopental and isoflurane in a model of forebrain ischemia in the rat. Anesth Analg 76:990–997
25. Busto R, Dietrich WD, Globus MYT et al (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729–738
26. Sano T, Drummond JC, Patel PM et al (1992) A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a rat model of incomplete forebrain ischemia. Anesthesiology 76:221–228
27. Chen Q, Chopp M, Bodzin G, Chen H (1993) Temperature modulation of cerebral depolarization during focal cerebral ischemia in rats: correlation with ischemic injury. J Cereb Blow Flow Metab 13:389–394
28. Morikawa E, Ginsberg MD, Dietrich WD et al (1992) The significance of brain temperature in focal cerebral ischemia: histopathological consequences of middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 12:380–389
29. Ridenour TR, Warner DS, Todd MM, McAllister AC (1992) Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. Stroke 23:733–738
30. Todd MM, Hindman BJ, Clarke WR, Torner JC (2005) Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 352:135–145

31. Dietrich WD, Busto R, Valdes I, Loor Y (1990) Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 21:1318–1325
32. Chan KH, Dearden NM, Miller JD et al (1993) Multimodality monitoring as a guide to treatment of intracranial hypertension after severe brain injury. Neurosurgery 32:547–552
33. Patel PM, Drummond JC, Cole DJ et al (1991) Delayed institution of phenylephrine induced hypertension during focal cerebral ischemia in the rat: effect on brain edema. Acta Neuropath (Berl) 81:339–344
34. Cole DJ, Matsumura JS, Drummond JC et al (1990) The effect of hypertension on reperfusion cerebral blood flow following temporary middle cerebral artery occlusion. J Neurosurg Anesthesiol 2:211–216
35. Siesjo BK, Katsura K, Mellergard P et al (1993) Acidosis-related brain damage. Prog Brain Res 96:23–48
36. Wagner KR, Kleinholz M, Courten-Myers Gd, Myers RE (1992) Hyperglycemic versus normoglycemic stroke: topography of brain metabolites, intracellular pH and infarct size. J Cereb Blood Flow Metab 12:213–222
37. Warner DS, Gionet TX, Todd MM, McAllister AM (1992) Insulin-induced normoglycemia improves ischemic outcome in hyperglycemic rats. Stroke 23:1775–1780; discussion 1781

Chapter 59

Challenges in perioperative medicine: neuroanaesthesia

K.J. Ruskin

Endoscopic third ventriculostomy (ETV) is a widely accepted minimally invasive surgical technique. Lespinasse, who coined the term *neuroendoscopy*, first attempted the procedure in 1910, and Mixter [1] performed the first successful third ventriculoscopy. ETV has become established as a therapeutic alternative in the management of patients with hydrocephalus. The procedure is most commonly used to create an alternative orifice for cerebrospinal fluid (CSF) to exit the ventricle in patients with obstructive hydrocephalus. ETV is now being used in the management of some forms of communicating hydrocephalus and is also being offered as a treatment of shunt malfunction [2]. The advent of stereotactic neurosurgery, combined with endoscopic techniques, has expanded the utility of this procedure, and more complicated surgery, such as endoscopic biopsy of ventricular tumours and drainage of ventricular haematomas, is now possible.

Although ETV is performed through a small burr hole and uses relatively simple instruments, it can cause significant alterations in intracranial physiology. The procedure involves penetration of brain parenchyma and instrumentation of the third ventricle. As a result, significant changes in the composition of CSF, intracranial pressure (ICP) and cerebral blood flow can occur during the procedure. Management of the patient undergoing ETV therefore requires close cooperation between the surgeon and anaesthesiologist. This chapter provides an overview of ETV and explores its anaesthetic implications.

Surgical technique

Endoscopic third ventriculostomy is most commonly performed with the patient's head in a rigid frame (i.e. a Mayfield head holder). Occasionally, however, the patient's head may be placed on a doughnut or other soft support [3]. After the patient is positioned, a parasaggital skin incision is made. Access to the cranial vault is through a small burr hole. After the skull has been entered, a small incision is made in the dura mater. Either a rigid or flexible endoscope is then introduced, providing access to the third ventricle (Figs. 1 and 2). If ETV is being performed as a treatment for hydrocephalus or to drain a cyst, a small hole is then made with a laser or with the tip of the endoscope. The hole may then be dilated using a Fogarty balloon catheter. At the completion of the procedure, the endoscope is withdrawn and the dura and scalp are closed.

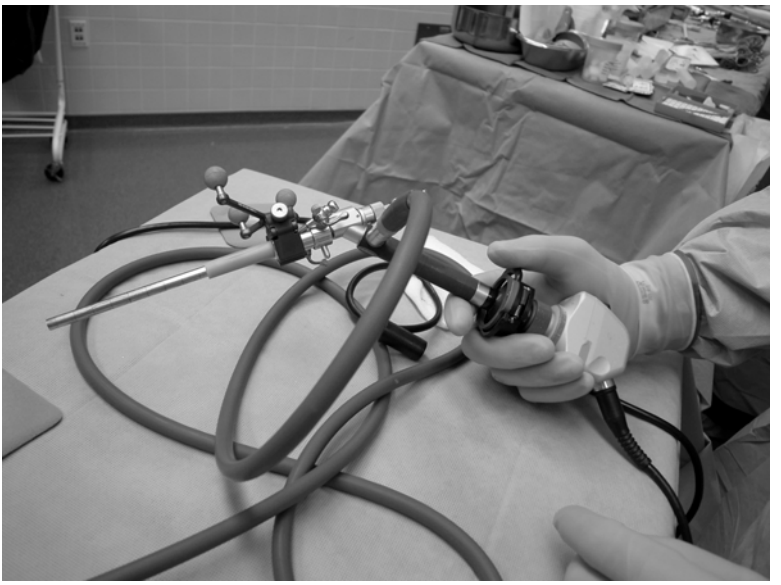


Fig. 1. An endoscope. Three spheres arranged in a triangle are used by the neuronavigator to determine the position of the endoscope relative to the patient

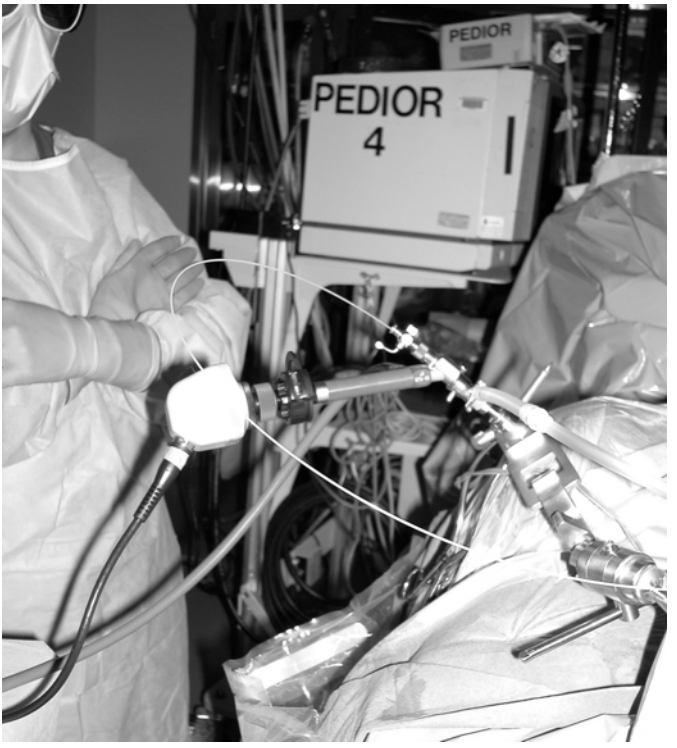


Fig. 2. Endoscope inserted into the skull

Stereotactic ETV uses computed tomography (CT) or magnetic resonance imaging (MRI) data to facilitate accurate identification of the surgical location and placement of the endoscope. Modern neuronavigation equipment uses optical identification instead of mechanically connecting the surgical instruments to a computer through an arm and series of transducers. Information from the CT or MRI is uploaded into a computer prior to the surgical procedure, and is then correlated with the location and orientation of the patient's head during a process called registration. After registration, the computer displays the location of the tip of the endoscope within the brain. Neuronavigation allows highly accurate, real-time orientation of the endoscope during the surgical procedure, and facilitates removal of large intraventricular tumours (Fig. 3).

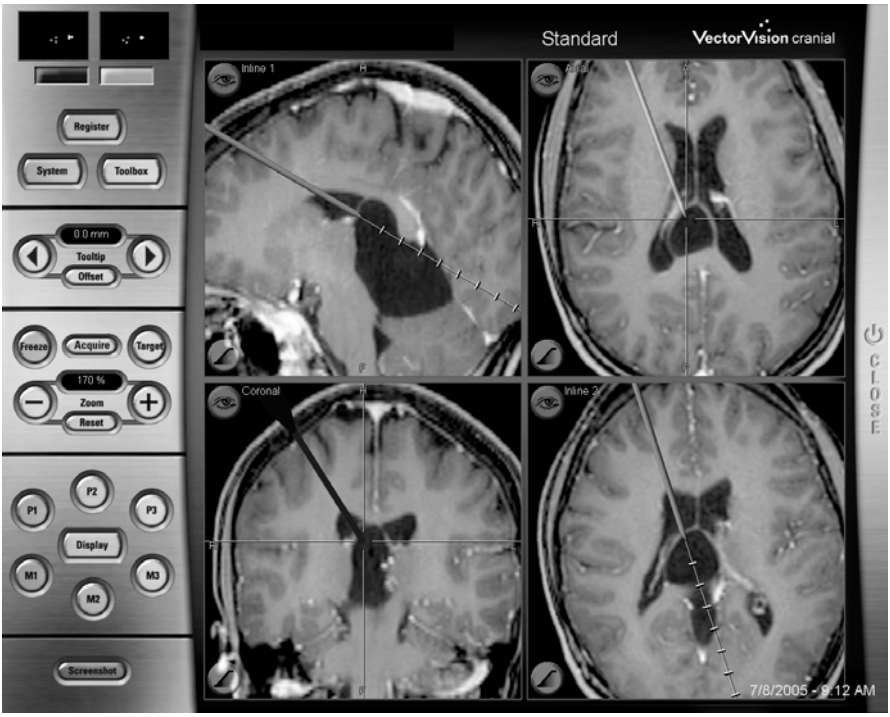


Fig. 3. Neuronavigation display. Note that each panel shows the endoscope in a different plane. The endoscope is depicted as a solid line, while the calculated trajectory is a hashed line. The two small windows in the upper left corner show the images generated by the two cameras

Anaesthetic implications

Endoscopic third ventriculostomy can cause significant changes in intracranial physiology. Most of these changes are caused by irrigating fluid, which is instilled through the endoscope during the procedure to maintain a clear view of the surgical field [4]. Intracranial pressure can very quickly rise to dangerous levels if the irrigating fluid is instilled too rapidly, if the outflow line is occluded, or if there is insufficient space between the endoscope and the introducer sheath. The abrupt increase in ICP can result in a Cushing reflex, which includes profound bradycardia and hypertension that may be preceded by tachycardia [5]. Although the classic description of the Cushing reflex includes bradycardia associated with systemic hypertension, tachycardia occurred more commonly than bradycardia in one study of cardiac events during ETV. In some of these patients, the tachycardia was associated with hypertension and an abrupt increase in ICP, leading the authors to suggest that an atypical Cushing reflex was responsible [6].

Factors other than the Cushing reflex may also be responsible for bradydysrhythmias that occur during ETV. In a case report of a cardiac arrest during ETV, the authors postulated that the event was caused by high-pressure irrigation, which caused distortion of the autonomic nuclei in the hypothalamus [7]. Some studies suggest that intraoperative bradycardia may result from either a sympathetic or a parasympathetic response to stimulation of the hypothalamic nuclei on the floor of the third ventricle [5, 6]. Another episode occurred during ETV in a patient with an infected shunt and aqueductal stenosis [8]. The irrigating solution may consist of 0.9% (normal) saline solution or lactated Ringers solution. Use of saline solution for the irrigation fluid can cause systemic hypertension [6], which may then produce bradycardia that occurs as a result of the pressor reflex.

During ETV, the endoscope passes through the brain parenchyma, and may come into contact with critical neurological structures. This may also cause significant physiological changes. Irritation of some areas of the brain during ETV can cause seizures. Occasionally, patients undergoing ETV develop central hyperthermia as a result of ependymal irritation or manipulation of the hypothalamus. The tip of the endoscope is frequently close to the basilar artery, and several case reports of basilar artery injury have been reported. There have also been reports of a traumatic basilar artery aneurysm, hemiparesis and cardiac arrest. Electrolyte disturbances occur only rarely [9]. Small haematomas that occur along the path taken by the endoscope have also been observed following ETV. These are usually found incidentally and are not clinically significant. Clinically significant haematomas and infection rarely occur.

Preoperative evaluation

In addition to the routine pre-anaesthetic examination, evaluation of the patient about to undergo ETV should ideally include a careful assessment of the patient's neurological status. Because many patients present for urgent surgery with an

altered mental status, however, management decisions must sometimes be made for patients without a complete history or laboratory studies. Patients may present with a history of multiple shunt infections and altered mental status. Many patients with hydrocephalus have congenital defects involving multiple organ systems and may be developmentally delayed. The cause of intracranial hypertension or hydrocephalus (e.g. hydrocephalus, shunt malfunction or an arachnoid cyst) should be determined.

Initial evaluation should consist of a complete history and physical examination. It may be possible to elicit signs of intracranial hypertension, including a history of gait disturbances, personality changes, headache, nausea, vomiting and visual disturbances. In many cases, hydrocephalus can increase ICP, decreasing cerebral perfusion and causing cerebral ischaemia. For this reason, a thorough examination should document the patient's baseline neurological status. The physical examination should include special attention to the state of consciousness, posturing, and pupillary signs. The nature of the planned surgical procedure should be reviewed with the surgeons, as this will affect the position of the patient and potentially which monitoring techniques are used. Preoperative laboratory tests should include a complete blood count and electrolyte panel, since the irrigating solution used during ETV can alter the composition of the CSF. Coagulation studies should be obtained since bleeding may be difficult to control through the endoscope.

Intraoperative management

Most preoperative medications, including steroids and anticonvulsants, should be continued in the perioperative period. Sedatives and anxiolytics may interfere with assessment of the patient's neurological status. These drugs may also cause hypoventilation, which can exacerbate existing intracranial hypertension. Administration of sedatives should therefore be avoided unless the patient is in a monitored setting. If the patient is extremely anxious, an anxiolytic such as midazolam may be administered in small, incremental doses immediately prior to surgery, while the patient is under continuous observation.

The goal of the anaesthetic management is to provide a smooth induction while preventing abrupt increases in ICP while ensuring patient immobility during the procedure [10]. Significant changes in cardiac rhythm and systemic blood pressure may occur during ETV, especially if ICP rises. Routine monitors, including ECG, non-invasive blood pressure and pulse oximeter, are always applied. The use of an intra-arterial catheter is recommended in order to facilitate beat-to-beat blood pressure monitoring and ensure detection of significant changes in systemic blood pressure. At least one large-bore peripheral intravenous catheter should be placed to facilitate fluid resuscitation. After induction of anaesthesia, insertion of a urinary bladder catheter should be considered if a long procedure is expected or if diuretics will be used to decrease ICP.

Either propofol or an ultra-short-acting barbiturate such as thiopental can be used for induction of general anaesthesia and control of ICP. Induction of anaesthe-

sia with propofol is associated with shorter times to eye opening, response to commands, and tracheal extubation at the end of the surgical procedure. This drug produces dose-dependent myocardial depression similar to that of thiopental, and should be used with caution if the patient is haemodynamically unstable.

Maintenance of anaesthesia can be accomplished with a potent volatile anaesthetic, such as sevoflurane, combined with judicious use of a narcotic such as fentanyl. The patient should be awake and alert at the end of the procedure, so short- or intermediate-acting agents are preferred. Nitrous oxide should be avoided during ETV. Nitrous oxide increases cerebral blood flow and therefore increases ICP. It also expands existing air spaces within the brain and may produce pneumocephalus. It may also rapidly enlarge any air bubbles that may have been trapped in the ventricle during the procedure.

Moderate hyperventilation (i.e. arterial $PaCO_2$ to between 25 and 30 mmHg) is commonly used during craniotomy to decrease brain swelling, to improve surgical exposure, and to treat intracranial hypertension. It is possible, however, that use of this manoeuvre during ETV may decrease the size of the ventricles and make the procedure more difficult for the surgeon. The use of hyperventilation should therefore be discussed with the surgeon.

It is imperative that the patient be immobile during the procedure. The tip of the endoscope is frequently near critical structures such as the basilar artery. Unexpected patient movement may therefore result in severe neurological injury or life-threatening haemorrhage. Neuromuscular blocking agents should therefore be used throughout the procedure, and an adequate depth of anaesthesia should be maintained. Perforation of the floor of the third ventricle may be painful, so the patient should be closely monitored during this portion of the procedure.

A report of at least one series of patients describes the benefits of performing ETV procedures under local anaesthesia with light sedation and analgesia [11]. The proposed benefits include the avoidance of general anaesthesia and the ability to communicate with the patient during the procedure. Because of the proximity of the endoscope to critical structures and the potentially disastrous complications that can occur if the patient moves, this procedure is not recommended for most ETV procedures. It may be considered in a patient in whom general anaesthesia carries a significant risk, and who can be guaranteed to remain completely still throughout the procedure.

Intracranial pressure can rise precipitously, so close monitoring of both blood pressure and heart rate is essential. Should significant changes in blood pressure, heart rate, or cardiac rhythm be observed during the operation, the surgeon should be asked to discontinue the flow of irrigating fluid or withdraw the endoscope. If haemodynamic stability is not restored by removal of the endoscope, pharmacological means to restore heart rate or blood pressure should be employed.

Hyperglycaemia substantially worsens neurological outcome following ischaemic injury. The proposed mechanism of injury is anaerobic lactate production from metabolism of cerebral glucose. Glucose also interferes with post-ischaemic cerebral perfusion. Although ETV is considered to be a minimally invasive procedure, hyperglycaemic patients should therefore be aggressively treated with insu-

lin, and glucose-containing solutions should be avoided. Blood glucose should be monitored frequently if the patient is diabetic or is receiving steroids and maintained between 80 and 180 mg/dl.

Conclusions

Endoscopic third ventriculostomy is a safe and effective technique that is used in the management of patients with a variety of neurosurgical problems. Although ETV is considered to be a minimally invasive neurosurgical technique, it can cause significant physiological changes. Careful attention to vital signs throughout the procedure is essential in order to detect a precipitous increase in ICP or a haemodynamic response to stimulation of the floor of the third ventricle. Management of patients who undergo this procedure requires careful anaesthetic management and close cooperation between the anaesthesia and surgical teams.

References

1. Mixter WJ (1923) Ventriculoscopy and puncture of the third ventricle. Boston J Med Surg 188:277–278
2. Murshid WR (2000) Endoscopic third ventriculostomy: towards more indications for the treatment of non-communicating hydrocephalus. Minim Invas Neurosurg 43:75–82
3. Gumprecht H, Trost HA, Lumenta CB (2000) Neuroendoscopy combined with frameless navigation. Br J Neurosurg 14(2):129–131
4. El-Dawatly AA, Murshid W, El-Khwsky F (1999) Endoscopic third ventriculostomy: a study of intracranial pressure vs. haemodynamic changes. Minim Invas Neurosurg 42:198–200
5. El-Dawatly AA, Nurshid WR, Elshimy Magboul MA et al (2000) The incidence of bradycardia during endoscopic third ventriculostomy. Anesth Analg 91:1142–1144
6. van Aken J, Struys M, Verplancke T et al (2003) Cardiovascular changes during endoscopic third ventriculostomy. Minim Invas Neurosurg 46:198–201
7. Ramani R (2003) Minimally invasive neurosurgery: anesthetic implications. Seminars in Anesthesia, Perioperative Medicine and Pain 22:43–49
8. Handler MH, Abbott R, Lee M (1994) A near-fatal complication of endoscopic third ventriculostomy: case report. Neurosurgery 35:525–527
9. El-Dawatly AA (2004) Blood biochemistry following endoscopic third ventriculostomy. Minim Invas Neurosurg 47:47–48
10. Ambesh PA, Kumar R (2000) Neuroendoscopic procedures: anesthetic considerations for a growing trend. J Neurosurg Anesth 12:262–270
11. Longatti PL, Barzol G, Paccagnella F et al (2004) A simplified endoscopic third ventriculostomy under local anesthesia. Minim Invas Neurosurg 47:90–92

Chapter 60

Does anaesthesia influence the apoptosis pathway?

G. Delogu, M. Signore, A. Antonucci

Apoptosis: a brief description

The biological phenomenon called apoptosis is defined as physiological, molecular, programmed cell death. The process has been discovered and rediscovered by various biologists over the past two centuries and has acquired a number of names. The term 'apoptosis'(A_O) was coined by Currie et al. in 1972 to represent a common type of cell death that is mechanistically distinct from necrosis as evidenced by several functional and morphological features [1]. First, apoptosis characteristically involves scattered, single cells and not cell groups as necrosis does. Second, damage to the cell membrane is a crucial event during the necrotic process; thus, necrotic cells release their contents into the interstitium, leading to a local inflammatory response. Conversely, plasma membrane integrity is relatively maintained in cells undergoing apoptosis, which is associated with rapid phagocytosis and degradation of apoptotic cells by adjacent cells or resident macrophages. This accounts for the absence of inflammation and injury in neighbouring host cells [2].

Apoptosis can thus be viewed as a form of 'cellular suicide,' characterised by specific morphological and biochemical phenomena involving both cytoplasm and nucleus. Cytoplasmic changes include aggregation of cytoskeletal filaments and rearrangement of rough endoplasmic reticulum to form concentric whorls. Nuclear changes are characterised by aggregates of chromatin in the centre of the nucleus, and chromatin condensation is the earliest apoptotic event observed by electron microscopy. A hallmark of cells dying by apoptosis is the fragmentation of DNA into 200-bp fragments through the activation of several putative endonucleases, such as DNase I, DNase II, NUC-18, and caspase-activated deoxyribonuclease.

Cell shrinkage is another typical structural change of programmed death, and is thought to be consequential to the movement of water out of the cell, resulting in cytoplasmic condensation. Membrane alterations include changes in the redistribution of phosphatidylserine, in membrane glycosylation, and in lipid profiles as well as in the expression of surface receptors [3].

Membrane blebbing and the formation of apoptotic bodies are also typical events occurring during apoptosis. The production of apoptotic bodies is observed only at a late stage of the death process and has been noted in vitro, but less commonly in vivo. The conventional idea of a net opposition between apoptosis and necrosis has been criticised by a few researchers, who have emphasised that the two phenomena share at least the following mechanisms:

- The same toxin can induce apoptosis and necrosis
- Myocardial and neuronal pathologies labelled as 'necrotic' are now known to involve apoptosis.
- Manipulation of the ATP level can influence the choice between the two models of cell death [1, 4].

The cell death program is regulated by intrinsic genetic factors as well as by environmental, extrinsic factors. Intrinsic genetic factors can act 'positively,' by activating genes whose function is to kill the cell, or 'negatively,' by acting as survival regulators. Among the inducers of apoptosis, the most well-studied are the death receptors belong to the tumour necrosis factor receptor (TNFR) gene superfamily, such as TNFR1, death receptor-3, -4, -5, and Fas/APO-1/CD95.

Caspases are cysteine proteases that have been highly conserved through-evolution, and are considered the central executioners of the apoptotic pathway. Over a dozen caspases have been identified in humans and about two-thirds of them have been suggested to function in apoptosis. Caspases engage in a cascade of sequential activation, indicating that they can participate in autoamplification. In fact, caspases themselves are substrates for other caspases and they activate each other in positive feedback loops. These proteases are constitutively expressed as pro-enzymes that contain three domains. Caspase activation, which involves proteolytic processing between domains, results in direct disassembly of cellular structures leading to dismantling and clearance of dying cells [5, 6]. The caspase cascade also consists of recognised initiator caspases that are activated through regulated protein–protein interactions, and of effector caspases that are activated by an upstream caspase. However, the ultimate molecular mechanisms mediating initiator caspase activation have not been clearly established.

The most well-known apoptosis antagonists belong to the *Bcl-2* gene family, since overexpression of these cell-death regulators has been shown to prolong cellular survival by blocking the apoptotic process. Indeed, Bcl-2 and the closely related Bcl-x1 and Mcl-1 are able to protect cells from a wide range of death-inducing stimuli, whereas other Bcl-2 members, including Bax and Bak proteins, exhibit pro-apoptotic activity, probably by altering the permeability or the conductance of the mitochondrial membrane [6, 7]. In addition to genetic factors, environmental extracellular regulators can influence the commitment of cells to undergo apoptosis. Among these death regulators, both pro-inflammatory and ant-inflammatory cytokines have been shown to play a crucial role in modulating the apoptotic fate of different cell types [8].

The intricate process of programmed cell death can be subdivided into three theoretical phases, which, although simplistic, allow us to better understand the apoptotic pathway: (1) in the induction phase, the cell receives apoptosis-triggering stimuli; (2) in the effector phase, various pro-and anti-apoptotic signals are coordinated; and (3) in the degradative phase, the well-known biochemical and ultrastructural features of apoptosis become detectable (Fig. 1).

During the initiation stage, numerous death inducers are involved, including the ligation of receptors [Fas/APO-1/CD95, tumour necrosis factors receptor (TNF-R)] or the activation of molecular mediators, such as kinases, ceramide, and Ca_2^+

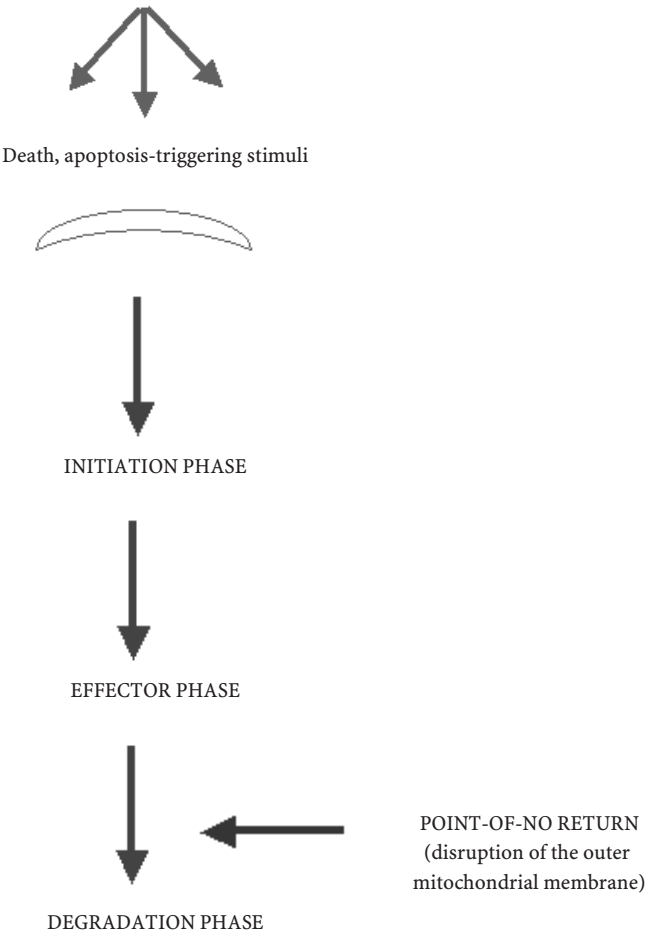


Fig. 1. The canonical phases of the apoptotic process

as well as toxins, chemotherapeutic agents, and reactive oxygen species [9]. Multiple signalling pathways to death have been identified and the pathway employed by the cell depends on the cell type, initial death triggers, and the delicate balance between the amounts of pro-apototic and anti-apoptotic proteins in the cell. These pathways, called 'private' as they are strictly dependent on the initial death inducer, ultimately trigger the common step of apoptosis, which comprises the effector and degradation phases. 'The point of no return' of the apoptotic cascade corresponds to the execution phase [1, 10, 11].

Today's overwhelming consensus is that mitochondria play a central role in the apoptotic machinery, as major changes in mitochondrial structure/function have been observed early during apoptosis. Mitochondria are central integrators of

apoptotic signals, and disruption of the outer mitochondrial membrane is often the event associated with the point of no return in cell death [12].

At present, it is generally assumed that two main pathways lead to apoptosis: the extrinsic (or death-receptor) pathway and the intrinsic (or stress) pathway (Fig. 2). The former involves activation of the plasma-membrane receptor of the TNF-recep-

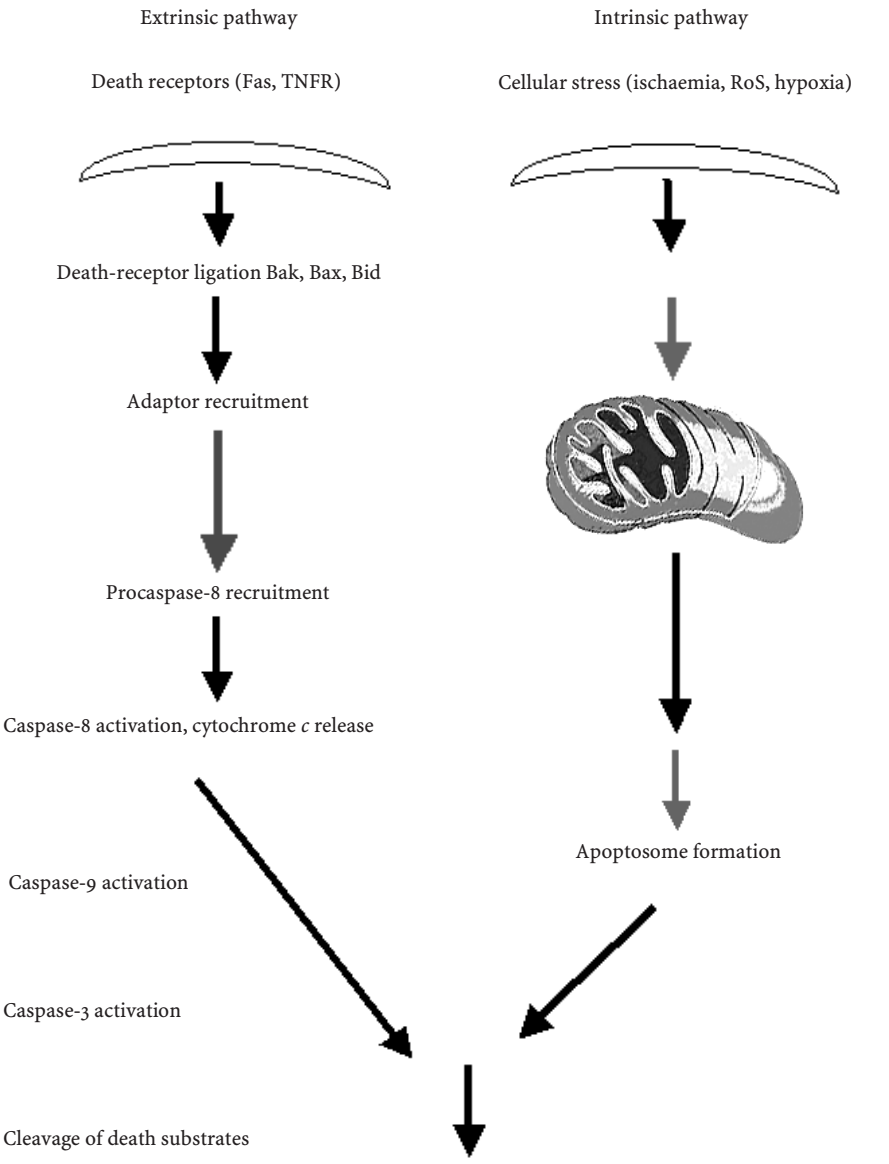


Fig. 2. The extrinsic and intrinsic pathways of apoptosis. *Bax* Bcl_2-associated x protein, *BaK* Bcl_2 agonist/killer, *Bid* BH_3- interacting-domain death agonist

tor superfamily (Fas/APO1/CD95, DR_3, and DR_4), which results in activation of caspase-8 and the subsequent proteolytic activation of other caspases. The intrinsic, mitochondrial-mediated pathway involves caspase-9 and, at the biochemical level, is characterised by mitochondrial membrane disruption, bioenergetic failure, and the release of potentially lethal proteins from the mitochondrial intermembrane space. The death receptor and mitochondrial pathways converge at the level of caspase 3 activation. In addition to these two pathways, in which executioner caspases orchestrate the death program, alternative, caspase-independent cell death (CICD) has been suggested by mounting recent evidence. For example, a serine protease, granzyme A, is able to induce a cell death pathway that is insensitive to caspase inhibitors [13–15]. Thus, in the modern era of apoptosis research there is still much to discover before the multiple pieces of the apoptotic puzzle can be ordered.

A piece of the apoptotic puzzle: anaesthesia and apoptotic pathways

Recently, a number of studies has focused on the relationship between surgical/anaesthesia trauma and apoptosis. Peripheral lymphocytes have been the most frequently studied cells, as post-surgical immune suppression has been attributed for the most part to the decrease of circulating T-cells that occurs in the early post-operative period. Indeed, unregulated activation of lymphocyte programmed death has been observed in patients undergoing surgery and general anaesthesia. Oka et al. found that surgical stress was able to trigger the apoptotic program in circulating lymphocyte by activation of the Fas/FasL pathway, and Sugimoto et al. confirmed the detection of exaggerated T-cell apoptosis following major surgical procedures [16, 17].

Treading in these researchers' footsteps, our study group investigated which apoptotic pathway might be involved in lymphocyte death following surgical/anaesthesia trauma, and the role played by anaesthesia itself in such a setting.

We found that in the early postoperative period the increased rate of lymphocyte apoptosis was associated with enhanced expression of the Fas/FasL system and down-regulation of anti-apoptotic factors, such as bcl-2. In addition, mitochondrial perturbations, including disruption of mitochondrial transmembrane potential and pro-oxidant oxidation–reduction status, were observed in T-cells of patients undergoing surgery/general anaesthesia. These findings strongly suggested that, following surgery, the two main pathways of programmed death could be activated in circulating lymphocytes due to up-regulated expression of Fas/FasL and severe mitochondrial dysfunction in those cells [18, 19].

The increased apoptotic death of T-cells following surgery/anaesthesia trauma may be partly explained by the strict relationship linking inflammatory cytokines and the apoptosis machinery. It is now well-established that during stressful events, including operative procedures, various cytokines are released locally and into the systemic circulation. For instance, previous studies provided evidence that plasma levels of interleukin 6 (IL-6), an integral part of the inflammatory response, constitute a crucial marker of the extent of surgical trauma. Notably, it was found

that caspases, the central executioners of cell death, also mediate the maturation of various cytokines, and our study group observed in surgical/anaesthesia trauma patients an exaggerated lymphocyte commitment to apoptosis associated with IL-10 overproduction [20–22].

To better understand the specific impact of anaesthesia on apoptosis, we exposed in vitro, freshly isolated peripheral lymphocytes to several anaesthetic agents, namely, pancuronium bromide, fentanyl, and propofol. Clinically relevant concentrations of these drugs were used and the laboratory experiments evidenced the following findings. Propofol did not exhibit any significant pro-apoptotic effect, confirming the observations of other researchers, who showed that propofol is even able to protect certain cell lines from apoptotic death [23, 24].

However, we did find that fentanyl can induce time-dependent apoptosis through alteration of mitochondrial redox metabolism, and this ability is similar to that of other opioids, including morphine [25]. Pancuronium also was able to promote programmed death; in fact, in lymphocytes cultured in the presence of this compound, increased expression of death receptors, such as Fas, FasL and ICEp20, as well as dissipation of mitochondrial membrane potential were detected. These findings were consistent with the larger number of apoptotic cells compared to control cultures [26].

In a further work on lymphocytes treated with pancuronium or fentanyl, we found that these drugs, at concentrations that promoted apoptosis, were able to induce an elevated rate of telomeric associations [27]. Interestingly, new insight into the strong link between the 'suicidal' cell program and genomic instability was provided by Artandi et al. [28].

Furthermore, also local anaesthetics are able to trigger apoptosis, and a recent investigation confirmed the capacity of lidocaine to induce mitochondrial injury and caspase activation in a neuronal cell line [29].

However, in addition to their pro-death effects, anaesthesia substances are able to protect different cells types from apoptosis, as demonstrated in animal models and in humans. Sevoflurane and propofol reduced the concentration of the apoptosis-inducing protein Bax after cerebral ischaemia and perfusion [30]. Propofol revealed an anti-apoptotic capacity, via suppression of caspase-3 activities, and a similar ability to prevent the death program has been shown in neuronal cells exposed to isoflurane [31]. Furthermore, apoptosis was significantly inhibited in human neutrophils incubated with sevoflurane in vivo [32].

Overall, these findings allow us to answer in the affirmative the question 'does anaesthesia influence the apoptosis pathway?' Compounds commonly used for general and local anaesthesia affect the apoptotic program in immunological cells, i.e. peripheral lymphocytes, and in other cell types by either priming or suppressing activation of the intracellular cell-death circuitry (Table 1).

Such an interference could occur at level of both extrinsic and intrinsic apoptosis pathway, but novel signalling pathways may also be implicated. The clinical impact of anaesthesia's influence on cell death represents an interesting field for further study. The aim is to optimise the use of anaesthetic drugs by inducing minimal harm while obtaining the maximal advantage for the patient.

Table 1. Drugs currently used in anaesthesia practice that demonstrate the influence of apoptosis pathways on different cell types.

Drug effect	Pro-apoptotic effect	Anti-apoptotic	Cell type	Possible mechanism of action
Lidocaine	+	–	Neurons	Mitochondrial dysfunction
Fentanyl	+	–	Lymphocytes	Mitochondrial injury, genomic instability
Propofol	–	+	Neurons	Down-regulation of Bax protein
			Lymphocytes	Suppression of Caspase-3 activation
			Astrocytes, osteoblasts	Antioxidant effect
Pancuronium	+	–	Lymphocytes	Mitochondrial injury, genomic instability
Ketamine	+	–	Neurons	Caspase-3 activation
Sevoflurane	–	+	Neurons	Down-regulation of Bax protein
			Neutrophils	Mitochondrial protection
Isoflurane	–	+	Neurons	Delay in activation of caspases

References

1. Kerr JF, Wyllie AH, Currie AR (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239–257
2. Penninger JM, Kroemer G (1998) Molecular and cellular mechanisms of lymphocyte apoptosis. Adv Immunol 68:51–144
3. Hengartner MO (2000) The biochemistry of apoptosis. Nature 407:770–776
4. Meier P, Finch A, Evan G (2000) Apoptosis in development. Nature 407:796–801
5. Cohen GM (1997) Caspase: the executioners of apoptosis. Biochem J 326:1–16
6. Vaux DL, Strasser A (1996) The molecular biology of apoptosis. Proc Natl Acad Sci USA 93:2239–2244
7. Kim R (2005) Unknotting the roles of Bcl-2 and Bcl-xL in cell death. Biochem Bioph Res Co 333:336–343
8. Joshi VD, Kalvakolanu DV, Cross AS (2003) Simultaneous activation of apoptosis and inflammation in pathogenesis of septic shock: a hypothesis. FEBS Lett 555:180–184
9. Waring P (2005) Redox active calcium ion channels and cell death. Arch Biochem Biophys 434:33–42
10. Otsuki Y (2004) Tissue specificity of apoptotic signal transduction. Med Electron Microsc 37:163–169
11. Damal NN, Koromeyer DJ (2004) Cell death: critical control points. Cell 116:205–219
12. Green DR, Reed JC (1998) Mitochondria and apoptosis. Science 281:1309–1312
13. Chipuk JE, Green DR (2005) Do inducers of apoptosis trigger caspase-indipendent cell death? Nat Rev Mol Cell Bio 6:268–275

14. Dong C, Li Q, Lyu S-C et al (2005) A novel apoptosis pathway activated by the carboxyl terminus of P21. Blood 105:1187–1194
15. Martinvalet D, Zhu P, Lieberman J (2005) Granzyme A induces caspase-independent mitochondrial damage, a required first step for apoptosis. Immunity 22:355–370
16. Oka M, Hirazawa K, Yamamoto K et al (1996) Induction of Fas-mediated apoptosis on circulating lymhocytes by surgical stress. Ann Surg 223:434–440
17. Sugimoto M, Shimaoka M, Hosotsubo K et al (1998) Up-regulation of Fas ligand (FasL) mRNA expression in peripheral blood mononuclear cells (PBMC) after major surgery. Clin Exp Immunol 112:120–125
18. Delogu G, Moretti S, Antonucci A et al (2000) Apoptosis and surgical trauma. Dysregulated expression of death and survival factors on peripheral lymphocytes. Arch Surg 135:1141–1147
19. Delogu G, Moretti S, Famularo G et al (2001) Mitochondrial perturbation and oxidant stress in lymphocytes from patients undergoing surgery and general anesthesia. Arch Surg 136:1190–1196
20. Helmy SA, Wahby MA, El-Nawaway M (1999) The effect of anaesthesia and surgery on plasma cytokine production. Anaesthesia 54:733–738
21. Kang SJ, Wang S, Kuida K et al (2002) Distinct downstream pathway of caspase-11 in regulating apoptosis and cytokine maturation during septic shock response. Cell Death Differ 9:1115–1125
22. Delogu G, Famularo G, Moretti S et al (2001) Interleukin-10 and Apoptotic Death of Circulating Lymphocytes in Surgical/Anesthesia Trauma. J Trauma 51:92–97
23. Acquaviva R, Campisi A, Murabito P et al (2004) Propofol attenuates peroxynitrite-mediated DNA damage and apoptosis in cultured astrocytes. Anesthesiology 101:1363–1371
24. Chen R-M, Wu G-J, Chang H-C et al (2005) 2,6-Diisopropylphenol protect osteoblasts from oxidative stress-induced apoptosis through suppression of caspase-3 activation. Ann NY Acad Sci 1042:448–459
25. Delogu G, Moretti S, Antonucci A et al (2004) Apoptogenic effect of fentanyl on freshly isolated peripheral blood lymphocytes. J Trauma 57:75–81
26. Delogu G, Moretti S, Marcellini S et al (2003) Pancuronium bromide, a non depolarising muscle relaxant which promotes apoptosis of blood lymphocytes in vitro. Acta Anaesthesiol Scand 47:1138–1144
27. Delogu G, Antonelli A, Signore M et al (2004) Chromosome instability in T-cells cultured in the presence of pancuronium or fentanyl. Acta Anaesthesiol Scand 48:968–972
28. Artandi SE, Attardi LD (2005) Pathway connecting telomeres and p53 in senescence, apoptosis and cancer. Biochem Bioph Res Co 331:881–890
29. Johnson MJ, Uhl CB, Spittler K-H et al (2004) Mitochondrial injury and caspase activation by the local anesthetic lidocaine. Anesthesiology 101:1184–1194
30. Engelhard K, Werner C, Eberspächer E et al (2004) Sevoflurane and propofol influence the expression of apoptosis regulating proteins after cerebral ischaemia and perfusion in rats. Eur J Anaesth 21:530–537
31. Kawaguchi M, Drummond JC, Cole DJ et al (2004) Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. Anesth Analg 98:798–805
32. Tyther R, O'Brien J, Wang J et al (2003) Effect of sevoflurane on human neutrophil apoptosis. Eur J Anesth 20:111–115

Chapter 61

Anaesthesia in orthopaedic surgery

B. Borghi, J. Frugiuele, A. Adduci

Regional anaesthesia (RA), general anaesthesia (GA), and RA integrated with mild GA (IA) are the options available to the anaesthetist in orthopaedic and traumatology surgery. Choosing the most appropriate anaesthetic depends on the anaesthetist's habits and technical skills. Estimated bleeding, operation time, and postoperative pain and stress should be borne in mind, because of the physical and psychological repercussions they entail. The advantages of RA are the control of endocrine–metabolism reactions induced by surgical stress [1, 2], reduced perioperative bleeding [3], and reduced postoperative morbidity [1, 4]. GA provides sedation and protection from the surgical environment (noise, smells, emergencies) and enables the patients to stay in uncomfortable positions for a long time. However, it fails to inhibit hormonal and endocrine responses to stress, even with the help of high plasma concentrations of opioids [5, 6].

Although there is no evidence to suggest that one type of anaesthetic reduces the intra- and postoperative death rate more than another, some anaesthesiological procedures can provide a better postoperative outcome and/or enable easier patient management during surgery, especially with regards to pain therapy. A Cochrane review has shown that the rate of deep-vein thrombosis and the risk of postoperative acute respiratory failure were lower when using epidural–spinal anaesthesia as opposed to GA in adult femoral fracture treatment. In total hip and total knee arthroplasty, epidural anaesthesia enables better postoperative pain control than spinal anaesthesia [7, 8].

A recent study of patients undergoing elective total hip arthroplasty under general anaesthesia showed a significant delay in the resumption of haemopoiesis. The circulating erythrocyte mass was calculated preoperatively, and on the first, second, and third day after surgery by Mercuriali's formula, which takes into consideration autologous and homologous blood transfusions, erythropoiesis, and bleeding. The delay may have been due to the role of nitrogen protoxide in inhibiting erythropoiesis [9].

Unilateral epidural anaesthesia

We evaluated the effects of turning the tip of the Tuohy needle 45° toward the operative side before threading the epidural catheter (45°-rotation group, $n = 24$) compared to a conventional insertion technique with the tip of the Tuohy needle

oriented at 90° cephalad (control group, $n = 24$) on the distribution of 10 ml of 0.75% ropivacaine with 10 μg sufentanil in 48 patients undergoing total hip replacement. The 45°-rotation group had preferential distribution of sensory and motor block toward the operative side, reduction of the incidence of intraoperative hypotension, lower volume of crystalloid and HES infused, accelerated recovery profile of the non-operative side, lower rate of bladder catheterisation, and lower volume of local anaesthetic solution to maintain postoperative pain control [10].

Unilateral spinal anaesthesia

The following procedure must be carried out rigorously when performing unilateral spinal anaesthesia:

- Put the patient in lateral decubitus with the treated side down.
- Point the needle bevel downwards
- Use a hyperbaric local anaesthetic (e.g. hyperbaric 0.5% bupivacaine)
- Avoid aspirating the liquor, even before injecting the anaesthetic
- Inject the anaesthetic slowly (about 1 min)
- Keep the patient in lateral decubitus for 15 min

This method is widely used in outpatient surgery, because low doses of anaesthetic permit adequate surgical planning, and the anaesthetic's effects (motor block, sensitive block, and spontaneous resumption of diuresis) are compatible with the patient's early discharge from hospital [11–14].

Peripheral continuous blockade

In the scope of regional anaesthesia techniques, there is a growing interest in peripheral blockades. They can provide the same efficacy as central blockades in intra- and postoperative pain control by more selective and specific analgesia, and above all the rate of undesired effects and complications is lower.

The ability to extend the analgesic effect of peripheral blockades into the postoperative period, by continuous infusion of the local anaesthetic through a specific perineural catheter, has overcome the limitations of the single-shot peripheral blockade. These limitations were due to the short duration of the anaesthetic's analgesic effect, which, depending on the individual patient's needs, should cover at least the first 24–48 h after surgery. In fact, several clinical studies [15–33] have shown the usefulness and efficacy of continuous peripheral blockades, not only because they control acute postoperative pain, but also because they continue to provide analgesic cover in the subsequent rehabilitation and functional recovery phase, and at home, and are without the side effects that characterise opioid analgesia (respiratory depression, nausea and vomit, constipation and urinary retention, sedation and pruritus) and NSAIDs (kidney failure, gastropathy, and increased risk of bleeding) [23, 28].

In patients undergoing total knee arthroplasty, regional anaesthesia (3-in-1

block and sciatic nerve block) combined with femoral perineural infusion of local anaesthetic has led to a 90% reduction of the more severe postoperative complications and a 20% reduction in hospitalisation time compared to a group of patients treated under GA or epidural anaesthesia. Postoperative bleeding and the consumption of morphine were also significantly lower [15, 29].

Continuous femoral infusion combined with catheterising the sciatic nerve (to be used only if the pain in the back of the knee is moderate-severe) is the best alternative to epidural analgesia or patient controlled anaesthesia PCRA with morphine for postoperative pain control and immediate rehabilitation after total knee arthroplasty [16].

The lumbar plexus blockade has some important advantages over epidural anaesthesia: absence of sympathetic blockade, increased haemodynamic stability, absence of urinary retention, and low risk of severe complications.

In recent years, improved knowledge about blockade techniques, the commercialisation of appropriate, safe equipment (new needles, catheters, fixation systems, and infusion systems), and the introduction into clinical practice of new, long-lasting, safer local anaesthetics, such as ropivacaine and levobupivacaine, as well as knowledge about their side effects and toxicity, have enabled the development of safe and efficacious postoperative analgesic techniques. Moreover, these can be managed at home by the patient, thus reducing hospitalisation times and hospital costs [24, 25, 27, 30, 32].

The continuous interscalene blockade as a single anaesthesiological technique, as described by Chelly et al. [26], is able to reduce intra- and postoperative times in patients undergoing rotator cuff surgery, from the arrival of the patient in the operating room to the start of surgery, and from the end of surgery to the patient's departure from the operating room. Furthermore, it reduces hospitalisation times by 66% compared to continuous interscalene blockade combined with GA, and by 40% compared to GA with infiltration of local anaesthetic in the treatment area [26].

All these elements suggest that peripheral continuous blockades will be a valid alternative in the future, not only to most single-shot peripheral blockades, but also to continuous epidural analgesia in several orthopaedic operations. Some studies carried out so far have shown that continuous postoperative perineural analgesia at home can be performed to the great satisfaction of patients. The analgesic technique consists of inserting a perineural catheter, in most cases before surgery, and thus used during surgery; alternatively, in some patients it is even inserted several days after surgery due to the inadequacy of and/or intolerance to systemic analgesic therapy. The following blocks were performed: interscalene, infraclavicular, femoral, and sciatic by subgluteal approach [31–33].

Infusion systems and doses for continuous perineural analgesia

Currently, there are two types of infusion systems on the market for the long-lasting release of drugs, which can be used in hospitals and at home: (1) elastomer pump with a constant infusion speed, and (2) electronic pumps that can be controlled by

the patient PCRA, not only with regard to the basal speed of infusion, but also to the delivery of additional boluses with varying lockout times, depending on the patient-controlled mode. Although PCRA pumps minimise the volume of local anaesthetic in relation to analgesic effect, they are usually only used to control pain during hospitalisation, whereas at home patients are provided with disposable elastomer pumps, which are less expensive and less bulky. In our experience, the doses used to maintain the analgesic blockade consisted of continuous infusion by elastomer pump (Baxter ref C1009), at a speed of 5 ml/h and a total capacity of 250 ml of 0.4% ropivacaine (Naropin). The pump, loaded with 10 mg Naropin/ml (100 ml and 150 ml physiologic solution), was connected to the antibacterial filter of the catheter by an extension with a three-way tap to enable the patient to stop the infusion temporarily in case of motor insufficiency or reduced analgesic requirement. Ropivacaine was chosen because of its long-lasting local anaesthetic effect, with greater motor sensitive differential blockade and less toxic potential than bupivacaine, thus making it perfect for domestic continuous perineural analgesia [34–37].

Regional analgesia managed by the patient at home

In our personal experience, regional analgesia managed by the patient at home consisted of perineural infusion of local anaesthetic by disposable elastomer pump, with the above-described infusion mode, which was given to the patient when discharged from hospital independently of the type of blockade or operation. Patients that were indicated for this type of analgesia gave their informed written consent, and were instructed on how to use the pump correctly, and how to recognise adverse effects provoked by the drugs used. They were also informed on how to get to the nearest hospital, and given phone numbers to call at any time to contact the doctor in charge. For correct domestic management of the analgesic, the patient received precise written instructions.

If the patient felt slight or severe pain during the infusion of local anaesthetic, the anaesthetic was integrated with NSAIDs (30 mg ketorolac or 50 mg ketoprofene 1 cp, repeatable 3 times a day) and/or central analgesics as rescue analgesia (tramadol SR 100 1 cp, repeatable 3 times a day) by mouth. If there was excessive insensitivity in the limb or difficulty in moving it, infusion was stopped by turning off the tap, which could be turned on again when the symptoms subsided. When the pain had completely disappeared, the patient could begin to suspend the infusion for progressively longer times, until stopping altogether and then removing the catheter. This is done according to the needs of the patient, who can resume infusion if the slightest pain is felt or before physiotherapy.

At the time of discharge, after placing the catheter, the patients filled in a form including their personal details, date, and type of continuous blockade used. Then patients were asked to include: the intensity of pain felt in the morning and in the evening (9 am and 7 pm), on a scale of 0 to 4: 0 = absent, 1 = slight, 2 = nagging, 3 = severe, and 4 = unbearable; the number of hours of infusion a day of the local

anaesthetic; the presence or not of motor paralysis; the need to take additional pain killers by mouth; the length of time the catheter remained in place up until its removal, and who removed it (the patient, a relative, or a doctor . . .); the onset of any complications; the degree of satisfaction; and any other comments. This form enabled the period of convalescence to be monitored after hospital discharge. The anaesthetic container, which was already full when given to the patient before discharge, could be refilled, if necessary with the help of an anaesthetist at the patient's nearest hospital. However, refilling instructions were written on the form and explained to the patients and their relatives. The anaesthetic container was not to be removed from the rest of the system under any circumstances; otherwise the pain therapy treatment would be suspended. The catheter did not normally need to be dressed at home, because the fixation device used excluded the risk of contamination. Therefore, the patient was instructed not to remove the dressing, for any reason, until the catheter was removed. If the dressing became partially undone by accident, or if bleeding, swelling, or infection occurred at the catheter insertion site, the patient was told to contact the family doctor. If pain was absent 24–36 h after suspending the infusion of local anaesthetic, the patient was allowed to remove the catheter, alone or with the help of a relative or family doctor.

Based on this experience, it was concluded that: peripheral continuous blockade is a reliable method, without evident side effects, and better accepted by the patient than general anaesthesia. Joints treated by surgery can benefit from immediate pain-free movement, and the peripheral continuous blockade contributes to reducing social costs of orthopaedic-traumatology surgery.

Several studies have supported the usefulness of patient-controlled domestic analgesia. For example, an American randomised, double-blind, controlled study with the use of a placebo investigated the efficacy of this type of analgesia on placing an infraclavicular perineural catheter and connecting it to a continuous infusion pump [31]. The results showed that the infusion of ropivacaine ($n = 15$) reduced markedly pain when compared to the placebo ($n = 15$; $P < 0.001$). For example, pain after moving (1–10 scale) on the first day after surgery was 6.1 ± 2.3 in the placebo group compared to 2.5 ± 1.6 in the ropivacaine group ($P < 0.001$). The use of oral analgesics and the rate of their side effects was reduced in the group treated with ropivacaine. Furthermore, the patient's personal satisfaction was significantly greater in the group treated with ropivacaine and no complications connected to local anaesthetics occurred. On the basis of the literature and our personal experience, we can thus summarise the advantages of regional anaesthesia:

- Preventive action against surgical stress
- Reduction of risks for patients with respiratory diseases
- Lower pharmaceutical impact on the patient
- Extended postoperative analgesia
- Reduced discomfort due to fasting, nausea, and/or vomiting
- Reduced need for perioperative assistance
- Obviation of possible complications connected to general anaesthesia
- Better psychophysical recovery, especially useful in elderly patients.

Patients of all age groups can benefit from regional anaesthesia, either in

elective or emergency surgery. The complications of any technique should be diagnosed accurately and quickly, in order to act confidently.

In conclusion, rather than wondering about what technique should be used, we think it is better to consider what skills we want to add to our technical arsenal. In the light of what is reported in the literature, and based on our personal experience it is indispensable for the anaesthetist, the orthopaedic surgeon, and the operating-room nurse to become familiar with relieving pain by continuous infusion of local anaesthetics.

References

1. Spencer L, Carpenter RL, Neal JM (1995) Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology 82(6):1474–1506
2. Kehlet H (1984) Epidural analgesia and endocrinometabolic response to surgery. Update and perspectives. Acta Anaesthesiol Scand 28:125–127
3. D'Ambrosio A, Borghi B, D'Amato A et al (1999) Reducing perioperative blood loss in patients undergoing total hip arthroplasthy. Int J Artif Organs 22:47–51
4. Rodgers A, Walker N, Schug A et al (2000) Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 321:1493
5. Anonymous (1990) Editorial views: Does opioid 'anesthesia' exist? Anesthesiology 73:1–4
6. Philbin DM, Rosow CE, Schneider RC et al (1990) Fentanyl and sufentanil anesthesia revisited: how much is enough? Anesthesiology 73:5–11
7. Parker MJ, Handoll HHG, Griffiths R (2005) Anaesthesia for hip fracture surgery in adults. At http://www.cochrane.org/cochrane/revabstr/AB000521.htm (last accessed Sept 09 2005)
8. Choi PT, Bhandari M, Scott J et al (2005) Epidural analgesia for pain relief following hip or knee replacement. At http://www.cochrane.org/cochrane/revabstr/AB003071.htm (last accessed Sept 09 2005)
9. Borghi B, Laici C, Iuoro S et al (2002) Anestesia epidurale vs generale. Minerva Anestesiol 68:171–177
10. Borghi B, Agnoletti V, Ricci A et al (2004) A prospective, randomized evaluation of the effects of epidural needle rotation on the distribution of epidural block. Anesth Analg 98(5):1473–1478
11. Kaya M, Oguz S, Aslan K (2004) A low-dose bupivacaine: a comparison of hyperbaric and hypobaric solutions for unilateral spinal anesthesia. Reg Anesth Pain Med 29(1):17–22
12. Borghi B, Stagni F, Bugamelli S et al (2003) Unilateral spinal block for outpatient knee arthroscopy: a dose-finding study. J Clin Anesth 15(5):351–356
13. Casati A, Fanelli G (2001) Unilateral spinal anesthesia. State of the art. Minerva Anestesiol 67(12):855–862
14. Kiran S, Upma B (2004) Use of small-dose bupivacaine (3 mg vs 4 mg) for unilateral spinal anesthesia in the outpatient setting. Anesth Analg 99(1):302–303
15. Chelly J, Greger G, Gebhard R et al (2001) Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. J Artrhoplasty 16(4):436–445
16. Ben-David B, Schmalenberger K, Chelly JE (2004) Analgesia after total knee arthropla-

sty: is continuous sciatic blockade needed in addition to continuous femoral blockade? Anesth Analg 99(3):954–955
17. Borgeat A, Perschak H, Bird P et al (2000) Patient-controlled interscalene analgesia with ropivacaine 0.2% versus patient-controlled intravenous analgesia after major shoulder surgery: effects on diaphragmatic and respiratory function. Anesthesiology 92:102–108
18. Rawal N, Allvin R, Axelsson K et al (2002) Patient-controlled regional analgesia (PCRA) at home. Controlled comparison between bupivacaine and ropivacaine brachial plexus analgesia. Anesthesiology 96:1290–1296
19. Capdevila X, Barthelet Y, Biboulet P et al (1999) Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after minor knee surgery. Anesthesiology 91:8–15
20. Chelly JE, Casati A, Al-Samsam T et al (2003) Continuous lumbar plexus block for acute postoperative pain management after open reduction and internal fixation of acetabular fractures. J Orthop Trauma 17(5):362–367
21. Van Oven H, Agnoletti V, Borghi B et al (2001) Analgesia regionale controllata dal paziente (PCRA) nella chirurgia del gomito anchilotico: elastomero vs pompa elettronica. Minerva Anestesiol 67:117–120
22. Klein SM, Greengrass RA, Gleason DH et al (1999) Major ambulatory surgery with continuous regional anesthesia and a disposable infusion pump. Anesthesiology 91(2):563–565
23. Fries JF, Miller SR, Spitz PW et al (1989) Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. Gastroenterology 96:647–655
24. Rawal N, Allvin R, Amilon A et al (2001) Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol and paracetamol. Anesth Analg 92:347–351
25. Ilfeld BM, Morey TE, Kayser Enneking F (2002) Continuous infraclavicular brachial plexus block for postoperative pain control at home. Anesthesiology 96:1297–1304
26. Chelly JE, Greger J, Al Samsam T et al (2001) Reduction of operating and recovery room times and overnight hospital stays with interscalene blocks as sole anesthetic tecnique for rotator cuff surgery. Minerva Anestesiol 67:613–619
27. Macaire P, Gaertner E, Capdevila X (2001) Continuous post-operative regional analgesia at home. Minerva Anestesiol 67:109–116
28. Pavlin DJ, Rapp SE, Polissnar NL et al (1998) Factors affecting discharge time in adult outpatients. Anesth Analg 87:816–826
29. Jankowski CJ, Horlocker TT, Rock MJ et al (1998) Femoral 3-in-1 nerve block decreases recovery room time and charges and time to hospital discharge after outpatient knee arthtroscopy. Reg Anesth Pain Med 23:S60
30. Rawal N, Axelsson K, Hylander J et al (1998) Postoperative patient-controlled local anesthetic administration at home. Anesth Analg 86:86–89
31. Mehrkens HH, Geiger PK (1998) Continuous brachial plexus blockade via the vertical infraclavicular approach. Anaesthesia 53(S2):19–20
32. Jankovic D, Wells C, Borghi B (2002) Anestesia regionale (Ed italiana). Masson, Milano, pp 316–320
33. Casati A, Chelly JE, Fanelli G et al (2001) Blocchi periferici per l'arto inferiore: il plesso lombare. Minerva Anestesiol 67:98–102
34. McClure JH (1996) Ropivacaine. Br J Anaesth 76:300–307
35. Mak PH, Tsui SL, Ip WY et al (2000) Brachial plexus infusion of ropivacaine with patient-controlled supplementation. Can J Anaesth 47:903–906

36. Borgeat A, Kalberer F, Jacob H et al (2001) Patient controlled interscalene analgesia with ropivacaine 0.2% versus bupivacaine 0.15% after major open shoulder surgery: the effects on hand motor function. Anesth Analg 92:218–223
37. Borgeat A, Perschak H, Bird P et al (2000) Patient-controlled interscalene analgesia with ropivacaine 0.2% versus patient-controlled intravenous analgesia after major shoulder surgery: effects on diaphragmatic and respiratory function. Anesthesiology 92:102–108

CRITICAL BLEEDING AND TRANSFUSION

Chapter 62

Severe bleeding in critical care

M. Girardis, S. Busani, M. Marietta

Severe bleeding and haemorrhagic shock are frequent and challenging conditions in anaesthesiologic and intensive-care clinical practice. Major haemorrhage may occur in trauma patients, during and after surgery, and in other variety of critical pathologies, such as oesophageal bleeding in cirrhotic patients and intracranial haemorrhage. Uncontrolled haemorrhage is the most common cause of death in trauma patients and accounts for at least 60% of deaths in patients after hospital admission [1]. Mortality after an episode of intracerebral haemorrhage is very high (20–40%), and 80% of the survivors suffer severe neurological impairment [2]. Perioperative bleeding depends on the extent and complexity of surgical procedures and on the coagulation status of the patient. However, unexpected and massive bleeding may complicate any surgical procedure, leading to a significant increase in perioperative mortality from < 1% up to 20% [3]. Despite the significant improvement in surgical technique, major surgery for liver diseases, such as partial hepatectomy and orthotopic liver transplantation (OLT), is still associated with significant blood losses due to both technical factors and poor haemostasis of cirrhotic patients. The degree of blood losses during OLT has important effects on postoperative infection, graft survival, intensive-care stay, and mortality [4]. Excessive bleeding is a crucial problem also in cardiac surgery: massive blood loss is associated with an eight-fold increase in the odds of death [5], and up to 5% of patients need a second operation to control severe post-operative bleeding [6].

The most common cause of intraoperative and postoperative bleeding is inadequate surgical haemostasis, and more than 70% of episodes are due to technique problems. Moreover, surgical technique per se affects the rate of postoperative bleeding [7, 8]. Nevertheless, surgery exposes patient to haemostatic stress, testing, in extreme conditions, the limits of the haemostatic system in maintaining a delicate balance between bleeding and clotting (thrombosis). Therefore, in patients with inherited or acquired defects in coagulation processes (e.g. haemophilia, liver dysfunction, anticoagulant therapy), severe bleeding can occur also following minimal procedure with faultless surgical technique. Whatever the cause, massive bleeding and its therapeutic correction lead to an unavoidable secondary coagulopathy caused by consumption and dilution of clotting factors, acidosis, and hypothermia [3]. Of these risk factors, hypothermia is without doubt the most important as it causes a depression in platelet activity, hinders the reactions of clotting enzymes, and impairs the fibrinolytic balance. At temperatures lower than 34°C, the dysfunction of haemostasis is equivalent to that observed in haemophilia B patients

with a 33% deficiency of factor IX activity. In addition, low body temperature impairs the activity of fibrinolysis inhibitors with a consequent quicker clot lysis [3, 9]. Dilutional thrombocytopoenia is also very common in patients with severe bleeding, particularly in those receiving transfusion volumes in excess with a platelet count decreased by about 60% after replacement of one blood volume [2]. The factors described above induce a vicious cycle that amplifies the coagulation dysfunction and may lead to uncontrollable bleeding.

Surgical bleeding: conventional therapy and new options

The initial resuscitation of a surgical patient with severe haemorrhage is based on surgical control of the bleeding source, and on the rapid replacement of blood losses by means of fluid and blood derivatives infusion. Each effort should be aimed at stopping the ongoing bleeding. Standard treatment includes surgical ligation of the vessels responsible for the bleeding, packing the bleeding area, and, as last resort, radiological intervention on vessels leading to the bleeding area. Medical therapy with fluid and blood derivatives usually plays a role in supportive therapy, but it can be also decisive in patients with primary (e.g. haemophilia) or secondary (e.g. oral anticoagulant) coagulopathy [2, 10].

During the last several years, there have been many advances in our knowledge of haemostatic processes, and different innovative therapies have been proposed. Nevertheless, the medical therapy of a bleeding patient is still largely empirical. One of the major limitations is the lack of real-time, accurate, and bed-side testing to evaluate the various haemostatic pathways and processes. In this field, thromboelastography appears to be a very promising technique, since it allows real-time and bedside analysis of clot formation and lysis [10]. However, the widespread use of this technique is scarce and it is instead restricted to specific settings, such as cardiac and transplantation surgery. Therefore, in clinical practice therapeutic decisions are often based on nonspecific physiological parameters and on the experience of the operative team. In addition, the effectiveness of many haemostatic drugs has been tested only in specific subgroups of patients and thus cannot be simply applied to all bleeding settings. For instance, tranexamic acid and ε-aminocaproic acid, two antifibrinolytic drugs, are very effective in the control of bleeding in patients with congenital coagulopathies who have undergone dental extraction or with oesophageal varices haemorrhage, and their use in cardiac surgery reduces the requirement of blood transfusion and the incidence of re-thoracotomy for postoperative bleeding [11, 12]. However, the efficacy of these two drugs is very modest when used in other types of surgical bleeding. Similarly, desmopressin, which exerts its effect by increasing plasma levels of factor VII and von Willebrand factor, has been successfully used to prevent and reduce surgical bleeding in patients with acquired or congenital defects of haemostasis (e.g. haemophilia A, uraemia, cirrhosis) [13, 14]. Nevertheless, its effect is poor in bleeding patients with normal haemostasis. To sum up, many haemostatic drugs still lack documented efficacy and they should never be used as a substitute for surgical control of bleeding.

Surgical therapy is sometimes not immediately available (i.e. trauma in a secondary hospital) or it is unable to stop the bleeding. At the same time, replacement and medical therapy are often incapable of maintaining adequate blood volume, and a large number of infusions can lead to secondary coagulation disorders and pulmonary oedema, both of which strongly influence patient outcome [10]. In this setting, recombinant activated factor VII (rFVIIa) appears to be a promising adjunctive therapy to manage life-threatening bleeding also in non-haemophiliac patients [15, 16]. Based on current insight into the function of blood coagulation, the pro-coagulative action of rFVIIa is due to: (a) the generation of thrombin after binding with tissue factor (TF), exposed at the site of tissue injury or vascular lesion; (b) the generation of a thrombin burst after binding on the surface of activated platelets; this mechanism depends only in part on TF exposure; (c) inhibition of fibrinolysis by activation of thrombin-activated fibrinolysis inhibitor [17]. These mechanisms explain the localised and time-limited effects of rFVIIa and, thereby, its low thrombotic potential.

rFVIIa has been available for the management of bleeding in haemophilia patients with inhibitors for many years. However, a growing body of literature suggests that rFVIIa can also be regarded as a potent pro-haemostatic agent either in patients with various primitive coagulation disorders or in patients with otherwise normal haemostasis but who experienced severe bleeding due to trauma and surgery [17]. In this latter class of patients, initial experiences with rFVIIa appear to be very encouraging. Apart from its use as a preventive strategy to reduce intra-operative bleeding, rFVIIa provided effective control of bleeding with a significant decrease in transfusion requirement when used in surgical patients with excessive and life-threatening haemorrhage, and in whom all other therapeutic measures had failed [15–17]. In two surveys, carried out in the UK and Australia, on the use of rFVIIa as a rescue therapy for severe haemorrhage [18, 19], 65% of patients received rFVIIa after a surgical procedure, with a decrease or cessation of ongoing bleeding in about 80% of cases. A recent retrospective single-centre analysis on ten patients with excessive bleeding showed that rFVIIa therapy reduced the transfusion requirement but did not increase survival rate compared to patients who had not received rFVIIa [20]. However, in the treated patients rFVIIa was used as a 'last ditch' response to control bleeding, i.e. in patients who were transfused before rFVIIa administration. It is obvious that, under such a condition, patient survival depends on the extent of organ failure induced by blood loss and transfusions rather than on the late control of bleeding. Unfortunately, there are no randomised clinical trials on the use of rFVIIa in such patients, which is not surprising since massive blood loss is not a day to day occurrence.

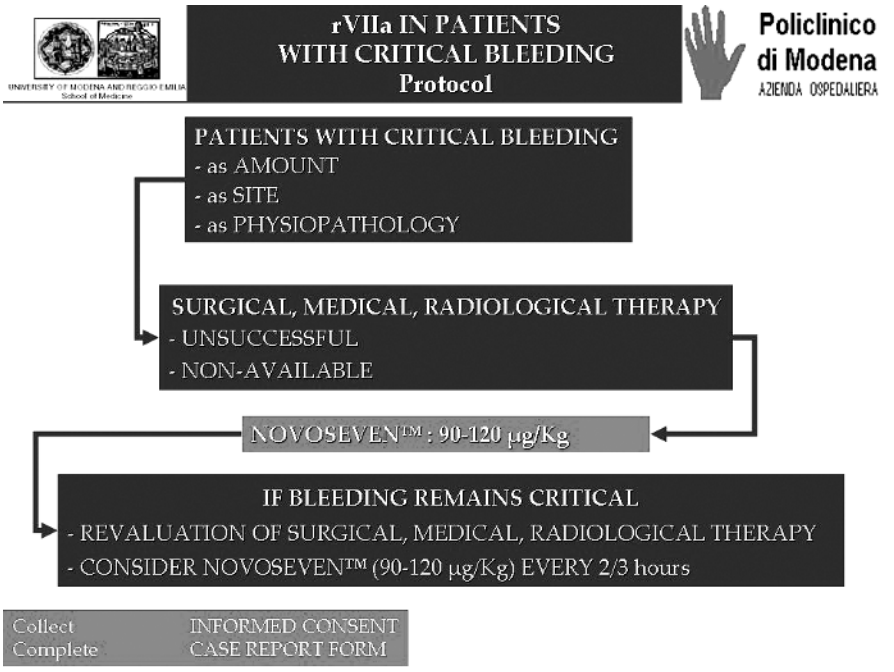
A particular type of critical bleeding occurs in patients with intracerebral haemorrhage (ICH). It was recently reported that ICH expands over time because of persistent bleeding from the primary source and mechanical disruption of the surrounding vessels [21]. The volume of the haematoma is a critical determinant of mortality and functional outcome; thus, prevention of haematoma enlargement by ultrahaemostatic therapy should be a primary goal in the management of ICH patients [22]. To this aim, rFVIIa would seem to be a very attractive option, based

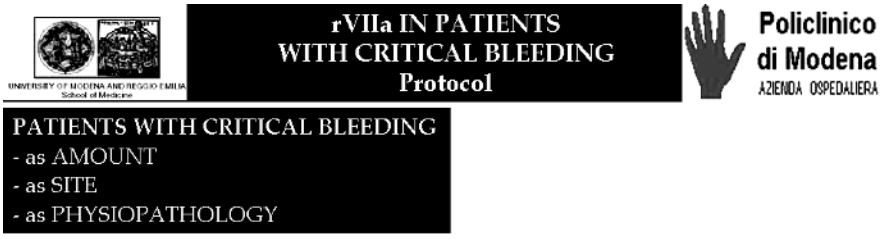
on its rapid pan-haemostatic effect; this hypothesis was confirmed in a recent randomised trial [23]. The use of rFVIIa within 4 h after the onset of ICH limited spreading of the haematoma and decreased mortality or severe disability from 69% to 53% of patients. A small increase (from 2% to 7%) in the number of adverse thromboembolic events (i.e. myocardial ischaemia and cerebral infarction) was observed in patients treated with rFVIIa, but the overall frequency of fatal or serious adverse events did not differ from that of placebo. Therefore, rFVIIa can be considered as a first-line therapy to improve survival and functional outcome in patients with ICH.

rFVIIa in life-threatening bleeding: personal experience

In our institution the use of rFVIIa in non-haemophilic patients with life-threatening bleeding has been guided by an internal protocol since September 2003. The protocol was established by a multidisciplinary group that included specialists involved in the management of critical bleeding, and it is aimed at providing clinicians with a useful tool for the treatment of such difficult patients (Fig. 1a, b). In accordance with this protocol, between October 2003 and June 2005, 22 patients received rFVIIa for severe uncontrolled bleeding: ten patients in the perioperative period, four after trauma, three with ICH, and five with miscellaneous causes of bleeding. A pre-existing coagulopathy was present in nine patients: six with severe liver disease, two with anticoagulant therapy and two with an acquired thrombocytopoenia. A single dose of 90 mg rFVIIa/kg was used in 15 patients, two doses in four patients and three doses in three patients. The mean time period between subsequent administrations was 4 h (2–12 h). Seventeen patients (77%) achieved complete or partial control of bleeding after rFVIIa; among these patients the survival rate at ICU discharge was 88%. In five patients (23%) rFVIIa was ineffective: two of the patients had massive bleeding during OTL, one patient had uncontrolled haemorrhage during vascular surgery, and two patients were treated after thoracic trauma. None of these patients survived and the cause of death was haemorrhagic shock. Nonetheless, as reported in all clinical experiences published thus far, the transfusion requirements in our patients were significantly reduced after rFVIIa administration. The number of transfusions of red packed cells was reduced from a mean of 2.5 U/h before to 1.7 U/h after drug administration, and the need for fresh frozen plasma decreased from 450 ml/h to 350 ml/h after rFVIIa. Clinical, instrumental, and post-mortem examinations did not reveal any sign of vascular thrombosis in the treated patients.

In spite of growing evidence that rFVIIa may have an important role in the management of severe bleeding, there are still a few unresolved issues regarding its use in surgical patients. Neither the optimal dose of rFVIIa nor how often the dose should be repeated has been precisely defined. A wide range of doses have been used in trauma and surgical patients, but for the most part clinicians administer doses up to 90 μg/kg, as suggested for haemophilia patients. The half-life of rFVIIa is about 2 h; thus, it may be reasonable to repeat rFVIIa administration





as AMOUNT

- INTRAOPERATIVE > 500-1000 ml/h for 1 h
- POSTOPERATIVE > 200-500 ml/h for 2 h
- BLUNT/OTHER > 2 gr Hb/h for 1 h

as SITE

- INTRACEREBRAL
within 3 hours from bleeding-re-bleeding
ICH score : 2-3
- INTRAHEPATIC
progressive increase by echo evaluation

as PHYSIOPATHOLOGY

inherited/acquired platelet dysfunction

JC Hemphill et al.
Stroke 2001, 32: 891-897

	Score		
GCS			
3-4	2		
5-12	1	**Score**	**Mort 30d.**
13-15	0		
Volume		0	0%
> 30 ml	1	1	15%
< 30 ml	0	2	60%
Site		3	75%
Sovratent	0	4	99%
Sottotent	1	5	100%
IVH			
Yes	1		
No	0		
Age			
> 80 years	1		
< 80 years	0		

Fig. 1a-b.

every 2–3 h if haemorrhage persists. However, so far, only few studies have reported the need for multiple doses of rFVIIa in surgical or trauma patients. While rFVIIa treatment of patients with disseminated intravascular coagulation (DIC) is controversial, recent reports described its successful use in several patients with DIC [24, 25]. Therefore, the contraindication of rFVIIa in patients with DIC should be re-considered. Another unanswered question regards the optimal timing of rFVIIa administration. From a theoretical point of view, the earlier the control of bleeding, the lower the complications related to haemorrhage, such as secondary coagulopathy, acidosis, and hypothermia. In this respect, some authors sustain that rFVIIa should be given as early as possible [15, 17]. Unfortunately, the lack of a safety profile in non-haemophilia patients hinders the use of rFVIIa as a first step drug in the management of severe surgical bleeding. Apart from its use in treating intracerebral haemorrhage, rFVIIa should currently be considered as a second-line therapy, to be used when conventional therapies are not available or are unable to control ongoing bleeding.

References

1. Lynn M, Jeroukhimov I, Klein Y, Martinowitz U (2002) Updates in the management of severe coagulopathy in trauma patients. Intensive Care Med 28(Suppl 2):241–247
2. Qureshi AI, Thurim S, Broderick JP et al (2001) Spontaneous intracerebral hemorrhage. N Engl J Med 344:1450–1460
3. Lawson JH, Murphy MP (2004) Challenges for providing effective hemostasis in surgery and trauma. Semin Hematol 41(Suppl 1):55–64
4. Mor E, Jennings L, Gonwa TA et al (1993) The impact of operative bleeding on outcome in transplantation of the liver. Surg Gynecol Obstet 176:219–227
5. Karkouti K, Wijeysundera DN, Yau TM et al (2004) The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 44:1453–1462
6. Rady MY, Ryan T, Starr NJ (1998) Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. Crit Care Med 26:225–235
7. Miller E, Paull DE, Morrissey K et al (1988) Scalpel versus electrocautery in modified radical mastectomy. Am Surg 54:284–286
8. National Prospective Tonsillectomy Audit (2004) Tonsillectomy technique as a risk factor for postoperative haemorrhage. Lancet 364:697–702
9. Eddy VA, Morris JA, Cullinane DC (2000) Hypothermia, coagulopathy, acidosis. Surg Clin North Am 80:845–854
10. Koh MB, Hunt BJ (2003) The management of perioperative bleeding. Blood Rev 17:179–185
11. Henry DA, Moxey AJ, Carless PA et al (2001) Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 1:CD001886
12. Casati V, Sandrelli L, Speziali G et al (2002) Hemostatic effects of tranexamic acid in elective thoracic aortic surgery: a prospective, randomized, double-blind, placebo-controlled study. J Thorac Cardiovasc Surg 123:1084–1091
13. Carless PA, Henry DA, Moxey AJ et al (2004) Desmopressin for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 1:CD001884
14. Levi M, Cromheecke ME, de Jonge E et al (1999) Pharmacological strategies to decrease

excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 354 :1940–1947
15. Grounds M (2003) Recombinant factor VIIa and its use in severe bleeding in surgery and trauma: a review. Blood Rev 17:S11–S21
16. Ghorashian S, Beverly JH (2004) Off license use of recombinant activated factor VII. Blood Rev 18:245–259
17. Levi M, Peters M, Büller HR (2005) Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: A systematic review. Crit Care Med 33:883–890
18. O'Connell NM, Perry DJ, Hodgson AJ et al (2003) Recombinant FVIIa in the management of uncontrolled hemorrhage. Transfusion 43:1649–1651
19. Eikelboom JW, Bird R, Blythe D et al (2003) Recombinant activated factor VII for the treatment of life-threatening haemorrhage. Blood Coagul Fibrinolysis 14:713–717
20. Clark AD, Gordon WC, Walker ID, Tait RC (2004) 'Last-ditch' use of recombinant factor VIIa in patients with massive haemorrhage is ineffective. Vox Sang 86:120–124
21. Brott T, Broderick J, Kothari R et al (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 28:1–5
22. Mayer SA (2003) Ultra-early hemostatic therapy for intracerebral hemorrhage. Stroke 32:224–229
23. Mayer SA, Brun NC, Begtrup K et al (2005) Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 352:777–785
24. Kenet G, Walden R, Eldad A et al (1999) Treatment of traumatic bleeding with recombinant factor VIIa. Lancet 354:1879
25. Tobias JD, Berkenbosch JW, Muruve NA et al (2002) Correction of a coagulopathy using recombinant factor VII before removal of an intra-aortic balloon pump. J Cardiothorac Vasc Anesth 16:612–614

Chapter 63

Transfusion triggers in surgery

P. Van der Linden

The adequacy of any haemoglobin concentration in a given clinical situation depends on whether a sufficient amount of oxygen is carried to the tissues to meet their metabolic requirements. Therefore, the decision to transfuse a given patient cannot be based solely on the haemoglobin level. Rather, rigid adherence to an arbitrarily pre-defined transfusion threshold will result in the over-transfusion of some patients, but also in the under-transfusion of others [1]. A better knowledge of the physiologic responses that develop during acute isovolaemic anaemia and of the clinical factors that can limit the ability of the organism to maintain adequate tissue oxygenation in these situations will allow the clinician to better define the transfusion trigger for each patient in the pre- and post-operative periods.

Physiologic response to acute anaemia

The maintenance of tissue oxygen delivery during an acute reduction in red blood cell concentration depends on both an increase in cardiac output and an increase in blood oxygen extraction [2]. These two mechanisms require 'normovolaemic conditions,' i.e. the preservation of an ample circulating blood volume.

The cardiac output response

Cardiac output increases during isovolaemic anaemia, mainly through an increase in stroke volume [2]. Heart rate may also contribute, but only in awake patients [3]. The rise in stroke volume appears closely related to the decrease in haematocrit [4], with the reduced blood viscosity resulting in an augmented venous return and a decreased total peripheral vascular resistance. The latter results essentially from the reduced blood viscosity but might also be related to a decreased scavenging capacity of blood to inactivate nitric oxide [5]. These changes in cardiac loading conditions lead to improved myocardial function, while direct enhancement of myocardial contractility has also been described [6]. Finally, the adequate cardiac output response to isovolaemic anaemia also depends on the presence of an intact autonomic nervous system and α-adrenergic tone [2, 7].

The oxygen extraction response

The second compensatory mechanism, allowing blood oxygen extraction to increase, aims at a better matching of oxygen delivery to oxygen demand at the tissue level. This mechanism entails physiologic alterations occurring at both the systemic and the microcirculatory level.

At the systemic level, a better matching of oxygen delivery to tissue oxygen demand requires a redistribution of blood flow to areas of high demand, such as the brain and the heart, such that the oxygen held in the venous blood is utilised more effectively [8]. This exceptional increase in blood flow to the brain and the heart occurs because these organs are 'flow-dependent' tissues, in contrast to others, e.g. the splanchnic area, the kidneys, and the skin, which are 'flow-independent.' 'Flow-dependent' organs extract most of the oxygen available, even under basal conditions, and cannot increase oxygen extraction further to meet their metabolic requirements.

Coronary blood flow increases even more than cerebral blood flow as myocardial oxygen demand increases during anaemia. When haematocrit is reduced to 10–12%, myocardial oxygen consumption more than doubles [9]. Under these conditions, coronary vasodilatation is near maximal. Below a haematocrit of 10%, coronary blood flow can no longer match the increased myocardial oxygen demand, and ischaemia develops, resulting in cardiac failure. This is in accordance with experimental data showing a decrease in systemic oxygen uptake at haematocrit values close to 10% [10].

Excess of perfusion of the brain and heart occurs at the expense of 'flow-independent' organs. Relative vasoconstriction occurs in some tissues so that renal, mesenteric, and hepatic blood flows are proportionately less than the total cardiac output response. This regional blood flow redistribution among organs is partly due to α-adrenergic stimulation but is unaltered in the presence of β-adrenergic blockade [11].

At the microcirculatory level, several physiologic adjustments contribute markedly to provide a more efficient utilisation of the remaining oxygen content of the blood [12]. The main effect of haemodilution on the microcirculation is an increase in red blood cell velocity, which allows the red blood cell flux in the capillaries to be maintained up to a systemic haematocrit of 20%. This increased flow velocity stimulates arterial vasomotion and provides a more homogeneous distribution of the red cells within the capillary network [12]. By shortening the transit time, the increase in red blood cell velocity may also reduce the loss of oxygen before it reaches the capillaries, and thereby improve oxygen transfer to the tissues.

An increase in the ratio of the microcirculatory to systemic haematocrit has also been demonstrated [13]. This phenomenon has been related to the complex interactions between axially migrating red blood cells (Fahraeus effect) and the heterogeneous nature of the microcirculatory network.

Finally, changes in the dynamics of the haemoglobin molecule could result in more efficient tissue oxygen delivery in anaemia. Indeed, a right shift of the oxyhaemoglobin dissociation curve, which enhances oxygen release at constant

oxygen tension, begins at haemoglobin level of 9 g/dl and becomes more prominent when levels are below 6.5 g/dl [14]. This phenomenon, resulting from increased synthesis of 2,3 diphosphoglycerate, appears with declining haemoglobin after 12–36 h.

Tolerance and clinical limits of anaemia

'Critical' level of anaemia

Maintenance of adequate tissue oxygenation during acute isovolaemic anaemia depends on the physiologic adjustments described above. Several studies have demonstrated that both the cardiac output response and the oxygen extraction response are involved already in the early stages of isovolaemic anaemia [15]. These responses allow the maintenance of tissue oxygen balance until the haematocrit falls to about 12–10%. Below this 'critical' value, oxygen delivery can no longer match tissue oxygen demand and cellular hypoxia will develop. Critical haemoglobin value could therefore be defined as the value of haemoglobin below which oxygen uptake becomes delivery-dependent.

Experimental studies in animals have demonstrated this critical haemoglobin value to be around 4.0 g/dl [16]. Corresponding values are obviously difficult to obtain in humans. Weiskopf et al. [17] showed, in healthy conscious volunteers, that tissue oxygenation remains adequate during severe isovolaemic haemodilution up to an haemoglobin value of 5 g/dl. Carson et al. [18] observed that the risk of death is low in patients with postoperative haemoglobin concentration between 7 and 8 g/dl. However, as postoperative haemoglobin value falls, the risk of mortality and/or morbidity rises and becomes extremely high below 5–6 g/dl. Van Woerkens et al. [19] studied a Jehovah's Witness patient who died from extreme haemodilution and observed a critical haemoglobin value of 4 g/dl. Tolerance to severe acute isovolaemic haemodilution not only depends on the integrity of the compensatory mechanisms but also on the level of tissue oxygen demand. For a given cardiac output and oxygen extraction response, any increase in tissue oxygen demand will require a higher haemoglobin level and therefore will reduce the patient's tolerance of haemodilution.

Factors associated with decreased tolerance of isovolaemic anaemia

Any factor altering either the cardiac output response or (and) the oxygen extraction response will also reduce the patient's tolerance of acute anaemia (Table 1). Maintenance of adequate volume replacement is of paramount importance. The cardiac output response to haemodilution may be reduced in the presence of altered myocardial contractility. Acute administration of negative inotropic agents, such as β-blocking agents, results in a decreased cardiac output response during haemodilution [20].

Table 1. Factors altering the physiologic response to isovolaemic anaemia

Factors associated with decreased cardiac output response
- Hypovolaemia
- Cardiac failure, negative inotropic agents (i.e. β-blocking agents)
- Coronary and valvular diseases
Factors associated with decreased O_2 extraction response
- Sepsis
- Acute respiratory distress syndrome (ARDS)
- Systemic inflammatory response syndrome (SIRS)
- Ischaemia-reperfusion syndrome
- Vasodilating drugs
Factors associated with altered gas exchanges
- ARDS
- Chronic obstructive pulmonary disease
Factors associated with increased O_2 consumption
- Fever
- Pain, stress, anxiety
- Sepsis, SIRS
- Hyperventilation syndromes

Coronary artery disease will obviously limit the tolerance of the heart to isovolaemic haemodilution. As myocardial oxygen extraction is already nearly maximal in resting conditions, the maintenance of myocardial oxygen consumption depends essentially on the increase in coronary blood flow. Therefore, the coronary reserve (the ratio between maximal coronary blood flow and resting coronary blood flow) is significantly reduced during haemodilution—especially in coronary artery disease patients, who already have decreased maximal coronary blood flow. The lowest tolerable haematocrit in coronary artery disease patients is not known but experimental data on animals with extrinsically applied coronary stenosis have demonstrated a significant increase in the critical haematocrit level to 17–18% [21]. Even if coronary artery disease patients may tolerate some degree of haemodilution intraoperatively, they will require a higher haematocrit in the early postoperative period in order to meet the increased tissue, and especially cardiac, oxygen demand. Cardiovascular disease patients having a lower preoperative haematocrit have a higher risk of death than non-cardiovascular disease patients with the same preoperative haematocrit [22]. A similar interaction was observed between cardiovascular disease and postoperative haemoglobin level [18].

In patients with no evidence of cardiovascular disease, age alone does not seem to be a major factor in determining tolerance to anaemia, although compensatory mechanisms to an acute reduction in blood oxygen content might be less efficient [23].

Respiratory insufficiency will also limit the physiologic adjustment to acute anaemia. On the one hand, altered arterial oxygenation participates in the decreased oxygen-carrying capacities of the blood; on the other hand, haemodilution may have a deleterious effect on pulmonary gas exchange, possibly through attenuation of hypoxic pulmonary vasoconstriction [24]. Although the optimal haematocrit during respiratory insufficiency is not known, patients with chronic respiratory failure develop polycythaemia in an attempt to maintain adequate tissue oxygen

delivery. Szegedi et al. [25] recently observed that, during one-lung ventilation, mild haemodilution impairs gas exchange in patients with chronic obstructive pulmonary disease, but not in patients with normal lung function.

In critical illness, most of the compensatory mechanisms for anaemia are reduced by the presence of hypovolaemia, hypoxaemia, depressed myocardial function, and/or altered tissue oxygen extraction capabilities. In addition, tissue oxygen demand is often increased in these situations, due to fever, pain, stress, and increased respiratory work. It is therefore not surprising that anaemia is associated with an increased risk of morbidity and mortality in critically ill patients, especially in those with cardiovascular disease. However, there is no evidence in the literature that the use of a more liberal transfusion strategy in this 'at risk' population is associated with a better outcome [26].

Anaesthesia (or sedation) and ventilatory support have been used in severely anaemic patients in an attempt to reduce their oxygen consumption. However, anaesthesia can alter the physiologic adjustments to isovolaemic haemodilution at different levels (Table 2). Because most anaesthetic agents depress in a dose-dependent manner the cardiovascular and the autonomic nervous system, it could be hypothesised that the most striking effect of anaesthesia would be a decreased cardiac output response to isovolaemic haemodilution. This hypothesis has been confirmed recently (Fig. 1) [3]. As anaesthesia decreases the cardiac output response to isovolaemic haemodilution, but could also decrease tissue oxygen demand, the effects of anaesthesia on patient's tolerance to severe anaemia ('critical' haemoglobin level) will depend on the balance between these two effects. Recent experimental data demonstrated that increasing the depth of anaesthesia is associated with a greater depressant effect on the cardiac output response than the reduction of the metabolic demand, resulting in a decreased tolerance to acute isovolaemic anaemia [27].

Table 2. Possible effects of anaesthetic agents on the physiological response to haemodilution

Effects on the cardiac output response
- Alteration in cardiac loading conditions
- Negative inotropic properties
- Depressed autonomic nervous system activity
Effects on the O_2 extraction response
- Vasodilation
- Depressed autonomic nervous system activity
Effects on gas exchange
- Decreased functional residual capacity
Effects on tissue oxygen demand
- Relief of pain, stress, anxiety
- Decreased myocardial oxygen demand (negative inotropic and chronotropic effect)
- Decreased muscular activity

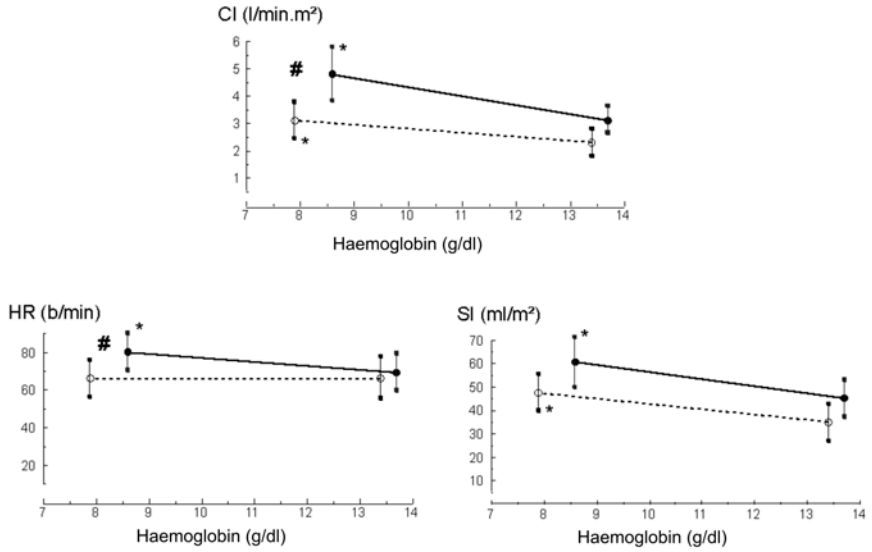


Fig. 1. Effects of anaesthesia on cardiac output response to isovolaemic haemodilution. *Closed circles, plain lines* Awake patients (n = 20), *open circles, dotted lines* anaesthetised patients (n = 20);* ~0.01 vs baseline; # significant different response to acute normovolaemic haemodilution between groups. (Adapted from [3])

The transfusion trigger

The adequacy of any haemoglobin concentration in a given clinical situation depends on whether a sufficient amount of oxygen is carried to the tissues to meet their oxygen requirements. Clinical signs of inadequate tissue oxygenation during anaemia (e.g. tachycardia, postural hypotension, dizziness) are very sensitive, but non-specific. Moreover, they are usually absent in sedated or anaesthetised patients. In critically ill patients, the mixed venous oxygen saturation (SvO_2) is frequently used to detect the development of an imbalance between oxygen supply and uptake. In a Jehovah's Witness patient dying from extreme haemodilution, the critical haemoglobin level was reached at a SvO_2 value of 56% and an oxygen extraction ratio of 44% [19]. Several clinical observations have led to the suggestion that SvO_2 (or the oxygen extraction ratio) might be a reliable physiologic guide to transfusion [28, 29].

Only a few well-conducted studies have evaluated the efficacy of transfusion strategies based on the haemoglobin level. Carson et al. [30] recently reviewed the ten randomised trials comparing the effects of a 'liberal' vs 'restrictive' transfusion strategy, based on a specified haemoglobin (or haematocrit) concentration, on short-term outcome ($n = 1780$ patients). Application of a restrictive strategy significantly reduced the likelihood of a patient requiring transfusion and the number of blood units transfused, without affecting the patient's outcome. It must be emphasised, however, that none of theses studies evaluated very anaemic patients (haemoglobin level < 7.0 g/dl). Even in patients with acute coronary syndrome, the application of a more 'liberal' transfusion strategy remains controversial [31–33]. The major problem with studies assessing the effectiveness of different transfusion strategies is that they also evaluate the efficacy of red blood cell transfusion. Most of the studies evaluating the efficacy of transfusion strategies were carried out before the implementation of universal leukoreduction, which by itself might have an impact on the mortality and morbidity associated with blood transfusion [34]. The real efficacy of allogeneic red blood cells older than several days to improve oxygen delivery at the tissue level remains discussed [35, 36].

In view of the current literature, it is unlikely that any level of haemoglobin can be used as a universal threshold for transfusion. The decision to transfuse an individual patient will depend on medical judgement taking into account not only the haemoglobin concentration, but also the physical status of the patient (his/her physiological reserve), the clinical conditions (ongoing blood loss, sepsis, sedation, etc.), and the available monitoring.

Conclusions

During anaemia, the acute decrease in blood oxygen-carrying capacities elicits physiologic adjustments, occurring at both the systemic and the microcirculatory levels, which result in an increased cardiac output and an increased tissue oxygen extraction. These are very efficient as they allow the maintenance of tissue oxygen delivery up to a systemic haematocrit of 10–15% in resting conditions. In pathophysiologic situations, tolerance to acute anaemia will depend on the ability of the organism to recruit each mechanism, and on the level of tissue oxygen demand. In any case, maintenance of adequate circulating blood volume is of paramount importance. In the perioperative setting, SvO_2, normally used to detect the development of an imbalance between oxygen supply and uptake, might be a reliable physiologic guide to transfusion. The decision to transfuse a given patient should not be based on the haemoglobin level only.

References

1. Goodnough LT, Brecher ME, Kanter MH et al (1999) Transfusion medicine. Blood transfusion. N Engl J Med 340:438–447
2. Chapler CK, Cain CM (1986) The physiologic reserve in oxygen carrying capacity: studies in experimental haemodilution. Can J Physiol Pharmacol 64:7–12
3. Ickx B, Rigolet M, Van der Linden P (2000) Cardiovascular and metabolic response to acute normovolemic anemia: effects of anesthesia. Anesthesiology 93:1011–1016
4. Licker M, Ellenberger C, Sierra J et al (2005) Cardiovascular response to acute normovolemic hemodilution in patients with coronary artery diseases: assessment with transesophageal echocardiography. Crit Care Med 33:591–597
5. Doss DN, Estafanous FG, Ferrario CM et al (1995) Mechanism of systemic vasodilation during normovolemic hemodilution. Anesth Analg 81:30–34
6. Habler OP, Kleen MS, Podtschaske AH et al (1996) The effect of acute normovolemic hemodilution (ANH) on myocardial contractility in anesthetized dogs. Anesth Analg 83:451–458
7. Glick G, Plauth WH, Braunwald EB (1964) Role of the autonomic nervous system in the circulatory response to acutely induced anemia in unanesthetized dogs. J Clin Invest 43:2112–2124
8. Tuman KJ (1990) Tissue oxygen delivery: the physiology of anemia. Anesthesiol Clin North Am 8:451–469
9. Von Restorff W, Hofling B, Holtz J et al (1975) Effect of increased blood fluidity through hemodilution on coronary circulation at rest and during exercise in dogs. Pfuegers Arch 357:15–24
10. Cain SM (1977) Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 42:228–234
11. Crystal GJ, Ruiz JR, Rooney MW et al (1988) Regional hemodynamics and oxygen supply during isovolemic hemodilution in the absence and the presence of high-grade beta-adrenergic blockade. J Cardiothorac Vasc Anesth 2:772–780
12. Messmer K (1991) Blood rheology factors and capillary blood flow. In: Gutierrez G, Vincent J-L (eds) Tissue oxygen utilization. Springer, Berlin pp 103–113
13. Lindbom L, Mirhashemi S, Intaglietta M et al (1988) Increase in capillary blood flow relative to hematocrit in rabbit skeletal muscle following acute normovolemic anemia. Acta Physiol Scand 134:503–512
14. Sibbald WJ, Doig GS, Morisaki H (1995) Role of RBC transfusion therapy in sepsis. In: Sibbald WJ, Vincent J-L (eds) Clinical trials for the treatment of sepsis. Springer, Berlin, pp191–206
15. Spahn DR, Leone BJ, Reves JG et al (1994) Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of nonoxygen-carrying and oxygen-carrying solutions. Anesth Analg 78:1000–1021
16. Van der Linden P, De Groote F, Mathieu N et al (1998) Critical haemoglobin concentration in anaesthetized dogs: comparison of two plasma substitutes. Br J Anaesth 81:556–562
17. Weiskopf RB, Viele MK, Feiner J et al (1998) Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 279:217–221
18. Carson JL, Noveck H, Berlin JA et al (2002) Mortality and morbidity in patients with very low postoperative hemoglobin level who decline blood transfusion. Transfusion 42:812–818
19. van Woerkens ECSM, Trouwborst A, van Lanschot JJB (1992) Profound hemodilution:

what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human ? Anesth Analg 75:818–821
20. Lieberman JA, Weiskopf RB, Kelley SD et al (2000) Critical oxygen delivery in conscious humans is less than 7.3 ml 02.kg-1.min-1. Anesthesiology 92:407–413
21. Levy PS, Kim SJ, Eckel PK et al (1993) Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. Am J Physiol 265:H340–H349
22. Carson JL, Duff A, Poses RM et al (1996) Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 348:1055–1060
23. Janvier G, Annat G (1995) Are there limits to haemodilution? Ann Fr Anesth Réanim 14(Suppl 1): 9–20
24. Deems S, Bishop MJ, Alberts MK (1995) Effect of anemia on intrapulmonary shunt during atelectasis in rabbits. J Appl Physiol 79:1951–1957
25. Szegedi LL, Van der Linden P, Ducart A et al (2005) The effects of acute isovolemic hemodilution on oxygenation during one-lung ventilation. Anesth Analg 100:15–20
26. Hébert PC, Wells G, Blajchman MA et al (1999) A multicenter randomized controlled clinical trial of transfusion requirements in critical Care. N Engl J Med 40:409–417
27. Van der Linden P, De Hert S, Mathieu N et al (2003) Tolerance to acute isovolemic hemodilution: effect of anesthetic depth. Anesthesiology 99:97–104
28. Fontana JL, Welborn L, Mongan PD et al (1995) Oxygen consumption and cardiovascular function in chidren during profound intraoperative normovolemic hemodilution. Anesth Analg 80:219–225
29. Paone G, Silverman NA (1997) The paradox of on-bypass transfusion thresholds in blood conservation. Circulation (Suppl II):II205–II209
30. Carson JL, Hill S, Carless P et al (2002) Transfusion triggers: a systematic review of the literature. Transfus Med Rev 16:187–199
31. Wu WC, Rathore SS, Wang Y et al (2001) Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 345:1230–1236
32. Rao SV, Jollis JG, Harrington RA et al (2004) Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 292:1555–1562
33. Hébert PC, Yetisir E, Martin C et al (2001) Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med 29:227–234
34. Hébert PC, Fergusson D, Blajchman MA et al (2003) Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 289:1941–1949
35. Marik PE, Sibbald WJ (1993) Effects of stored blood transfusion on oxygen delivery in patients with sepsis. JAMA 269:3024–3029
36. Walsh TS, McArdle F, McLellan SA et al (2004) Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med 32:364–371

TRAUMA AND DISASTER MEDICINE

Chapter 64

Pre-hospital trauma care: controversial aspects

G. Berlot, B. Bacer, S. Rocconi

No one doubts that opening the airways and clearing them from foreign bodies (A = airways), promoting gas exchange (B = breath) and making the blood deliver oxygen to the tissues (C = circulation) represent the fundamental steps in the treatment of trauma patients. Actually, if one translates the ABC priorities into the corresponding procedural steps, it is possible to create a new acronym, namely VIP (ventilation, infusion and pump [or perfuse]). Yet, despite these widespread persuasions, there is not as much agreement upon the ways to achieve these goals. As a matter of fact, the entire (relatively) brief history of critical care has been marked by some hotly debated issues, including the 'crystalloid–colloid controversy', the 'stay and play vs scoop and run' approach to severely injured patients, the computed tomography vs chest x-ray for the diagnosis of pneumothoraces, the optimal levels of positive end-expiratory pressure, etc. Despite the relevance of the debated points and the high scientific ranks of the advocates of the different approaches, no study has definitely demonstrated that one given option is always the best in all circumstances. In other words, an up-to-date reader of the scientific journals dealing with these issues can hardly draw a firm conclusion on the strategy to adopt in his or her daily clinical work.

Securing of the airways

It is worthwhile to recall that the immediate tracheal intubation (TI) of trauma patients has two main goals: namely (a) the prevention and/or treatment of hypoxaemia, which is rather common in the immediate post-traumatic phase and which is considered, along with arterial hypotension, the main factor responsible for secondary brain injury [1, 2]; and (b) the prevention of aspiration in patients unable to protect their airways [3]. Despite these advantages, different authors have demonstrated that patients intubated at the scene of the accident presented a worse prognosis as compared with those who received the TI on their arrival at the emergency department (ED). In a poorly randomised study performed on a paediatric population, Gausche et al. [4] demonstrated that both survival and the neurological outcome were similar in patients who were treated with bag-valve mask (BVM) and in those who were tracheally intubated on the scene; interestingly, TI was successful in only 57% of children in whom it was attempted and several misplacements or mislodgements of the tube occurred in this group. In other

words, in this patient population TI apparently caused more harm than good. In another study [5] comparing major trauma patients treated with BVM or TI performed by emergency medicine technicians (EMT) without the assistance of sedatives and muscle relaxants, a remarkably better outcome was demonstrated in the BVM group. In the TI group, the mortality exceeded 90%. However, it must be remarked that the feasibility of TI without drugs is a strong indicator of a grim prognosis [6], thus making it difficult to conclude positively that TI is harmful by itself. Recently, Di Bartolomeo et al. [7] demonstrated that the outcome of severely head-injured patients was not affected by either the levels of intervention (advanced trauma care performed by experienced anaesthetists involved in the helicopter emergency medical system [HEMS] vs expanded basic life support performed by registered nurses) or the type of transportation to the ED (helicopter vs ground ambulance); the authors attributed this result to the high level of training of the ground ambulance teams who were specifically trained in trauma care. Independently from the relevant role played by highly trained personnel working in the ground ambulances, these results are in sharp contrast with a previous study from the same group in which a remarkably better outcome was demonstrated in patients treated by the HEMS [8]. If these studies clearly indicate that on-the-scene TI could be harmful or ineffective in terms of outcome improvement, other investigators demonstrated exactly the opposite. Winchell et al. [9] reported a better outcome in tracheally intubated patients with impending or established apnoea associated with a depressed level of consciousness as compared with patients treated with BVM only (the mortality rates were 26.0 and 36.2%, respectively). Interestingly again, the rate of successful TI was only slightly higher than 50%, and this could have contributed to the higher mortality in patients in whom TI could not be performed, who were treated with the BVM. Another study demonstrated that the introduction of physicians specifically trained in critical-care medicine in helicopter-transported teams previously manned by paramedics was associated with both an increased rate of on-the-scene TI (51 vs 10%) and an overall improvement of the outcomes [10]. As stated above, it is difficult to draw definite conclusions from these conflicting studies, yet some considerations can be made.

First, as underlined by a recent statement of the Eastern Association for the Surgery of Trauma [11], the maintenance of oxygenation and the prevention of asphyxia are the cornerstones of the treatment of trauma victims unable to breath spontaneously and/or at risk of aspiration. Although different devices have been developed and used to this aim, including laryngeal mask airways, Combitube, etc., TI remains the gold standard against which all these approaches must be challenged. However, its use is not risk-free and requires both an appropriate level of manual skill and the safe use of drugs whose actions and side-effects must be known and recognised. As it appears from the above-quoted studies, in trauma patients TI appears safe and cost-effective in terms of outcomes, provided that (a) it is performed by adequately trained professionals, able either to secure the airways in a short time in the vast majority if not all patients; and (b) the same individuals must be able to adopt alternative measures when TI is unfeasible. These operative capabilities apply to physicians particularly trained in the management of the

airways. Second, a safe and rapid TI may not be sufficient to prevent death or disabling neurological consequences: other conditions exist in trauma patients, which may contribute to these poor outcomes. Indeed, in a study in 1994, Stocchetti et al. [12] demonstrated that roughly 10% of in-hospital early post-traumatic deaths were clearly preventable and that the underlying causes were hypoxaemia or hypotension occurring alone or in association. It must be recalled that both conditions may be caused by pneumothorax (PNX), whose deleterious effects can be precipitated by the mechanical ventilation used after the TI. Then, it follows that, although the appropriate management of the airway remains an absolute priority, this is only the beginning and the on-the-scene subsequent care of trauma patients must be performed by professionals specifically trained in the recognition and treatment of these harmful conditions. In settings where emergency care is provided by professionals with heterogeneous training and background (EMT, trained police officers and fire fighters, volunteers, etc.), these goals are hardly accomplished. Conversely, when skilled physicians are involved, these complications are fully diagnosed and treated: in a recent study comparing the effect of different approaches on the outcome of trauma patients [13], TI and PNX drainage were performed in 91 and 25% of patients treated by HEMS-operating anaesthetists, as compared with much lower rates of these procedures performed by ground ambulance teams, which, in the vast majority of cases, did not include these professionals. In our region, similar rates of TI and PNX drainage by means of a small-sized thoracotomy performed in the pre-flight phase have been accomplished by the anaesthetists operating in the regional HEMS.

Finally, the TI–BVM controversy should not be considered as a component of the wider 'scoop and run vs stay and play' debate. Although there is no doubt that in the presence of active bleeding, the definitive care must be supplied in the surgical suite, yet it is not conceivable even in the most extreme conditions that an asphyxiating patient could be rushed to the hospital without securing the airways and looking for other immediate life-threatening injuries. This applies also to situations where multiple patients must be triaged and cared for simultaneously. In a recent paper dealing with the treatment of the victims of terrorist attacks in Israel, the only immediate procedures were the TI and the needle decompression of PNX, which were performed either on-the-scene or en route to the ED [13]. Again, these manoeuvres require specific training, which cannot be acquired only theoretically or with minimal practice. Actually, a suboptimal level of both basic and advanced training could account for the negative results present in some studies dealing with the high rate of complications of TI performed by medics [14] and the worse outcome of patients in whom a considerable pre-ED time was spent in attempting to establish an intravenous line [15].

In conclusion, there is no firm evidence that the TI is associated with detrimental effects, provided that is it is performed by trained physicians with a full knowledge of the TI-related drugs, the related complications and the available alternatives.

Restoration of tissue perfusion

Along with maintenance of oxygenation, organ perfusion is the cornerstone of the treatment of injured patients. Several reports indicate that, besides the severity of injures, the appropriateness of the initial approach heavily influences the clinical course and possibly the long-term consequences of trauma [16–18] and that the inflammatory response eventually leading to the development of a later multiple organ dysfunction syndrome (MODS) is primed by factors acting immediately after the trauma [19]. This led to the concept of the 'golden hour', which represents a theoretical timeframe during which the biological response to trauma is triggered and every effort should be done to restore perfusion and tissue oxygenation in order to prevent the activation of the mechanisms ultimately leading to a widespread tissue inflammation and apoptosis [20, 21].

However, everyone involved in the pre-hospital treatment of trauma patients recognises that the 'golden hour' hardly can be used as intended. At best, it means 'the sooner, the better'. In everyday life, a 'silver day' intended as an interval to correct tissue hypoxia appears a more realistic goal [22]. Behind this statement, a number of open questions exist despite decades of investigations and thousands of papers focused on the topic. First, is it safer to initiate a fluid resuscitation in the field or to rush the patient(s) to the most appropriate hospital? Second, which are the endpoints of the treatment in the pre-hospital phase? This latter question appears to be particularly relevant, as both under- and overtreatment can worsen the outcome and cause avoidable deaths. Actually, a number of circumstances contribute to delay the restoration of the perfusion, including a prolonged extrication time, difficulties in securing an intravenous line, environmental factors, etc.

Two mutually exclusive lines of thinking have been developed, each with its own rationale, advocates and detractors. The 'scoop and run' policy basically aims to avoid further time gaps between the rescue and the prompt treatment of surgically amenable injuries. Accordingly, only not-delayable, life-saving procedures are performed, including securing the airways and decompressing tensive PNX by means of needle puncture or field toracosthomy. This approach is the opposite to the 'stay and play' strategy, which mandates a full stabilisation (i.e. restoration of acceptable blood arterial pressure values) before the transportation. Yet in the early 1990s, Bickell et al. [23] demonstrated that patients with penetrating torso injuries who underwent an aggressive fluid resuscitation in the pre-hospital phase had a worse prognosis compared to patients who were rapidly rushed to the hospital; the authors attributed this result to different factors, including a longer time elapsing between the injury and the definitive surgical repair of the bleeding injuries, the resuscitation fluid-associated dilution of the coagulation factors and a higher arterial pressure facilitating the escape of blood throughout torn blood vessels. As stated above, other authors also demonstrated a worse outcome in patients fluid-resuscitated in the field, even if they attributed this finding more to the considerable time spent in attempting to establish an intravenous line than to the fluid resuscitation itself [15].

Due to the lack of clinical trials compatible with the evidence-based medicine

(EBM) criteria, in 2001 the Cochrane Group stated that, at the time, there were insufficient data to conclude that early and/or large-volume administration is of any benefit in uncontrolled haemorrhage [24], and the situation has not yet changed. However, if taken to its extreme consequences, this statement could lead to a pretty nihilistic attitude during the pre-hospital and the immediately post-admission phase, delaying the restoration of volaemia until the diagnostic workup has been completed. This approach could increase the already elevated rate of potentially avoidable deaths of trauma patients, which are mostly caused by untreatable hypotension resulting from advanced hypovolaemia, alone or in association with hypoxaemia [17, 25]. Moreover, there are circumstances in which an aggressive fluid resuscitation and/or the use of vasopressors is warranted, as in the case of a coexisting head trauma, when a prolonged hypotension sets the stage for the occurrence of secondary brain injuries, which carry devastating consequences, or in patients with extensive burns and massive musculoskeletal injuries [26, 27].

Thus, although in the absence of the above-quoted clinical indications, the administration of large volumes of fluids is not advisable until active bleeding focuses have been excluded; nevertheless, it can be concluded that: (a) the positioning of multiple large-bore intravenous lines is mandatory provided that this manoeuvre does not imply a substantial delay in transportation; (b) in the presence of penetrating injuries of the torso or other clearly exanguinating injuries (i.e. major vessel injuries), the time spent on the scene cannot be justified by the obtainment of 'normal' arterial pressure values; and, finally, (c) fluid resuscitation as well as the concomitant use of vasopressors should be titrated more on the clinical condition and on some therapeutic target, rather than on algorithms that do not take into account the ongoing change of perfusion.

The endpoints of volume resuscitation

Similar to all pathological states, if one decides to start fluid resuscitation, some clues are needed to up- or down-regulate the volume administered. This point appears vital as severe clinical consequences can derive from an inappropriate administration of fluids. Unfortunately, the most common markers of hypovolaemia and/or hypoperfusion monitored in the pre-hospital phase, the arterial pressure (AP) and the heart rate (HR), are also the least reliable to drive the therapy [28, 29]. Moreover, these signs can also be influenced by factors apart from the trauma itself, including the effect of drugs and alcohol, the presence of medullary injuries, the action of drugs, etc. Under-resuscitation can lead to a poor outcome through two different pathways. In the first case, the hypoperfusion is severe and acute, ultimately leading to irreversible damage of the brain and/or death. This scenario appears relatively common, as a considerable number of in-hospital preventable deaths still occur in the early post-admission phase due to hypovolaemia [17, 25]. In the second case, a less severe but long-lasting hypoperfusion is present, leading to a gradual deterioration of organ function till a full-blown MODS occurs [20]. A hypoxia-driven translocation of germs and/or germ-derived sub-

stances from the gut lumen to the bloodstream likely plays a major role in the initiation and maintenance of this condition [20, 21].

As a matter of fact, the diagnostic tools to investigate both the presence and the extent of hypovolaemia in the pre-hospital setting are rather limited. One should recognise that the commonly observed alteration in some haemodynamic variables, including AP, HR and the presence of peripheral cyanosis, can be caused by factors different from hypovolaemia, including PNX, pain and hypothermia. Keeping in mind these limitations, two approaches are possible [30–33]. The first starts by considering as hypovolaemic every severely injured patient; based on this assumption it appears safer to err on the overtreatment side and start an aggressive volume infusion immediately and continue it until the diagnostic investigations have confirmed or excluded a source of bleeding.

The continuation of the volume resuscitation en route to the hospital constitutes a third policy of the treatment of trauma patients, namely the 'run and play' approach. The pro and cons of this extended 'stay and play' attitude have been described earlier. The second approach is based on the gross evaluation of the clinical conditions: in the presence of a disturbance of the consciousness it is safer to obtain a relatively elevated arterial pressure (systolic arterial pressure 120–130 mmHg) to prevent the occurrence of a secondary brain injury, whereas lower values (systolic arterial pressure 90 mmHg) are tolerated in trauma patients without any neurological injury, provided that the arrival to the destination hospital does not exceed 30–40 min. This latter strategy, practically consisting of a hypotensive resuscitation, closely resembles a well-known and time-honoured anaesthesiological practice, namely controlled hypotension, currently used in neurosurgery and in other procedures requiring a blood-free surgical field.

As a matter of fact, despite the development of a number of diagnostic tools aimed to detect both the efficacy of fluid resuscitation and tissue hypoperfusion in critically ill patients, their application in the pre-hospital phase appears limited due to the hopefully short time elapsing between the rescue and the admission, and the technical limitations associated with the various techniques. Moreover, it should be underlined that in critically ill patients, the time trends of biological variables are more valuable than absolute values by themselves and the use of point-of-care diagnostic technologies on the scene of trauma could supply, at best, a panel of initial markers (i.e. blood lactate, base excess, etc.), whose variations should be monitored in a more advanced phase of treatment. With these limitations in mind, capnometry appears the only monitoring tool suitable for the pre-hospital phase, as it can supply real-time information not only about the correct position of the endotracheal tube, but also on both the haemodynamic and the pulmonary function in tracheally intubated and mechanically ventilated patients [34, 35].

Conclusions

Despite decades of studies and experiences, an EBM-based consensus on the most appropriate treatment of trauma patients in the out-of-hospital setting has not yet

been achieved. As a matter of fact, different approaches exist and no one has been demonstrated clearly superior over the others for all the circumstances and for all patients. A number of factors likely account for this finding. First, as the ABC represents a goal, the different levels of training and expertise of professionals trying to achieve it can be associated with different outcomes. Second, the most appropriate approach differs in patients with penetrating or blunt injuries. Third, similar to what has been hypothesised in other fields of critical-care medicine, perhaps the mortality rate is a rather rough, albeit unequivocal, marker of either outcome and/or appropriateness of care, and should be substituted with other indices, including changes of some biological variables or the quality of life of survivors. Finally, and likely most important, the on-scene treatment is the critical link between the out-of-hospital chain-of-survival and the in-hospital system of delivery of care, and weak points of either system can influence the outcome independently from the others.

References

1. Stocchetti N, Furlan A, Volta F (1996) Hypoxemia and arterial hypotension at the accident scene. J Trauma 40:764–767
2. Ravussin P, Bracco D, Moeschler O (1999) Prevention and treatment of secondary brain injury. Curr Opin Crit Care 5:511–516
3. Gillahm M, Parr JA (2002) Resuscitation for major trauma. Curr Opin Crit Care 15:167–172
4. Gausche M, Lewis RJ, Stratton SJ et al (2000) Effect of out-of-hospital pediatric endotracheal intubation on survival and neurologic outcome. JAMA 283:783–790
5. Eckstein M, Chan L, Schneir A et al (2000) Effect of prehospital advanced life support on outcomes of major trauma patients. J Trauma 48:643–648
6. Lockey D, Davies G, Coats T (2001) An observational study of the survival of trauma patients who have pre-hospital tracheal intubation without anesthesia or muscle relaxants. Br Med J 323:1410
7. Di Bartolomeo S, Sanson G, Nardi G et al (2001) Effects of two patterns of prehospital care on the outcome of patients with severe head injury. Ann Surg 136:1293–1300
8. Nardi G, Massarutti D, Muzzi R et al (1994) Impact of emergency medical helicopter service on mortality for trauma in north east Italy: a regional prospective audit. Eur J Emerg Med 1:69–77
9. Winchell RJ, Hoyt DB (1997) Endotracheal intubation on the scene improves survival in patients with severe head injury. Arch Surg 132:592–597
10. Garner A, Rashford S, Lee A, Bartolacci R (1999) Addition of physicians to paramedics helicopter services decreases blunt trauma mortality. Aust N Z J Surg 69:697–701
11. Dunham CM, Barraco RD, Clark DE et al (2003) Guidelines for emergency tracheal intubation immediately after traumatic injury. J Trauma Inj Infect Crit Care 55:162–179
12. Stocchetti N, Pagliarini G, Gennari M et al (1994) Trauma care in Italy: evidence of in-hospital preventable deaths. J Trauma 36:401–405
13. Karch SB, Lewis T, Young S et al (1996) Field intubation of trauma patients: complications, indications and outcomes. Am J Emerg Med 14:617–619
14. Peleg K, Ahronson-Daniel L, Stein M et al (2004) Gunshot and explosion injuries:

characteristics, outcomes and implications for care of terror-related injuries in Israel. Ann Surg 239:311–318
15. Sampalis JS, Tamin H, Denis R et al (1997) Ineffectiveness of on-site intravenous line: is prehospital time the culprit? J Trauma Inj Infect Crit Care 43:608–617
16. Desbourough JP (2000) The stress response to trauma and surgery. Br J Anaesth 85:109–117
17. Stocchetti N, Furlan A, Volta F (1996) Hypoxemia and arterial hypotension at the accident scene. J Trauma 40:764–767
18. Ravussin P, Bracco D, Moeschler O (1999) Prevention and treatment of secondary brain injury. Curr Opin Crit Care 5:511–516
19. Gillahm M, Parr JA (2002) Resuscitation for major trauma. Curr Opin Crit Care 15:167–172
20. Keel M, Trenta O (2005) Pathophysiology of polytrauma. Injury 36:691–709
21. Nolan JP, Parr MJA (1997) Aspects of resuscitation in trauma. Br J Anaesth 79:226–240
22. Hocthkiss RS, Schmieg RE, Swanson PE et al (2000) Rapid onset of intestinal epithelial and lymphocytic death in patients with trauma and shock. Crit Care Med 28:3207–3217
23. Blow O, Magliore L, Claridge JA et al (1999) The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. J Trauma Inj Infect Crit Care 47:964–969
24. Bickell WH, Wall MJ Jr, Pepe PE et al (1994). Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Eng J Med 331:1105–1109
25. Kwan I, Bunn F, Roberts I, on behalf of the WHO Pre-Hospital Trauma Care Steering Committee (2003) Timing and volume of fluid administration for patients with bleeding. The Cochrane Database of Systematic Reviews 2003, Issue 3. CD002245, DOI:10.1002/14651858
26. Chiara O, Scott JD, Cimbanassi S et al (2002) Trauma deaths in an Italian urban area: an audit of pre-hospital and in-hospital trauma care. Injury 33:553–562
27. Gueugniaud PY, Carsin H, Bertin-Maghit M, Petit P (2000) Current advances in the initial management of major thermal burns. Intensive Care Med 26:848–854
28. Holt SG, Moore KP (2001) Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. Intensive Care Med 27:803–811
29. McGee S, Abernethy WB, Simel DL (1999) Is this patient hypovolemic? JAMA 281:1022–1029
30. Deakin CD, Low L (2000) Accuracy of the advanced trauma life support guidelines for predicting systolic blood pressure using carotid, femoral and radial pulses: observational study. Br Med J 321:673–674
31. Elliott DC (1998) An evaluation of end points of resuscitation. J Am Coll Surg 187:536–547
32. Porter JM, Ivatury RR (1998) Search of the optimal endpoints of resuscitation in trauma patients: a review. J Trauma Inj Infect Crit Care 44:908–914
33. Bilkowsi RN, Rivers EP, Horts HM (2004) Targeted resuscitation strategies after injury. Curr Opin Crit Care 10:529–538
34. Tisherman SA, Barie P, Bokhari F et al (2004) Clinical practice guidelines: endpoints of resuscitation. J Trauma Inj Infect Crit Care 57:898–912
35. Silvestri S, Ralls GA, Krauss B et al (2005) The effectiveness of the out-of-hospital continuous end-tidal CO_2 monitoring on the rate of unrecognized misplaced intubation within a regional emergency medical services system. Ann Emerg Med 45:497–503

Chapter 65

The unstable trauma patient

G. Gordini, M. Menarini, E. Bigi

Major trauma patients demonstrate, with notable frequency, relevant alterations to their principal physiological parameters, which are manifested at the scene of the event. These alterations cause 'instability'—a condition in which, without intervention, the patient's vital functions can be seriously compromised (even fatally). 'Instability' is commonly referred to as haemodynamic alterations.

In this analysis, focusing in particular on the patient's treatment from the pre-hospital stage to arrival in the emergency room, the main problems that determine the haemodynamic instability of the patient, the approach methodologies and evaluations and the need for a solid pre-hospital link will be examined.

The ideal response to major trauma is a trauma system

The survival of patients who have been victims of large-scale trauma indubitably improves with a system approach. Research led primarily in the USA shows that the reduction of morbidity and mortality due to a trauma is possible only through a system approach, thus using all the available resources in the best way. The urgent, various and often very complex diagnostic and therapeutic requirements of severe trauma call for appropriate means, a multidisciplinary approach and a whole organisation able to integrate the different professional competencies.

The development of an integrated system for the care of trauma patients primarily involves the setting up of trauma centres of reference for the regional network, facilities with integrated functions able to guarantee a timely assistance and continuity of care during the different phases of the emergency.

The methodological approach to trauma patients

There is still no general agreement on what is the best strategy to approach the trauma victim in the pre-hospital field. The concept of the 'golden hour' is still said to be the critical time during which certain interventions, such as airway management, fluid therapy and spinal stabilisation, may keep the patient alive or prevent further deterioration until definitive care can be delivered.

This definitive care often, but not always, involves surgical interventions for the control of bleeding or drainage of intracranial haemorrhage. Realistically, however,

many patients do not reach the operating theatre until more than 1–2 hours have elapsed since their injury, even in major urban trauma centres. A 'golden hour' is also an unrealistic expectation for a patient with uncontrolled major haemorrhage and profound hypotension, when the chances of survival and a good recovery expire within minutes [1].

This affirmation becomes even more important when this is reported: 'Intensive care is a process, not a location. In the critically ill injured patient, it should be started as early as possible without compromising or delaying emergency interventions. Invasive monitoring and the involvement of clinicians trained in intensive care should be routine in the emergency department' [2].

From the first pre-hospital evaluation of the patient, it is evident that the execution of vital support manoeuvres capable of maintaining the principal physiological functions is of great importance, without interruption in the successive phases.

Patients with haemodynamic instability

The theme of the patient with haemodynamic instability is highly relevant when discussing the initial phases of treatment, from the pre-hospital phase to the emergency room. Studies on preventable death show still elevated percentages of possibly preventable and definitely preventable deaths. A recent study by Chiara et al. [3] shows that: 'A majority of avoidable deaths were found in patients with treatable CNS injuries combined with haemorrhage or hypoxia. We believe that early, aggressive field management of airway and haemorrhage by experienced, trained pre-hospital personnel may have reduced the number of these deaths.'

The American College of Surgeons defines shock as a circulatory system abnormality resulting in inadequate organ and tissue oxygen delivery. Shock can be present in many forms, but the most common form in blunt and penetrating injury that decreases circulating volume is haemorrhagic shock.

In the case of penetrating injury, as shown in Bickell's classic study [4], the initial strategy is the immediate transport of the patient to the hospital, without wasting time positioning intravenous lines and beginning infusion (Bickell indicates positioning an intravenous line during transport).

Regarding closed trauma, which constitutes the majority of cases in European countries, there have been recent revisions relative to the strategy of infusion. Fluid administration has been the cornerstone treatment for haemorrhagic shock; therefore, reaching normal pressure values was considered as the primary objective. The rationale for fluid administration is that, by restoring normal volaemia and normalising blood pressure, it guarantees a cardiac output and a perfusion pressure sufficient to maintain the vital organs.

The objective is to find a way to support the circulation adequately to allow the perfusion of the vital organs while trying to keep the risk of further bleeding as low as possible. Maintaining arterial pressure values under normal pressure values is a strategy that aims to reach this result.

To be exact, there are two possible strategies in trauma: delayed resuscitation, where fluid is withheld until haemostasis is definitively achieved; and permissive hypotension, when fluid is given but the endpoint for resuscitation is lower than normotension.

Research in studies of large animals [5] with uncontrolled haemorrhage found that thrombus dislodgement occurred at a systolic blood pressure (SBP) of 80 mmHg (the expression 'popping the clot' describes this phenomenon). There is still no definitive data regarding humans. A study by Dutton [6] concludes: 'Titration of initial fluid therapy to a lower than normal SBP during active haemorrhage did not affect mortality in this study. Reasons for the decreased overall mortality and the lack of differentiation between groups likely include improvements in diagnostic and therapeutic technology, the heterogeneous nature of human traumatic injuries and the imprecision of SBP as a marker for tissue oxygen delivery'.

Patients presenting in haemorrhagic shock were randomised to one of two fluid resuscitation protocols: target SBP > 100 mmHg or target SBP of 70 mmHg. However, it emerges from the data analysis that the average arterial pressure was 114 ± 12 mmHg in the first group and 100 ± 17 mmHg in the second, a difference that is statistically significant but which evidently shows that the target of 70 mmHg was not respected. A very high rate of severely traumatised patients who are maintaining normal vital signs and urine output still suffer subnormal oxygen delivery, evidenced by increased lactate. The Eastern Association for the Surgery of Trauma guidelines report: 'Standard haemodynamic parameters do not adequately quantify the degree of physiologic derangement in trauma patients. The initial base deficit, lactate level or gastric pH can be used to stratify patients with regard to the need for ongoing fluid resuscitation, including packed red blood cells and other products, and the risks of MODS and death' [7].

One aspect of great importance for the continuity of care of the patient is represented by activation of the trauma team. Their activation, which can predict different criteria for different realities in which they find themselves, both clinical and organisational, assumes notable relevance in cases of patients who are haemodynamically unstable.

The fact that hypotension, or better still, the presence of signs and symptoms of shock, are valid criteria for the activation of the trauma team is generally agreed upon. Franklin [8] writes: 'Prehospital hypotension remains a valid indicator for trauma team activation. Even though most of the non DOA patients (492 of 598) were stable on arrival to the ED, nearly 50% required operative intervention, and an additional 25% required operative intervention, and an additional 25% required intensive care unit admission. The trauma team should be activated and involved with these patients early'.

Chan [9] comes to an interesting conclusion in a study that compares traumatised patients with a pre-hospital arterial pressure of < 90 mmHg and normotensive patients, and concludes that: 'The injured patients who were hypotensive in the out-of-hospital setting but normotensive upon ED arrival were more severely injured and had more potential for blood loss than were the patients who were both in the out-of-hospital setting and in the ED. Out-of-hospital hypotension may be a

clinical predictor of severe injury, even in the face of normal ED SBP. Prospective studies are indicated to validate this hypothesis.'

The strategy of permissive hypotension, whose efficacy needs to be proven in future studies, should keep two vital elements in mind: the tolerance levels of elderly trauma patients (less efficient physiologic compensatory mechanism, blood pressure levels normally higher than younger patients) and the duration of controlled hypotension (how long it is possible to maintain pressure levels below normal, taking into consideration that times for definitive haemostasis are usually quite high).

Moreover, in the patient with severe head injury, where cerebral perfusion requires pressure values higher in respect to a blunt trauma without cerebral lesions, the target of blood pressure probably needs to be higher, even if randomised studies are lacking for this patient group.

Hypertonic solutions: what role?

The discussion on ideal fluid resuscitation in the unstable trauma patient has, for many years, centred on which liquid to use: crystalloids or colloids? In recent years hypertonic solutions have become more common. Two recent reviews have highlighted some interesting conclusions.

On the use of colloids and crystalloids [10]: 'There is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of randomised controlled trials.'

On the use of the hypertonic solution [11]: 'This review does not give us enough data to be able to say whether hypertonic crystalloid is better than isotonic and near isotonic crystalloid for the resuscitation of patients with trauma, burns or those undergoing surgery. However, the confidence intervals are wide and do not exclude clinically significant differences. Further trials which clearly state the type and amount of fluid used and that are large enough to detect a clinically important difference are needed'.

An unpublished multicentric study on the use of hypertonic saline solutions in trauma patients in hypovolaemic shock conducted in Italy (coordinated by Prof. O. Chiara) demonstrates the safety of hypertonic solution infusions and the need for minor infusions of liquid to reach pressure targets forecast in the studio (in this case SBP = 110 mmHg).

In terms of outcome it has not been possible to demonstrate a positive effect of hypertonic solutions on patients treated with these kinds of solutions; an analysis of a subgroup of patients with severe head injury has shown an increase in survival rates due to the improved control of intracranial pressure.

The effect on intracranial pressure is undoubtedly of great interest, and it

can be said that 'it is certainly an oversimplification to consider hypertonic solution solely as an osmotic agent that extracts water from oedematous cerebral tissue' [12].

Other interesting properties are connected with hypertonic solutions; those worth a special mention are their effects on microcirculation (de-swelling of the endothelial cells with an improvement of the peripheral perfusion) and an action on immunomodulation, with a reduction of polymorphonuclear neutrophil activation and infiltration in the lungs (and the development of acute respiratory distress syndrome [ARDS]).

One of the most stimulating aspects of the use of hypertonic solutions, other than the necessity to demonstrate their efficacy on the patient in a state of shock, is the scenario of their use as a therapy for specific groups of trauma patients.

Pre-hospital ultrasound and early surgical intervention

The trauma sonogram has become an essential tool in trauma resuscitation. Many different studies have highlighted and recommended its usage (level II) as the initial screening to exclude haemoperitoneum, particularly after closed trauma. Focused abdominal sonogram for trauma (FAST) may be considered as an initial diagnostic modality to exclude haemoperitoneum. In the presence of a negative or indeterminate FAST result, diagnostic peritoneal lavage and computed tomography have complementary roles.

FAST has the objective of locating liquids in the intraperitoneal cavity: it can be implemented quickly and could be used in the pre-hospital stage, as its utility in the early stages of hospital treatment is so consolidated.

One study [13] considered 84 patients. FAST performed in flight showed an overall accuracy of 96.4% with a sensitivity of 81% and a positive predictive value of 100%. Another study [14] has shown less positive results. A total of 71 patients were taken into consideration (83% with blunt trauma). FAST examinations could not be performed in 34 patients (48%) due to insufficient time (67%), inadequate patient access, or combativeness. Technical difficulties (difficult screen visualisation due to ambient lighting, battery failure, machine malfunction) prevented scanning in seven (19%) of the 37 in whom it was attempted. The authors concluded that 'Significant advances in training, technology and/or patient access will be necessary for aeromedical FAST to be feasible'.

This conclusion is also shared by Polk et al. [13]. In the civilian emergency medical services sector, it appears that flight crews and emergency medical services teams with the proper qualifications can perform ultrasound examinations in the field or in flight, giving the awaiting trauma team an idea as to what is wrong with the patient before the patient even arrives. Knowing whether the patient has haemoperitoneum prior to his or her arrival at the hospital may have significant triage implications. Patients with haemodynamic instability and a reliably positive haemoperitoneum could perhaps be triaged directly to the operating room and bypass the trauma room. Patients without haemoperitoneum and with stable vital

signs could potentially be rerouted to level 2 or 3 centres if other patients are more in need of the level 1 centre's care.

As confirmed above, and not forgetting the problems posed by the execution of FAST in the pre-hospital stage (technical limitations, environmental influences, personnel training, operator dependency), there is an essential element: the prospective of a link between pre-hospital efficiency and an ability to save time.

Permissive hypotension has been mentioned before and for the time period it may be allowed. Bypassing of the emergency room, with the advanced life support level guaranteed by the pre-hospital team, can, without a doubt, be a time saver, taking into consideration that the trauma centre can be better prepared to treat the patient.

Administration of recombinant factor VIIa

Recent studies have analysed the role of administering recombinant factor VIIa (rFVIIa) in trauma patients with severe bleeding. rFVIIa is commonly used in haemophiliac patients. Recently, the effects of its administration in cases of acquired coagulopathy after trauma and surgery have been evaluated, in both animals and humans. Factor VIIa is a prohaemostatic agent – more specifically an initiator of thrombin generation. The mechanism of action of VIIa favours an enhancement of haemostasis limited to the site of injury without systemic activation of the coagulation cascade. Various studies have collected data on the use of rFVIIa.

Boffard et al. [15] conducted a large placebo-controlled trial of rFVIIa (400 μg/kg in three doses) in 301 patients with severe blunt and/or penetrating trauma. In this study, 277 patients were analysed (143 with blunt trauma and 134 with penetrating trauma). The authors reported that rFVIIa decreased red blood cell transfusion requirements in major traumatic haemorrhage, while showing a good safety profile in high-risk patients. The trends seen towards reduced multiple organ failure and ARDS were noted but non-statistically significant (this study was sponsored by Novo Nordisk S/A).

A retrospective analysis of patients with blunt trauma ($n = 8$) and uncontrolled haemorrhage has shown a significant reduction in the necessity to transfuse red blood cells, fresh frozen plasma and platelets [16]. Treatment with rFVIIa reduced or stopped bleeding in all patients. The conclusion was: 'Administration of rFVIIa seems to be beneficial in blunt trauma patients with uncontrolled bleeding, but the optimal timing and dose of administration remain to be established. Also, prospective randomised trials with emphasis on safety, survival rates and transfusion consumption are needed to elucidate the role of rFVIIa as an adjunct to bleeding control in blunt trauma.'

In another review on the efficacy and safety of rFVIIa in the treatment of severe bleeding [17], the authors concluded: 'Recombinant factor VIIa appears to be relatively safe with a 1–2% incidence of thrombotic complications based on published trials. More randomised controlled clinical trials are required to assess the efficacy and safety of recombinant factor VIIa for patients without a pre-existent coagulation

disorder and with severe bleeding. In the meantime, off-label use of recombinant factor VIIa may be considered in patients with life-threatening bleeding.'

What is missing is the experience with early administration of rFVIIa in the earlier stage of massive haemorrhage, during the phase of pre-hospital care and during transport to the trauma centre.

Blunt thoracic trauma, blunt cardiac trauma and haemodynamic instability

Among the causes of haemodynamic instability after a major trauma, we undoubtedly think of closed thoracic trauma, with an elevated energy. Special attention should be paid here to cardiac trauma. An unclear definition of cardiac trauma (blunt cardiac trauma is favoured to myocardial contusion) has made it difficult to compare data collected from different studies. Mattox et al. [18] suggest that the term 'blunt cardiac trauma' be used only in the presence of pump failure or malignant cardiac rhythms.

Blunt trauma can induce myocardial lesions in several ways:

(1) Direct transfer of energy during the impact on the thorax
(2) Rapid deceleration of the heart
(3) Compression of the heart between the sternum and the spine [19]

Hypotension in a trauma patient is initially seen to be a consequence of the haemorrhage: in other words, it often means a late hypothesis of cardiac damage. It should also be noted that a late diagnosis of blunt cardiac trauma and a late treatment can lead to severe complications. The diagnostic criteria of blunt cardiac trauma have a reduced predictive value: both the ECG and the transthoracic echogram are also unreliable.

As for the ECG, it can be said that the predictive positive values are limited while the predictive negative values can be up to 95% (in other words, patients with a thoracic trauma but with a negative ECG have a very low probability of developing grave cardiac complications).

As regards the echocardiogram, the transoesophageal echocardiogram undoubtedly has a greater accuracy, but in reality it is not possible to have this type of procedure for at least 24 hours. Its presence in a trauma centre is now seen as fundamental.

The traumatised myocardium leads to the release of troponin T and I, and a co-relation exists between the quantity of troponin in the blood and the amount of energy absorbed by the myocardium. The negative predicted value of troponin is high, while the positive predicted one is low: therefore it depends on the fact that hypoperfusion of the myocardium (as a consequence of haemorrhagic shock) can determine the release of troponin, even without a direct trauma to the heart [20].

Some preliminary studies seem to indicate that the sensitivity and specificity of troponin as a marker of blunt cardiac trauma are linked in a relevant way to the interval between the trauma and the taking of blood (in particular around the eighth hour). More studies of this pathology are necessary to define the best diagnostic modalities and therapeutic approaches.

Bearing in mind that among the causes of haemodynamic instability are aortic injuries (for which no specific analysis is needed), it is worth underlining how severe pulmonary contusions are associated with conditions of haemodynamic instability linked with myocardial dysfunction.

One study investigated whether factors that determine myocardial performance (preload, afterload, heart rate and contractility) are altered after isolated unilateral pulmonary contusion. The conclusion was: 'Ventricular performance can be impaired by depressed myocardial contractility and increased right ventricular afterload even with normal left ventricular afterload and preload. It is thus conceivable that occult myocardial dysfunction after pulmonary contusion could have a role in the progression to cardiorespiratory failure even without direct cardiac contusion' [21].

Haemodynamic instability due to complex pelvic trauma

Pelvic fractures are very common in high-energy trauma. They are the third most frequent type of injury found in victims of motor vehicle crashes. The main cause of morbidity and mortality in patients with pelvic fractures is uncontrolled haemorrhage. The goal in resuscitation of the haemodynamically unstable patient with pelvic trauma is to identify the preponderant site of the haemorrhage. Potential sites of intrapelvic bleeding include fractured bone edges, soft tissues, venous and arterial vascular injuries.

The opening of the pelvic ring, with a consequent increase of pelvic volume ('open book'), creates a space potential that favours the establishment of an uncontrolled retroperitoneal haemorrhage. O'Neil et al. [22] has shown how it is possible to hypothesise which arteries and veins have been damaged, from the type of pelvic lesion. 'Posterior arterial bleeding (internal iliac or its posterior branches) was statistically more common in patients with unstable posterior pelvic fractures, and anterior arterial bleeding (pudendal or obturator) was more common in patients with lateral compression injuries. The superior gluteal artery was the most commonly injured vessel associated with posterior pelvic fractures.'

Therefore, it is necessary to adopt a strategy of accurately monitoring all vital functions, combined with an aggressive infusional therapy, in all patients with pelvic fractures until they are admitted to the emergency department.

In a polytraumatised patient with a haemodynamically unstable pelvic fracture, the initial management must be rapidly to identify the predominant site of haemorrhage. The use of FAST finds universal consensus: 'FAST-based algorithm for blunt abdominal injury was more rapid, less expensive, and as accurate as an algorithm that used computer tomogram or diagnostic peritoneal lavage only' [23].

An echogram positive for haemoperiton provides immediate indications for laparotomy, therefore the patient will be re-evaluated regarding the pelvic lesions and an eventual loss of haemodynamic stability after abdominal surgical intervention.

It is worth remembering that a laparotomy increases pelvic volume and there-

fore retroperitoneal bleeding is favoured. As Ghanayem reminds us, it 'supports reduction and temporary stabilization of unstable pelvic injuries before or concomitantly with laparotomy' [24].

If a haemoperiton is not present in the FAST, it is necessary to identify the type of pelvic fracture, in particular, whether the pelvic ring is open and whether it is susceptible to closure. In the case of a pelvis susceptible to closure (open book), an external fixator or c-clamp is used. In our situation a c-clamp is positioned immediately in the emergency room; the positioning time in the hands of an expert is approximately 10 minutes.

Grimm et al. [25] stated that low-pressure venous haemorrhage may be tamponaded by an external fixator, given that enough fluid volume is present in the pelvic retroperitoneum. An external fixator may not generate sufficient pressure to stop arterial bleeding. A large volume of fluid must be lost into the pelvis before an external fixator can have much effect on retroperitoneal pressure.

A pelvic fracture not susceptible to closure or unstable haemodynamics even after the positioning of a c-clamp indicates an angiography with vascular embolisation. Some types of pelvic fractures find little benefit from the positioning of a c-clamp to reduce bleeding. Bassam noted: 'We conclude that patients with anterior-posterior compression type 2 and 3, lateral compression type 2 and 3, or vertical shear injuries who are haemodynamically unstable as a result of their pelvic fracture, should undergo immediate angio if laparotomy is not indicated' [26].

Conclusions

As seen previously, the successful treatment of a trauma unstable patient represents a great challenge for the trauma system. The revision of best strategies, the application of diagnostic protocols and therapeutic innovations, and the search for continuity in treatment from the scene of the accident to the trauma centre are essential elements that appear to help improve the outcome for this patient group. The availability of scientific evidence, of answers to different problems, requires correct methodological studies that do not confuse 'apples and oranges', but which are able to group homogeneous patients, with defined objectives that are clear and unequivocal.

The outcome of a trauma unstable patient is time-dependent, but only with an accurate diagnosis can the speed of treatment ensure that this outcome is positive.

References

1. Parr MJ, Joseph AP (2001) Resuscitation for major trauma. Resuscitation 48:1–3
2. Oakley PA, Coleman NA, Morrison PJ (2001) Intensive care of the trauma patient. Resuscitation 48:37–46
3. Chiara O, Scott JD, Cimbanassi S et al (2002) Trauma deaths in an Italian urban area: an audit of prehospital and in hospital trauma care. Injury 33:553–562
4. Bickell WH, Wall MJ Jr, Pepe PE et al (1994) Immediate versus delayed resuscitation for hypotension patients with penetrating torso injuries. N Engl J Med 331:1105–1109
5. Mapstone J, Roberts I, Evans P (2003) Fluid resuscitation strategies: a systematic review of animal trials. J Trauma 55:571–589
6. Dutton RP, Mackenzie CF, Scalea TM (2002) Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 52:1141–1146
7. Hoff WS, Holevar M, Nagy KK et al (2002) Practice management guidelines for the evaluation of blunt abdominal trauma: the EAST practice management guidelines work group. J Trauma 53:602–615
8. Franklin GA, Boaz PW, Spain DA et al (2000) Prehospital hypotension as a valid indicator of trauma team activation J Trauma 48:1034–1039
9. Chan L, Bartfield JM, Reilly KM (1997) The significance of out-of-hospital hypotension in blunt trauma patients. Acad Emerg Med 4:785–788
10. Roberts I, Alderson P, Bunn F et al (2004) Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 4:CD000567
11. Bunn F, Roberts I, Tasker R et al (2004) Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 3:CD002045
12. Doyle JA, Davis DP, Hoyt DB (2001) The use of hypertonic saline in the treatment of traumatic brain injury. J Trauma 50:367–383
13. Polk JD, Fallon WF, Kowach B et al (2001) The Airmedical F.A.S.T. for trauma patients: the initial report of a novel application for sonography. Aviat Space Environ Med 72:432–436
14. Melanson SW, McCarthy J, Stromski CJ et al (2001) Aeromedical trauma sonography by flight crews with a miniature ultrasound unit. Prehospital Emerg Care 5:399–402
15. Boffard KD, Warren B, Iau P et al (2004) Decreased transfusion utilization and improved outcome associated with the use of recombinant factor VIIa as an adjunct in trauma. J Trauma 57:451
16. Geeraedts LM, Kamphuisen PW, Kaasjager HA et al (2005) The role of recombinant factor VIIa in the treatment of life-threatening haemorrhage in blunt trauma. Injury 36:495–500
17. Levi M, Peters M, Buller HR (2005) Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med 33:883–890
18. Mattox KL, Flint LM, Carrico CJ et al (1992) Blunt cardiac trauma (formerly termed myocardial contusion). J Trauma 33:649–650
19. Orliaguiet G, Ferjani M, Riou B (2001) The heart in blunt trauma. Anaesthesiology 95:544–548
20. Edouard AR, Benoist JF, Cosson C et al (1998) Circulating cardiac troponin I in trauma patients without cardiac contusion. Intensive Care Med 24:988–995
21. Moomey CB, Fabian TC, Melton A et al (1998) Determinants of myocardial performance after blunt chest trauma. J Trauma 45:988–996
22. O'Neil PA, Riina J, Sclafani S et al (1996) Angiographic findings in pelvic fractures. Clin Orthop 329:60–67

23. Boulanger BR, McLellan BA, Brenneman FD et al (1999) Prospective evidence of the superiority of a sonography-based algorithm in the assessment of blunt abdominal trauma. J Trauma 47:632–637
24. Ghanayem AG, Wilber JH, Lieberman JM et al (1995) The effect of laparotomy and external fixator stabilization on pelvic volume in an unstable pelvic injury. J Trauma 38:396–400
25. Grimm MR, Vrahas MS, Thomas KA (1998) Pressure-volume characteristics of the intact and disrupted pelvic retroperitoneum. J Trauma 44:454–459
26. Bassam D, Cephas GA (1998) A protocol for the initial management of unstable pelvic fractures. Am Surg 64:862–867

Chapter 66

What to do next: major chest trauma beyond the 'recipe books'

F. Plani, J. Goosen

Thoracic injury constitutes one on the most heterogeneous groups of trauma pathology, and the one that encompasses the most organs and systems within its jurisdiction. It is also one of the most lethal: Of the 180 000 deaths per year in the United States in the 1990s, thoracic injury was solely responsible for 25% and played a major role in another 25% [1]. Thoracic injury also accounted for 37% of the soldiers killed in action in Vietnam, before the widespread use of Kevlar vests. Out of 1 198 penetrating injuries to the heart in South Africa, only 6% of victims presented to hospital alive [2]. Clearly, the immediate recognition and management of life-threatening injuries must be within the grasp of any doctor treating trauma patients, however infrequently this may be [3].

Advanced thoracic surgical techniques are required in a higher percentage of patients than was reported in the earlier literature [4], with up to 31% of patients in a recent large multicentre study requiring thoracotomies and 25% requiring major lung resections.

This review aims to analyse the finer points of the current teachings on the main categories of chest trauma and its management, and then identify other serious conditions and syndromes for which a consensus concerning their management is lacking or only just beginning to be advanced.

Basic principles of chest trauma management proposed by the Advanced Trauma Life Support Program for Doctors

The Advanced Trauma Life Support Program for Doctors (ATLS) originated in the United States in the late 1970s, and has now spread to over 37 countries worldwide, training over half a million doctors. On successful completion of the course, participants are able to identify and treat in the primary survey six immediately life-threatening injuries, and another 12 potentially life-threatening injuries in the secondary survey. The first group of actual or potential immediately life threatening injuries consists of airway obstruction in the chest, tension pneumothorax, open pneumothorax, flail chest, massive haemothorax, and cardiac tamponade. The second group comprises simple pneumothorax, haemothorax, pulmonary contusion, tracheobronchial tree injuries, blunt cardiac injury, traumatic aortic disruption, traumatic diaphragmatic injury, mediastinal traversing

wounds, plus various thoracic fractures, subcutaneous emphysema, and oesophageal injuries.

Since the ATLS course is geared towards emergency physicians, only basic surgical skills are taught, such as needle thoracentesis, insertion of chest drains, and pericardiocentesis. However, mention is made of the need for emergency-room thoracotomy, flexible bronchoscopy for the extraction of foreign bodies and blood, and the possible need for ventilation in flail chest. Attention is also drawn to the possibility of massive haemothorax even if the standard 1500 ml are not drained immediately, and to subtle signs of cardiac tamponade and to pericardial blood draining into the pleura.

Despite the success of ATLS, a number of questions on the immediate management of chest trauma are too controversial for simple rules. Examples originating directly from the pathological entities described in ATLS are, to mention but a few:

- Is there effective damage control after emergency-room thoracotomy?
- How should a haemopneumothorax in a chest with extensive pleural adhesions be dealt with?
- What is the outcome of draining a large chronic haemothorax?
- Is pneumonectomy a survivable procedure in acute trauma?
- How can life-threatening myocardial contusions be identified?
- How can diaphragmatic rupture while ventilating on positive pressure ventilation be detected?
- How can delays in detecting penetrating oesophageal injuries be avoided?
- What is a practical protocol to investigate transmediastinal gunshot wounds?
- What are the best modalities for dealing with a traumatic aortic injury?

Definitive Surgical Trauma Care for surgeons

In 1999, the International Association for the Surgery of Trauma and Surgical Intensive Care (IATSIC) designed and started offering the Definitive Surgical Trauma Care (DSTC) course to complement the teachings of ATLS for trauma surgeons and surgical residents who go on to operate on and care for trauma patients beyond ATLS-based resuscitations [1]. This course has been offered to surgeons and surgical trainees in the UK, South Africa, Australia, Austria, the Netherlands, Greece, Scandinavia, Turkey, Yemen, and other countries. It is less rigidly organised than ATLS, has a number of optional modules, and aims at teaching the theory of injury, surgical decision-making, trauma surgery of individual organ systems, trauma systems, and scoring systems. Lectures, mortuary sessions, operations on anaesthetised animals, and group discussions are used to teach a more advanced surgical approach to trauma patients.

Upon completion of a DSTC course, surgeons and residents will be familiar with:

- Operative, nonoperative, and video-assisted modalities in chest surgery
- Different types of thoracotomies, including emergency-room thoracotomy and pleural toilet

- The ventilation of patients with pulmonary contusion and those with persistent pneumothoraces
- The suturing of cardiac wounds while avoiding the coronary arteries
- Management of penetrating injuries of the great mediastinal vessels by primary repair
- Management of penetrating trauma to the oesophagus
- Internal splinting and external stabilisation for flail chest
- Techniques of tractotomy and stapling of pulmonary wounds.

Life-threatening conditions beyond the scope of the 'Recipe Books'

The first medical practitioners to resuscitate victims of major trauma are likely to be emergency physicians, anaesthesiologists, and trauma surgeons, and not cardiothoracic surgeons or pulmonologists. While the teachings of ATLS and DSTC will allow them to deal with the vast majority of thoracic emergencies, there are some potentially fatal conditions that require some extra thinking and interventional skills. These may present in the course of the resuscitation, during surgery, or in the early intensive-care management of the patients. In the combined experience of the Johannesburg Hospital Trauma Unit of the University of the Witwatersrand in Johannesburg, South Africa, these have been the following:

1. Exsanguinating haemoptysis
2. Acute airway obstruction in the ventilated patient
3. Acute pulmonary oedema during resuscitation or surgery
4. Life threatening pulmonary contusion
5. Massive bleeding into the chest cavity
6. Deterioration despite successful repair of cardiac injury
7. Life threatening myocardial contusion.

In other situations, controversial points requiring rapid decision-making are: (1) use of noninvasive ventilation (NIV) in acute trauma; (2) current management of traumatic aortic injury; and (3) ideal management of flail chest.

Exsanguinating haemoptysis

Haemoptysis can be life-threatening, especially in a polytrauma patient, in whom it may be just one of many injuries, all potentially fatal [5]. On its own, mortality due to haemoptysis varies between 23 and 85%, and is mainly the result of flooding of the tracheobronchial tree down to the alveoli, with subsequent asphyxiation of the patient. Haemoptysis has many aetiologies, mainly nontraumatic, such as cancer, tuberculosis, vascular malformations, and bleeding disorders such as encountered in acute renal failure [6]. Trauma accounts for less than 10% of haemoptysis cases (but for 100% of cases seen by trauma surgeons).

Massive haemoptysis has been variously described as being of between 600 and 1000 ml in 24 h, with major haemoptysis being > 200 ml/24 h. Most authors seem to favour a surgical approach to treating massive haemoptysis [7], which leads to

a reduction in morbidity and mortality when compared to less aggressive management. In trauma, bleeding can vary from blood-stained sputum to exsanguinating bleeding of over 150 ml/h, which may make intubation, let alone ventilation, difficult or impossible.

Anatomically speaking, the problems may be due to the following: (1) bleeding from injury to the base of the skull or face, flooding the airways from above; (2) penetrating neck injuries, with bleeding into the larynx or trachea; and (3) bleeding from tracheobronchial or lung parenchymal lacerations.

A number of options exist in the management of haemoptysis, namely, bronchoscopic irrigation with cold saline or with vasoconstrictors, plugging with Surgicel into the bleeding bronchus, detachable Fogarty balloons, Arndt blocker tubes [7–11], and bronchial and nonbronchial systemic arterial embolisation [10].

The insertion of double-lumen endotracheal tubes for bronchial isolation may be tried if simpler methods fail, to be followed by surgery and resectional lobectomy if the bleeding continues. The operative approach is associated with significant mortality and morbidity [11], but may be the only option in massive haemoptysis in trauma, where one is likely to find major bronchial arterial and airway destruction.

Management in the resuscitation room varies with the level of origin of the bleeding:

- Base of skull, face, neck (blunt or penetrating injury): The patient should lie on one side, or sit up if the cervical spine is not at risk while preparations are made for securing a definitive airway. Injection of local anaesthetic in the area of the cricothyroid membrane is followed by one attempt at orotracheal intubation. If this fails, a percutaneous/surgical cricotyroidotomy is carried out using a size 7 percutaneous tracheostomy set.

Following successful surgical intubation, an orogastric tube is inserted, and the nose and mouth packed until the bleeding has largely stopped, followed by angiography and embolisation, CT scanning, or immediate surgery in unstable patients should then be carried out. The cricothyroidotomy can be converted to a tracheostomy when convenient. Flexible bronchoscopy should be carried out immediately after, to remove the inevitable large amounts of blood, clots, and aspirate from the tracheobronchial tree.

- Neck with evidence of laryngeal destruction: The procedure is the same as above, but no attempts at intubation should be made. A semi-open percutaneous tracheostomy can be carried out under local anaesthesia in the unintubated patient. Subsequent management parallels that of the situations described above.
- Bleeding from within the endotracheal tube: Ensure that the tube is of a size adequate for instrumentation (change using a tube exchanger if smaller than size 8.0).

1. Try to suction, use cold saline, and apply high PEEP if not contraindicated by the severity of the head injury.
2. Use a flexible bronchoscope to identify bleeding bronchi: try to stop bleeding with vasoconstrictors. Surgicel should only be used by clinicians with previous

experience. Following cessation of bleeding, clear the rest of the bronchial tree. It may be necessary to angio-embolise the bleeding vessel later.

3. If bleeding persists: introduce a left-sided double-lumen tube over a tube exchanger, ventilate only the non-bleeding side, and transfer the patient to surgery for thoracotomy and resectional surgery.

In summary, trauma patients may present with airway, tracheobronchial, and lung bleeding of any degree of severity, from minor to torrential. The treating trauma surgeon must quickly identify those patients who respond to simple methods, possibly followed by angio-embolisation, and act on the ongoing bleeds with lung isolation and surgery.

Acute airway obstruction in the ventilated patient

The incidence of acute bronchial obstruction in patients with severe head injuries is very high. Up to 33% of brain-dead patients up for lung donation in Paris were found to have significant aspiration not detected on plain chest radiographs, and up to 5% of patients with significant head and facial trauma who arrived intubated at two large trauma centres in Johannesburg required emergency room bronchoscopy to clear obvious right upper lobe atelectasis and the bronchial tree in general (personal series).

Fibre-optic bronchoscopy has been evaluated for safety, effectiveness in clearing atelectasis, and superiority to physiotherapy [12] in the ICU setting. It was found to be effective mainly for lobar and segmental atelectasis but its use was accompanied by hypoxaemia, hypercapnia, elevation of ventilatory pressures, haemodynamic instability, worsening of cardiac ischaemia, and elevation of intracranial pressure (ICP). Comparisons to repeated, 4-hourly physiotherapy treatments do not apply in the resuscitation setting. The addition of insufflations to flexible bronchoscopy has been found to confer further advantages in a number of studies [13, 14]. Often, inspissated secretions, food, and dry blood behave like foreign bodies, and are found in the main-stem bronchi in two thirds of patients, mainly in the right bronchial tree [15].

In summary, early flexible bronchoscopy is the preferred method of bronchial clearance in the resuscitation room and during early ICU admission, when ventilation is difficult and there is evidence of aspiration and atelectasis. A large endotracheal tube is necessary to avoid some of the complications associated with flexible bronchoscopy in patients with head injuries and haemodynamic instability.

Acute pulmonary oedema during resuscitation or surgery

Neurogenic pulmonary oedema (NPO), negative pressure pulmonary oedema (NPPO), and cardiogenic pulmonary oedema (CPO) can all be encountered in the resuscitation of trauma patients.

Neurogenic pulmonary oedema is encountered in about 5% of cases of severe

head injuries, and can be life-threatening [16]. Hypoxaemia is due either to increased extravascular lung water, through a hydrostatic mechanism and capillary hypertension, or to increased permeability of the alveolar capillary wall. High tidal volumes and high PEEP are normally sufficient to reverse it, but these procedures may be contraindicated in patients with severe head injuries with increased intracranial pressure. However, PEEP has less of an effect on intracerebral pressures than originally postulated, and the effects of hypoxia in raising intracerebral pressure are far more pronounced than that of PEEP.

Alveolar recruitment manoeuvres have been shown to encourage rapid recovery from acute lung contusion and acute lung injury [17], but often rely on inverse ratios and high PEEP. Prone positioning, however, being a form of slow recruitment, has been successful in the treatment of early ARDS [18], and has recently also been used successfully in NPO [16], as long as the head is not turned to one side and the trunk is elevated. The role of prone positioning in the management of neurogenic pulmonary oedema awaits further studies.

Negative pressure pulmonary oedema normally has nothing to do with trauma, being encountered mainly in healthy individuals following extubation and unwitnessed upper airway obstruction [19]. It is thought to be caused by excessive intrathoracic force from inspiration against a critical obstruction of the upper airway. This creates transudation of fluid from the pulmonary capillaries to the interstitium and the alveoli [20]. Its treatment is re-intubation and positive pressure ventilation with PEEP.

NPPO is encountered occasionally in trauma resuscitations, following energetic ventilation and suctioning through a thin endotracheal tube, or biting onto an endotracheal tube by an awake or restless patient. This will then have the same effect as pushing against a closed glottis.

Cardiogenic pulmonary oedema is characterised by a PAWP of 18 cm of water or above, and is usually due to fluid overload, or a significant myocardial contusion. Diuretics and inotropic therapy will usually be successful in supporting the left ventricle, whereas it would be of no benefit in NPO or NPPO.

Life-threatening pulmonary contusion

Pulmonary contusion is very common in polytrauma patients, occurring in almost 17% of cases [21]. It was historically associated with blast injuries, from high explosives, and was later seen as a consequence of acceleration–deceleration injuries from traffic accidents, falls, and blunt or penetrating direct trauma to the chest. When associated with spinal injuries with spinal cord damage, its severity seems to be improved with early spinal fixation [30].

Anatomically, pulmonary contusion represents shearing or bursting of lung tissue, with an inertial and an implosion effect, mainly affecting the gas–liquid interphase, and the heavy–light interphases, leading to severe haemorrhages and hepatisation of the lung. The tissue damage caused by pulmonary contusion can be severe, to the extent that it has been found to be a more frequent cause of fat embolism syndrome than long bone fractures [29].

Ventilation is required in 20–50% of all patients, of whom 20–43 % will develop ARDS, and up to 35% will develop pneumonia.

These complications are much more marked in patients in whom over 20% of the lungs are affected by the contusion, as seen on chest CT scan. Such patients will develop ARDS in up to 90% of cases [22, 26]. Management has relied on selective intubation, ventilation on rotational beds, fluid resuscitation, adenosine-containing solutions [23], and, lately, alveolar recruitment manoeuvres [17, 23, 25, 26, 28].

Lung recruitment manoeuvres have been proposed for situations in which ventilation according to the ARDS.net guidelines failed to prevent deterioration and when there is CT scan evidence of lung contusion. Chest CT scanning is essential in order to quantify the damage to lung tissue, since plain chest radiographs may miss most lung contusions and haemothoraces [31].

The aim of lung recruitment is to keep alveoli open according to the open lung concept (OLC). Various methods have been used, including very high rates and inverse ratio, supine or sitting recruitment manoeuvres (RM), or prone positioning [33], associated with periods of 40–90 s of PEEP up to 50 mmHg, intermittent sighs, etc. This is somewhat in contrast to the classic teaching that RM are useful particularly for secondary ARDS, whereas in the context of severe lung contusion it is used for a primarily pulmonary condition.

Prone positioning was used as early as 1974 for ARDS, but has only been tried in the early phases of lung injury, irrespective of cause, by a few centres since the late 1990s [32]. Since mid-2005, we have used early prone position and RM on days 1–4 in a number of patients with severe lung contusion not responding to conventional ventilation, with rapid improvement of pulmonary function and radiographic picture in all the patients. Further studies are needed to assess the role and preferred types of alveolar RM in patients with early life-threatening lung contusion.

Massive bleeding into the chest cavity

There are no courses or elective cardiothoracic work that can prepare trauma surgeons on how to deal with exsanguinating bleeding from the chest, be it on first inserting an intercostal drain, opening the chest, or in trying to stem the bleeding at thoracotomy. The main culprits are the aorta and its branches [34–36], the cervicomediastinal venous system [37], the lung [38–40], intercostal and vertebral vessels, and the heart.

Penetrating injuries to the thoracic aorta are just as lethal now as they were 10 years ago, with 73% of victims of gunshots to the thoracic aorta arriving with an unrecordable blood pressure, and 100% mortality, irrespective of treatment. In less desperate cases, it has been suggested that femoral cardiopulmonary bypass should be instituted prior to thoracotomy, but this is only possible in patients not in extremis, such as those with a contained haematoma.

Cervicomediastinal venous injuries are probably even more frightening than major arterial injuries, mainly because of the difficulty in achieving rapid, safe control of flimsy, valveless vessels behind the sternoclavicular joints while the

patient is exanguinating. We believe the more stable the patient, the more likely is venous bleeding, and prefer to secure proximal venous control using cervical (internal jugular vein) and subclavicular (subclavian vein) incisions prior to sternotomy, whereby proximal arterial control can be secured. The key factor for a sternotomy is speed, often achieved best with a simple hammer and chisel (Lepske knife).

The lung can also bleed massively, to the extent that some damage control manoeuvre needs to be employed immediately upon opening the chest. The lung twist was described by Mattox et al., [38] and is essentially a 180° rotation, after dividing the inferior pulmonary ligament. In our institution, we routinely use a Foley catheter wrapped around the hilum of the lung extrapericardially and kept in place with an artery forceps, with excellent results.

Intercostal vessels, perivertebral vessels, and vertebral bodies can bleed profusely and persistently, particularly following high-energy gunshot wounds, with very few surgical options being available, especially for posterior injuries. One can try mobilisation of other intercostal muscles, pleural flaps, and rotating muscle flaps from outside the chest cavity, but all these methods are too unreliable and take too long for exsanguinating patients. Instead, a stepwise plan must be followed to achieve surgical control.

Because of their protected position under the furrow on the inferior aspect of the rib, indirect measures of control are often futile. We often resort to limited rib resection to rapidly control intercostals. For multiple rib fractures, we expose and secure the intercostal vessels by dissecting the mediastinal pleura over the vertebral bodies. Our best method is the use of Bio-Glue (Viking Pharmaceuticals) and Surgicel to help pack the holes, irrespective of surrounding tissue destruction. If nothing else works, damage control with tight gauze packing can be used at the first operation.

Transmediastinal gunshot wounds may vary from soft-tissue injuries to a combination of all of the injuries mentioned above, and associated oesophageal perforations [41]. Not all such patients need to be rushed to the operating room: 60% of patients presenting with a systolic blood pressure over 100 mmHg, and up to 50% of those with an initial systolic blood pressure between 60 and 100 mmHg can be treated nonoperatively. Patients with a systolic blood pressure (SBP) of less than 60 mmHg, however, must be taken immediately to the operating room, if it is near, ready, and easily accessible. If any delay in the operating room is expected, an immediate left or bilateral emergency-room thoracotomy, with Foley catheter cross-clamping of the aorta and of the hilum of the worse affected lung, must be carried out.

The timing and indications of thoracotomy for unspecified chest bleeding are controversial. Whereas the outcome of emergency room thoracotomies is generally worse than that for operating room procedures [42], it has been our experience that patients who look reasonably stable in the emergency room may deteriorate significantly in the 5–10 min that it takes to have the patient ready on the operating table.

Even patients with a systolic blood pressure of 90–100 mmHg, but requiring ongoing massive fluid resuscitation and continuing to bleed, therefore, may benefit

from an emergency room thoracotomy as the first step of their damage control management. These patients will then be treated with temporary chest wall closure, be it a Bogota Bag, towel clip closure, or other temporising measures, until they can undergo the mandatory re-look thoracotomy or sternotomy, in order to improve their survival [43]. Prospective controlled studies are, however, necessary to define this line of management.

Deterioration despite successful repair of cardiac injury

The overwhelming majority of victims of penetrating injuries to the heart die before reaching hospital. For example, 94% of 1198 patients included in a study in Natal died before reaching the hospital [2], and mortality is not much better for penetrating injuries of the chest in general, where only 16% of victims reach hospital alive.

All cardiac injuries continue to be considered a complex challenge even in centres that have to deal with them on a weekly basis [48]. The first factor to complicate the condition is the presence of other injuries to other regions or organs; the injury with the greatest blood loss will then take precedence [51].

Injuries to the coronary arteries worsen the prognosis, with mortality ranging between 5 and 50%. The lower figures are from centres using cardiopulmonary bypass [46]. Injured coronary arteries can be safely tied off if very distal, whereas proximal ones need to be grafted or stented-bypassed. Techniques used to restore distal flow in these cases are saphenous vein grafting and, more recently, intraluminal stenting applied under vision. We have used off-pump saphenous vein grafting in a small number of patients in our unit. The use of intra-aortic balloon pumps, to increase diastolic filling and reduce afterload and cardiopulmonary bypass, improved survival in a large series. A situation in which the use of cardiopulmonary bypass seems to confer a significant advantage is the presence of multi-chamber injuries [49].

Blunt or penetrating injuries to the atrioventricular conductive system have been associated with fatal or near fatal cardiac arrest from ventricular fibrillation, due to oedema, injury, or necrosis of the atrioventricular node and the proximal bundle of His [50].

Refractory hypoxaemia may occur after successful repair of penetrating cardiac injuries, and is a sign of right to left shunt somewhere in the heart; very rarely, it is caused by AV fistula in the proximal pulmonary circulation [47]. We have managed two such patients, one with a very obvious ventricular septal defect, and one with a totally silent atrial septal defect, in whom no murmur could be heard. Both patients were successfully treated by cardiopulmonary bypass.

Life-threatening myocardial contusion

Myocardial contusion is frequently suspected in blunt-trauma victims, and has been reported in anywhere between 3 and 56% of patients, most of whom were

asymptomatic and required no therapeutic intervention [52]. Evaluation using troponin T and I, specific cardiac markers, more accurately place the incidence at around 20% of patients with severe blunt chest trauma [54].

Since myocardial contusion is mainly associated with a sudden blow to the heart against the sternum and anterior rib cage, most of the injuries are found in the right ventricle. The histological findings range from oedema and haemorrhage to necrosis of the muscle fibres, similar to what is seen in myocardial infarction. In severe cases, there can be rupture of septi and cordi, pericardial effusions, and valvular rupture.

The effects of damage to the right ventricle are probably due to a reduction in right ventricular wall compliance leading to septal shift. This, together with the increased pulmonary artery resistance often found in chest trauma, leads to impairment of coronary flow and regional ischaemia [53]. The arteries most commonly affected are the LAD and the circumflex [56].

In cases of severe anatomic injury, myocardial contusion can lead to cardiogenic shock that is resistant to inotropic support, and to fatal arrhythmias [53], in around 15% of cases. Only occasionally is immediate surgery indicated, mainly for a ruptured right atrium or ventricle presenting with tamponade.

The accurate diagnosis of myocardial contusion is generally difficult, since most tests are only partially specific, and polytrauma patients can be unstable for a number of reasons. The lack of specificity rests with the fact that the ECG evaluates the larger left ventricle more accurately than the frequently injured right ventricle; thus, the ECG will be significant only when global heart ischaemia becomes apparent. The initial abnormalities may be limited to a right bundle branch block, arrhythmias, and tachycardia.

Cardiac enzymes are of very limited use as markers where there has been extensive skeletal muscle damage, whereas troponin T and I are very specific for myocardial injury, and are normally elevated from 4–6 h from the injury until 4–6 days after. If they are normal over 48 h from the injury, myocardial contusion can be safely excluded. In a recent study, patients were discharged if they had a normal ECG and normal troponin I for 8 h [57]. Elevated levels of troponin I are proportional to the severity of arrhythmia [55]. Transoesophageal echocardiography can demonstrate the anatomy, contractility, abnormal wall motion of the heart, and pericardial effusion, and is the investigation of choice in unstable patients. Positron emission tomography (PET), while promising, has not been evaluated in this setting.

In summary, myocardial contusion is often suspected and identified as a benign condition in a relatively high percentage of patients with severe chest trauma, in whom only follow up, similar to that following a minor myocardial infarction, is needed. In the few patients that are very unstable, inotropic support, aortic balloon pump, and surgery, with or without cardiopulmonary bypass, are required and are associated with a high mortality.

Controversial points requiring rapid decision-making

The following situations do not represent immediately-life threatening emergencies, and hours may be spent debating the best treatment modality. Nevertheless, trauma surgeons must be aware of the options from the moment the patient is stabilised enough to leave the resuscitation room, when different, divergent, and often clashing decisions needs to be made.

Use of noninvasive ventilation in acute trauma

Trauma patients often require ventilation for long periods of time, and are therefore at risk of ventilator-associated pneumonia [58]. Patients with a number of conditions require intubation and ventilation according to ATLS criteria, namely, oxygen saturation of less than 90%, a PaO_2 of less than 65 mmHg on room air, or a PaO_2/FiO_2 of less than 300 [59].

NIV was first advocated to treat acute respiratory failure in acute exacerbations of chronic obstructive pulmonary disease, acute pulmonary oedema, and immunocompromised states [60]. Its main advantages in hypoxaemic respiratory failure are fewer septic complications and ease of weaning. Good candidates for NIV are fully cooperative, able to protect their airways, and haemodynamically stable. In view of the need for a tight-fitting mask, the presence of a naso- or orogastric tube is a relative contraindication. Patients with head injuries, therefore, and trauma patients with copious secretions and difficult pain control, such as in multiple rib and vertebral fractures, may not do well with NIV. It is recommended that NIV be tried for not longer than 1 h, and if not successful, invasive ventilation be initiated. Absolute contraindications are previous cardiorespiratory arrest, facial trauma, upper airway obstruction, haemodynamic instability, strict supine positioning, and inability to clear secretions.

NIV has been advocated for short periods of weaning post-extubation, and we have used it in that capacity in a number of patients. Patients with flail chest may do very well or very poorly on NIV, and further studies are needed to identify good candidates among them.

We have also used NIV successfully in patients with spinal cord injury; in situations in which intubation or re-intubation and tracheostomy have been avoided; in fail chests, with mixed results; post-extubation in patients who had recovered from ARDS but still required some end-expiratory support; and, most surprisingly, in freshly extubated patients recovering from head injury with mild to moderate mental confusion, where they tolerated a tight fitting mask far better than an orotracheal tube, and in whom a tracheostomy had not been felt to be necessary.

Current management of traumatic aortic injury

The presence of a traumatic aortic rupture must be suspected in any patient with severe pelvic fractures, in those with ruptured diaphragms, and in any patient with

a significantly lower blood pressure in the lower limbs than in the upper limbs [67]. Rupture can occur anywhere in the thoracic aorta, even in the distal portion, if associated with vertebral fractures. It is classically found at the level of the isthmus, just below the origin of the left subclavian artery in horizontal mechanisms, and in the proximal arch in falls from heights.

The treatment of contained post-traumatic ruptures of the thoracic aorta has been a source of controversy since alternatives to mandatory thoracotomy and vascular grafting were first advocated in the early 1990s [62, 63]. Satisfactory results were found with nonoperative or delayed surgical treatment of contained ruptures without signs of pseudocoarctation. This has proved to be particularly useful in patients with serious associated injuries, mainly head, spinal, and abdominal injuries. Abdominal injuries with severe contamination, pancreatic, colonic injuries, and diaphragmatic injuries in particular militate against the early use of vascular grafts. Delaying surgery, however, is accompanied by lethal uncontained ruptures in at least 4% of patients, normally within the first week. Recently, a large study found that delay worsened overall mortality from 9 to 20% [64].

Surgery is not without dangers: a large number of patients start off shocked, mainly from extra-aortic causes, with cardiac risk factors, and severe associated injuries. Surgical mortality varies between 8 and 15% in various multicentre studies [66], irrespective of cardiopulmonary bypass, which, however, can lower the incidence of paraplegia from 19 to 2%, and is particularly indicated in the management of complex injuries [69].

Some patients are very poor candidates for either surgical or conservative management, such as patients with associated severe head injuries, requiring high mean arterial pressures, and those with unstable spinal injuries, in whom paraplegia may result as a direct consequence of positioning for a posterior thoracotomy.

Endovascular stent grafting was first introduced in the late 1990s following its successful use in abdominal aortic aneurysms, and its main advantages in the trauma setting are that it avoids a thoracotomy and need for ventilation. It can be carried out under local anaesthesia, does not require turning the patient, and avoids the sudden increases and decreases in intracranial pressure associated with aortic cross-clamping and unclamping. Stenting has been the method of choice in a number of units for the past few years, and it has been used more and more frequently in Johannesburg as well, mainly in the private sector, particularly for patients with the associated injuries described above. Thus, it is probably becoming the gold standard [68].

Ideal management of the flail chest

The management of flail chest aims at offering patients good pain control, avoidance of complications, such as pneumonia and respiratory failure, restoration of reasonable anatomical normality, and return to pretraumatic respiratory function [70]. The three basic methods of treatment are the following:

1. Conservative management relies on a combination of epidural analgesia, pleural blocks, transcutaneous nerve stimulation, opioids, nonsteroidals, and para-

cetamol [72] to obtain good pain control. This should be followed by physiotherapy and mobilisation.
2. Pneumatic stabilisation represents a form of internal stenting through invasive ventilation, and, more recently, NIV.
3. Surgical stabilisation consists of rib plating [71], and seems to offer significant advantages for early extubation, particularly in patients without significant lung contusion and major deformities. This approach is technically quite simple. Absorbable plates with 2-point or 1-point fixation can be used, and small incisions are made just over the areas requiring plating. No single method, however, can be recommended [72] for all categories of patients.

Patients with flail chests may have severe pulmonary contusion, and a debilitating deformity of the chest wall, or the condition may limited to ribs fractured posteriorly, and minimal signs and symptoms.

More patients than previously thought require intubation and ventilation [73]. Out of 11 patients in a prospective study, eight required intubation within 24 h, and two of these eight suffered significant complications because of a delay in treatment. All patients with significant associated injuries and co-morbidities should be intubated early, under controlled conditions. Among the patients requiring ventilation, early extubation after surgery is possible in 90% of patients without significant pulmonary contusion [76], while restoration of normal respiratory function and return to sport and work is significantly better after surgical management. Forced vital capacity is higher after surgery [75]

The incidence of acute pneumonia is significantly reduced with surgical stabilisation, as long as it is performed early, normally within 48 h.

Conclusions

Thoracic injuries rank among the most lethal encountered in blunt and penetrating trauma. Societal changes (sport utility vehicles, safety measures such as air-bags and traction control, etc.), coupled with improvements in pre-hospital response times and levels of care may allow patients with previously mortal conditions to reach the hospital in a very critical state, presenting with hitherto poorly recognised clinical scenarios.

- Haemoptysis may well respond to angio-embolisation and bronchoscopic interventions in a respiratory setting, but is more likely to require a double-lumen tube and surgery when due to an injured bronchial artery.
- Foreign bodies mean chunks of food and bone obstructing the bronchi and making ventilation impossible.
- Pulmonary oedema, be it neurogenic or negative-pressure-induced, is sometimes the final straw for a severe head injury or a severe lung contusion.
- Severe pulmonary contusion, likewise, may require ventilatory modalities previously only used in the management of secondary ARDS, such as prone positioning and alveolar recruitment.
- Unstoppable bleeding from the chest remains a constant reminder of a sur-

geon's limitations, and requires an extremely aggressive surgical approach.
- Most penetrating cardiac injuries require surgery within minutes from admission and may require cardiopulmonary bypass and coronary grafting in the middle of the night.
- Similarly, myocardial contusion, usually benign or irrelevant may be an unexpected source of mortality unless management correctly and aggressively.
- Non invasive ventilation has a very specific and unexpectedly widening place in trauma.
- Traumatic aortic injury requires early decision making
- Plating of ribs should be carried out in the first 2–3 days to avoid septic complications.

For these conditions, the literature is sketchy and experience limited. We have presented a series of novel clinical scenarios and our limited experience in dealing with them. These injuries require a paradigm shift from the conventional, and clinicians need to be able to think beyond the regularly reviewed guidelines such as ATLS and DSTC.

References

1. Boffard KD (2003) Manual of definitive surgical trauma care. Arnold, London, pp 75.1
2. Campbell NC, Thomson SR, Muckart DJ et al (1997) Review of 1198 cases of penetrating cardiac trauma Br J Surg 84:1737–1740
3. American College of Surgeons (1997) Advanced Trauma Life Support Programme, Committee on Trauma, Chicago, Ill., p 4
4. Jurkovich J, Wall M, Hoyt D et al (2001) Management of traumatic lung injury: a Western Trauma Association multicentre review. J Trauma 51:1049–1053
5. Valipour A, Kreuzer A, Koller H et al (2005) Bronchoscopy-guided topical haemostatic tamponade therapy for the management of life threatening haemoptysis. Chest 127:2113–2118
6. Kallay N, Dunagan DP, Adair N et al (2001) Haemoptysis in patients with renal insufficiency. Chest 119:788–794
7. Reisz G (2005) Topical haemostatic tamponade. Chest 127:1888–1889
8. Chinsky K (2005) Bleeding risk and bronchoscopy. Chest 127:1875–1877
9. Kabon B, Waltl B, Leitgeb J et al (2001) First experience with fiberoptically directed wire-guided endobronchial blockade in severe pulmonary bleeding in an emergency setting. Chest 120:1399–1402
10. Yoon W, Kim JK, Kang HK (2002) Bronchial and non bronchial systemic artery embolization for life-threatening haemoptysis. Radiographics 22:1395–1409
11. Jougon J, Ballester M, Delcambre M et al (2002) Massive Haemoptysis: what place for medical and surgical treatment? Eur J Cardiothorac Surg 22(3):345–351
12. Kreider M, Lipson DA (2003) Bronchoscopy for atelectasis in the ICU. Chest 124:344–350
13. Haenel JB, Moore FA, Moore EE (1992) Efficacy of selective intrabronchial air insufflation in acute lobar collapse. Am J Surg 164:501–505
14. Van Heerden PV, Jacob W, Cameron PD (1995) Bronchoscopic insufflation of room air for treatment of lobar atelectasis in mechanically ventilated patients. Anaesth Intensive Care 23:175–177

15. Dikensoy O, Filiz A (2002) Foreign body aspiration: clinical utility of flexible bronchoscopy. PMJ Online 78:399–403
16. Fletcher SJ, Atkinson JD (2003) Use of prone ventilation in neurogenic pulmonary oedema. Brit J Anaesth 90(2):238–240
17. Schreiter D, Reske A, Christoph J (2004) Alveolar recruitment in combination with sufficient positive end-expiratory pressure increases oxygenation and lung aeration in patients with severe chest trauma. Crit Care Med 32(4):968–975
18. Slutsky AS (2001) The acute respiratory distress syndrome, mechanical ventilation and the prone position. N Engl J Med 345:610–11
19. Ackland G, Mythen M (2005) Negative pressure pulmonary oedema as an unsuspected imitator of acute lung injury/ARDS. Chest 127:1867–1868
20. Goli AK, Roy TM (2003) Spontaneous negative pressure changes: an unusual case of noncardiogenic pulmonary oedema. J Ky Med Assoc 101(8):317–320
21. Cohn S (1997) Pulmonary contusion: review of the clinical entity. J Trauma 42(5):973–979
22. Miller P, Croce M, Fabian T (2001) ARDS after pulmonary contusion: accurate measurement of contusion volume identifies high-risk patients. J Trauma 51(2):223–230
23. Kelly M, Fabian T (2003) Novel resuscitation strategy for pulmonary contusion after severe chest trauma. J Trauma 55(1):94–105
24. Marini J (2001) Recruitment manoeuvres to achieve and 'open lung' – whether and how. Crit Care Med 29(8):1647–1648
25. Barbas V, Silvia C (2003) Lung recruitment manoeuvres in ARDS and facilitating resolution. Crit Care Med 31(4):S265-S271
26. Gattinoni L, Pelosi P, Goodman L (2001) What has CT taught us about ARDS? Resp Crit Care Med 164(9):1701–1711
27. Chae-Man L, Jung H, Kim WD (2003) Effect of alveolar recruitment manoeuvre in early acute respiratory distress syndrome according to antiderecruitment strategy, etiological category of diffuse lung injury, and body position of the patient. Crit Care Med 31(2):411–418
28. Grasso S, Brochard L, Slutsky A et al (2002) Effects of Recruiting Manoeuvres in patients with ARDS ventilated with protective ventilatory strategy. Anesthesiology 96(4):795–802
29. Aydin MD, Gundogdu C (2005) Cerebral fat embolism: pulmonary contusion is a more important aetiology than long bone fractures. Clin Neuropathol 24(2): 86–90
30. Kerwin AJ, Frykberg ER (2005) The effect of early spine fixation on non neurologic outcome. J Trauma 58(1):15–21
31. Massarutti D, Berlot G, Carchietti E (2004) Abdominal ultrasonography and chest radiography are of limited value in the emergency room diagnostic work-up of severe trauma patients with hypotension on the scene of accident. Radiol Med (Torino) 108(3):218–224
32. Hormann C, Hartlieb S (1994) The prone position in ARDS. A successful therapeutic strategy. Anaesthetist 43(7):454–462
33. Broccard A (2003) Prone position in ARDS. Chest 123(5):1334–1336
34. Demetriades D, Velmahos G, Berne TV (1996) Mortality and prognostic factors in penetrating injuries of the aorta. J Trauma 40(5):76–79
35. Hoffberger J, Savage E (2005) Penetrating trauma of the aortic arch: a case report. J Trauma 58(2):381–383
36. Dosios T, Emmanuel MD (2000) Blunt and penetrating trauma of the thoracic aorta and aortic branches. J Trauma 49(4):696–703

37. Nair R, Robbs JV, Muckart DJ (2000) Management of penetrating cervicomediastinal venous trauma. Eur J Vasc Endovasc Surg 19:65–69
38. Wilson A, Wall M, Mattox K (2003) The pulmonary hilum twist as a thoracic damage control procedure. Am J Surg 186(1):49–52
39. Karmy-Jones R, Knudson MM, Hoyt D (2001) Management of traumatic lung injury: a western trauma association multicentre review. J Trauma 51(6):1049–1053
40. Cothren C, Moore EE, Burch J (2002) Lung-sparing techniques are associated with improved outcome compared with anatomic resection for severe lung injury. J Trauma 53(3):483–487
41. Renz B, Feliciano D, Rozycki G (2000) Transmediastinal gunshot wounds: a prospective study. J Trauma 48(3):416–421
42. Balkan ME, Oktar GL, Ergul EG (2002) Emergency room thoracotomy for blunt thoracic trauma. Ann Thorac Cardiovasc Surg 8 (2):78–82
43. Vargo, DJ, Battistella FD (2001) Abbreviated thoracotomy and temporary chest closure: an application of damage control after thoracic trauma. Arch Surg 136(1):21–24
44. Campbell NC, Muckart DJ, Thomson SR (1997) Review of 1198 cases of penetrating cardiac trauma. Br J Surg 84:1737–1740
45. Bowley D, Boffard KD, Davis S (2002) Off-pump cardiac revascularization after a complex stab wound. Ann Thorac Surg 74(6):2192–2193
46. Fedalen P, Garcia J (2001) Intraluminal shunt placement and off-pump coronary revascularization for coronary artery stab wound. J Trauma 50(1):133–135
47. Dairywala I, Herbert P, Talucci R (2005) Severe refractory hypoxemia following a gunshot injury. Chest 127:398–401
48. Asensio JA, Soto SN, Demetriades D (2001) Penetrating cardiac injuries: a complex challenge. Surg Today 31(12):1041–1053
49. Baker JM, Battistella FD (1998) Use of cardiopulmonary bypass to salvage patients with multiple-chamber heart wounds. Arch Surg 133(8):855–860
50. Inoue H, Nishida N (2004) Case report: an autopsy case of fatal arrhythmia induced by injuries of the atrioventricular conduction system. Med Sci Law 44(4): 353–358
51. Saadia R, Degiannis E, Levy RD (1997) Management of combined penetrating cardiac and abdominal trauma. Injury 28(5–6):343–347
52. Sybrandy KC, Cramer MJM, Birgersdijk C (2003) Diagnosing cardiac contusion: old wisdom and new insights. Heart 89:485–489
53. Penney DJ, Parr MJA (2002) Intra-aortic balloon counterpulsion for cardiogenic shock due to cardiac contusion in an elderly trauma patient. Resuscitation 55(3):337–340
54. Lang-Lazdunski L, Mouroux J, Jancovici R (1997) Role of videothoracoscopy in chest trauma. Ann Thorac Surg 63(2):327–333
55. Rajan GP, Zellweger R (2004) Cardiac Troponin I as a predictor of arrhythmia and ventricular dysfunction in a trauma patient with myocardial contusion. J Trauma 57(4):801–808
56. Naseer N, Frishman WH (2003) Circumflex coronary artery occlusion after blunt chest trauma. Heart Dis 5(3):184–186
57. Velmahos GC, Salim A, Asensio J et al (2003) Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. J Trauma 54(1):45–51
58. Garfield MJ, Howard-Griffin RM (2000) Non invasive positive pressure ventilation for severe thoracic trauma. Br J Anaesthesia 85(5):788–790
59. Vidhani K, Parr M (2002) Should we follow ATLS® guidelines for the management of traumatic pulmonary contusion: the role of NIV. Resuscitation 52(3):265–268

60. Liesching T, Kwok H, Hill N (2003) Acute application of NIPPV. Chest 124:699–713
61. Nava S, Ceriana P (2004) Causes of failure of non-invasive mechanical ventilation. Respiratory Care 49(3):295- 303
62. Langanay T, Verhoye JP, Corbineau H et al (2002) Surgical treatment of acute traumatic rupture of the thoracic aorta. Eur J Cardiothorac Surg 21:282–287
63. Holmes JH, Hall RA, Karmy-Jones RC (2002) Natural history of traumatic rupture if the thoracic aorta managed non operatively. Ann Thorac Surg 73:1149–1154
64. Hemmila M, Rowe S, Wahl W (2004) Delayed repair for blunt thoracic aortic injury: is it really equivalent to early repair. J Trauma 56(1):13–23
65. Amabile P, Piquet P (2004) Surgical versus endovascular treatment of traumatic thoracic aortic rupture. J Vasc Surg 40(5):873–879
66. Jahromi AS, Safar HA, Cina CS (2001) Traumatic rupture of the thoracic aorta. J Vasc Surg 34:1029–1034
67. Ochsner MG Jr, Champion HR (1989) Pelvic fracture as an indicator of increased risk of thoracic aortic rupture. J Trauma 29(10):1376–1379
68. Uzieblo M, Sicard GA (2004) Endovascular repair of traumatic thoracic aortic disruptions: should endovascular surgery become the gold standard. Vasc Endovasc Surg 38(4):331–337
69. Miller PR, Meredith JW (2003) Complex blunt aortic injury repaired: beneficial effects of cardiopulmonary bypass use. Ann Surg 237(6):883–884
70. Bloomer R, Willett K, Pallister I (2004) The stove-in chest: a complex flail chest injury. Injury 35(5):490–493
71. Voggenreiter G, Neudeck F, Neuerburg KPS (1998) Operative chest wall stabilization in flail chest: outcome with or without pulmonary contusion. J Am Coll Surg 187(2):130–138
72. Karmakar MK, Ho AM (2003) Acute pain management of patients with multiple fractured ribs. J Trauma 54(3):615–625
73. Velmahos GC, Demetriades D (2002) Influence of flail chest on outcome among patients with severe thoracic cage trauma. Int Surg 87(4):240–244
74. Mayberry JC, Mullins RJ (2003) Absorbable plates for rib fracture repair: preliminary experiences: J Trauma 55(5):835–839
75. Tanaka H, Shimazaki S (2002) Surgical stabilization or internal pneumatic stabilization? A prospective randomized study of management of severe flail chest patients. J Trauma 52(4):727–732
76. Lardinois D, Ris HB (2001) Pulmonary function testing after operative stabilization of the chest wall for flail chest. Eur J Cardiothorac Surg 20(3):496–501

Chapter 67

Application of new educational methodologies in disaster medicine

F. Della Corte, A. Gratarola, F. La Mura

Commonly, Disaster Medicine educational issues are often related to the Emergency Medicine domain, even though in Europe there is no clear definition about these two subjects. Yet, following the extraordinary succession of natural and technological disasters in Europe during the past several years (e.g. Chernobyl, flooding, forest fires), the governments belonging to the European Union are putting increasing pressure on national entities (ministries, universities, hospitals, local governments, etc.) to develop official plans, protocols, and guidelines that can be implemented in case the regular 'pathways' fail at any level. The study of disaster situations is included in the core curriculum of many schools at the undergraduate and post-graduate level (ranging from Architecture to Computer Science to Economics), and the possibility of short-, medium-, and long-term chain-reaction effects involving the environment and affected population are being examined. At least in Europe, the body of knowledge belonging to the study of Medicine, despite being very rich and formally exhaustive, is mostly oriented to the ideal situation of doctor and patient, rather than to the occurrence of any type of system failure causing a massive number of casualties and the need to provide treatment, even in hostile environments and over time. Two core subjects, Epidemiology and Occupational Medicine, offer students the possibility to think in terms of hundreds to millions of patients. Disaster Medicine attempts to be multidisciplinary [1], and ideally includes:

1. Emergency Medicine
2. Epidemiology/Public Health
3. Internal Medicine
4. Psychiatry
5. Infectious Disease
6. Occupational Medicine

Of course, such an extensive range of subjects is not enough to either distinguish Disaster Medicine as a distinct teaching area, nor to differentiate it from Emergency Medicine as a new chapter in Medical Science. The need/resource ratio [2] is often used to define an emergency (ratio tending to zero) versus a disaster (ratio tending to 1) situation, following the form of a bi-dimensional plot. Disaster Medicine enlarges the scope of this matrix, in that it has a third dimension, time (disasters last days, weeks, months, years), and its base is not the strict time and place where medical emergencies physically occur and are recognised as such. Thus, while Emergency Medicine teaching and training help students to face sudden events in

the best possible way, the word 'sudden' is not the main connotation of disasters and 'training' is not the keystone of the educational effort and learning process.

The tentative difference between Education and Training helps to understand the need for a new educational entity devoted to Disaster Medicine (as a body of knowledge, official school subject, etc.).

Education addresses:

1. Problem solving
2. Conditions of uncertainty
3. Data that are difficult to interpret or messy or missing
4. 'Time' factors that are difficult to estimate
5. Making new hypothesis, proving them
6. Making new hypothesis on the basis of previous success/mistakes

Training has to do with:

1. Gaining skills
2. Following protocols
3. Making decisions, even quickly and under hostile conditions, on the basis of pre-determined pathways and possibilities, perhaps by using highly branched decision trees

While the potential theatre for Emergency Medicine is based on the space–time–action unity triad, those three variables are neither clearly related nor easily depicted in a disaster scenario.

Use of computer-based tools for real-time simulations in emergency and disaster medicine teaching

Overview

Over the past 20 years, three distinct classes of distributed, interactive real-time applications have become prominent: military simulations [3], networked virtual environments (NVEs) [4], and multiplayer computer games (MCGs) [5]. The focus of scientific research has shifted from military simulations (the 1980s) to NVEs (the 1990s), and, currently, to MCGs. Moreover, the entertainment industry is investing seriously in MCGs, mobile gaming, and online gaming in general.

Military simulations are mentioned here for their approach to the simulation of a team working in a hostile environment. The United States Department of Defense has been developing networked military simulations since the 1980s. The first developed protocol was SIMNET, which was aimed at providing interactive networking for real-time, human-in-the-loop battle engagement simulation, and war-gaming [6]. To achieve this goal, SIMNET attempted to provide functional fidelity rather than accurate physical reproduction. Current military research efforts concentrate on developing systems based on high-level architecture (HLA), which was issued as IEEE Standard 1516 in 2000 [7]. HLA aims at providing a general architecture and services for distributed data exchange. It does not prescribe any specific implementation or technology.

Networked virtual environments are mainly designed for local use and to support only a small number of participants. Usually, NVEs also pay closer attention to virtual representations of the participants (i.e. avatars) and to collaboration between participants (e.g. operating at the same time with a shared object). Reality Built For Two (RB2), BrickNet, DIVE, MASSIVE, and COVEN are some of the historically important NVE implementations.

Multiplayer computer games have been dealt with only marginally in the scientific literature, until recently. The reports have usually concentrated on simple games and limited problem settings. Current efforts at the European level consider MCGs as main parts of granted projects, such as e-DISTRICT CiPro [8] (European DIStance TRaining Interactive and Collaborative Tools for Civil Protection) and I-SEE [9] (Interactive Simulation Exercise for Emergencies), both of which are supported by the EU Leonardo da Vinci Project 2000–2006.

Goals and pitfalls in the use of virtual reality in emergency and disaster medicine

Medical literature has for several years predicted a break-through in virtual reality technologies for medical education. While there probably is a great potential for this technology, there seems to be a wide gap between expectations and actual possibilities, at least at present. The majority of publications about virtual reality (VR) and medicine, are focused on surgical education for undergraduates and postgraduate students, and the authors' main goals and concerns seem to be how to provide the best three-dimensional representation of reality, with high-level accuracy, for micro-/gross anatomy, physiology and pathology. Such programs are often described as 'flight simulators for doctors,' they aim to ensure the most effective off-patient training, in which a single trainee faces his/her virtual patient (VP) in a one-on-one setting. But as a matter of fact, the degree of graphical accuracy does not represent any degree of 'realism,' and many other factors are known to play an active role in the virtual recreation of reality, especially considering that a VP is not only 'anatomy,' but a complex software agent that ideally puts the physician in the most 'real' scenario. A phenomenological study published in 2003 by Bearman indicated that a constructed, computer-based VP can have substantial emotional effects on medical students [10], and that the emotions are not likely only to occur in the presence of a 'cold' even if detailed graphical environment. Nevertheless, the occurrence of emotional reactions during a VP simulation session may somewhat be considered as a fair approximation to realism. If surgical simulations seem to be a cost-effective training approach to surgical practice, no major evidence can be found in the literature about similar benefits of VR applied to other fields of Medicine, such as Emergency Medicine and, to some extent, Disaster Medicine. The characteristics that clearly differentiate emergency medical care from remaining hospital medical practice involve the fact that, in the latter, the patients are grouped according to age and nature of illness or injury and the patient load is controlled, planned, and predictable [11]. In emergency situations, the classical vertical pathway of medical thinking in patient care is most of the time reversed, changing from 'diagnosis > therapy' to 'therapy > diagnosis,'

the latter meaning that the doctor must have high flexibility and interdisciplinary knowledge in order to establish the right treatment priorities that make the difference between life and death in critical settings. While the triage of priorities related to a single or a few patients is one of the principal characteristics of 'classical' Emergency Medicine, the tentative triage of both patients and resources comprises one of the main aspects of Disaster Medicine.

The Hospital Disaster Preparedness (HDP) modular course as a framework for research, education, and specific training in Disaster Medicine

The HDP course [12], issued within the European Master in Disaster Medicine (EMDM), has as its main goal how to set up hospital preparedness for the admission of a large number of casualties in the hospital. One of the course's motivations is that almost everywhere in the world well-defined laws exist that define the need for a hospital plan concerning the admission of a large number of patients after a mass casualty/disaster. However, very often, even if such a plan has been created, it has never been tested with a drill or in real emergencies. The main objective of the course are therefore the following: (1) to identify the possible risk factors in a given area, (2) to manage resources that will be used to implement the plans, and (3) to test the plans within a simulated disaster through a simulation game provided in a proper simulation environment.

Identifying the possible risk factors in a given area: Welcome to Riceland

The virtual HDP geopolitical area is called Riceland, and every virtual citizen (actually users from the whole world) is given a 'passport' and a virtual identity to enter. Riceland is composed of towns, mountains, rivers, lakes, and industrial infrastructures. Every player has a clearly defined role, such as Mayor, Hospital Director, Minister, etc, and she/he is expected to interact both with the other players and with the Game Masters. The land is provided as a digital land embedded in a web-based e-learning environment.

Managing the resources that will be used to implement the plans: Spending two months in Riceland

The citizens are expected to play the game during a time-frame of 2 months (in the EMDM version of HDP). This differentiates Riceland from any other existing MCGs; i.e. the simulation of 'real life' in the sense that the effects of political, economic, logistical, and medical decisions have consequences over time and may contribute to preventing a disaster situation, or to decreasing the risk of one. While Riceland provides a graphical interactive representation of what happens in the digital land, it also has the characteristics of a role-playing game. At the end of the

2 months, the players and their teams—who are led to a completely new situation compared to the initial one (and always different from previous 'matches' played on the same platform)—must upload their own Hospital Disaster Preparedness plan onto the e-learning environment. The teams have the possibility to ask for structural changes in the buildings (e.g. one more back-up hospital entrance), and must face the eventuality that large failures in infrastructure occur following a disaster simulated in Riceland. The disasters are not driven by Artificial Intelligence agents, but are administered by the team of Masters supervising the game, and implemented and experienced within the game platform. The current game platform is called "HDPnetS" [14].

Testing the plans within a simulated disaster through a simulation game provided in a proper simulation environment

Once the teams are satisfied with their work, the HDP plans belonging to each single hospital in Riceland (there are 5–6 main towns and hospitals currently) is tested using a networked virtual environment for real-time disaster simulation. Every hospital (and all the teams) are confronted with a massive influx of casualties, issues related to the communications with the EMS during the virtual drill, communications (or lack thereof) with other hospitals and structures, the occurrence of sudden infrastructure failure, such as failure of buildings or even the hospital itself, roads, etc. The very next day after the virtual real-time simulation, EMDM students take part in a real-size drill that is organised and arranged as it was in Riceland on the day of the virtual disaster. During the live-in course of the Fifth Edition of the EMDM, 30 students from all over the world participated in the drill, which was organized in the town of Casalvolone (Novara, Italy). Almost the entire town was the setting of the simulation, with real building failures (fires, etc), real policemen, firemen, Red Cross, and more than 50 casualties played by undergraduate sixth-year medical students, who 'learned' Disaster Medicine by being 'realistic' victims and changing their status according to good or bad moves made by the players.

Conclusions

Training tools alone are not likely to be effective without an instructional framework to lend them sense. Even the best performance obtained using a training tool such as a basic life support (BLS) or advanced life support (ALS) manikin (and a student's retention curve and its optimisation over time [13]) will not result in making a person a good healthcare provider. Moreover, the tools commonly used for training in Emergency Medicine are not necessarily the best ones within a Disaster Medicine educational setting, since they mostly focus on post-event reduction of the level of 'improvisation' within the acute phase and occur in a narrow time-frame and a very specific area, rather than enlarging the scope to a wider area (metropolitan, national, international) and a wider time-frame (including the pre-disaster assessment phases, etc.). The HDP–Riceland experience was very

encouraging, from the teachers' and the learners' perspective, and by fulfilling the possible criteria for effective simulation exercises in Disaster Medicine. The results of this experience will be published in the near future.

References

1. Delooz H, Debacker M, Della Corte F (2003) The European Master Program in Disaster Medicine. International Journal of Disaster Medicine 1:35–41
2. de Boer J (1999) Order in chaos: Modeling medical management in disasters. Eur J Emerg Med 6(2):141–148
3. United States Department of Defence. Defence Modeling and Simulation Office. http://www.dmso.mil/
4. Singhal S, Zyda M (1999) Networked virtual environments: design and implementation. Addison Wesley, New York
5. Smed J, Kaukoranta T, Hakonen H (2001) Aspects of networking in multiplayer computer games. In: Sing LW, Man WH, Wai W (eds) Proceedings of International Conference on Application and Development of Computer Games in the 21st Century. Hong Kong SAR, China, Nov 2001, pp 74–81
6. Alluisi EA (1991) The development of technology for collective training: SIMNET, a case history. Hum Factors 33(3):343–362
7. United States Department of Defence, Defence Modeling and Simulation Office. High Level Architecture. http://www.dmso.mil/public/transition/hla/
8. e-DISTRICT CiPro, European DIStance TRaining Interactive and Collaborative Tools for the Civil Protection, EU Leonardo da Vinci project 2000–2006. http://www.edci-pro.org
9. I-SEE, Interactive Simulation Exercise for Emergencies, EU Leonardo da Vinci project, 2000–2006. http://www.iseeproject.org
10. Bearman M (2003) Is virtual the same as real? Medical students' experiences of a virtual patient. Acad Med 78(5):538–545
11. Delooz H (1992) Emergency medicine: An anaesthesiologist's concept. Baillieres Clin Anaesthesiol 6(1):1–23
12. Della Corte F, La Mura F, Petrino R (2005) E-learning as educational tool in emergency and disaster medicine teaching. Minerva Anesthesiol 71:181–195
13. Wik L, Myklebust H, Auestad BH et al (2002) Retention of basic life support skills 6 months after training with an automated voice advisory manikin system without instructor involvement. Resuscitation 52(3):273–279
14. HDPnetS^{TM}, Hospital Disaster Preparedness networked Simulator^{TM}, www.hdpnets.com

Chapter 68

Terrorist attacks: what have we learned?

P. Singer

Terrorism and mass casualties have become a part of modern life. Such events, in Madrid, Istanbul, Tel Aviv, New York, or, recently, London, just outside the British Medical Association House, have made it to clear to members of the medical profession that any doctor may be called upon to treat and manage patients injured in explosions [1]. Explosions are by far the most common cause of casualties associated with terrorism. Following the description by Zuckerman [2] of injuries caused by explosives during World War II, and the initial management guidelines contained within the Advanced Trauma Life Support (ATLS), advice and guidance on the management of casualties have progressed and improved in terms of medical approach and ethical considerations. The use of metallic objects to inflict penetrating injuries in crowded civilian settings is nowadays relatively frequent, with implications for triage, diagnosis, treatment, hospital organisation, and of surgical capacity [3]. Finally, increased attention is being given to the moderately injured, as they may face immediate life-threatening injuries, including multiple soft-tissue entry sites, and thus require rapid diagnosis and damage control. The challenging issues raised by the increased need to treat victims of terrorist attacks are detailed in this chapter.

Epidemiology data

Israeli experience

In a recent review [4], we summarised the incidents reported in Israel related to terrorist acts committed with conventional weapons. In the period of the second intifada, from September 29, 2000 to July 13, 2005, 7 307 people (5 102 civilians and 2 205 security-force personnel) were injured and 1 058 (740 civilians and 318 security-force personnel) were killed [5]. The epidemiology of terror-related traumatic injury has been described in adults [6, 7] and in children [8] (Table 1). From a total of 561 adult patients with terror-related injuries, 26% needed intensive care, 55% suffered from open wounds, and 31% from internal injuries. In children, there were 138 hospitalisations due to terror compared with 8 363 for non-terror-related injuries. The terror victims were older (12.3 ± 5.1 vs 6.9 ± 5.3 years, $P < 0.0001$) and more frequently sustained penetrating injuries (54% vs 9%). The main injuries were internal injuries to the torso, open wounds of the head, and critical injuries.

These required more intensive-care resources (33% vs 8% in the comparison group), longer hospitalisation, and greater need for rehabilitation.

Table 1. Epidemiology of terror-related versus non-terror-related traumatic injury in adults and children (adapted from [5, 6])

	Adults			Children		
	Terror	Non-terror	*P* value	Terror	Non-terror	*P* value
Number	561	22 487		138	8 363	
Age years	61% (15–29 years)	23% (15–29 years		12.3 ± 5.1	6.9 + 5.3	0.001
Penetrating wounds	55%			54%	9%	0.001
Torso wounds	38%			11%	4%	0.001
Open wounds to head		Not reported		13%	6%	0.001
ICU	26%	8%		33%	8%	0.001
Median length of hospital stay	5 days	3 days	0.001	5 days	2 days	0.001
Rehabilitation				17%	1%	0.001

World experience

Arnold et al. [9] described 29 terrorist bombings, producing 8 364 casualties, 903 immediate deaths, and 7 461 immediately surviving injured. Immediate mortality rates and hospitalisation rate were, respectively, 25% and 25%, 8% and 36%, and 4% and 15% in structural collapse, confined spaces, and open spaces. Unique patterns of injury were found in all bombing types and are described below.

The data obtained can teach us that most of the deaths were immediate and untreatable. Between 48% and 94% of the victims arrived in emergency rooms, 15–36% were hospitalised, and the mortality rate was less than 1%.

The lesions encountered vary according to environment and type of bombing. Many events have been included in this study, including structural collapse, such as occurred in Bologna [10], Beirut, Buenos Aires, Oklahoma [11], Dharan, and Nairobi; explosions in a confined space, such those in Belfast, London, Birmingham, Paris, Berlin, Jerusalem [12], Istanbul, and Bali [13]; or explosions in open space, as in Belfast, London, Tel Aviv, and Jerusalem [14].

The outcome of 29 mass casualty terrorist bombings showed that a large number of injuries and deaths occurred immediately after structural collapse. There were 4 257 injured and 213 immediate deaths in Nairobi in 1998, and 759 injured and 163 immediate deaths in Oklahoma City in 1995. Confined space or open-air explosions resulted in far fewer victims. Combining the data from all of the mass casualty injuries resulting from the above-listed incidents, the median number of injured was 94; per event, 76 immediately survived the attack and 18 required prolonged hospitalisation. The rate of immediate mortality was 25%, 8%, and 4% for structural collapse, confined space explosions, and open-air explosions, respectively. Thus, in injured survivors, the three types of mass-casualty terrorist

bombings produce unique patterns with respect to mortality, the number of injured victims who immediately survived, the need for hospitalisation, and injury rates. Table 2 lists the injury rates by bombing type and according to the environment.

Table 2. Injury rates according to bombing type. All values are pooled percentage, with 95% CI followed by median percentage with IQR (adapted from [9, 18])

Injury	Structural collapse	Confined space	Open space
Pulmonary blast	5 (2–7)	21 (0–46)	7 (4–11)
Pneumothorax	1 (1–2)	13 (4–29)	3 (1–6)
Blast lung syndrome	1 (0–3)	16 (0–37)	5 (3–9)
Tympanic rupture	2 (1–4)	35 (16–54)	5 (0–15)
Penetrating soft tissue	66 (61–71)	41 (14–67)	86 (58–100)
Intestinal perforation	1 (0–6)	3 (0–6)	0 (0–2)
Eye	4 (1–10)	6 (0–15)	1 (0–3)
Penetrating abdomen	1 (0–1)	2 (0–4)	3 (0–8)
Penetrating vascular	2 (1–3)	2 (0–5)	1 (0–3)
Fracture	13 (11–15)	20 (0–48)	6 (3–11)
Amputation	2 (0–3)	3 (0–6)	1 (0–4)
Intracranial injury	2 (1–3)	3 (0–6)	1 (0–3)
Liver or spleen	1 (0–2)	2 (0–4)	1 (0–3)
Burn	1 (1–2)	22 (16–28)	1 (0–2)
Inhalation	2 (1–4)	NR	NR
Crush	3 (0–8)	NR	NR

Description of lesions

Most terrorist attacks have involved explosive devices. Bombs such as those used in Madrid [15] or London [3] are easy to produce and can injure or kill many people. Improvised devices can also inflict severe injuries, especially if they are loaded with metallic objects. A recent review [16] described the different types of blast injury. Primary blast injury is caused by barotrauma, and the direct effect of over or under pressurisation can lead to rupture of the tympanic membrane, pulmonary damage, and rupture of hollow viscera. Secondary injury is induced by metallic fragments and other particles present in the explosive devices, or by projectiles. Penetrating injury can be tremendously devastating. Tertiary blast injury is caused by structure collapse and large airborne fragments, leading to crush injury and extensive blunt trauma. Finally, quaternary blast injury is related to diseases or complications, such as burns, asphyxiation, radiation, and inhalation of dust, or other complications not linked to primary, secondary, or tertiary blast injury.

Peleg et al. [7] compared the injuries induced by terrorist gunshot wound (GSW) and by explosion. In 1 033 patients, 54% were victims of explosion, 36% had suffered GSW, and 10% had been injured by other means. Most of the patients were young males. Open wounds were found in a higher proportion in GSW (63%) than in blast (53%) victims. Fractures were also more frequent in the GSW group (42% vs 31%). However, injuries to multiple body regions were significantly more fre-

quent in explosion victims (62% vs 47%). ICU median stay was 4 (2–9) days in the explosion group and 3 (1–5) days in the GSW group. Explosion victims had more fatal but also more minor injuries, and longer hospital stay. A larger proportion of gunshot victims died during the first day (97% vs 58%). Overall mortality was 7.8% in the GSW group and 5.3% in the explosion group.

Israel was the field of intense terrorist activity between September 2000 and November 2004. The 135 successful attacks led to a casualty toll of 1 058 killed and 7 307 injured. Most of the suicide bombings occurred in open spaces, buses, and semi-confined spaces. Almogy et al. [17] reviewed the experience of the six trauma centres registered by the National Trauma Registry. Open-space attacks had a median number of 28 (range 4–60) victims and one (range 0–3) fatality. Bus attacks were more dramatic, with a median of 40 victims (range 22–50) and nine fatalities (range 7–15). Attacks in semi-confined space attacks resulted in a larger number of injured (median 70; range 55–119) and a higher number of fatalities (15/attack, range 12–16). The presence of shrapnel in the explosive device increased the number and severity of the injuries. The universal response of hospitals to attacks in crowded places has been:

- Evacuation of the emergency room
- Cessation of operating room activity
- Mobilisation of personnel.

Triage aspects

The lessons we have learned in Israel from those 4 years of experience have been mainly at the triage level [18]. Many victims are brought to the admitting area over a period of minutes by pre-hospital personnel and by private means. The response procedure that has evolved is as follows:

- A trauma-qualified surgeon waits at the entry of the emergency room to perform triage. Homodynamic instability and severe respiratory distress are always suspected. Evaluation and treatment of the severely injured are initiated.
- Attention is given to identify those patients suffering from blast-induced lung injury and those with multiple-entry-site wounds and extensive tissue damage. Both groups require high-level care or surgery.
- Chest drains have to be inserted quickly in case of acute respiratory distress after the blast.
- The surgeon and the intensive care specialist have to reevaluate the patients many times, weighing the need for imaging studies, surgical procedures, and admission to the ICU. Hypotensive victims of suicide bombing attacks who have abdominal/thoracic injuries believed to contribute significantly to their instability are taken to the operating room. Many of these victims have shrapnel injuries, and since the attackers usually approach victims from behind, many entry-site injuries are located on the patients' backsides. Almogy et al. [17] proposed modifying the approach to damage control of these patients and to achieve haemostasis of lesions located in the back before positioning the patient in the supine position for routine abbreviated laparotomy. The London experience,

which involved nail bombings, resulted in a recommendation of debridement without any reconstructive procedures, and of delaying closure/split skin grafting [3].

ICU issues

Epidemiological studies demonstrated that the victims of terror-related trauma had a higher ISS, and were admitted at a higher rate to the adult and paediatric intensive care departments (22.8% of hospitalised adults and 36% of children) than patients with non-terror-related medical conditions [7, 8]. Victims of terrorist attacks also had a longer hospital stay. Thus, in case of terrorist attacks, ICU beds should be made available.

Blast injury of the lungs

Tympanic-membrane rupture serves as a sensitive marker for blast injury. However, patients without ruptured tympanic membranes may also develop blast lung injury [19]. As shown in one study [19], 142 victims had perforated eardrum and 31 had combined otic and pulmonary injuries. From the Madrid train bombing, rupture of tympanic membranes occurred in 99 of the 243 victims and chest injury in 97 [15]. The lung is the second most susceptible organ to primary blast injury. Pizov et al. [20] proposed a blast lung injury (BLI) score based on a retrospective study of 15 patients with primary BLI resulting from explosions on civilian buses. Patients were classified as severe, moderate, or mild according to their PaO_2/FIO_2, radiological findings, and existing barotrauma (pneumothorax or bronchopleural fistula). In this series, five patients had mild BLI (PaO_2/FiO_2 200 mmHg, localised lung infiltrates on chest radiograph, no evidence of bronchopleural fistula), six had moderate BLI (PaO_2/FiO_2 60–299 mmHg, bilateral and asymmetric chest infiltrates), and four had severe BLI (PaO_2/FiO_2 60 mmHg, massive bilateral infiltrates, bronchopleural fistula present). Respiratory failure was the major cause of death in two patients with severe BLI but in none of those with mild or moderate BLI. Ventilatory support was mandatory in all patients with severe BLI. In 17 victims of BLI, a pressure-limit strategy was applied and no victims developed barotraumas. Despite the subsequent hypercapnia, patients remained haemodynamically and metabolically stable [21]. In case of head injury, permissive hypercapnia may be less acceptable. High-frequency oscillatory ventilation has been proposed [20] to prevent overdistension and damage to the alveoli, and some preliminary results show encouraging results [20]. The use of extracorporeal membrane oxygenation may aggravate pulmonary haemorrhage and should be carefully prescribed.

Air embolism is another recognised complication of BLI and may be due to disruption of alveolar septae and interstitial vessel walls [22]. Autopsy studies demonstrated that air embolism exists in most patients suffering from adult respiratory distress syndrome. In addition, animals exposed to different levels of blast were depleted in antioxidants, such as vitamin C, vitamin E, and glutathione,

and had increased levels of nitric oxide and lipid peroxidation [23]. Hypoxia may generate free-radical reactions, thereby destroying lung and vessel walls.

Bleeding and factor VII

Initial ICU management is directed to achieving optimal oxygenation and perfusion. Shock resulting from external or internal haemorrhage should be treated following a procedure similar to that used for military- or crime-related injuries. However, two additional points should be stressed. As discussed earlier, bleeding control of wounds located in the back and caused by shrapnel injuries should be suspected and diagnosed early, before other surgical procedures. A careful examination should be performed to prevent profuse bleeding, hypothermia, and haemorrhagic shock during surgical procedures or early ICU stay. Therefore tailored protocols should be instituted.

Recombinant activated factor VIIa (rFVIIa) has been successfully used to treat bleeding patients with various coagulopathies [24]. Animal studies have been very convincing and have shown significant improvement in mean prothrombin time, mean arterial blood pressure and mean blood loss in hypothermic coagulopathic pigs after administration of rFVIIa [25]. In a series of 37 patients who received rFVIIa for surgical bleeding of different aetiologies (Table 3), bleeding was stopped in most of the patients and overall survival was 18% [26]. This therapy is an additional tool in the treatments available for terror victims. Additional, prospective randomised studies will define the best indications of this expensive drug.

Table 3. Use of recombinant factor VIIa in trauma victims vs in surgical patients

	Number of patients	Survival 24 h (%)	Survival 7 days (%)	Survival 30 days (%)
Trauma	11	55.6	27.3	18.2
Surgical	12	83.1	58.7	17.2
Transplant	7	86.6	57.4	29.2

Abdominal lesions

While the decision to perform surgery is easy to make in patients with acute abdominal symptoms, careful observation and repeated radiological examinations as well as diagnostic peritoneal lavage should be done in patients with suspected abdominal injury and perforation [27, 28]. Intramural haematomas, depending of their location, size, position relative to the mesenteric artery, and whether or not the pattern of haemorrhage appears diffuse or confluent, are important factors in the prediction of later perforation. In all cases of haemodynamic instability or unexplained sepsis, aggressive assessment of the abdomen should be performed, since it is a possible source of perforation and sepsis. Based on recent experience, all victims with multiple shrapnel wounds should be exa-

mined by total body computed tomography as soon as the initial chaos in the hospital has subsided.

Ethical issues of mass casualties

Definition

Mass casualty is characterised as resulting from an event in which the number of victims is very high. This can happen during a terrorist act. In these situations, the imbalance between the number of victims and health representatives imposes organisational dilemmas and the need for ethical rules.

From the ethical point of view, the rules issued by the WMA in disasters [29] and the WADEM [30] incompletely take into account the ethical decisions that must be made during mass casualty. The Israel Medical Association [31] recently issued a position paper based on general ethical rules, such as beneficence, autonomy, nonmaleficence, and justice, in addition to the right of the health worker to individual security and the rights of society and the nation.

Beneficence: It is the responsibility of the physician to do his or her best and to assure that the health system will do all that it can to ensure the best possible treatment to the victims. In case of mass casualties and disaster, fast and effective triage is mandatory, according to the conditions at the scene. Patients with survival chances should have the highest priority. Second priority should be given to victims requiring immediate therapy but who are not in immediate danger of death. Third priority should given to patients who can wait, without risk of worsening of their conditions. Fourth priority should be given to patients without a reasonable immediate chance of survival.

Autonomy: The patient has the right to decide about his or her future health. The patient should be informed regarding the hospital destination. He or she can refuse all therapy or to receive a specific type of treatment. The physician has to take the patient's decisions into account; however, the physician has the right to overrule the patient's decision in case of logistical problems that conflict with the patient's wishes, such as regarding hospital destination.

Nonmaleficence: A reasonable standard of care is mandatory in mass-casualty situations.

Justice: Priorities should be given according to medical decision and triage criteria. Medical decisions will be based on the goal of saving the largest number of human lives, even if some individuals could not be treated. The triage will not introduce factors such as sex, age, religion, nationality, profession, or social rank into account.

Security of health professionals

Since the location of the disaster is not always secured, at least at the beginning of the triage action, the entry of health professionals into the scene is not obligatory

and even futile as long as there are risks for the health care providers. This rule is particularly relevant in case of biological threat.

Health professionals have to adhere to the following rules: the physician is not obliged to endanger him- or herself in order to save the lives of others. However, escape and refusal to take part in mass casualty management is unethical and unacceptable. In case of a predictable event (future conflict, war, danger of building collapse, etc.) the medical team has to optimally prepare itself (material, protection, training, vaccination, etc.) so that it will be able to work under the conditions imposed by the conflict. Without possibility of preparation, the medical team will have to do its best willingly and efficiently.

Education

The ability to cope with mass casualty has become an integral part of the basic educational medical syllabus. Schools of medicine have to include this subject in the medical curriculum of all physicians. Medical doctors, medical schools, and medical and paramedical associations need to teach their respective students how to deal with mass casualties. Medical doctors have to take an important part in designing protocols of care, and in educating the general population on how to respond in case of a mass casualty event.

Research

Studies should be performed in accordance with decisions made by ethics committees. Special consideration has to be taken regarding the administration of drugs or the use of methods/techniques without possible approval. Results from research should be published after approval of the institutions where the studies were performed.

The knowledge acquired during a mass casualty event is not the sole property of researchers but also of the ethics committee of the scientific society to which the researcher belongs (society of emergency medicine, critical care, surgery). Each study related to response organisation and the treatment of victims of mass casualty must receive the approval of the scientific society involved in evaluating the treatment.

Bioterrorism

Society has to protect its medical teams from danger of contamination in case of bioterrorism. In case of practical risk, health authorities must provide health professionals with all the necessary protection. Every health professional has the right to refuse this assistance. All health professionals who receive the required protection must take care of victims of bioterrorism according to medical standards.

Conclusions

In light of the increasing risk of bombing attacks, physicians and intensive care specialists should familiarise themselves with the characteristics of explosive devices and the injuries inflicted by blasts, explosions, and shrapnel. Triage has become an important part of the management of these patients. The ICU should focus on the possibility of pulmonary, bleeding, and abdominal conditions. Finally, an ethical code for responding to mass casualty is proposed in this chapter.

References

1. Chaloner (2005) Blast injury in enclosed spaces. Br Med J 331:119–120
2. Zuckerman S (1940) Experimental study of blast injuries to the lungs. Lancet ii:219–224
3. Hart AJ, Mannion S, Earnshaw P et al (2003) The London nail bombings: the St Thomas' Hospital experience. Injury 34:830–833
4. Singer P, Cohen J, Stein M (2005) Conventional terrorism and critical care. Crit Care Med 33:S61–S65
5. Israel Defence Force official web site. Available at: http://idf.il/daily_statistics/english
6. Peleg K, Aharonson-Daniel L, Stein M, Shapira SC (2003) Patterns of injury in hospitalized terrorist victims. Am J Emerg Med 21:258–262
7. Peleg, Aharonson-Daniel L, Stein M et al (2004) Gunshot and explosion injuries. Characteristics, outcomes and implications for care of terror-related injuries in Israel. Ann Surg 239:311–318
8. Aharonson-Daniel L, Waisman Y, Dannon YL, Peleg K (2003) Epidemiology of terror-related versus non-terror-related traumatic injury in children. Pediatrics 112:281–285
9. Arnold JL, Halpern P, Tsai MC et al (2004) Mass casualty terrorist bombings: a comparison of outcomes by bombing type. Ann Emerg Med 43:263–273
10. Brismar B, Bergenwald L (1980) The terrorist bomb in Bologna, Italy, 1980: an analysis of the effects and injuries sustained. J Trauma 22:216–220
11. Teague DC (2004) Mass casualties in the Okhahoma bombing. Clin Orthop Relat Res 422: 77–81
12. Leibovici D, Gofrit ON, Stein M et al (1996) Blast injuries: Bus versus open-air bombings —a comparative study of injuries in survivors of open-air versus confined-space explosions. J Trauma 41:1030–1035
13. Stephens DP, De Keulenaer BL, Collins S et al (2003) Operation Bali assist— the Royal Darwin Hospital Intensive Care Unit. Anaesth Intensive Care 3:300–305
14. Stein M, Hirshberg A (1999) Medical consequences of terrorism. The conventional weapon threat. Surg Clin North Am 79:1537–1551
15. Gutierrez de Ceballos JP, Fuentes FT, Diaz DP et al (2005) Causalties treated as the closest hospital in the Madrid, March 11, terrorist bombings. Crit Care Med 33:S107–S112
16. DePalma RG, Burris DG, Champion HR et al (2005) Blast injuries. N Eng J Med 352:1335–1342
17. Almogy G, Belzberg H, Montz Y et al (2004) Suicide bombing attacks. Update and modifications to the protocol. Ann Surg 239:295–303
18. Halpern P, Tsai MC, Arnold JL et al (2003) Mass-casualty, terrorist bombings: implications for emergency department and hospital emergency response. Prehospital Disaster Med 18:235–241

19. Katz E, Ofek B, Adler J, Abramowitz HB, Krausz MM (19890 Primary blast injury after a bombing explosion in a civilian bus. Ann Surg 209:484–488
20. Pizov R, Oppenheim-Eden A, Matot I et al (1999) Blast lung injury from an explosion on a civilian bus. Chest 115:165–174
21. Sorkine P, Szold O, Kluger Y et al (1998) Permissive hypercapnia ventilation in patients with severe pulmonary blast injury. J Trauma 45:35–38
22. Cernak I, Wang Z, Jiang J et al (2001) Ultrastructural and functional characteristics of blast injury-induced neurotrauma. J Trauma 50:695–706
23. Elyased NM, Gorbunov NV (2003) Interplay between high energy impulse noise (BLAST) and antioxidants in the lung. Toxicology 189:63–74
24. Martinowitz U, Keneth G, Segal E et al (2001) Recombinant activated factor VIIa for adjunctive hemorrhage control in humans. J Trauma 51:4318
25. Shreiber MA, Hoomb JB, Hebner U et al (2002) The effects of recombinant factor VIIa on coagulopathic pigs with grade V liver injuries. J Trauma 53:252–257
26. Blank N, Singer P, Stein M (2005) Treatment with activated recombinant factor VIIa (rFVIIa) in non hemophilic patients with coagulapathic bleeding. Medical thesis, University of Tel Aviv, Sackler School of Medicine
27. Cripps NPJ, Cooper GJ (1997) Risk of late perforation in intestinal contusions caused by explosive blast. Br J Surg 84:1298–1303
28. Paran H, Neufeld D, Shwartz I et al (1996) Perforation of the terminal ileum induced by blast injury: delayed diagnosis or delayed perforation. J Trauma 40:472–475
29. World Medical Association (1994) Medical Ethics in the event of Disasters. Bull Med Ethics 102:9–11
30. WADEM (2001) Guidelines for evaluation and research in the Utstein style version: Geneva. http://wadem.medicine.wise.edu/Ch9.htm
31. Singer P, Halpern P, Feingelman I et al (2005) Ethical guidelines in mass casualties management. IMAJ (in press)

PAEDIATRICS

Chapter 69

Difficult airway

G.A. Marraro

The small size of the larynx and trachea makes airway obstruction life-threatening in infants and children. Airway obstruction can appear after a simple inflammation of the upper airways and may progressively deteriorate until emergency stage. Hypoxia due to impairment of airway is a frequent cause of morbidity and mortality in the paediatric age group [1–3]. Airway obstruction, due to the severity of complications and possible evolution of hypoxia into cardiac arrest, must be treated immediately. The treatment is devoted to maintaining patency of airways and ensuring adequate ventilation.

Difficult airway is due to alteration of the upper respiratory tract (e.g. nasal cavity, nasal–pharynx, and larynx) and lower respiratory tract (e.g. trachea, bronchi and bronchioles) and can derive from congenital and acquired malformations, infectious diseases, oedema and trauma.

Congenital and acquired malformations

Congenital and acquired malformations can affect the paediatric airway in different ways and may become evident at birth in the delivery room or may appear when the child is older and somatic growth has made the airway impairment more evident. Congenital airway abnormalities may improve, worsen, or remain the same as craniofacial structures mature.

Craniofacial dysostosis

The craniofacial dysostosis syndrome includes congenital abnormalities, of which the most common are Apert, Crouzon and Pfeiffer's syndromes. All have craniosynostosis with some degree of midface hypoplasia and other abnormalities, including hypertelorism and proptosis. The mandible can be of normal size but appears to be relatively prognathic secondary to the midface hypoplasia. The palate is high and arched, while the nasal passages are small with some degree of choanal stenosis. As a result, these children are primarily mouth breathers. Closure of the mouth occludes the oral airway as the tongue fills the smaller oral cavity, while the small nares and choanal stenosis offer resistance to airflow via the nasal route. Children whose craniofacial dysostosis causes severe airway problems often have obstructive apnoea. Other structural defects of the airway include vertebral abnormalities that may limit neck motion.

The airway abnormalities make management of the airway by mask difficult. Fitting the mask may be problematic because of the small midface and proptosis. Intubation of the trachea is not as difficult unless there is a major problem with neck mobility. However, a slightly smaller than expected endotracheal tube, because of tracheal ring abnormalities, is necessary. Nasal intubation is not contraindicated but may also require a smaller tube.

Lip and palate malformations

Cleft lip and/or palate is the most common type of craniofacial disorder; it may exist by itself or be associated with other craniofacial syndromes [4]. Patients with isolated cleft lip usually do not have airway problems. However, cleft palate can cause difficulties during airway management. If the tongue falls into the cleft, it may obstruct the nasal airway, and when relaxation of the oropharyngeal musculature allows the tongue to fall posteriorly, the tongue may obstruct the oropharynx completely [5]. Cleft palate may be associated with other structural abnormalities, e.g. Pierre–Robin sequence of micrognathia, glossoptosis and respiratory obstruction [6].

Airway management in patients with simple cleft lip and palate is usually straightforward. The use of an oropharyngeal airway will keep the tongue from occluding the airway. Intubation difficulties may depend on whether the cleft is unilateral or bilateral. In unilateral cleft, the laryngoscope blade will tend to fall into a left-sided cleft during intubation, as the tongue gets swept to the left side and alters the line of vision. In bilateral clefts, the premaxilla is angled anteriorly, altering the line of sight and hampering insertion of the laryngoscope blade.

Hemifacial microsomia

Hemifacial microsomia is characterised by varying degrees of mandibular hypoplasia, auricular abnormalities, overlying soft-tissue loss and facial nerve weakness. The position and shape of the ramus may grade deformity of the mandible in hemifacial microsomia [7]. As the severity of deformation increases, the degree of difficulty in airway management also increases. Intubation is often more difficult after reconstruction of the jaw because this procedure may be followed by soft-tissue contractures that restrict mouth opening.

Microsomia may present bilaterally and be easily confused with Pierre–Robin's syndrome. In this case, management of the airway ranges from easy to impossible for either mask ventilation or tracheal intubation.

Goldenhar's syndrome, a variant of hemifacial microsomia, has the added features of macrostomia and may have fused or hemivertebrae resulting in limitation of neck flexion and extension and increasing the difficulty of intubation [8]. Care must be taken in manipulating children affected by this syndrome because any forceful movement of the neck can cause neurological injury. Airway morphology may change as the child grows or as a result of surgical intervention.

Myopathic dysplasia

Freeman–Sheldon syndrome, whistling face syndrome—craniocarpotarsal dysplasia—is a rare pathology characterised by contraction of the facial musculature and other soft tissues. The patient has a mask-like face with circumoral fibrosis and microstomia. In addition to microstomia and circumoral fibrosis, children often have contractures that limit mobility of the neck, making airway management and intubation very difficult [9]. These patients are at higher risk of malignant hyperthermia [10].

Limitation of flexion and extension of the neck

Klippel–Feil syndrome is characterised by severe limitation of flexion/extension of the neck as a result of fusion of cervical vertebrae and atlanto-occipital abnormalities, spinal canal stenosis and scoliosis. For these reasons, care must be taken in manipulating and positioning the child because any forceful movement of the neck could cause neurological injury. Other skeletal deformities may also be present, with Sprengel's syndrome being the most common. It is usually easy to manage the airway by mask, but the limitation of neck movements makes intubation extremely difficult. Fibreoptic tracheal intubation or use of a laryngeal mask airway is the technique of choice to manage the airway [11].

Goldenhar's syndrome, with the presence of fused or hemivertebrae, and Freeman–Sheldon syndrome with neck contractures, can result in limitation of neck flexion and extension and increase the difficulty of airway management.

Jaw malformations and dysfunction of the temporomandibular joint

Hypoplasia of the jaw (Pierre–Robin syndrome), associated with other craniofacial abnormalities (e.g. Treacher–Collins and Goldenhar syndrome), is a congenital defect that can favour airway obstruction during spontaneous breathing. Hypoplasia can be associated with atresia and coanal stenosis, reduction of the nose–pharynx space and malformations of the palate (palatoschysis and bifid uvula). The malformation tends to be less evident with age (4–6 years) but can create in any cases difficult intubation and airway obstruction.

Airway management in patients with Pierre–Robin syndrome or associated craniofacial syndromes may involve the use of alternative techniques for securing the airway. The patient can be ventilated by mask according to the history of snore or sleep apnoea. If the patient has a history that indicates lack of airway patency during sleep, successful ventilation by mask is unlikely and in consequence the techniques for intubation must be altered.

Patients with Treacher–Collins syndrome (mandibulofacial dysostosis) have maxillary, zygomatic and mandibular hypoplasia. Secondary problems include cleft palate and velopharyngeal incompetence. Other prominent features include small mouth, high arched palate, laterally sloping palpebral fissures, notched lower eyelids, coloboma of the eye, and hearing loss because of atresia of the internal and

external ears. Patients with these abnormalities can suffer severe airway obstruction, and mask ventilation and tracheal intubation are difficult to achieve and impossible if there are associated temporomandibular joint (TMJ) abnormalities. As children grow, increasing basilar kyphosis of the cranial base may make airway management even more difficult. The respiratory function of these patients should be monitored to identify the obstructive problems early [12]. As intubation and ventilation by mask are difficult in this group of patients, the techniques of choice are fibreoptic intubation or use of a laryngeal mask [13]. Procedures to close the cleft palate or correct velopharyngeal insufficiency by creating a pharyngeal flap often are associated with postoperative airway obstruction.

Hyperplasia of jaw (Ramon or cherubism syndrome) is a rare but familiar malformation characterised by upper and lower jaw hypertrophy. Tongue dislocation makes visualisation of the glottis difficult during laryngoscopy.

Dysfunction of the temporomandibular joint is a rare congenital malformation characterised by agenesis of condilus. Generally it is acquired pathology and follows trauma (forceps application during delivery) or inflammation (septic arthritis). In both conditions, the final result is reduced motility and anchilosis of the TMJ. Acquired micrognatia can be severe and can compromise jaw movements and mouth opening, and airway management appears to be difficult.

Malformations of mouth and tongue

Microstomia, reduced opening of the mouth, is present in several congenital malformations such as Freeman–Sheldom, Hallermann–Streiff and oto-palato-digital syndromes. Acquired forms are connected with burns and caustic lesions. Microstomia hinders the introduction of the laryngoscope blade, visualisation of the glottis and endotracheal intubation.

Macroglossia is present in congenital malformations such as Beckwith–Wiedemann, trisomia 21/Down's and Hurler syndromes, and in hypothyroidism, haemoangioma and lymphoangioma of the tongue. Lymphatic malformation generally involves the submandibular space and neck but can be extended to the tongue, vallecula, epiglottis and soft palate.

Large tongue, reduction of the oral cavity and tumefaction of the submandibular space can favour airway obstruction. Airway obstruction due to these pathological conditions may increase apnoea sleep syndrome. Macroglossia is frequently associated with dysphagia, dysphonia, orthodontic and aesthetic problems.

Beckwith–Wiedemann syndrome is characterised by macroglossia, exomphalos and gigantism. The large, protuberant tongue is the primary cause of respiratory distress and, in extreme cases, the tongue may obstruct the airway so severely that cor pulmonale occurs [14]. The key to airway management in patients with macroglossia is not to attempt mask ventilation (which requires keeping the tongue in the mouth) but to use nasotracheal intubation. Direct laryngoscopy is easy to perform because the tongue can be moved out of the way. Hyperplasia of the kidneys and pancreas also characterise this syndrome and cause patients to be prone to hypoglycaemia [15].

Down's syndrome, trisomy 21, is the most common chromosomal abnormality characterised, in addition to other abnormalities, by a narrowed nasopharynx, a relatively large and protuberant tongue and cleft lip/palate. The larynx and cricoid ring tend to be small, predisposing to acquired subglottic stenosis. There is a high incidence of atlantoaxial subluxation, which can make extension of the neck hazardous. Airway management includes keeping the relatively large tongue from occluding the airway. The enlarged tongue can cause or worsen obstructive sleep apnoea.

Hurler syndrome, congenital mucopolysaccharidoses, is a genetic disorder characterised by deficiencies in enzyme production that lead to accumulation of mucopolysaccharides throughout the body. In the airway, infiltration by mucopolysaccharide deposits leads to tongue enlargement, thickening and redundancy of the soft-tissue mucosa of the oropharynx, and blockage of nasal passages. Progressive airway obstruction leads to severe respiratory compromise [16, 17], and mask ventilation and tracheal intubation become impossible. Individuals with mucopolysaccharidoses, in the past, often died of cardiomyopathy because of the effects of mucopolysaccharide accumulation in the heart. Bone marrow transplantation has proven an effective way to reverse mucopolysaccharide deposition by supplying the missing enzyme and this treatment can actually reverse airway obstruction [18].

Malformation of the nose, palate and pharynx

Choanal atresia, unilateral or bilateral, results in respiratory distress shortly after birth because many newborns breathe only through the nose. Immaturity of coordination between respiratory efforts and oro-pharyngeal motor/sensory input accounts in part for obligatory nasal breathing. Obstructive symptomatology disappears during crying and reappears during feeding and in the absence of crying. Clinical symptomatology is less evident in cases of unilateral presentation.

Tracheal intubation is not mandatory and neither is tracheostomy. In cases of partial stenosis, choanal dilatation can be performed.

Nasal masses are rare malformations that can create airway obstruction and difficult laryngoscopy and intubation. Intubation can be more difficult if it is associated with palatoschisis and the mass can invade the mouth.

Palatoschisis can be associated with difficult airway when it is associated with Pierre–Robin, Treacher–Collins, Goldenhar and Klippel–Feil syndromes. A special prosthesis, which partially reconstructs the lip and palate, can be useful for safe and easy intubation.

Malformation of the larynx

Congenital atresia of the larynx is a life-threatening condition unless it is recognised immediately at birth and treated promptly. Emergency cricostomy or fissuration of the trachea in some cases can allow ventilation.

Laryngomalacia is due to lack of the usual rigidity of the laryngeal cartilage. The glottis, the arytenoid cartilages and supraglottic structures collapse toward the glottis during inspiration and this leads to inspiratory stridor, which is exacerbated by crying or distress. Laryngotracheomalacia is a frequent complication of prolonged intubation and use of an incorrect tracheal tube (large diameter, rigid structure, cuffed).

Congenital laryngeal webs occur at the level of the glottis and usually are thin membranes that partially occlude the tracheal opening. They produce symptoms of feeble cry and dyspnoea after birth.

Laryngeal cysts and laryngoceles are soft-tissue masses that protrude into the glottis lumen and result in respiratory distress and inspiratory stridor.

Vocal-chord paralysis, unilateral or bilateral, may be present at birth or acquired later. Vocal-chord paralysis is the second most common cause of congenital obstruction of airways in infants. Congenital causes include idiopathic forms, birth trauma of the vagal nerve, hydrocephalus, Arnold–Chiari syndrome and encephalocele. Acquired vocal-chord paralysis derives from neurological disorders and post-surgery complications. Thoracic and neck surgical operations are the most frequent causes. Left-sided chord paralysis is more common because of the lengthy path followed by the left recurrent laryngeal nerve. The unilateral form can be asymptomatic, while the bilateral form can create inspiratory stridor, severe airway obstruction, cyanosis and apnoea. The unilateral form does not require treatment, while the bilateral form can require intubation and/or tracheostomy. Aspiration can be frequent in both unilateral and bilateral forms. Acquired forms generally resolve spontaneously, which is not the case for congenital forms.

Laryngeal granuloma follows prolonged and traumatic intubation but can also appear in infants and children intubated for a short time. Symptomatology is progressive and is characterised by hoarseness, stridor during inspiration, voice alteration and dyspnoea. Airway obstruction is connected with the size of the granuloma, which can obstruct laryngeal additus and can create severe respiratory distress.

Subglottis stenosis

Congenital subglottis stenosis may be asymptomatic at birth but often becomes symptomatic when tracheal oedema causes severe inspiratory stridor. This may be diagnosed initially as laryngo-tracheo-bronchitis, but it recurs with subsequent upper respiratory infection. This form can resolve spontaneously with age according to the severity of malformation. Subglottis stenosis may be a frequently acquired disease following tracheal intubation. Individual susceptibility, traumatic intubation, movement and size of the endotracheal tube, use of cuffed tubes and duration of intubation can cause the lesion. The most serious forms may require surgery or application of a special prosthesis.

Congenital vascular malformations

Haemangioma occurs most commonly on the face and upper torso. It may involve any part of the airway, causing severe airway obstruction. Stridor is frequent, as is alteration of voice tone, dyspnoea, cyanosis and difficulty in feeding. Laryngoscopy shows the unilateral subglottis mass and angiography may be necessary to confirm the diagnosis. Although haemangiomas grow rapidly in infancy, they then involute spontaneously over a year or two.

Arterio-venous malformations involving the face and airway are relatively uncommon. These lesions grow as the child grows, and can cause erosion and distortion of adjacent structures, so a lesion involving the airway may make securing the airway difficult.

Venous lymphatic malformations, previously called cystic hygroma, comprise a mixture of venous and lymphatic elements. They may be of various sizes at birth and may continue to grow postnatally. Occasionally, they can become infected or dramatically increase in size as a result of internal haemorrhage.

Malformations of trachea and bronchi

In bronchomalacia and intrathoracic tracheomalacia, the cartilaginous components of the upper airway lack their characteristic rigidity and the mechanism of breathing is altered due to an obstacle of exhalation. A congenital weakness or deficiency of the cartilage that supports the trachea and bronchi causes primary congenital tracheomalacia, which is rare. Acquired tracheomalacia may occur from extrinsic compression of the airway and in long-term ventilated infants. Suggestive symptoms are severe cyanotic episodes, often preceded by crying and agitation. Diagnosis can be made with airway fluoroscopy or bronchoscopy [2]. Laryngo-tracheo-oesophageal cleft is a congenital defect due to a failure of dorsal fusion of cricoid lamina, between the posterior laryngeal wall and, sometimes, the trachea and the oesophagus. A severe form of the malformation is a persistent oesophago-trachea, incompatible with life.

Tissue masses, congenital cysts and sequestration

Tissue masses may reduce the calibre of the tracheal lumen, either by extrinsic compression (e.g. cystic hygroma), or by growth into the tracheal lumen from the tracheal wall (e.g. haemangioma). The trachea may be compressed by the presence of an abnormal vascular structure. The innominate artery is the most common vessel causing tracheal compression. Vascular rings and slings, and enlarged tracheal compression are other vascular abnormalities. Congenital cysts and sequestration, and bronchospastic disorders (e.g. asthma, bronchiolitis and bronchopulmonary dysplasia) can also obstruct the airways.

Children present various symptoms as stridor, wheezing, lobar atelectasis, or recurrent pulmonary infections up to severe respiratory failure.

Infectious diseases

More common infective pathologies that can create airway obstruction are listed below but it is necessary to remember that several other infective diseases, such as diphtheria and rubella, can create obstructive symptomatology due to the formation of adherent tracheal and laryngeal membranes.

Laryngo-tracheo bronchitis

Laryngo-tracheo bronchitis affects children from 6 months to 3 years of age and is caused by a variety of infectious agents, occurring mainly during the winter. Airway compromise is due to swelling of the tracheal mucosa in the subglottis region. The trachea has a progressive narrowing of its lumen, with the narrowest point just below the vocal chords, while the upper glottis is normal.

Epiglottitis

Epiglottitis is a bacterial infection of the supraglottic tissues caused by *Haemophilus influenzae* type B and is frequently confused with laryngo-tracheo bronchitis because both present inspiratory stridor and respiratory distress. Diagnosis can be confirmed by anterior–posterior and lateral neck radiography in which the trachea appears normal and the epiglottis is markedly swollen and oedematous.

Peritonsillar abscess is typical of the early second decade of life and the child may present a muffled voice and drooling. If the abscess is sufficiently wide, the child presents severe respiratory distress and trismus.

Retropharyngeal abscess

Retropharyngeal abscess is characterised by a progressive symptomatology with sore throat, fever and dysphasia. The posterior oropharyngeal wall may bulge, but most commonly the findings are unremarkable. Rupture of the abscess can spill the contents into the tracheo-bronchial tree. An inspiratory radiograph of the lateral neck may show thickening of paravertebral soft tissue and possible mediastinal extension of infection.

Laryngeal papillomatosis

Laryngeal papillomatosis is the most common benign tumour of the larynx occurring between infancy and 4 years of age, and can cause respiratory obstruction, which may injure or kill the patient.

Angio-oedema

Angio-oedema is a well-localised oedema involving the deep layers of skin, including the subcutaneous tissue. It may occur in response to a variety of systemic disorders and may lead to swelling of the soft tissue of the face, particularly the eyes and lips. If the oedema involves the soft tissues of the upper respiratory tract, laryngeal obstruction and respiratory failure may result.

Trauma

Traumatic injury to the upper airway may be divided into oral facial trauma and laryngeal or tracheal trauma. Oral facial trauma exposes the risk of upper airway obstruction. The swelling of soft tissues and inhalation of blood may lead to airway compromising and acute respiratory distress syndrome (ARDS). Injury to the larynx and trachea may occur following blunt trauma such as road accident or following penetrating trauma. The development of subcutaneous emphysema is evidence that a laryngeal fracture or tracheal tear has occurred.

Burn injury of the upper airway may complicate the management of a burn victim. Because of the very efficient cooling capacity of the upper air passages, thermal injury to the airway below the vocal chords is uncommon, occurring in less than 5% of cases.

Airway obstruction may also be produced by aspiration of a variety of foreign bodies, nuts being one of the most frequent. The airway may be blocked from the posterior pharynx to the bronchi and symptoms vary according to the site of the foreign body and the degree of obstruction it produces. If the foreign body produces valve bronchial obstruction, hyperinflation of the involved lung will be seen at an expiratory chest x-ray. Long-term aspiration can provoke lobar atelectasis.

Aspiration of gastric material is a severe syndrome that can evolve into chemical pneumonia and ARDS.

Finally, airway obstruction can be connected with various facial and neck malformations in which airway patency can be lost from reduction of the muscle tone of the neck.

General considerations in the management of the difficult airway

Structurally, the airway consists of bony and soft-tissue elements. The effects of these elements on airway structure may be interdependent or independent of each other. When assessing airway management, the various areas of the airway to consider include the oral cavity, anterior mandibular space, maxilla, TMJ and vertebral column.

The oral cavity can be viewed as a box bounded by the bony structures of the maxilla and the mandible, and filled to some extent by the soft tissue of the tongue. The ratio of volume of the oral cavity to the tongue indicates the likelihood of upper

airway obstruction. Maxillary or mandibular abnormalities will change the volume of the box. Craniofacial disorders are often associated with tongue enlargement, rarely with decreased tongue size. As the ratio of tongue to volume of the oral cavity increases, the probability of airway obstruction increases.

The anterior mandibular space is the space within the mandible into which the soft tissue of the tongue can be displaced during laryngoscopy. Any condition that makes this space small relative to the size of the tongue will make laryngoscopy and tracheal intubation difficult, e.g. Pierre–Robin syndrome.

Maxillary hypoplasia can change the mass-to-volume ratio of the upper airway in a similar manner to tongue hyperplasia or mandibular hypoplasia, making airway obstruction more likely.

The function of the TMJ, the hinge that opens the upper airway and also translocates the lower jaw forward, is fundamental to visualise laryngeal additus. Restricted opening of the TMJ is more common than failure of translocation. Causes of fixed rigidity of the TMJ include congenital conditions or previous trauma. In cases of restricted opening, it is important to determine if rigidity is fixed or may be overcome once the patient is anaesthetised.

The vertebral column, particularly the atlanto-occipital section and the lower cervical region, allows flexion and extension of the neck and affects the ability to manage the airway. Vertebral fusion, hemivertebrae and arthritic changes may decrease cervical mobility to the extent that tracheal intubation is difficult or impossible. Other disease processes or congenital conditions may cause instability of the vertebral column and put the spinal chord in danger of impingement. In these circumstances, motion of the neck must be avoided and alternative methods (e.g. fibrescopic laryngoscopy) of intubation sought.

Soft-tissue abnormalities that cause difficult airway usually fall into two categories: those that limit movement of the airway and those that distort the airway by mass effects. Soft-tissue problems that limit airway movement usually affect mouth opening. Mass effects on the airway because of soft-tissue abnormalities may be congenital in origin, the result of surgical interventions, or the result of diseases that develop later in life. Of the congenital problems, macroglossia is one of the most common. Other problems that cause mass effects include soft-tissue tumours and various forms of arterio-venous malformations. Sometimes these can cause secondary problems by erosion or mechanical obstruction of different structures.

Techniques suggested in the treatment of difficult airway

The treatment of difficult airway is devoted to restore airway patency and to improve and maintain adequate ventilation. First of all, the patency of airway can be obtained with simple manoeuvres that include correct positioning of the neck and the head, clearing the mouth and the pharynx and dislocating the jaw and the neck, alone or in combination with lateral decubitus [3, 19].

In cases of visible foreign body, its rapid removal using laryngoscope and forceps is indispensable for restoration of patency of the airways.

Non-invasive oral and nasal devices can restore and maintain airway patency because they facilitate the passage of gases into the pharynx and the larynx, avoiding the nostril and mouth [2, 3].

Oral devices

Oral devices are useful in cases of non-patency of nostril and choane, in the presence of macroglossia, hypotonic muscle of chin triangle and of neck, and when the mouth is difficult to maintain adequately open. The use of an oral device can stimulate vomiting if an incorrect calibre is used and may worsen respiratory insufficiency. During manual ventilation it can favour the passage of gases into the stomach and aspiration.

Nasal devices

Nasal devices may be useful in cases of impossible access to the mouth because of anomalies of maxillo-facial structures, in tumours and head trauma. A nasal tube positioned with the tip in the posterior pharynx can be utilised. A larger diameter tube than that used in tracheal intubation is sufficient. Proper length may be estimated as distance from nares to angle of mandible. Lower tube placement stimulates coughing and vomiting and favours the passage of gases into the oesophagus. In cases of facial trauma with problematic patency of nares and choanae, positioning is difficult because a wrong route can be created.

Laryngeal mask

The laryngeal mask airway (LMA) has an established role in the management of the difficult adult airway. Its use in the difficult paediatric airway is less well documented, but the LMA is increasingly used to secure the airway and to act as an aid to tracheal intubation [20] in infants and children. The LMA allows maintenance of airway patency in the majority of cases but does not resolve all ventilatory problems. Complications connected with its use are difficult insertion and easy displacement, partial or complete airway obstruction, laryngo-spasmus in cases of insufficient plane of anaesthesia, uvular, pharyngeal and laryngeal trauma. The laryngeal mask is not indicated in the presence of vomiting, regurgitation and full stomach and in emergency. It is difficult to use in chronic lung disease and large quantities of secretions, in hypertrofic tonsils and in malformation of the oral cavity.

Many children with severe facial malformations that make tracheal intubation hazardous, or even impossible, can benefit from use of the LMA, since a tracheal tube can be introduced through the tube and advanced blindly into the trachea. Intubation via the LMA is a recognised technique for securing the difficult airway in paediatric patients. The correct position of the LMA in relation to the laryngeal inlet can be confirmed by fibrescopic examination [21–24].

Tracheal intubation

Tracheal intubation is the optimum invasive method to control patency of airways and ventilate adequately the lungs. It can be performed under direct laryngoscopy with children under sedation or during general anaesthesia. In difficult airway, volatile halogenate anaesthetics are useful as they allow sedation of the patient, maintenance of spontaneous breathing and bronchodilatory effect [2, 25].

Difficult intubation can be suspected or unexpected. In the case of suspected difficult intubation, a well-planned and flexible approach must be taken. Idoneous equipment has to be used and a well-trained specialist should be present. Reduced complications and failures in intubation have been reported in well-programmed situations.

Difficult intubation can be divided into two major groups. In the first group, direct visualisation of the glottis is difficult or impossible; in the second group, visualisation of the larynx is possible under direct laryngoscopy but the passage through the glottis and trachea of the usual size endotracheal tube is impossible [2, 3].

Techniques suggested in difficult intubation due to non-visualisation of glottis and vocal chords

In cases of difficult intubation [26] due to non-visualisation of laryngeal additus, several methods have been proposed to intubate the trachea, but only one can be effective in 90% of cases using a fibreoptic laryngoscope [27]. All airway management algorithms [28, 29] show fibreoptic bronchoscopy as the final step in the management of a difficult airway but, in our opinion, the anticipation of its use can be recommended in expected difficult airway.

The availability of increasingly smaller calibre fibreoptic laryngoscopes [30] has led to their widespread use in paediatrics, facilitating difficult intubation and diagnostic bronchoscopy. Fibreoptic bronchoscopes are available in various sizes, the smallest being 1.8 mm. The apparatus allows continuous oxygen supplementation directly into the airways, as well as bronchosuctioning, except with a 3.5-mm diameter or smaller fibreoptic laryngoscope [31].

Tracheal intubation with fibreoptic endoscopy is a technique particularly well suited for patients who are awake because the use of this instrument may be rendered more difficult during general anaesthesia due to the loss of tone in the muscles that support the tongue and, indirectly, the epiglottis [32].

In infants and children, collapse of these structures under general anaesthesia does not represent a major burden during the procedure, due perhaps to the better tone of these structures in the early years of life. However, loss of patency of the child's airway can occur rapidly with hypoxaemia and desaturation due to high baseline oxygen consumption. Therefore, during airway manipulation, administration of oxygen as well as atropine to prevent bradycardia and to dry secretions is an essential step to ensure the success of this technique in infants and children.

One of the problems that can be encountered during fibreoptic intubation is the trauma to the nasal mucosa caused by the passage of the endoscope. This complication can be mild to moderate but does not impede visualisation with the

endoscope. In rare cases, fibreoptic intubation can be unsuccessful due to excessive bleeding and secretions; this occurred after several attempts to intubate with direct laryngoscopy [27].

Lighted stylet (Lightwand), Bullard Laryngoscope [33] and several laryngoscope blades have been proposed for intubation during difficult airways. Belscope, an angulated laryngoscope and rigid tubular laryngoscope have been proposed to visualise the glottis in the presence of severe oedema of the additus laryngeus or a large and occluding tongue in order to perform tracheal intubation [34]. The equipment is used almost exclusively in adolescents and adults, and use in newborns and infants has yet to be demonstrated.

Techniques suggested in difficult intubation due to laryngeal and tracheal stenosis [3]

In cases of oedema, inflammation or patent anomalies of laryngeal additus and trachea, it is necessary to improve the passage of air through the vocal chords and trachea in order to guarantee gas exchange when performing endotracheal intubation. Oral rather than nasal intubation is preferred, as the former is easier to perform in emergency.

All material necessary for intubation must be previously prepared and checked. Straight and curved laryngoscope blades and different sizes of tubes, starting from 2 mm ID, must be immediately available. Tracheal intubation can be performed with children under sedation or during general anaesthesia in 100% oxygen and spontaneous breathing. At this time muscle paralysis is contraindicated.

Having visualised laryngeal additus by laryngoscope, a semi-rigid tracheal tube of suitable diameter is advanced into the larynx in order to allow tracheal intubation. Once a safe airway and sufficient ventilation have been assured, the child can be paralysed. A short-acting curare drug is preferred in order to return rapidly to spontaneous breathing.

Laryngeal additus and/or tracheal stenosis are successively dilated using well-lubricated progressive sizes of semi-rigid tubes, positioned one after the other, until a maximal size tube is introduced according to stenosis and normal anatomy.

At the end of dilatation, the patient must remain nasal intubated with a soft endotracheal tube (PVC Ivory or silicone rubber) of 1/2 calibre less than the maximum reached during dilation. Nasal intubation is preferred for long-term treatment as it allows the tube to be stable fixed, so avoiding accidental extubation, dislocation and selective bronchial intubation.

Continuous positive airway pressure and spontaneous breathing can be used if mechanical ventilation is not required. A progressive positive end-expiratory pressure (PEEP) level from 5 to 15 cm H_2O must be applied in order to create an 'air pillow' around the tube and favour progressive dilation of the inflamed/stenotic area. In spontaneous breathing, if a small diameter tube is used, the resistance created can be reduced by pressure support of 5–10 cm H_2O over PEEP level. Pressure-support ventilation may overcome muscle fatigue and increase in oxygen consumption.

Humidified and warmed gases are indispensable during the treatment, both to

maintain fluid secretions and to facilitate bronchosuction. Gas leakage round the vocal chords may favour spontaneous resolution of inflammation and oedema. Improved stenosis is confirmed by increasing air leakage.

Non-severe oedema, e.g. post-intubation oedema, and inflammatory stenosis (e.g. acute laryngitis and epiglottitis) resolve spontaneously in 4–5 days. In cases of difficult extubation and if leakage does not appear, the dilation manoeuvre can be repeated two or three times after 3–4 days. If difficult extubation persists after 1 month, other treatments must be considered to resolve the pathology (e.g. prosthesis application).

Percutaneous Cricothyroidotomy

Percutaneous cricothyroidotomy is a life-saving technique, which can resolve severe and life-threatening situations such as massive facial trauma, oro-pharyngeal haemorrhage, severe upper airway obstruction and impossibility to ventilate. It is to be used only in emergency and when other non-invasive approaches have been inefficacious. All physicians should be familiar with the technique. The positioning of the needle into the trachea, through the cricothyroid membrane, to allow ventilation, may easily damage cricothyroid cartilages because the cricothyroid membrane is of small width in infants and children. It can result in subsequent laryngeal stenosis and permanent damage to speech [2, 3, 35].

Threading a small-bore plastic catheter into the lower cervical trachea through the needle used to perform cricothyroidotomy, it is possible to perform transtracheal ventilation. The tip of the catheter is positioned 2–3 cm above the carina in order to avoid accidental selective bronchial intubation. The catheter positioning allows the application of jet ventilation.

Tracheotomy

Tracheotomy is not considered an emergency procedure today. Prolonged tracheal intubation has replaced tracheostomy, particularly since the introduction of soft, long-lasting, atoxic endotracheal tubes that are well tolerated and suitable for long-term use.

Tracheotomy could be limited to iatrogenic injury to the upper airway, in laryngeal disruption and complex craniofacial injury, in basal skull fractures with cerebrospinal fluid leak and/or nasal fractures or deformities that contraindicate a nasotracheal tube, in arch bars and jaw wiring, and in chronic patients needing some ventilatory support.

In newborns, infants and young children, tracheotomy is to be avoided because of the damage to the airways due to the smaller size of the child's trachea compared to that of the adult. Severe stenosis and difficult decannulation are frequent conditions after tracheotomy in the paediatric age group [2, 3].

General considerations

Difficult airway in infants and children must be manipulated with delicacy in order to assure continuously a minimum passage of air in the trachea and to avoid laryngo- and/or bronchospasm. High oxygen concentration must be administered in order to guarantee sufficient PaO_2 during spontaneous breathing, and until access to the trachea has been ensured and ventilation is controlled. Muscle relaxants are contraindicated in cases of difficult airway and suspicion of failed intubation, and when manual ventilation by mask may be difficult.

References

1. McNiece WL, Dierdorf SF (2004) The pediatric airway. Semin Pediatr Surg 13:152–165
2. Marraro GA (2004) Airway obstruction and difficult intubation in pediatrics. In: Khilnani P (ed) Practical approach to pediatric intensive care. Jaypee, New Delhi, pp 114–128
3. Marraro G (2002) Airway management. In: Bissonnette B, Dalens BJ (eds) Principles and practice of pediatric anesthesia. McGraw-Hill, New York, pp 778–814
4. Milerad J, Larson O, Hagerg C et al (1997) Associated malformation in infants with cleft lip and palate. A prospective, population based study. Pediatrics 100:180–186
5. Shar AE (1992) Mechanisms of airway obstruction in Robin sequence: implications for treatment. Cleft Palate Craniofac J 29:224–231
6. Figueroa A, Glupker TJ, Fitz MG et al (1991) Mandible, tongue and airway in Pierre Robin sequence. A longitudinal study. Cleft Palate Craniofac J 28:425–434
7. Mulliken JB, Kahan LB (1987) Analysis and treatment of hemifacial microsomia in childhood. Clin Plast Surg 14:91–100
8. Madan R, Trikha A, Vankataraman RK et al (1990) Goldenhar's syndrome: an analysis of anaesthetic management. Anaesthesia 45:49–52
9. Laishley RS, Ry WL (1982) Freeman Sheldon syndrome: report of these cases and the anaesthetic implications. Can Anaesth Soc J 33:388–393
10. Jones R, Dolcourt JL (1992) Muscle rigidity following halothane anesthesia in two patients with Freeman Sheldon syndrome. Anesthesiology 77:599–600
11. Dunn REO, Jones DJ (1988) Fibreoptic intubation in Klippel Feil syndrome. Anaesthesia 43:18–21
12. Kreiborg S, Dahl E (1993) Cranial base and face in mandibulofacial dysostosis. Am J Med Genet 47:753–760
13. Takefumi L, Kumiko F, Kazuya T et al (1995) Orotracheal intubation through the laryngeal mask airway in paediatric patients with Treacher Collins syndrome. Paediatr Anaesth 5:129–132
14. Friede H, Figueroa AA (1985) The Beckwith-Wiedemann syndrome. A longitudinal study of the macroglossia and dentofacial complex. J Craniofac Genet Dev Biol 1:179–182
15. Smith DF, Mihin FG, Flynn M (1982) Chronic alveolar hypoventilation secondary to macroglossia in the Beckwith-Wiedemann syndrome. Pediatrics 70:695–697
16. Mahowald WM, Iber CI, Rosen J et al (1989) Sleep disordered breathing in mucopolysaccharide storage disorders. Sleep Research 18:348
17. Sjgren P, Pedersen T, Steinmetz H (1987) Mucopolysaccharidoses and anaesthetic risks. Acta Anaesth Scand 31:214–218

18. Guffon N, Souillet G, Maire I et al (1998) Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. J Pediatr 133:119–125
19. Galloway DW (1990) Upper airway obstruction by the soft palate: influence of position of head, jaw and neck. Br J Anaesth 64:383P–384P
20. Selim M, Mowafi H, Al-Ghamdi A et al (1999) Intubation via LMA in pediatric patients with difficult airways. Can J Anaesth 46:891–893
21. Rowbottom SJ, Simpson DL, Grubb D (1991) The laryngeal mask airway in children. A fibreoptic assessment of positioning. Anaesthesia 46:489–491
22. Walker RW (2000) The laryngeal mask airway in the difficult paediatric airway: an assessment of positioning and use in fibreoptic intubation. Paediatr Anaesth 10:53–58
23. Hashan F, Kumar CM, Lawler PGP (1991) The use of the laryngeal mask to assist fibreoptic intubation. Anaesthesia 46:891
24. Thomas PB, Parry MG (2001) The difficult paediatric airway: a new method of intubation using the laryngeal mask airway. Cook airway exchange catheter and tracheal intubation fibrescope. Paediatr Anaesth 11:618–621
25. Brooks P, Ree R, Rosen D et al (2005) Canadian pediatric anesthesiologists prefer inhalational anesthesia to manage difficult airways. Can J Anaesth 52:285–290
26. Frei FJ, Ummenhofer W (1996) Difficult intubation in paediatrics. Pediatr Anaesth 6:251–263
27. Blanco G, Melman E, Cuairan V et al (2001) Fibreoptic nasal intubation in children with anticipated and unanticipated difficult intubation. Paediatr Anaesth 11:49–53
28. Benumof JL (1991) Management of the difficult adult airway. Anesthesiology 75:1087–1110
29. Anonymous (1993) Practice guidelines for management of the difficult airway. A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 78:597–602
30. Ovassapian A (2001) The flexible bronchoscope. A tool for anesthesiologists. Clin Chest Med 22:281–299
31. Wringley SR, Black AE, Sidhu VS (1995) A fibreoptic laryngoscope for paediatric anaesthesia: a study to evaluate the use of the 2.2 mm Olimpus (LF-P) intubating fibrescope. Anaesthesia 50:709–712
32. Crosby ET, Cooper RM, Douglas MJ et al (1998) The unanticipated difficult airway with recommendations for management. Can J Anaesth 45:757–776
33. Baraka A, Muallem AM (1994) Bullard laryngoscopy for tracheal intubation in a neonate with Pierre-Robin syndrome. Paediatr Anaesth 4:111–113
34. Cooper MG, Donnelly J, Overton JH (1993) Assessment of an angulated laryngoscope for difficult intubation. Paediatr Anaesth 3:33–36
35. Wong DT, Lai K, Chung FF et al (2005) Cannot intubate-cannot ventilate and difficult intubation strategies: results of a Canadian national survey. Anesth Analg 100:1439–1446

Chapter 70

Rationale for the use of noninvasive ventilation in children

C. Gregoretti, F. Racca

Although the basics of respiratory physiology are similar in adults, older children, and infants, significant developmental differences nonetheless exist with respect to age-specific disorders, maturational differences in airway size, and the evolution of respiratory mechanics [1]. In addition, in the absence of preexisting illness, acute respiratory failure is relatively rare in children. Invasive respiratory support with an endotracheal tube is a core feature of intensive care. Age and behavioural conditions can limit a child's understanding and cooperation, necessitating the enhanced use of sedatives and muscle relaxants to minimise self-injury and unplanned endotracheal tube removal [2]. Invasive mechanical ventilation should be theoretically discontinued as soon as the patient can sustain spontaneous breathing with adequate gas exchange [3, 4].

Noninvasive mechanical ventilation (NIV) is an area of expanding interest, but there are few reports on its application in children. So far, case series constitute the vast majority of the available knowledge, both in the acute setting and at home. Furthermore, many of the published case series typically report the results of treatment of a mixed group of medical conditions in children, making it even more difficult to draw conclusions with respect to any specific disease [1, 2].

The present chapter deals with the important differences in respiratory mechanics, breathing pattern, dead space, and spontaneous breathing ventilation–perfusion ratio between children and adults, and infants and children in order to find a rationale for using NIV in young patients.

Respiratory mechanics

The goal of a ventilatory control system placed in the brain stem and receiving input from several sources (chemoreceptors, stretching receptors in the lung, variation of metabolic status, and others) is to generate the timing and the intensity of the phrenic nerve signal. The target of the output resulting from the contraction of the respiratory muscles (pressure, flow, and volume) is to provide a breathing pattern able to generate the minimal work of breathing required for obtaining optimum arterial blood gases [5, 6].

During spontaneous breathing, the pressure applied to the respiratory system ($P_{app.rs}$) at any instant is equal to the pressure generated by the respiratory muscles (P_{musc}) [7].

$$P_{app.rs} = P_{musc} \text{ (Eq. 1)}$$

The respiratory system consists of the lung and the surrounding structures, commonly referred to as the 'chest wall.' The pressure applied to the respiratory system is dissipated against: (a) the resistance of the patient's lung and of the chest wall (R_{tot}), (b) the elastance (Est) of the patient's lung and chest wall, (c) the pressure needed to accelerate the lung mass (P_{in}), and (d) the intrinsic positive end-expiratory pressure ($PEEP_i$), when it is present. Under these circumstances, the act of breathing in a spontaneously breathing patient can be described at any instant as follows:

$$P_{musc} = P_{res} + P_{el} + P_{in} + PEEP_i \text{ (Eq. 2)}$$

P_{res} represents the resistive pressure and is a function of flow (P_{res} = flow × R_{tot}) and P_{el} represents the elastic recoil pressure and is a function of volume (P_{el} = volume × Est).

The pressure to accelerate lung mass (P_{in}) is negligible in adults. Conversely, infants have a relatively heavier lung per unit volume than adults and they breathe at a higher frequency. The force required to accelerate the lungs into motion is likely to be greater. In addition, the infant often breathes through the nose. As a consequence, the equation of motion can be re-written as follows [8]:

$$P_{musc} = P_{res} \text{ (upper airways + lower airways)} P_{el} + P_{in} + PEEP_i \text{ (Eq. 3)}$$

The neonate has a relatively stiff lung and a very compliant chest wall, which, unopposed, would lead to a functional residual capacity (FRC) of only 15% of total lung capacity. In the infant and in contrast to adults, the lung base is within the closing volume range, whereas the apex is on the ideal portion of the pressure–volume curve.

Due to high chest wall compliance, neonates have significantly lower relative relaxation volumes than adults. There are several mechanisms to overcome the tendency of the lung to collapse and to secure a proper end-expiratory lung volume (EELV) [8–10]:

1. Laryngeal breaking [11] or glottic closure during inspiration
2 Maintenance of the post-inspiratory tone in the muscles of the chest wall [12]
3. Tonic activity of the diaphragm throughout the respiratory cycle
4. The use of respiratory rates fast enough to make the expiratory time less than the time constant of the respiratory system

The combination of a relatively rapid respiratory rate and short expiratory time results in the generation of PEEPi [8].

The compliant chest wall also impedes the neonate's ability to generate adequate tidal volumes (VT) [13, 14]. The transition to a more relaxed pattern of respiratory flow occurs between 6 and 12 months [8].

Unlike in the early adult [8], the low transpulmonary distending pressure and the tendency to closure of the small intrapulmonary airways combined with their small diameter make the infant vulnerable to airway obstruction. Airway resistance has been found to be relatively lower at birth than at 2–3 months of age. This is due to the different growth patterns of lung and alveoli. Conversely, in the premature infant the airways are more compliant, with a tendency to collapse during expiration [8].

The mechanics of the respiratory system are further hampered by the high-flow resistance of the nasal airway, because the infant often breaths through the nose and small airways [15]; thus, there is increased propensity to hypertrophy of the adenoids and tonsils [16].

Furthermore, during the stage of rapid eye movement (REM) sleep, decreased muscle tone increases the flow resistance of the upper airways, which may lead to sleep apnoea during this sleep stage [17, 18].

The Respiratory pump

The high chest-wall compliance affects poor recoil of the rib cage (horizontal ribs), allowing it to distort, thereby causing low tidal volume and decreasing effective alveolar ventilation. In addition, a small zone of apposition of the diaphragm [19] that predisposes to obstruction and immature muscles in the very young [20] reduces the ability of the infant to cope with the added respiratory load and accentuates growth retardation [14, 19].

The energy expenditure of the respiratory pump is much higher in infants than in adults. However, as in adults, muscle tone is particularly low during REM sleep, contributing to a further decrease in FRC and in the power of the expiratory pump.

While oesophageal monitoring remains the gold standard for detecting pleural pressure, it is an invasive manoeuvre. Alternative to oesophageal monitoring include measuring the pulse transit time (PTT) [21, 22]. PTT is the time needed for the pulse wave to travel from the aortic valve to the periphery, estimated as the delay between the R wave in the ECG and the arrival of the pulse wave at the finger as determined by pulse oximetry. PTT discloses acute changes in arterial pressure generated by increased oscillations in pleural pressure due to the inspiratory effort.

Breathing pattern and body position

The effect of the irregular spontaneous breathing pattern and of posture on the spatial distribution of ventilation in neonates (23 ± 22 days, weight 2.4 ± 0.44 kg) free from respiratory disease were investigated by the non-invasive imaging method of electrical impedance tomography [23]. This study identified the significant effect of breathing pattern and posture on the spatial distribution of lung ventilation in spontaneously breathing neonates. The results showed that breathing pattern did not differ with regard to posture. In the right lateral position, the distribution of ventilation during tidal breathing of the dependent and non-dependent lung was similar, as opposed to the situation in adults. However, ventilation was preferentially directed towards the dependent lung regions during spontaneous deep breaths. Thus, the ventilation distribution under these conditions was identical to the adult pattern. An examination of regional lung ventilation in the prone position surprisingly revealed lower ventilation in the left than in the right lung region during tidal breathing. Also, in the prone posture, the abdominal wall is compressed, its

compliance is reduced and, consequently, respiratory mechanics are modified.

Finally, as above mentioned, apnoeas are more frequent in neonates than in adults, especially during REM sleep [17, 18].

Dead space

In children with acute lung injury, there is an increase in minute ventilation (VE) and inefficient gas exchange due to a high level of physiologic dead space ventilation (VD/VT). Any increase in dead space will cause a decrease in the efficiency of CO_2 removal and a consequent increase in the VE requirements out of proportion to the level of metabolic demand for gas exchange. Increased metabolic demands and ventilatory support were found to be the major determinants of VE requirements in children with ARDS (mean age 5.5 ± 4.6 years)

Positive end-expiratory pressure, when used in critically ill patients to correct hypoxaemia, may contribute to increased VD/VT [24].

Effect on arterial blood gases

The process of alveoli formation is nearly complete at the end of the perinatal period but only finally ends by the age of 3 years [8]. Several factors contribute to maintaining a relatively low arterial oxygen tension in infants and very young children. The tendency of the peripheral airways to collapse, resulting in a low Va/Q ratio in the dependent lung region, could explain the difference with adults, in whom perfusion at the lung base is increased but ventilation is decreased due to the lack of support of the lung tissue by the highly compliant chest wall.

The metabolic rate of children is approximately double that of the adult [8], thus increasing the risk of hypoxaemia, the risk of which is even further increased in the presence of parenchymal lung disease The hypoxaemic respiratory response is also attenuated in the infant [8]. Arterial blood gases tend to normalise in children age 4–5 years.

Rationale of using noninvasive ventilation

The rationale of using NIV requires an understanding of the difference between noninvasive continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NPPV) and thus of the equation of motion. As can be seen by Eq. 1, during spontaneous breathing the pressure applied to the respiratory system ($P_{app.rs}$) at any instant is the pressure generated by the respiratory muscles (P_{musc}) [7]. As a result, only unassisted breaths are generated during continuous positive airway pressure breathing [25], which can be considered as spontaneous ventilation when $P_{app.rs}$ follows Eq. 1.

Conversely, during assisted breaths $P_{app.rs}$ during the inspiratory phase always

exceeds the expiratory pressure. As a result, breaths during mechanical ventilation are always defined as assisted and the patient-ventilator interaction can be also described by using the equation of motion, where the total $P_{app.rs}$ includes the pressure generated by the respiratory muscle (P_{musc}) and the pressure applied by the ventilator (P_{vent}):

$$P_{app.rs} = P_{musc} + P_{vent} \quad \text{(Eq. 4)}$$

Under these circumstances, the act of breathing in an active mechanically ventilated patient can be described at any instant as follows:

$$P_{musc} + P_{vent} = \text{PEEPi} + P_{res} + P_{el} \text{ (Eq. 5)}$$

The rationale for the use of NIV in acute respiratory failure is essentially to avoid endotracheal intubation with all of its directly related complications, such as tracheal injury, gastric aspiration, hypotension, and predisposition to nosocomial pneumonia, as well as difficulties with sedation of the intubated child [26]. Avoiding endotracheal intubation is certainly most important in the immunocompromised patient, but it is also desirable to prevent the child experiencing possible discomfort and psychological trauma, despite sedative and analgesic treatment, while being intubated. Allowing for spontaneous breathing during NIV lowers the need for heavy sedation and assures better mobilisation. Finally, the child's ability to speak at least a few words, to cough, and to swallow can be maintained [27].

The interface is a crucial determinant of the success of NIV, and the patient cannot tolerate and accept NPPV in the case of facial discomfort, skin injury, or significant air leaks. In addition, facial deformity can occur in children due to the pressure applied by the mask on growing facial structures [28].

The use of non-invasive CPAP in infants and in small children early in the development of respiratory distress syndrome may prevent impending respiratory failure, with subsequent restoration of end-expiratory lung volumes (EELV) and thus an improvement of ventilation/perfusion mismatch. The mechanisms thought to be activated in this situation are: (1) a 'stenting' effect of continuous positive pressure on the large bronchi; (2) an increase in EELV that is dependent on the CPAP level [29]; (3) a reduction of the work of breathing by counteracting chest wall distortion. In addition, CPAP allows the administration of oxygen concentrations in the inspired air that are higher than those provided by simple oxygen delivery systems because there is no entrainment of ambient air. Noninvasive CPAP has also been found useful to treat problems related to upper airway obstruction by acting as a mechanical stenting of the upper airways [30, 31].

In children, NPPV has been demonstrated to support the respiratory muscle or even allow them to rest [1, 27, 32, 33] but convincing evidence is still scarce [1, 2].

Extubation failure rates in paediatric intensive care units range from 2.7 to 22% [4, 34]. In adults NIV did not prevent the need for re-intubation or reduce mortality in unselected patients who had respiratory failure after extubation [35]; however, paediatric patients have not been surveyed yet.

A poor prognosis and high mortality rate in children who underwent bone marrow transplantation and required mechanical ventilation due to pulmonary infection were recently reported by Jacobe et al [36]. This raises the question whether an alternative approach that avoids tracheal intubation, such as NIV, is

appropriate in these patients. Recently, NIV using a new device, the helmet, was tested in oncology patients with ARDS [33]. This new interface offers important advantages, including improved tolerability compared to other interfaces, a fixation system with a lower risk of cutaneous injury, and the possibility of fitting the helmet to any patient, regardless of facial contour [37].

Conclusions

Noninvasive ventilation has been shown to have a potential role in the treatment of acute respiratory failure of paediatric patients, although further studies are needed [1].

Many differences exist between adults, children, and infants regarding both respiratory mechanics and treatment of acute respiratory failure, although experience acquired in one field can be applied to the others. A significant fraction of patients with paediatric acute lung injury/ARDS can be identified in the early stage. These patients provide a valuable group in whom new therapies can be tested. Consequently, clinical trials in which paediatric patients with acute respiratory failure were randomised either to a noninvasive ventilation strategy with NIPPV or CPAP or to receiving supplemental oxygen could readily be organised [38, 39]. The results of these types of study would show whether clinical outcome, such as the need for endotracheal intubation and mechanical ventilation, or even mortality, can be improved by NIV.

References

1. Nørregaard O (2002) Noninvasive ventilation in children. Eur Respir J 20:1332–1342
2. Akingbola OA, Hopkins RL (2001) Pediatric noninvasive positive pressure ventilation. Pediatr Crit Care Med 2:164–169
3. Kurachek SC, Newth CJ, Quasney MW et al (2003) Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. Crit Care Med 31:2657–2664
4. Manczur T, Greenough A, Pryor D et al (2000) Assessment of respiratory drive and muscle function in the pediatric intensive care unit and prediction of extubation failure. Pediatr Crit Care Med 1:124–126
5. Squadrone E, Gregoretti C, Ranieri VM (2005) Patient ventilator interaction. In: Fink MP, Abraham E, Vincent JL, Kochanek PM (eds) Textbook of critical care. Elsevier-Saunders, Philadelphia, pp 505–510
6. Mead J (1960) Control of respiratory frequency. J Appl Physiol 15:325–336
7. Mead J, Whittenberger JL (1953) Physical properties of human lungs measured during spontaneous respiration. J Appl Physiol 5:770–796
8. Taussig ML (1996) Introduction. In: Stocks J (ed) Infant respiratory function testing. Wiley, New York, pp 1–18
9. Kosch PC, Stark AR (1984) Dynamic maintenance of end-expiratory lung volume in full-term infants. J Appl Physiol 57:1126–1133

10. Stark AR, Cohlan BA, Waggener TB et al (1987) Regulation of end-expiratory lung volume during sleep in premature infants. J Appl Physiol 62:1117–1123
11. Mortola JP, Fisher JT, Smith JB et al (1982) Onset of respiration in infants delivered by caesarean section. J Appl Physiol 52:716–724
12. Lopes J, Muller NL, Bryan MH et al (1981) Importance of inspiratory muscle tone in maintenance of FRC in the newborn. J Appl Physiol 51:830–834
13. Hagan R, Bryan AC, Bryan MH et al (1977) Neonatal chest wall afferents and regulation of respiration. J Appl Physiol 42:362–367
14. Howard SE (1987) Diaphragmatic work of breathing in normal infants and in infants with chronic lung disease. MSc dissertation, York University, Toronto, Canada
15. Lacourt G, Polgar G (1971) Interaction between nasal and pulmonary resistance in newborn infants. J Appl Physiol 30:870–873
16. Levy AM, Tabakin BS, Hanson JS (1967) Hypertrophied adenoids causing pulmonary hypertension and severe congestive heart failure. N Engl J Med 277:506–511
17. Rosen CL, D'Andrea L, Haddad GG (1992) Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. Am Rev Respir Dis 146:1231–1234
18. Young T, Palta M, Dempsey J et al (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235
19. Hershenson MB (1992) The respiratory muscles and the chest wall. In: Beckerman RC, Brouilette RT, Hunt CE (eds) Respiratory control disorders in infants and children. Williams and Wilkins, Baltimore, pp 28–46
20. Keens TG, Bryan AC, Levison H (1978) Developmental patterns of muscle fiber types in human ventilatory muscle. J Appl Physiol 44:909–913
21. Smith RP, Argod J, Pepin JL et al (1999) Pulse transit time: an appraisal of potential clinical applications. Thorax 54:452–457
22. Pagani J, Villa MP, Calcagnini G et al (2003) Pulse transit time as a measure of inspiratory effort in children. Chest 124:1487–1493
23. Frerichs I, Schiffmann H, Oehler R et al (2003) Distribution of lung ventilation in spontaneously breathing neonates lying in different body positions. Intensive Care Med 29:787–794
24. Coss-Bu JA, Walding DL, David YB et al (2003) Dead space ventilation in critically ill children with lung injury. Chest 123:2050–2056
25. Gregory GA, Kitterman JA, Phibbs RH et al (1971) Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333–1340
26. Orlowski JP, Ellis NG, Amin NP et al (1980) Complications of airway intrusion in 100 consecutive cases in pediatric ICU. Crit Care Med 8:324–331
27. Rimensberger PC (2000) Noninvasive pressure support ventilation for acute respiratory failure in children. Schweiz Med Wochenschr 130:1880–1886
28. Fauroux B, Lavis JF, Nicot F et al (2005) Facial side effects during noninvasive positive pressure ventilation in children. Intensive Care Med 31:965 –969
29. Elgellab A, Riou Y, Abbazine A et al (2001) Effects of nasal continuous airways pressure on breathing pattern on spontaneously breathing newborn infants. Intensive Care Med 11:1782–1787
30. Miller MJ, DelFiore JM, Strohk KP et al (1990) Effect of nasal CPAP on supraglottic and total pulmonary resistance in pre-term infants. J App Physiol 1:141–146
31. Gaon P, Lee S, Hannan S et al (1999) Assessment of effect of nasal continuous positive pressure on laryngeal opening using fiberoptic laryngoscopy. Arch Dis Child Fetal Neonatal Ed 3, F230–232

32. Thill PJ, McGuire JK Baden HP et al (2004) Noninvasive positive-pressure ventilation in children with lower airway obstruction. Pediatr Crit Care Med 5:337–342
33. Piastra M, Antonelli M, Chiaretti A et al (2004) Treatment of acute respiratory failure by helmet-delivered non-invasive pressure support ventilation in children with acute leukemia: a pilot study. Intensive Care Med 30:472–476
34. Farias JA (2001) A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. Intensive Care Med 27:1649 –1654
35. Esteban A, Frutos-Vivar F, Ferguson ND et al (2004) Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 350:2452–2460
36. Jacobe SJ, Hassan A, Veys P et al (2003) Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. Crit Care Med 31:1299 –1305
37. Antonelli M, Conti G, Pelosi P, et al (2002) New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med 30:602–608
38. Flori HR, Glidden DV, Rutherford GW et al (2005) Pediatric acute lung injury prospective evaluation of risk factors associated with mortality. Am J Resp Crit Care Med 171:995–1001
39. Cogliati A, Conti G, Tritapepe et al (2002) Noninvasive ventilation in the treatment of acute respiratory failure induced by all-transretinoic acid (retinoic acid syndrome) in children with acute promyelocytic leukemia. Pediatr Crit Care Med 3:70–73

Chapter 71

Neonatal helmet–continuous positive airway pressure in preterm infants

D. Trevisanuto, N. Doglioni, N. Grazzina

Continuous positive airway pressure (CPAP) is increasingly being used in the care of premature infants [1, 2]. CPAP is effectively used in patients immediately after extubation to prevent atelectasia, and to reduce apnoea episodes and the need for re-intubation [3]. In addition, in the centres adopting an 'early CPAP approach' for the treatment of infants with respiratory distress syndrome (RDS), the incidence of chronic lung disease appears lower in comparison with those using mechanical ventilation [4, 5].

In preterm infants, CPAP can be performed by means of nasal prongs or nasopharyngeal tubes, nasal masks or face masks, and nasal cannulae [1, 2]. The advantages and disadvantages of these various methods of delivering CPAP have been reported recently by Polin and Sahni [1].

Actually, the most used method for administering CPAP is by nasal prongs; however, it may fail for several reasons (Table 1). All these issues remain to be resolved and, in particular, improvement of the patient–ventilator interface seems to be crucial to achieve a prolonged and effective application of CPAP in preterm infants. Recently we developed a new device (neonatal helmet–CPAP) to administer CPAP in preterm infants [6]. We postulated that the neonatal helmet–CPAP could possess important advantages in comparison with conventional nasal CPAP (Table 2).

Table 1. Causes of nasal CPAP failure

Insufficient applied pressure
Insufficient circuit flow
Inappropriate prong size or placement
Airway obstruction from secretions
Baby's open mouth creating a large leak and lowering the pharyngeal pressure
Increased work of breathing
Improper position of CPAP prongs
Abdominal distension from swallowing air
Nasal septal erosion and necrosis
Discomfort of the patient

Table 2. Postulated advantages of neonatal helmet–CPAP in comparison with nasal CPAP

Ease of application
Good tolerability
Reduced risk of disconnection from CPAP system
Absence of air leakage due to baby's open mouth, maintaining a stable pressure in the system
Fixation system avoiding the risk of cutaneous lesions

The neonatal helmet–CPAP (Starmed, Mirandola, Modena, Italy) is made of rigid transparent polycarbonate. It is a bed that consists of two basic parts. In the superior part of the bed, there is a sealed hood, to which the inspiratory line of the circuit is directly connected by a dedicated port. At this level, pressure, fraction of inspired oxygen (FiO_2) and temperature in the chamber are detected and continuously displayed (Sensor OPT, Starmed, Mirandola, Modena, Italy). Another port is provided for expiratory exit in which an adjustable positive end-expiratory pressure valve allows regulation of the desired pressure in the system. The sealed hood has a simple opening system to permit the prompt accessibility to the infant's face, if necessary. In addition, in the upper part of the hood there is a pressure release (pop-off) valve that prevents excessive pressure build-up in the system (10 cmH_2O). The pressure chamber is kept separated from the rest of the bed by a transparent latex-free polyurethane membrane. The cone-shaped membrane has a hole in the middle to allow the patient's head to pass through it. Due to the pressure in the chamber, the soft membrane becomes a loose collar around the neck, adhering to the shoulders of the patient with a sealing and atraumatic effect. A soft diaper system positioned in the lower part of the patient's body allows proper sealing and shoulder contact of the patient to the soft membrane (Fig. 1a, b). The space around the head of the patient within the pressure chamber is approximately 2.5 l; however, because of the high continuous flow of fresh gases delivered through the chamber (ranging between 8 and 10 l/min), the dead-space effect is negligible. The neonatal helmet–CPAP is available in two different sizes: a small size for patients with birth weight < 1 500 g (diameter of the hole in the membrane = 3 cm) and a large size for neonates with birth weight 1 500–2 500 g (diameter of the hole in the membrane = 4 cm).

In a short-term physiological study, we compared the effectiveness of neonatal helmet–CPAP with a conventional nasal CPAP system (Infant Flow Driver Infant Flow Device; Hamilton Medical, Reno, NV, USA; Electro Medical Equipment Ltd, Brighton, UK) [7] in 20 preterm neonates (median birth weight 815 g, range 599–1 440 g; gestational age 27 weeks, range 24–32 weeks) needing continuous distending pressure for apnoea and/or mild RDS. Each infant was studied for two consecutive 90-min periods, alternating between neonatal helmet–CPAP and nasal CPAP. Neonatal Infant Pain Scale (NIPS) score [8] was significantly lower when the infants were on the neonatal helmet–CPAP than when they were on nasal CPAP (0.26 ± 0.07 to 0.63 ± 0.12, $p < 0.01$) (Fig. 2). The other studied parameters did not differ between the neonatal helmet–CPAP and nasal CPAP: fraction of inspired oxygen (%) 32 ± 2 vs 33 ± 2; transcutaneous saturation (%) 93 ± 0.6 vs 92 ± 0.4;

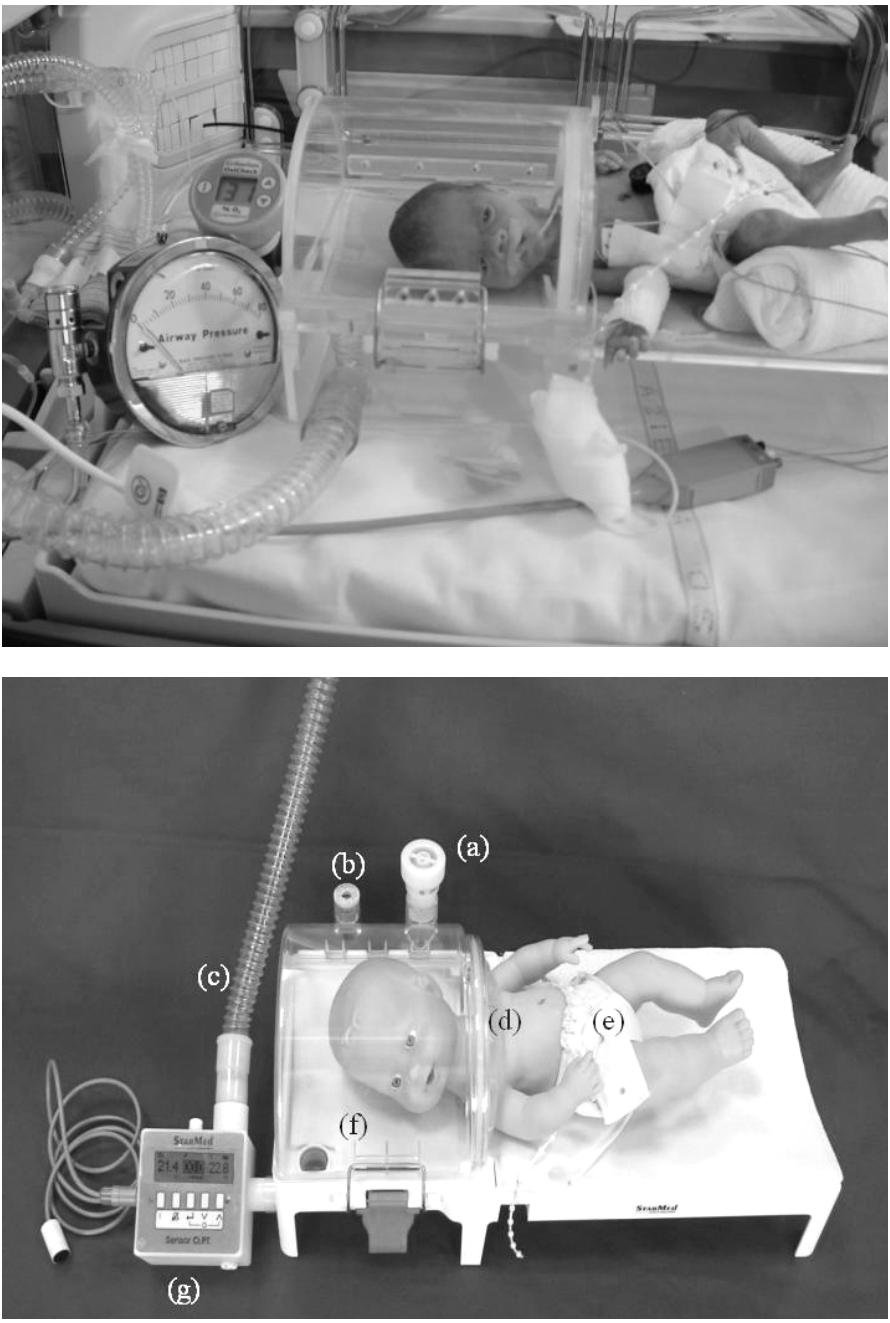


Fig. 1. **(a)** Neonatal helmet–CPAP (see text for explanation): (*a*) positive end-expiratory valve; (*b*) pressure-release valve; (*c*) inspiratory line; (*d*) membrane; (*e*) soft diaper system; (*f*) sealed hood; (*g*) monitor OPT. **(b)** Neonatal helmet–CPAP prototype used in a patient

heart rate (beats/min) 134 ± 5 vs 143 ± 2; respiratory rate (breaths/min) 56 ± 3 vs 50 ± 3; mean arterial pressure (mmHg) 46 ± 1 vs 48 ± 2; transcutaneous PCO_2 (mmHg) 53 ± 3 vs 52 ± 2; transcutaneous PO_2 (mmHg) 60 ± 4 vs 57 ± 4.

This short-term physiological study shows that the neonatal helmet–CPAP appears to be a feasible device for managing preterm infants needing continuous distending pressure, with better tolerability and oxygenation than nasal CPAP.

In 1971, Gregory et al. were the first to describe the use of a simple device to provide CPAP as a way to maintain lung gas volumes in preterm infants with RDS [9]. Their system consisted of a plastic pressure chamber around the infant's head. Differently from the Gregory et al.'s original system [9], in which 'the infant's head was enclosed in the chamber with a loosely fitting collar about the neck', our 'new head CPAP' leaves the neck free and the pressure in the system is guaranteed by a membrane that lays on the shoulders of the patient. In this way, the 'garrotting effect' of the collar and the consequent risks for cerebral haemodynamic complications [10], such as intraventricular haemorrhage and hydrocephalus, are avoided [11].

Factors determining the effectiveness of any nasal CPAP device include its associate work of breathing, flow characteristics, ease of application, and the comfort level of the infant once the device is in place [1, 2, 12–14]. Nasal prongs are commonly used to provide continuous or variable gas flow nasal CPAP [12, 14]. Even if differences in performance were reported among the different nasal CPAP devices [1, 2, 14], concerns exist about increased work of breathing with nasal prongs, compared with face mask CPAP [15]. Additionally, nasal prongs often

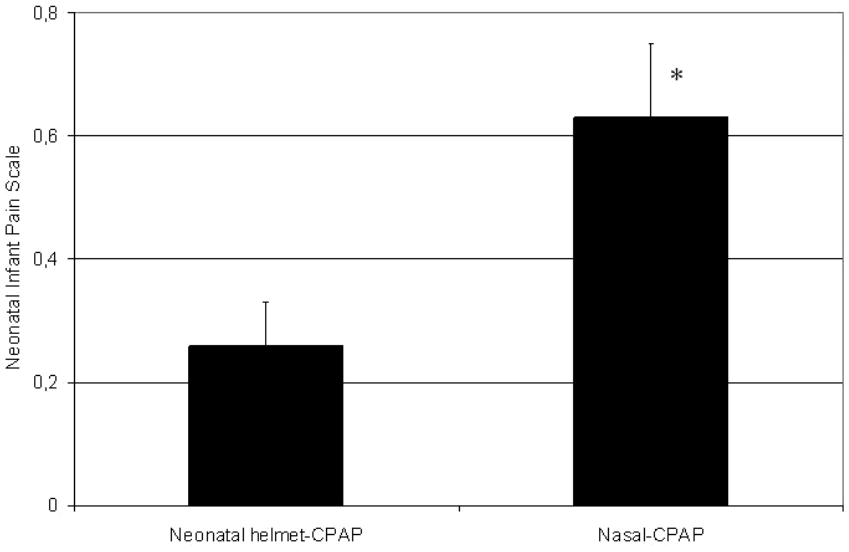


Fig. 2. Neonatal Infant Pain Scale score: neonatal helmet–CPAP versus nasal CPAP. * $p < 0.01$

become dislodged, making care of these infants difficult [1, 2]. Another factor that alters the efficacy of any nasal CPAP delivery system is the airway leak around the prongs [1, 2, 14]. Because the prongs are mechanically in parallel with the lungs, a larger leak around them results in lower effective nasal CPAP or less recruitment. Finally, nasal trauma has been reported with long-term use of nasal CPAP [16].

The helmet–CPAP was developed to overcome most of these problems: it is well tolerated by the patient, air leakage around the prongs or secondary to mouth opening and nasal trauma are eliminated and the dislocation of the device is very rare, making care of these infants easy.

Our results suggest that helmet–CPAP was better tolerated than nasal CPAP. In fact, NIPS scores were significantly lower in the helmet–CPAP trial period. Unfortunately, the study was not blind and one could argue that the attending nurse was influenced in scoring the infant's comfort. This hypothesis could be reasonable; however, the increased well being of the patients during helmet–CPAP treatment was confirmed also by the other, more objective physiological parameters, such as heart rate and blood pressure, although the differences were not statistically significant.

These advantages were previously demonstrated in adult patients with acute hypoxaemic respiratory failure, where a similar device (helmet) was used to administer non-invasive pressure-support ventilation. In fact, this new approach allowed the successful treatment of hypoxaemic acute respiratory failure, assuring a better tolerance than facial mask non-invasive pressure-support ventilation, with less complications [17, 18].

Another striking finding in our study was the decrease, although not statistically significant, in the number of desaturations documented while infants were receiving helmet–CPAP. The more stable method of fixation of the helmet–CPAP device and, consequently, a reduced disconnection from CPAP, could explain this difference. In fact, it is noteworthy that the most difficult aspects of using nasal CPAP are positioning and management of the device. In agreement with other authors [1, 2], we feel that nursing care is critical to the handling of the nasal CPAP devices to avoid technical problems. However, as we have been using nasal CPAP systems for several years in our unit, we consider the confidence and skill of our nurses with this device to be adequate. Instead, the experience with helmet–CPAP was at the beginning. Nevertheless, no particular concerns were expressed by the nursing staff over difficulties in correct insertion and management of the helmet–CPAP.

Limitations of the study

Due to safety reasons, we enrolled only clinically stable patients in this short-term physiological study. However, the design of this trial, with randomisation of the first technique of CPAP and then the crossover method using within-subject comparison, meant that any carry-over effect from one technique was balanced out.

We studied preterm babies after the acute phase of RDS needing relatively low oxygen concentrations and low CPAP pressures. The potential effectiveness of this

new device could be different for infants with RDS in the acute phase. Whether the head–CPAP, for example, could reduce the work of breathing or improve the lung recruitment remains to be demonstrated.

From a practical point of view, the CPAP would be interrupted at any time that the neonate required nursing care, since the patient is enclosed in a chamber. Disconnection from the CPAP system reduces the patient's airway pressures and, consequently, could have a negative effect on the management of the respiratory disease [1, 2].

Although we did not find any short-term complications, the size and the design of this study do not permit us to report on long-term effectiveness or limitations of this new device.

Furthermore, other important aspects previously evaluated in adult patients remain unresolved [18, 19]. For example, non-invasive ventilation with a helmet is associated with significantly greater noise than nasal and facial masks and a medium- and long-term exposure to loud noise could potentially impair ear function and increase the patient's discomfort [20]. Although heat and moisture exchanger filters (Hygrobac antimicrobial filter/HME, Mallinkrodt, Mirandola, Italy), ear plugs and sound traps may effectively decrease the discomfort caused by noise inside the helmet, this could be a real problem for the developing premature infant and needs further evaluation. In a recent physiological study including healthy adult volunteers, CPAP delivered by head helmet was as effective as CPAP delivered by facial mask in increasing end-expiratory lung volume and in compensating for airway pressure changes. However, higher gas flow rates were necessary to maintain a relatively low inspiratory CO_2 concentration [19]. In this pilot study, we used gas flow rates in the range of 8–10 l/min to maintain the airway pressures in the chamber. However, the optimal flow rate in this new neonatal CPAP system needs to be investigated further.

After this short-term physiological study in stable patients, it would be very interesting to evaluate whether the same results could be obtained in sicker infants and/or for a longer period of time.

In conclusion, CPAP is an increasingly popular method of respiratory support for preterm infants. Despite clinical evidence of effectiveness of nasal CPAP, some fundamental technological and clinical issues remain to be addressed in well-designed, prospective and randomised controlled trials [1, 2, 14]. The neonatal helmet–CPAP could be a useful alternative for the respiratory support of neonates needing continuous distending pressure. However, only larger, randomised controlled trials with specific end-points will allow us to define the role of this new device in the management of preterm neonates.

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References

1. Polin RA, Sahni R (2002) Newer experience with CPAP. Semin Neonatol 7:379–389
2. De Paoli AG, Morley C, Davis PG (2003) Nasal CPAP for neonates: what do we know in 2003? Arch Dis Child Foetal Neonatal Ed 88:F168–F172
3. Davis PG, Henderson-Smart DJ (2002) Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants. The Cochrane Library, Issue 1. Oxford, Update Software
4. Avery ME, Tooley WH, Keller JB et al (1987) Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 79:26–30
5. Van Marter L, Allred EN, Pagano M et al (2000) Do clinical markers of barotraumas and oxygen toxicity explain interhospital variation in rates of chronic lung disease? Pediatrics 105:1194–1201
6. Trevisanuto D, Grazzina N, Doglioni N et al (2005) A new device for administration of continuous positive airway pressure in preterm infants: comparison with a standard nasal CPAP continuous positive airway pressure system. Intensive Care Med 31:859–864
7. Moa G, Nilsson K (1993) Nasal continuous positive airway pressure: experiences with a new technical approach. Acta Paediatr 82:210–211
8. Lawrence J, Alcock D, McGrath P et al (1993) The development of a tool to assess neonatal pain. Neonatal Network 12:59–66
9. Gregory GA, Kitterman JA, Phibbs RH et al (1971) Treatment of the idiopathic respiratory distress system with continuous positive airway pressure. N Engl J Med 284:1333–1340
10. Vert P, Andre M, Sibout M (1973) Continuous positive airway pressure and hydrocephalus. Lancet 2:319
11. Zaramella P, Trevisanuto D, Freato F et al (2004) Does helmet-CPAP reduce cerebral blood flow by comparison with nasal CPAP in very low birth weight newborns? Pediatr Res 55:414A
12. Courtney SE, Pyon KH, Saslow JG et al (2001) Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatrics 107:304–308
13. Klausner JF, Lee AY, Hutchinson AA (1996) Decreased imposed work with a new nasal continuous positive airway pressure device. Pediatr Pulmonol 22:188–194
14. De Paoli AG, Davis PG, Faber B et al (2002) Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. The Cochrane Library, Issue 4. Oxford, Update Software
15. Goldman SL, Brady JP, Dumpit FM (1979) Increased work of breathing associated with nasal prongs. Pediatrics 64:160–164
16. Robertson NJ, McCarthy LS, Hamilton PA et al (1996) Nasal deformities resulting from flow driver continuous positive airway pressure. Arch Dis Child 75:F209–F212
17. Antonelli M, Conti G, Pelosi P et al (2002) New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med 30:602–608
18. Chiumello D, Pelosi P, Carlesso E et al (2003) Noninvasive positive pressure ventilation delivered by helmet vs standard face mask. Intensive Care Med 29:1671–1679
19. Patroniti N, Foti G, Manfio A et al (2003) Head helmet versus face mask for non-invasive continuous positive airway pressure: a physiological study. Intensive Care Med 29:1680–1687
20. Cavaliere F, Conti G, Costa R et al (2004) Noise exposure during noninvasive ventilation with a helmet, a nasal mask, and a facial mask. Intensive Care Med 30 1755–1760

Chapter 72

Helmet-delivered CPAP in children with acute hypoxaemic respiratory failure

G. Chidini, P. Pelosi, E. Calderini

During the past few years, noninvasive ventilation (NIV) has become an accepted approach not only for treating chronic respiratory failure in children, especially in the home setting, but also for providing ventilatory support in acute respiratory failure in children admitted to the paediatric intensive care unit (PICU). However, the large body of experience concerning NIV mostly derives from the adult population, and many of the published studies involving children report results from a mixed group of patients, making it difficult to draw conclusions about the efficacy of NIV in specific disease conditions.

Recently a consensus report summarised the state of the art on nasal mask ventilation as follows:

'At present nasal mask ventilation in children must be considered an investigational technique for use only by experienced centres. Further to our knowledge there are no published reports on the use of this technique in small children, and there are not generally accepted guidelines' [1].

In the adult intensive care setting, with encouraging results from several clinical trials, NIV during acute hypoxaemic respiratory failure has become an accepted treatment of non-chronic obstructive pulmonary disease (COPD)-related acute respiratory failure (ARF), e.g. due to acute lung injury/acute respiratory distress syndrome (ALI/ARDS), or acute pulmonary oedema [2–5].

Increased use of NIV in the PICU may be warranted for paediatric patients in attempts to decrease the rate of endotracheal intubation. With limited experience, it is difficult to define the ideal NIV candidate and the timing of application: infants and small children are at high risk of developing respiratory fatigue and ARF, and these physiological aspects may justify early NIV treatment as soon as clinical signs of impending respiratory failure develop and before clinical evidence of hypoxaemia and/or respiratory acidosis are present.

The aim of this article is to highlight some of the critical issues concerning certain aspects of NIV in infants/children: the selection of the patients that may benefit from NIV, the timing of initiation, and the type of interfaces that are better tolerated. We also describe our experience with helmet-delivered continuous positive airway pressure (HCPAP) in treating hypoxaemic ARF in infants admitted to our PICU.

Acute respiratory failure in children: pathophysiology, rationale for CPAP administration, and clinical studies

Healthy infants and young children are at increased risk of respiratory failure due to the relative instability of the developing respiratory system [6, 7]. The immature chest wall is highly compliant, and thus does not provide a stable platform to support the diaphragm and accessory respiratory muscles. Whereas the immature lung has exaggerated elastic recoil, and the immature rib cage is easily distorted, the predicted functional residual capacity (FRC) in young infants is close to total lung capacity. Increased laryngeal tone during expiration and other compensatory mechanisms are necessary to maintain FRC above its predicted level. For these reasons, for each significant derangement in respiratory mechanics, infants are prone to respiratory distress and alveolar hypoventilation. As dynamic lung compliance decreases, both the respiratory rate and dead-space-to-tidal-volume ratio nearly double. Because the chest wall is highly compliant, compensatory increases in diaphragmatic contraction manifest visibly in young infants as asynchronous movements of the thorax and abdomen (termed retractions or indrawing). A portion of the work done by the diaphragm in this situation is wasted through chest-wall distortion, instead of achieving a sufficient transrespiratory pressure gradient to sustain alveolar ventilation. Accordingly, early NIV treatment is justified as soon as clinical signs of impending respiratory failure develop and before clinical evidence of hypoxaemia and/or respiratory acidosis are present.

NIV can be provided either by bilevel respiratory support or by CPAP. The latter is a ventilatory technique by which the patient breathes spontaneously with a constant level of PEEP during in- and expiration. The benefits of this methods are related to the physiological effects of PEEP: increase in FRC, reduction in intrapulmonary shunt and increase in lung compliance by recruitment of underventilated alveoli, reduction in the work of breathing, prevention of atelectasis. The efficacy of CPAP in improving hypoxaemia has been well-documented since 1935, but its widespread use began after 1970, when CPAP was extensively applied in reversing hypoxaemia associated with respiratory distress syndrome (RDS) in neonates in the PICU. In the paediatric research field, data from large randomised clinical trials are lacking, and many of the studies involve children with chronic restrictive respiratory failure (neuromuscular diseases). There have been a few studies of acute hypoxaemic respiratory failure in the PICU setting, and the results have supported the use of bilevel noninvasive continuous nasal-mask positive airway pressure ventilation (BiPAP) in NIV. Padman et al. [8] reviewed a case series of 15 paediatric patients, age 4–21 years, with chronic respiratory failure (4 had cystic fibrosis, 11 had neuromuscular disease) who where admitted to the intensive care unit for acute ventilatory deterioration. All patients were given a trial of BiPAP. In 14 of 15 patients, an artificial airway could be avoided; baseline respiratory rates and PCO_2 levels improved significantly, but no differences in oxygenation were observed. Fortenberry and colleagues [9] presented observational data from 28 patients, age 0.3–17 years. with hypoxaemic ARF. All patients received BiPAP. The most common primary diagnosis was pneumonia ($n = 19$), nine patients had severe

underlying neurologic dysfunction or were immunocompromised. In patients on BiPAP, clinical and laboratory variables improved rapidly, i.e. a significant decrease in respiratory rate, improvement in arterial blood gas parameters (PaO_2, $PaCO_2$, and pH), calculated alveoloalveolar gradient, and PaO_2/FiO_2 ratio. Only three of 24 patients required intubation. In a prospective, non-controlled clinical study, Padman et al. [10] evaluated the efficacy of BiPAP applied by mask in critically ill children with underlying medical disease. Thirty-four patients, age 0.5–20 years, with respiratory distress requiring airway or gas-exchange support were enrolled in the study. The initiation of BiPAP was successful in 31 patients, and resulted in a decrease in dyspnoea score, respiratory rate, resting heart rate, and bicarbonate levels and an increase in room air saturation to normal levels. There were only three patients who failed to respond to this treatment and therefore required intubation and conventional mechanical ventilation.

A recent paper of Trevisanuto reported good efficacy of HCPAP in improve oxygenation in 20 very low birth weight, preterm babies requiring CPAP for RDS [11].

Indication and selection of patients for noninvasive ventilation

The determinants of the success of NIV–CPAP include a well-fitting and comfortable interface, which is the most critical factor, a delivery system adapted to the specific characteristics of the respiratory mechanics of the infant or child, and correct identification of candidates in whom intubation can most likely be avoided without increased risk for the patient. With the limited experience to date, it is difficult to clearly define the ideal paediatric patient for an NIV–CPAP trial in terms of the severity of respiratory illness. However, since children are at increased risk of rapidly developing respiratory failure, due to the structural and functional properties of their developing respiratory system, it may be justified to initiate NIV–CPAP in the small child or in infants early, as soon as clear signs of impending respiratory failure (i.e. severe dyspnoea, grunting, use of accessory muscles, intercostal retractions, and paradoxic abdominal motion) develop and before physiologic evidence of acute respiratory insufficiency with acute respiratory acidosis and/or acute hypoxaemia are present. The aim of such an approach would be to reduce the work of breathing and prevent respiratory fatigue, which in a small child can rapidly lead to severe hypoxic respiratory failure followed by apnoeas and cardiorespiratory arrest. Based on these reflections, the empirical criteria for patient selection can be formulated as: progressive hypoxic and/or hypercarbic respiratory failure or insufficiency in the absence of apnoea or impending collapse, and no immediate morbidity or mortality expected in case of failure of NIV. The patient should have intact upper airway protection, be relatively cooperative (mild sedation may be required), and haemodynamically stable. Absolute contraindications are: absence of upper airway protection, Glasgow Coma Scale < 8, ongoing emesis, excessive secretions, acute facial trauma.

Interfaces

The technique by which CPAP is delivered may alter its efficacy in neonates and infants. Goldman et al. reported an almost 100% increment in the work of breathing with nasal CPAP compared to facial mask. This adverse effect was attributed to flow resistance within the nasal attachment. A further disadvantage of nasal CPAP may be the leakage of breathing gas from the attachment or through the patient's mouth. In view of this limitation, an alternative, nasal CPAP delivery system has been developed (infant flow driver); however, there have been few studies comparing the efficacy of CPAP delivery methods. A comparison of continuous-flow CPAP via nasal prongs and variable-flow nasal CPAP demonstrated that lung recruitment was greater with the variable-flow system. Increments in the work of breathing and mask intolerance with facial skin breakdown are major causes of treatment failure with others interfaces (nasal and facial masks). For this reason, new interfaces that enhance comfort are needed to implement the feasibility of NIV in the paediatric population. Moreover, all of the existing studies have been carried out in the PICU and have involved RDS patients. To the best of our knowledge, trials involving infants and children with hypoxaemic respiratory failure are lacking.

A relatively new interface for CPAP delivery is the helmet. Potential advantages of this device include good tolerability, reduced needs of sedatives, and delivery of NIV for longer periods while avoiding the risk of skin breakdown. Moreover, this method can be applied to any patient, regardless of facial contour. In this research field, there is a large body of medical literature from studies carried out in adults. Several clinical trials involving adults patients reported that good efficacy was achieved in patients with several types of ARF who were treated with the helmet. Antonelli et al., in a large randomised controlled study [4], reported a significant reduction in intubation rate, rate of complication, length of ICU stay, and mortality in patients with ARF related to solid-organ transplantation who were randomised to receive either noninvasive pressure support (NIPPV) and medical treatment or only medical treatment. Another study, which compared patients treated with facial mask vs HCPAP, reported better tolerance of the helmet. In those patients, NIPPV could be administered for periods of time ranging from 18 to 48 h [12, 13]. All of the authors reported that the helmet dramatically reduces the incidences of facial-skin breakdown, thus avoiding the need to discontinue NIPPV. This is probably the main cause for the sustained improvement in gas exchange reported in the respective studies. There are few data on the use of the helmet in the paediatric population. Antonelli [14] used helmet-delivered NIV to successfully treat (ICM 2004[AQ2]) four children with ARF related to haematologic diseases, and showed a significant improvement in gas exchange and good tolerance of the interface. Trevisanuto [5] compared the efficacy of CPAP administered with a rigid neonatal helmet versus a conventional nasal CPAP system in a randomised, cross-over study. Twenty very low birth weight[AQ3], preterm babies were randomised to receive CPAP delivered by conventional system and helmet in random order for two subsequent periods of 90 min. Arterial blood gases, haemodynamics, and other physiological parameters did not differs between the two modes of CPAP, but the

neonatal infant pain score (NIPS) was significantly lower in HCPAP modes (0.26 ± 0.07 vs 0.6 ± 0.12). In this short-term physiological study, the neonatal HCPAP mode seems to be as good as the current gold standard for managing preterm infants needing CPAP for RDS.

Despite enthusiasm for the helmet, there is reason for caution: when CPAP is administered with a helmet a major concern is the risk of rebreathing, because of the large volume surrounding the head of the patients. To avoid CO_2 rebreathing it is critical that an elevated fresh gas flow, employing a continuous free-flow system, is delivered. Another concern is the exposure of the middle ear to positive pressure, with a theoretical risk of middle ear damage.

HCPAP for treating acute hypoxaemic respiratory failure in infants: our experience

Between January and May 2005, we conducted a clinical pilot study involving all infants meeting ARF criteria, eligible for treatment with HCPAP, who were admitted to the PICU in a tertiary children teaching hospital in Milan (IRCCS Ospedale Maggiore Policlinico, Terapia Intensiva de Marchi), Italy. Inclusion criteria were as follows: $pO_2/FiO_2 < 300$, tachypnoea, and respiratory effort score (RES) ≥ 2. In the latter, a respiratory severity score was calculated from the respiratory effort on admission: the nurse observed patient for intercostal, subcostal, and substernal recession, and nasal flaring, and assigned a score of 0, 1 or 2 for each factor. Each score was then multiplied by a weighting factor. The weighted scores were then totalled to obtain a final score for respiratory effort: 1 = mild, 2 = moderate, 3 = severe). In addition, patients enrolled in the study failed to show significant clinical improvement after at least 15 min of oxygen therapy via the Venturi system and conventional medical treatment (antibiotics, inhalational therapy with steroids and/or bronchodilators). Infants with any of the following were excluded: requirement of endotracheal intubation, cardiopulmonary resuscitation, failure of more than two organs, coma, recent orogastric surgery, and cystic fibrosis.

Equipment

The helmet (Castar© Starmed Italy) is made of transparent latex-free polyvinylchloride and is secured to a soft collar that adheres to the neck of the child. This collar provides a sealed connection during positive-pressure ventilation, and the system is secured by two pairs of hooks and clasps. The two ports of the helmet act as inlet and outlet for gas flow, and a PEEP underwater sealed valve is placed in the expiratory limb of the system. Adequate lavage of CO_2 by delivering CPAP using a continuous-flow system with 30 l fresh gas flow min^{-1}.

CPAP treatment

During the CPAP trial, the head of the bed was kept at a 45° angle. Once the helmet was in place, a PEEP level of 3 cmH_2O was set and was raised in steps of 2–3 cmH_2O in order to obtain $SpO_2 \geq 94\%$ with $FiO_2 < 0.6$, as well as a reduction in both accessory muscle activity and tachypnoea. The duration of the CPAP trial at admission was at least 2 h. A senior nurse recorded the patient's need for sedatives, his or her degree of comfort (VAS scale), and the RES.

Monitoring and weaning

All infants had continuous electrocardiography, noninvasive arterial pressure and arterial oxygen saturation monitoring. A central venous catheter and an arterial catheter were placed based on the clinical judgment of each member of the participating medical staff. CPAP was discontinued if the infant no longer had tachypnoea, or if the peripheral oxygen saturation was 90% without support, and in the absence of dyspnoea and activation of accessory muscles.

Criteria for intubation

Patients who failed CPAP trial were intubated and mechanically ventilated.

Criteria for endotracheal intubation and mechanical ventilation were as follows: impending neurological impairment, bradypnoea and respiratory arrest, haemodynamic instability, development of conditions requiring protection of the airway or management of secretions, inability of the patient to tolerate the CPAP helmet.

End points and measurements

The primary end points were an improvement in gas exchange, respiratory mechanics, rate of intubation at 24 h, and incidence of complications related to NIV (gastric distension, regurgitation, intolerance).

Secondary end points included ICU-related events such as nosocomial infections, length of PICU stay, and outcome in the PICU and in hospital.

PaO_2, $PaCO_2$, pH, bicarbonate, base excess, arterial blood pressure, heart and respiratory rate, and RES were determined at admission during O_2 mask (T0), after 2 h of CPAP (T1), and 1 h after the end of the CPAP trial (T2).

Sepsis, severe sepsis, and septic shock were defined according to consensus guidelines. Patients who were suspected of having ventilator-acquired pneumonia underwent quantitative tracheal aspirate. Bacterial pneumonia was diagnosed when at least 10^5 CFU/ml were measured in the lavage fluid.

A diagnosis of bloodstream infection was made on the basis of international consensus guidelines

Statistical analysis

Data are given as mean ± SD. Student's *t* test for paired samples was used to compare data obtained at different times. The test was significant for $p < 0.05$.

Results

From January 2005 to May 2005, 10 infants with ARF were enrolled in the study. The baseline characteristics of this are reported in Table 1. PRISM was calculated 24 h after admission; organ failures were defined according to the paediatric MSOFA score. Results are reported in Table 2.

Table 1. Baseline characteristics of population

Patients characteristics N° 10 (%)		
Male n°	4	(40)
PRISM	13.6	(7.9)
SOFA tot	2.5	(0.5)
SOFA res	2.5	(0.5)
Age (Mo)	5.6	(6)
GCS	14	(1)
Weight (Kg)	5.7	(0.9)
Conditions precipitating ARF		
Community Pneumonia	4	(40)
Viral infection	3	(30)
Bronchiolitis	3	(30)
Comorbid conditions		
Prematurity	4	(40)
Mechanical ventilation at birth	2	(20)

Table 2. Results

	Baseline To	**CPAP T1**	**After 1 h T2**	**p**
RES score	6.4 ± 1.2	2.0 ± 1.2	1.6 ± .12	< 0.05
PaO2/FiO2	119.4 ± 35.3	191 ± 65.8	117.4 ± 25.5	< 0.05
PCO2	48.5 ± 10	48.8 ± 7.5	43.6 ± 9.8	
PH	7.34 ± 0.009	7.35 ± 0.05	7.39 ± 0.03	
RR	67.8 ± 16.9	44.7 ± 9.5	41.6 ± 15.3	
HR	146.6 ± 29.5	145.8 ± 23.5	143 ± 27	

A first trial of CPAP (5 ± 1 cmH_2O) was applied for a mean duration time of 2.5 ± 0.8 h. The mean administration of CPAP in the first 24 h after admission was 7.8 ± 2.2 h and one patient was ventilated consecutively for 10 h. CPAP was associated with a significant improvement in pO_2/FiO_2 at T1 (To = 119.8 ± 35.3 vs T1 = 191 ± 65.8, $P < 0.05$). When CPAP was removed, PaO_2/FiO_2 returned to baseline values (117.4 ± 25.5) (Fig. 1). Respiratory rate (breaths per minute) was signifi-

cantly reduced at T1 (To = 67.8 ± 16.9 vs T1 = 44.7 ± 9.5 $P < 0.005$) and T2 (To = 67.8 ± 16.9 vs T2 = 41.6 ± 15 $P \sim 0.05$), as was RES (To = 2.6 ± 0.4 vs T1 = 1.6±1.5, $P < 0.001$; To = 2.6 ± 0.4 vs T2 = 1.6 ± 1.1, $P < 0.01$) (Figs. 2, 3). No differences were noted in $PaCO_2$, pH, bicarbonate, or base excess at the different time points.

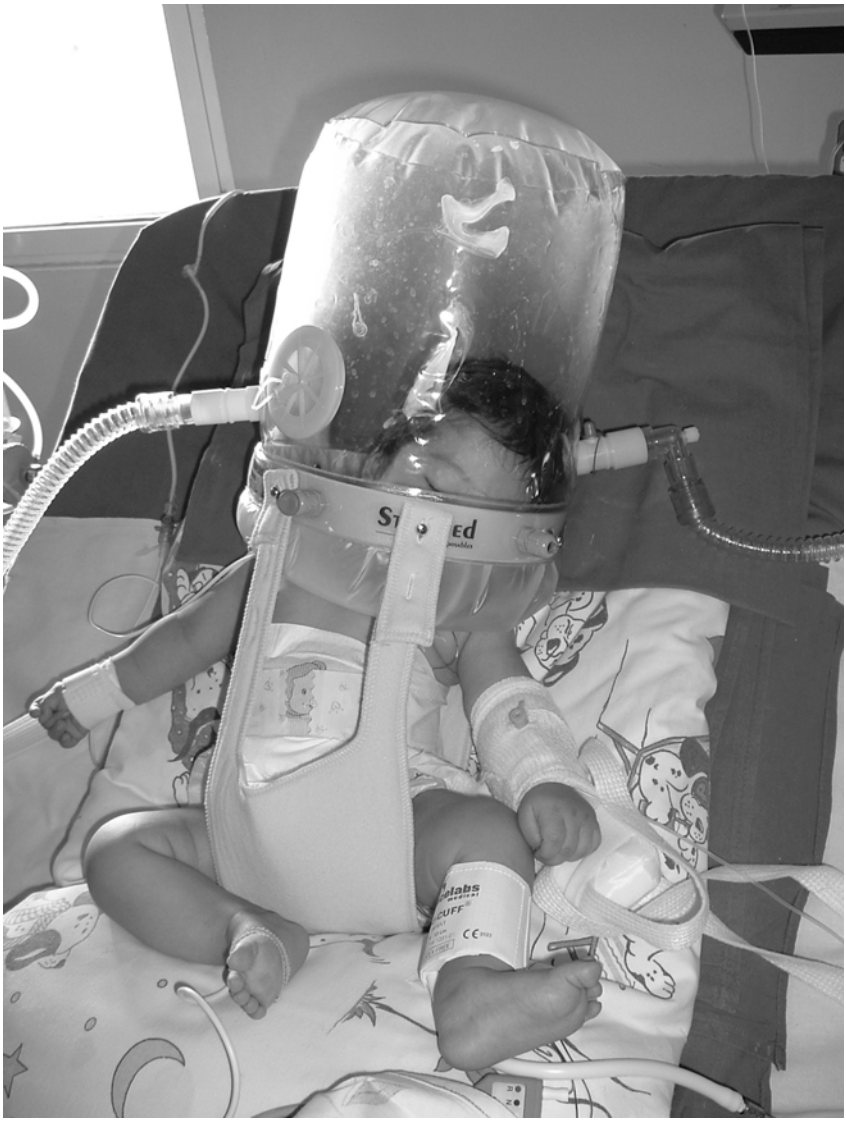
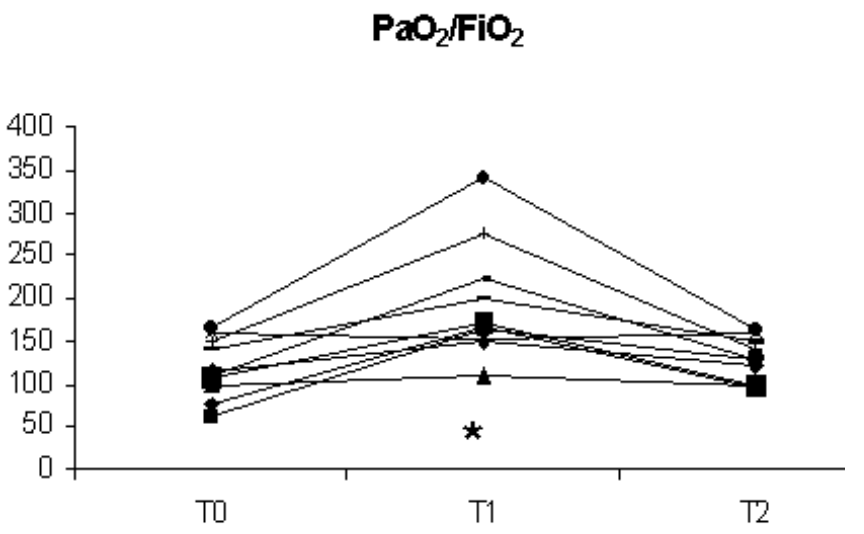


Fig. 1. The helmet (Castar© Starmed, Italy)



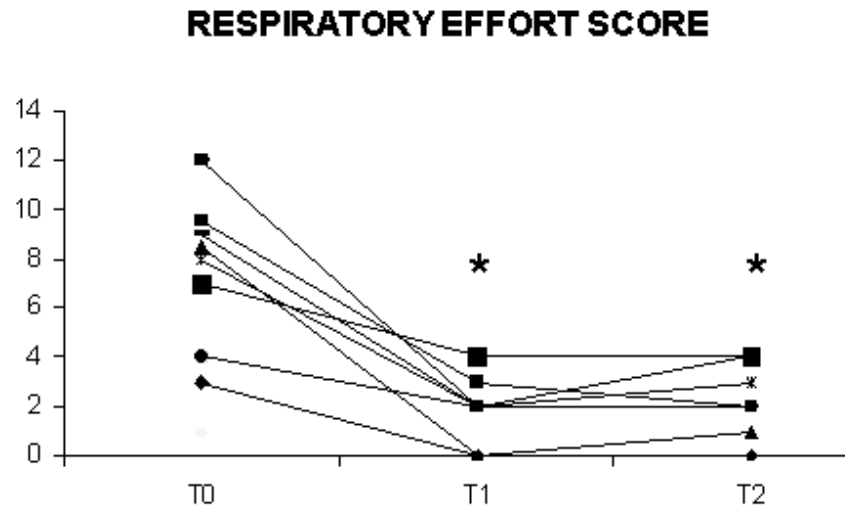


Fig. 2. Respiratory parameters at different time intervals. Data are shown as mean ± SD. *To*, admission during O_2 Venturi mask. *T1*, Helmet CPAP 2 h after enrolment; *T2*, Venturi mask 1 h after suspension of HCPAP; * $p < 0.05$

Complications

One patient was mechanically ventilated for impending respiratory failure not responsive to CPAP trial. No patients treated with CPAP developed skin necrosis or gastric distension, or had problem related to delivery of enteral feeding during CPAP. While one patient was intolerant and needed sedatives, a high level of tolerance of this method, as reported by the nurses (VAS 7.8 ± 2.2) was otherwise recorded. All infectious complications occurred after endotracheal intubation and were related to *Pseudomonas aeruginosa.* There was one case of ventilator-associated pneumonia (VAP) and severe sepsis due to *Pseudomonas* infection and one case of VAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) infection. No other severe complications were reported in patients treated with HCPAP.

Discussion

In this clinical pilot study, HCPAP was an efficient device to obtain an improvement in gas exchange and a reduction in respiratory effort. We observed a rapid improvement in pO_2/FiO_2 after 2 h CPAP, while a reduction in respiratory muscle activation was observed shortly after the institution of HCPAP. The improvement in respiratory mechanics and reduction in respiratory rate was sustained after discontinuation of HCPAP, while pO_2/FiO_2 returned to baseline values shortly after discontinuation. Normocapnia was maintained during the HCPAP trial, but we did not observe a reduction in pCO2 during the first trial. A positive trend was present but not significant, probably due to the small sample size. The lack of a reduction in pCO2 may be explained by the elevated dead space surrounding the head of the infant. CPAP mask intolerance is mainly due to discomfort, claustrophobia, and facial skin lesions. In order to avoid these complications, patients are often ventilated for short periods of time. By contrast, HCPAP devices are associated with good tolerability, reduction in air leakage, and an absence of skin necrosis, conjunctivitis, and eye irritation. The fixation system seems to be efficient and significant gas leakage or lesions related to fixation devices were not observed. In our population, good tolerance and elevated comfort of the HCPAP device were recorded. Only 1 patient needed sedatives in the first 24 h. Another patient was ventilated continuously for 10 h. Ideally, HCPAP allows infants to be ventilated for longer times than is possible with mask devices. Severe complications occurred only after endotracheal intubation, and did not develop in infants treated with HCPAP only.

Conclusions

Helmet CPAP is a new interface that allows an efficient ventilation over long times, even in infants with acute hypoxaemic respiratory failure. The device can be applied easily and quickly, and patients appear to well-tolerate the HCPAP without significant side effects. An improvement in gas exchange without hypercapnia and

a reduction in respiratory muscles activity are the hallmarks of HCPAP. While our results strongly suggest that this method provides safe and effective treatment of acute hypoxic and hypercarbic respiratory failure in children, well-controlled trials are needed to confirm these preliminary encouraging results. It might be reasonable to initiate HCPAP early, especially in small children, to avoid respiratory fatigue and to reverse impending respiratory failure. However, it is too early to recommend the use of HCPAP in acute or impending paediatric respiratory failure as a general first-treatment approach. Successful administration of HCPAP requires that the medical staff be familiar with the structural and functional properties of the developing respiratory system and be able to make an informed, appropriate choice at the right time. Larger clinical randomised trials are needed to further study the efficacy of HCPAP with respect to outcome in infants and children with ARF.

References

1. Make BJ (1998) Mechanical ventilation beyond intensive care unit: report of a consensus conference of the American College of Chest Physicians. Chest 113:289S–344S
2. Brochard L, Mancebo J, Wysocki M (1995) Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 333:817–822
3. Antonelli M, Conti G, Rocco M et al (1998) A comparison of noninvasive positive pressure ventilation and mechanical ventilation in patients with acute respiratory failure. N Engl J Med 339:429–435
4. Antonelli M, Conti G, Bufi M et al (2000) Acute respiratory failure in patients with solid organ transplantation: a prospective randomized evaluation of noninvasive ventilation. JAMA 283:235–241
5. Rusterholtz T (1999) Noninvasive pressure support ventilation with face mask in patients with acute pulmonary oedema. Intensive Care Med 25:21–28
6. Scharf SM, Feldman NT, Goldman MD et al (1978) Vocal cord closure: a cause of upper airway obstruction during controlled ventilation. Am Rev Respir Dis 117:391–397
7. Akingbola OA, Servant GM, Custer JR, Palmisano JM (1993) Noninvasive bi-level positive pressure ventilation: management of two pediatric patients. Respir Care 38:1092–1098
8. Akingbola O, Palmisano J, Servant G et al (1994) Bi-PAP mask ventilation in pediatric patients with acute respiratory failure. Crit Care Med 22:144 (abs)
9. Padman R, Lawless S, VonNessen S (1994) Use of BiPAP® by nasal mask in the treatment of respiratory insufficiency in pediatric patients: preliminary investigations. Pediatr Pulmonol 17:119–123
10. Fortenberry JD, Del Toro J, Jefferson LS et al (1995) Management of pediatric acute hypoxemic respiratory insufficiency with bi-level positive pressure (BiPAP) nasal mask ventilation. Chest 108:1059–1064
11. Padman R, Lawless ST, Kettrick RG (1998) Noninvasive ventilation via bilevel positive airway pressure support in pediatric practice. Crit Care Med 26:169–173
12. Trevisanuto D, Grazzina N, Doglioni N (2005) A new device for administration of continuous airway pressure in preterm infants: comparison with a standard nasal CPAP continuous positive airway pressure system. Intensive Care Med 31(6):859–864

13. Rocco M, Dell'Utri D, Morelli M (2004) Noninvasive ventilation by helmet or face mask in immunocompromised patients. Chest 126:1508–1515
14. Tonnelier JM, Prat G, Noweak E (2003) Noninvasive continuous pressure ventilation using a new helmet interface: a case control prospective pilot study. Intensive Care Med 29:2077–2080
15. Piastra M, Antonelli M (2004) Treatment of acute respiratory failure by helmet delivered noninvasive pressure support ventilation in children with acute leukemia: a clinical pilot study. Intensive Care Med 30:472–474

PAIN

Chapter 73

Organisation of an Acute Pain Service

M. Stadler, J. Boogaerts

Despite an increased focus on postoperative pain management programs, i.e. the development of new standards, extended quality, and outcome measures in pain management, many patients continue to experience intense pain after surgery [1, 2]. It is well-known that efficient and safe management of pain perioperatively reduces the risk of adverse outcomes. Sufficient treatment of pain may reduce thromboembolic, cardiac, and pulmonary complications as well as help to blunt autonomic and somatic reflex responses, thus restoring organ functions. The alleviation of pain enables early mobilisation and food intake, reduces fatigue and anxiety and consequently leads to improved subjective comfort and increased satisfaction. Advances in perioperative care, including fast-track surgery, optimised perioperative pain relief procedures and accelerated postoperative recovery programs decrease postoperative morbidity, length of hospital stay, and time of convalescence [3–5].

Taking into account all these facts, the ASA in 2004 reappointed a Task Force to revisit and update the 'Practice Guidelines for Acute Pain Management in the Perioperative Setting' of 1995 [6, 7]. Besides the recommendation of using multimodal techniques, administration of different analgesics and perioperative techniques, they strongly emphasised implementing institutional policies and procedures including anaesthesiologists providing perioperative pain management and Acute Pain Services.

Perioperative pathophysiology

The perioperative period can be divided into preoperative, operative, and postoperative parts, each of which impacts postoperative morbidity, length of hospital stay, and convalescence.

Preoperative evaluation

Postoperative morbidity is related to preoperative comorbidity [8]. The assessment of concomitant diseases is routine practice during preoperative visit and evaluation. The anaesthetist (together with the surgeon) has to assess the risks before operation and optimise the patient's condition.

Preoperative nutritional support should be provided, mainly in malnourished patients and elderly [9]. Recent clinical studies have shown that preoperative intake of a carbohydrate drink may reduce postoperative endocrine catabolic responses and improve insulin resistance [10].

Additionally, patient education of the postoperative care plan plays a major role in the perception of pain and recovery after surgery. The psychological preparation of patients—as has been proved—decreases pain perception as well as the requirement for analgesic drugs. It furthermore reduces preoperative anxiety, and therefore enhances recovery and shortens hospital stay [11, 12].

Operative period

Surgical injury induces a complex stress response characterised by profound endocrine–metabolic changes including hypermetabolism and catabolism, and inflammatory response with activation of humoral cascade systems, leading to malaise, hyperthermia, and immune suppression [13]. This stress response to surgery puts the patient at risk, especially if organ functions are already impaired before surgery. Various techniques are available to reduce stress, such as prevention of hypothermia, high inspired oxygen fraction and, most importantly, blockade of afferent neural stimuli from the surgical area by applying peripheral nerve blocks, or spinal or epidural anaesthesia. The metabolic effects of afferent blockade with local anaesthetics are further enhanced if the block is maintained during postoperative pain treatment.

Further protective interventions are the administration of glucocorticoids as a single dose preoperatively [14] and administration of β-blockers [15]. Nutritional support may confer beneficial effects in high-risk patients [16]. Active prevention of hypothermia is recommended to decrease wound infection, blood loss, and the incidence of cardiac events, thus facilitating the recovery process. In addition, the comfort of the patient must be considered. As a consequence of the reduced stress response and the inhibition of autonomic reflexes that occur after surgery, postoperative organ dysfunction may be attenuated.

Postoperative period

Postoperatively, all efforts should be made to mobilise the patient; this is only possible with effective pain relief.

To enhance early recovery, early enteral feeding should be at the goal; thus, the use of tubes, drains, and catheters should be restricted to absolute necessity. Many postoperative practices have evolved away from traditional approaches, and should be revisited to obtain scientific data regarding the effectiveness of newer, more patient-oriented practices [4].

Acute Pain Service

During the last decade, emphasis has been placed on the organisation of postoperative pain management programs and the importance of institutionalising pain relief procedures. In 1992, Gould was one of the first to describe the sequential introduction of an Acute Pain Service (APS) [17]. The focus was on the policy of providing pain relief after surgery such that every patient benefited after any type of surgery. Other authors introduced the anaesthesiologist-based APS, which focused on patients who had undergone major surgical interventions and thus often required more sophisticated techniques of postoperative pain control [18, 19]. In contrast, Rawal and Berggren [20] introduced a model of a low-cost APS in 1994. This nurse-based anaesthesiologist-supervised model provides pain treatment for all surgical patients and served as a blueprint for the implementation of an APS in our hospital.

In 2001, Harmer stated that standards for implementing an APS as well as better quality-assurance programs were warranted. To provide improvement over time, regular audits and quality tools, e.g. flowcharts, report cards, and quality manuals, should be introduced in the field of postoperative pain relief [21]. As Rawal and Berggren [20] stated, 'the solution to the problem of inadequate postoperative pain relief does not lie so much in the development of new techniques, but rather in the establishment of a formal organisation.'

From theory to practice: the nurse-based anaesthesiologist-supervised APS in Charleroi/Belgium

The creation of an APS in our hospital came as a result of a fatal incident involving a 40-year old, ASA I patient who died after an over-consumption of pain medication prescribed by five different physicians to treat postoperative pain. The medications were partly ordered by telephone, without a proper examination of the patient's health. This critical incident alerted the hospital manager and revealed the urgent need to improve pain management procedures.

A continuous quality-improvement program was set up by defining quality indicators and using quality tools. This program anticipated an enhancement of pain relief for all surgical inpatients postoperatively and the maintenance of this service over time. The study was conducted in a general hospital of 1 005 beds, 240 among them located on surgical wards. The process of quality management was divided into eight stages spanning over a 3-year period [22]. A brief recapitulation of the main components of this process is as follows:

- First, a pain management committee (PMC) was set up. It consisted of five anaesthesiologists, four surgeons, one pharmacist, 12 referent nurses, each of whom was responsible for pain management in a surgical unit, and one 'pain nurse.'
- A survey of nurses' attitudes and knowledge of pain management was conducted.
- Thereafter, educational programs for nurses and physician were provided. The

Visual Analogical Scale (VAS) device to assess in routinely relieving pain was introduced. Both nurses and physicians became familiar with guidelines concerning the management of postoperative pain.

- Regular consensus meetings were organised by the Department of Anaesthesia to establish a pain protocol accepted by all partners.
- The nurse-based APS, comprising acute pain nurses (APNs), acute pain anaesthesiologists, and day or night nurses, was introduced. The cornerstones of the service are: standardised treatment protocols, regular assessments of pain intensity every 4 h using the VAS, recording of treatment efficacy on a bedside vital-signs chart. The APN makes daily rounds on all surgical departments and registers patient satisfaction as well as problems regarding analgesia and side effects of treatment.
- Development of a clinical pathway to create an optimal regime of postoperative pain management [23].
- The analysis of flowcharts led to the definition of the most relevant quality indicators. A limited number of these indicators were graphed on report cards (patients' preoperative information, VAS scores, analgesic consumption, and patients' satisfaction). These report cards are produced monthly and enabled the PMC to identify problems and introduce necessary corrections.
- A quality manual was published and distributed in the post-anaesthesia care unit (PACU), to personnel working on surgical wards, and to surgeons and anaesthesiologists. The goal of the quality manual was to precise delineation of responsibilities and methods currently used. The process of postoperative pain management was divided into three clearly defined stages: pre-, peri- and postoperative care.

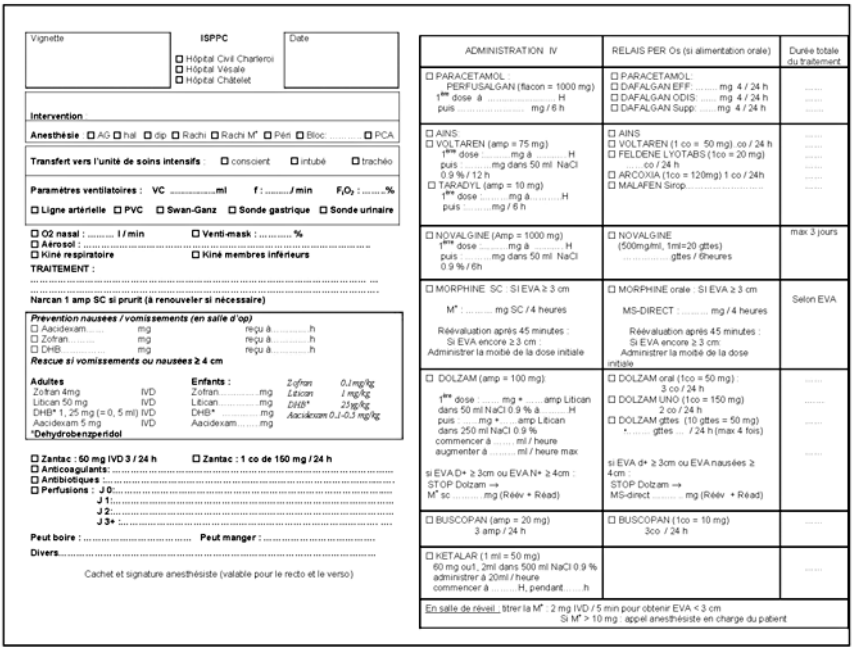
Multimodal approach to pain treatment

Current literature recommends the administration of different analgesic drugs, i.e. those acting by different mechanisms. The concept of so-called multimodal or balanced analgesia takes advantage of the additive or synergistic effects of combining multiple agents. Consequently, this leads to the need for a lower dose of each drug and to a concomitant reduction of side effects [24, 25].

In Charleroi, a multimodal analgesic regime was developed that combined different analgesic techniques. Every patient receives paracetamol and NSAIDs regularly (by the clock). This basic treatment is combined with morphine subcutaneously in case of VAS > 3 cm. Forty five minutes after morphine administration, the VAS is reassessed. If it remains above 3 cm, half of the initial morphine dose is readministered. An individual analgesic prescription sheet is established for all patients leaving the PACU (Fig. 1). Additionally, several regional techniques specific for the type of surgery as well as morphine-based patient controlled analgesia (PCA) are provided to patients who have undergone major surgical interventions. Safe management of these techniques on the ward is ensured by the requirement that bedside charts be filled out for every patient (Fig. 2). Ward nurses

monitor the patient every 4 h, measuring blood pressure, heart rate, respiratory rate, VAS at rest and movement, occurrence of vomiting and nausea, Bromage score, and brick test in case of epidurals. All side effects and incidents have to be noted carefully and the responsible physician must be alerted. In case of insufficient pain relief, the APN or the anaesthesiologist in charge of the APS, or the anaesthesiologist on call has to evaluate the patient following well-defined protocols.

Preoperatively, the patient is given an information pamphlet about the VAS device. Ward nurses explain the use of the VAS device, and the anaesthesiologist discusses preoperatively the anticipated postoperative pain regime, i.e. the analgesic technique. The patient is assured that pain, nausea, and vomiting will be closely checked and immediately treated, and that every effort will be made to maintain the patient's VAS below the previously defined threshold of 3 cm.


Vignette

ISPPC

☐ Hôpital Civil Charleroi
☐ Hôpital Vésale
☐ Hôpital Châtelet

Date

Intervention

Anesthésie : ☐ AG ☐ hal ☐ dip ☐ Rachi ☐ Rachi M° ☐ Péri ☐ Bloc: ..... ☐ PCA

Transfert vers l'unité de soins intensifs : ☐ conscient ☐ intubé ☐ trachéo

Paramètres ventilatoires : **VC** .....**ml** **f** : ...../ **min** **F_iO_2** : .....**%**

☐ **Ligne artérielle** ☐ **PVC** ☐ **Swan-Ganz** ☐ **Sonde gastrique** ☐ **Sonde urinaire**

☐ **O2 nasal** : ..... **l / min** ☐ **Venti-mask** : ..... **%**
☐ **Aérosol** : .....
☐ **Kiné respiratoire** ☐ **Kiné membres inférieurs**
TRAITEMENT :
.....
.....
Narcan 1 amp SC si prurit (à renouveler si nécessaire)

Prévention nausees / vomissements (en salle d'op)
☐ Aacidexam..... mg reçu à.....h
☐ Zofran..... mg reçu à.....h
☐ DHB..... mg reçu à.....h

Rescue si vomissements ou nausees ≥ 4 cm

Adultes		**Enfants** :		
Zofran 4mg	IVD	Zofran.....mg	*Zofran*	*0,1 mg/kg*
Litican 50 mg	IVD	Litican.....mg	*Litican*	*1 mg/kg*
DHB* 1, 25 mg (= 0, 5 ml)	IVD	DHB*.....mg	*DHB**	*25µg/kg*
Aacidexam 5 mg	IVD	Aacidexam.....mg	*Aacidexam 0,1-0,3 mg/kg*	

*Dehydrobenzperidol

☐ **Zantac : 60 mg IVD 3 / 24 h** ☐ **Zantac : 1 co de 150 mg / 24 h**
☐ **Anticoagulants**: .....
☐ **Antibiotiques** : .....
☐ **Perfusions** : **J 0**:.....
J 1:.....
J 2:.....
J 3*:.....

Peut boire : ..... **Peut manger** : .....

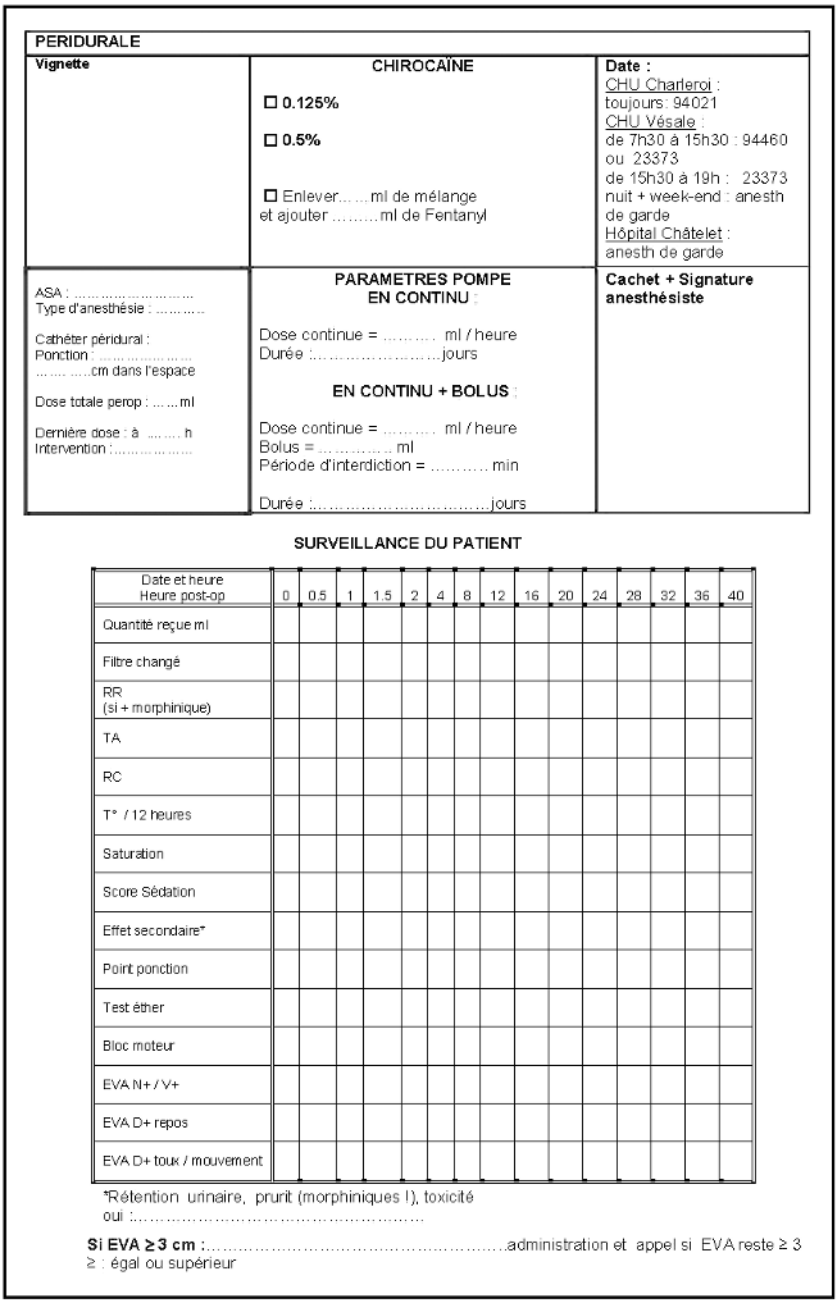
Divers.....

Cachet et signature anesthésiste (valable pour le recto et le verso)

ADMINISTRATION IV	RELAIS PER Os (si alimentation orale)	Durée totale du traitement
☐ PARACETAMOL : PERFUSALGAN (flacon = 1000 mg) 1ère dose à .....H puis ..... mg / 6 h	☐ PARACETAMOL : ☐ DAFALGAN EFF : ..... mg 4 / 24 h ☐ DAFALGAN ODIS : ..... mg 4 / 24 h ☐ DAFALGAN Supp : ..... mg 4 / 24 h	....
☐ AINS : ☐ VOLTAREN (amp = 75 mg) 1ère dose : ..... mg à .....H puis ..... mg dans 50 ml NaCl 0.9 % / 12 h ☐ TARADYL (amp = 10 mg) 1ère dose : ..... mg à .....H puis ..... mg / 6 h	☐ AINS : ☐ VOLTAREN (1 co = 50 mg) .co / 24 h ☐ FELDENE LYOTABS (1co = 20 mg) ..... co / 24 h ☐ ARCOXIA (1co = 120mg) 1 co / 24h ☐ MALAFEN Sirop.....	....
☐ NOVALGINE (Amp = 1000 mg) 1ère dose : ..... mg à .....H puis ..... mg dans 50 ml NaCl 0.9 % / 6h	☐ NOVALGINE (500mg/ml, 1ml=20 gttes) ..... gttes / 6heures	max 3 jours
☐ MORPHINE SC : SI EVA ≥ 3 cm M° : ..... mg SC / 4 heures Réévaluation après 45 minutes : Si EVA encore ≥ 3 cm : Administrer la moitié de la dose initiale	☐ MORPHINE orale : SI EVA ≥ 3 cm MS-DIRECT : ..... mg / 4 heures Réévaluation après 45 minutes : Si EVA encore ≥ 3 cm : Administrer la moitié de la dose initiale	Selon EVA
☐ DOLZAM (amp = 100 mg) 1ère dose : ..... mg + ...amp Litican dans 50 ml NaCl 0.9 % à .....H puis ..... mg + ...amp Litican dans 250 ml NaCl 0.9 % commencer à ..... ml / heure augmenter à ..... ml / heure max si EVA D+ ≥ 3cm ou EVA N+ ≥ 4cm : STOP Dolzam ⇒ M° sc ..... mg (Réév + Réad)	☐ DOLZAM oral (1co = 50 mg) : 3 co / 24 h ☐ DOLZAM UNO (1co = 150 mg) 2 co / 24 h ☐ DOLZAM gttes (10 gttes = 50 mg) +..... gttes .... / 24 h (max 4 fois) si EVA d+ ≥ 3cm ou EVA nausées ≥ 4 cm : STOP Dolzam ⇒ MS-direct ..... mg (Réév + Réad)	....
☐ BUSCOPAN (amp = 20 mg) 3 amp / 24 h	☐ BUSCOPAN (1co = 10 mg) 3co / 24 h	.....
☐ KETALAR (1 ml = 50 mg) 60 mg ou1, 2ml dans 500 ml NaCl 0.9 % administrer à 20ml / heure commencer à .....H, pendant.....h		.....

En salle de réveil : titrer la M° : 2 mg IVD / 5 min pour obtenir EVA < 3 cm
Si M° > 10 mg : appel anesthésiste en charge du patient

Fig. 1. Analgesic prescription sheet for any patient leaving the recovery room



PERIDURALE

Vignette	**CHIROCAÏNE** ☐ **0.125%** ☐ **0.5%** ☐ Enlever……ml de mélange et ajouter ……..ml de Fentanyl	**Date :** CHU Charleroi : toujours: 94021 CHU Vésale : de 7h30 à 15h30 : 94460 ou 23373 de 15h30 à 19h : 23373 nuit + week-end : anesth de garde Hôpital Châtelet : anesth de garde
ASA : …… Type d'anesthésie : …… Cathéter péridural : Ponction : …… …… ……cm dans l'espace Dose totale perop : ……ml Dernière dose : à ……h Intervention : ……	**PARAMETRES POMPE EN CONTINU :** Dose continue = ……. ml / heure Durée :……jours **EN CONTINU + BOLUS :** Dose continue = ……. ml / heure Bolus = …… ml Période d'interdiction = …… min Durée :……jours	**Cachet + Signature anesthésiste**

SURVEILLANCE DU PATIENT

Date et heure Heure post-op	0	0.5	1	1.5	2	4	8	12	16	20	24	28	32	36	40
Quantité reçue ml															
Filtre changé															
RR (si + morphinique)															
TA															
RC															
T° / 12 heures															
Saturation															
Score Sédation															
Effet secondaire*															
Point ponction															
Test éther															
Bloc moteur															
EVA N+ / V+															
EVA D+ repos															
EVA D+ toux / mouvement															

*Rétention urinaire, prurit (morphiniques !), toxicité
oui :……

Si EVA ≥ 3 cm :……administration et appel si EVA reste ≥ 3
≥ : égal ou supérieur

Fig. 2. Bedside chart for patients who received epidurals

APS: a continuous quality improvement program

The implementation of an APS is an ongoing process and is subject to change in case of poor results. Parameters such as VAS, postoperative nausea and vomiting (PONV), and other side effects, must be accurately monitored by APNs. All relevant variables are statistically evaluated once a year. An example is displayed in Table 1, in which side effects related to different pain relief procedures were recorded and compared between 2003 and 2004. In case of poor outcome, procedures are revisited, discussed among all responsible members of the APS, and new guidelines, if necessary, are introduced.

Table 1. Analysis of side effects in patients who received different analgesic techniques: 2003-2004

Nausea	2003		2004		Sedation	2003		2004	
None (%)	209	74.9	422	82.6	Present (%)	96	24.9*	84	16.4*
VAS 1-3 cm (%)	49	12.7*	33	6.5*	Absent (%)	290	75.1	427	83.6
VAS ≥ 3cm (%)	48	12.4	56	11.0					
	*$P = 0.003$					*$P = 0.002$			
Vomiting	2003		2004		Urine retention	2003		2004	
Yes (%)	36	9.4	34	6.7	Present (%)	12	3.1	10	2.0
No (%)	349	90.6	477	93.3	Absent (%)	374	96.9	500	98.0
	*$P = 0.136$					*$P = 0.272$			
Prurite	2003		2004		Headache	2003		2004	
Yes (%)	45	11.7*	32	6.3	Present (%)	3	0.8	17	3.3*
No (%)	341	88.3	479	93.7	Absent (%)	383	99.2	494	96.7
	*$P = 0.004$					*$P = 0.010$			
Respiratory rate > 8	2003		2004						
Yes (%)	23	6.0*	9	1.8					
No (%)	362	94.0	502	98.2					
	*$P = 0.001$								

As an example, the incidence of nausea and vomiting was significantly reduced following implementation of a protocol addressing the prevention and treatment of PONV. Educational programs dealing with all important aspects of PONV were offered to nurses and anaesthesiologists. By means of the protocol, nurses were able to administer drugs independently according to the above-mentioned prescription sheet. As a consequence, very early and efficient treatment of nausea and vomiting were established, which led to a high rate of satisfaction from patients and nurses.

A relatively high incidence of episodes of VAS > 3 cm in the orthopaedic department revealed the need for more continuous peripheral nerve blocks for postoperative pain relief. The anaesthesiologists were asked to improve their skills to provide these blocks, and the anaesthesiologist's assignments were more adapted to make optimal use of their particular capabilities. However, there is still need for further improvement.

In regular meetings (four times a year), all current problems are discussed and a rapid and satisfactory solution is usually found.

In the context of the inception of ISO 9001 in the Department of Anaesthesia, all procedures have to be reviewed, responsibilities redefined, and processes precisely described. This is the current state of the Continuous Quality Improvement (CQI) program of the APS in Charleroi.

Eight years after the successful implementation of a nurse-based anaesthesiologist-supervised APS in Charleroi, a major improvement in the provision of postoperative pain relief can be clearly seen. Nurses increasingly assess patients for the presence and intensity of pain as well as the consequences of its treatment. The fear of side effects of morphine administration has decreased significantly. VAS pain scores have become a standard tool in the assessment of postoperative patients regarding blood pressure or heart rate measurements. The satisfaction rate of nurses, surgeons, anaesthesiologists, and especially patients with the APS is very high. Further improvement in early feeding, decreased use of gastric tubes, and very early mobilisation are warranted, although these are mainly a problem of insufficient manpower.

To conclude, the postoperative recovery progress is basically dependent on the provision of efficient pain relief programs, primarily accomplished by Acute Pain Services. Sufficient postoperative care requires the implementation of 'perioperative care teams'; however, due to restricted financial resources, this remains a challenge for the next decade.

References

1. Apfelbaum JL, Chen C, Mehta S, Gan TJ (2003) Postoperative experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 97:534–540
2. Rocchi A, Chung F, Forte L (2002) Canadian survey of postsurgical pain and pain medication experiences Can J Anaesth. 49:1053–1056
3. Kehlet H, Wilmore DW (2002) Multimodal strategies to improve surgical outcome. Am J Surg 183:630–644
4. Kehlet H, Holte K (2001) Effect of postoperative analgesia on surgical outcome. Br J Anaesth 87:62–72
5. Kehlet H, Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 362:1921–1928
6. American Society of Anesthesiologists Task Force on Acute Pain Management (1995) Practice guidelines for acute pain management in the perioperative setting: a report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 82:1071–1081
7. American Society of Anesthesiologists Task Force on Acute Pain Management (2004) Practice guidelines for Acute Pain Management in the perioperative setting. An updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 100:1573–1581
8. Garcia-Miguel FJ, Serrano-Aguilar PG, Lopez-Bastida (2003) Preoperative assessment. Lancet 362:1749–1757

9. Anonymous (1991) Perioperative nutrition in surgical patients. The Veteran's Affairs Total Parenteral Nutrition Study Group. N Engl J Med 325:525–532
10. Nygren J, Soop M, Thorell A et al (1999) Preoperative oral carbohydrates and postoperative insulin resistance. Clin Nutr 18:117–120
11. Klafta JM, Roizen MF (1996) Current understanding of patients attitudes forward and preparation for anesthetic: a review. Anesth Analg 83:1314–1321
12. Carr DB, Goudas LC (1999) Acute pain. Lancet 353:2051–2058
13. Wilmore DW (2002) From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Ann Surg 236:643–648
14. Holte K, Kehlet H (2002) Perioperative single-dose glucocorticoid administration: pathophysiological effects and clinical implications. J Am Coll Surg 287:1435–1444
15. Auerbach AD, Goldman L (2002) Beta-blockers and reduction of cardiac events in non-cardiac surgery. JAMA 287:1445–1447
16. Wray CJ, Mammen JMV, Hasselgren PO (2002) Catabolic response to stress and potential benefits of nutrition support. Nutrition 18:971–977
17. Gould TH, Crosby DL, Harmer M et al (1992) Policy for controlling pain after surgery: effect of sequential changes in management. BMJ 305:1187–1193
18. Schug SA, Haridas RP (1993) Development and organizational structure of an Acute Pain Service in a major teaching hospital. Aust N Z Surg 63:8–12
19. Wheatley RG, Madej TH, Jackson IJ et al (1991) The first year's experience of an acute pain service. Br J Anaesth 67:353–359
20. Rawal N, Berggren L (1994) Organization of acute pain services: a low-cost model. Pain 57:117–123
21. Harmer M (2001) When is a standard, not a standard? When is it a recommendation? Anaesthesia 56:611–612
22. Bardiau FM, Taviaux NF, Albert A et al (2003) An intervention study to enhance postoperative pain management. Anesth Analg 96:179–185
23. Bardiau FM, Braeckman MM, Seidel L et al (1999) Effectiveness of an Acute Pain Service in a general hospital. J Clin Anesth 11:583–589
24. Kehlet H, Werner M, Perkins F (1999) Balanced analgesia. What is it and what are its advantages in postoperative pain? Drugs 58:793–797
25. Fengling J, Frances C (2001) Multimodal analgesia for postoperative pain control. J Clin Anesth 13:524–539

Chapter 74

Pain management and patient satisfaction

D. Caristi, L. Miotto, M. Piva

Effective pain relief is very important not only for humanitarian and ethical reasons, but also in order to avoid several postoperative complications and to obtain a faster recovery from surgery and an earlier discharge from hospital. Good pain management in the peri- and postoperative periods helps to ensure the best outcome for the patient [1]. Pain relief per se does not significantly improve the postoperative outcome, with the exception of patient satisfaction and pulmonary complications. Instead, postoperative morbidity and hospital stays are dependent on many factors, including preoperative information, quality of analgesia, and existing programs for postoperative care and rehabilitation, including orders for mobilisation, oral nutrition, and discharge criteria [2]. In recent years, the techniques for pain management in patients undergoing surgery have substantially improved. The choice of analgesic and the route and technique of administration can be tailored to the individual's need to optimise pain control and to avoid postoperative discomfort and suffering.

The recognition that unrelieved pain contributes to preoperative morbidity and mortality has inspired many institutions to develop an Acute Pain Service (APS) in an attempt to provide effective postoperative relief. The immediate and sustained formal support and authoritative recommendations of various medical and healthcare organisations have promoted the widespread introduction of APS [3–13]. This, in turn, has led to successful and safe implementation of multi-modal pain management strategies [14], and an increase in the use of specialised pain relief methods, such as patient-controlled analgesia (PCA) and epidural infusions of local anaesthetics/opioid mixtures, in surgical wards. Implementation of these methods represent real advances in improving patient well-being and in reducing postoperative morbidity [15]. However, although there is no reason why a patient should not receive appropriate analgesia, recent surveys have revealed that the incidence of moderate or even severe postoperative pain may be as high as 30–70% [16, 17].

Most patients, physicians, surgeons, and nurses still consider moderate to severe pain to be an acceptable consequence of surgical interventions. In spite of this fact, however, studies including assessment of patient satisfaction with postoperative pain management have repeatedly indicated that most patients still seem satisfied with their postoperative care. Recent studies carried out in accordance with the recommendations of the American Pain Society and the Agency for Health Care Policy and Research (AHCPR, 1992) indicated that this paradoxical relation-

ship between experienced pain and patient satisfaction still exists. Satisfaction is a subjective appraisal of personal care, while a number of factors seem to influence satisfaction with hospital care. Studies have shown that pain is a particularly important determinant of patient satisfaction. It is now recognised that many patients have been greatly under-treated for their postoperative pain in the past. Under-treatment of pain has been determined to have a negative impact on short-term recovery and may even have a detrimental long-term effect on health. Three reasons accounting for under-treatment of pain relate to fear of narcotic addiction, poor communication among staff, and perceptions by patients that pain medications are neither necessary nor good.

Most patients do not receive any information on pain and its possible methods of treatment, although information about the predictability and controllability of the painful stimulus is a major influence in pain expectation. The manipulation of patients' expectancies regarding the onset, duration, intensity, and sensory qualities of the stressful events by the provision of accurate preparatory information has been shown to minimise the distress of patients undergoing stressful invasive medical procedures [18]. Despite the results of studies showing that the amount of information requested by patients can vary considerably and that the introduction of pamphlets does not improve patient satisfaction [19], information leaflets should be formally assessed to ensure that patient knowledge is increased. The aim of the present study was to assess any association between different pre- and postoperative factors, particularly patient information, expected pain, and actual pain experienced, and overall patient satisfaction with pain management. A patient satisfaction questionnaire was developed for this study and administered postoperatively to two samples of postsurgical patients, one routinely informed and the second given maximum information about postoperative pain care.

Methods

After informed consent, and in accordance with accepted ethical requirements, a sample of 100 consecutive patients scheduled for major elective surgery was recruited in the order of their admission to the APS for postoperative pain management. The exclusion criteria were severe psychosis and dementia. During the preoperative anaesthesiologist's visit, the patients received routine verbal information plus maximum information via leaflets about postoperative pain management. This group (group B) was compared to a previous sample of 100 consecutive patients (group A) who had received only routine information. All of the postoperative patients were managed by a nurse-based, anaesthesiologist-supervised APS.

Routine postoperative analgesia, based on standard protocols, was commenced with intravenous boluses or continuous intravenous infusions of opioids combined or not with anti-inflammatory drugs (NSAID), or continuous epidural infusions of opioids and local anaesthetics. PCA was not used for pain relief in the present study. A visual analogue scale (VAS) was used for the collection of data on pain intensity, every hour during the first 3 h and four times daily during the first 3 days. Demo-

graphic data, type of surgery, route of administration of analgesic drugs, and side effects were collected by APS staff during pain treatment. At the end of the analgesic postoperative treatment, and before discharge from hospital, patients were administered a satisfaction questionnaire containing 17 items about fields of importance in pain management: patient's information, quality of analgesia (including adequacy of pain relief provided and side effects), actual pain experienced (intensity and frequency of pain perceived), patient's preoperative expectations, patient's satisfaction, and suggestions. To decrease the risk that patients would not respond honestly to the questions, the questionnaire was administered orally, by a specifically trained interviewer, not directly involved in the care or pain treatment of the patient. In spite of these precautions to avoid bias, it was still not possible to exclude completely the influence of a 'staff pleasing-factor.' No patient refused to complete the questionnaire. Four items pertained to patient information (informed or not, when informed, who informed, and understanding of the information), six items concerned the quality of analgesia (helpfulness of preoperative information when requesting medications; long waiting time for pain medication once requested; side effects, such as itching, numbness, sedation, and nausea or vomiting), and four items were about pain intensity (the worst pain, and milder pain experienced on a 0 to 10 pain scale; the frequency of peaks of perceived moderate to severe pain; the pre-operative expected pain on a verbal rating scale). The last three items explored overall satisfaction with pain management given in the postoperative phase, as assessed on a 5-category scale (very satisfied, satisfied, slightly satisfied, slightly dissatisfied, very dissatisfied), the patient's agreement, and suggestions on how to improve analgesic management.

Statistical analyses

Testing for trend in contingency tables was used to assess the correlation between pre-operative expectation and experienced pain. Hypergeometric distribution was used to study the association between age, sex, expected pain, information, and high level of satisfaction.

Results

Demographic data, kind of surgery, and postoperative analgesia are presented in Table 1. No significant difference was observed in either group regarding mean age and type of surgery. The epidural technique was used more often in group B.

There was more information prior to surgery in group B (98%) than in group A (46%), and it was given by the anaesthesiologist, before surgery in 89% of the patients in group B and in 23% of the patients in group A. No patient was informed by nurses and only 6% by surgeons. The vast majority of patients in group B understood the information received (96%), compared to only 42% in group A (Table 2).

Pre-operatively expected and postoperatively experienced overall pain intensi-

Table 1. Demographic data, type of surgery, and postoperative analgesia

Variable	Group A	Group B
Age	63.59 ± 15.5	63.74 ± 15.26
Sex (% female)	42%	52%
Type of surgery		
Abdominal	43%	43%
Urological	25%	18%
Chest surgery	6%	15%
Vascular	9%	11%
Orthopaedic	13%	6%
Plastic	2%	2%
Neurosurgical	2%	2%
Ears-nose-throat surgery	0%	3%
Route of administration of analgesic drugs		
Intravenous (boluses)	19%	12%
Continuous epidural (elastic pump)	9%	23%
Continuous intravenous (elastic pump)	72%	65%
Pain levels (mean, 0–10)		
Worst postoperative pain	VAS:3.74±2.68	VAS : 5.27 ± 2.04
Lowest postoperative pain	VAS:0.73 ± 1.22	VAS:1.09 ± 1.17

Table 2. Patient's information

	Group A	Group B
Did you have any information about postoperative treatment of pain in hospital?		
Yes	46%	98%
No	54%	2%
When did you have such information?		
Before surgery	41%	90%
After surgery	3%	3%
Before and after	2%	3%
I don't know	54%	4%
Who gave you this information?		
The anaesthetist	23%	93%
The surgeon	6%	0%
I don't know	71%	7%
Did you understand it?		
Yes	42%	96%
No	2%	0%
No answer	56%	4%

ty in groups A and B is summarised in Tables 3 and 4. In group A, more patients expected moderate to unbearable pain intensity (80%) than in group B (70%). The pain intensity experienced by patients in this group was lower than expected in the postoperative phase, whereas group B patients expected a lower intensity of pain than in group A, but reported that they experienced more pain than expected. The number of patients experiencing no or mild pain was considerably higher in group A (37%) than in group B (21%).

Table 3. Expected and experienced pain in group A

	Expected pain	Experienced pain
No pain	8	12
Mild pain	12	25
Moderate pain	31	36
Severe pain	41	25
Unbearable pain	8	2

Table 4. Expected and experienced pain in group B

	Expected pain	Experienced pain
No pain	24	4
Mild pain	6	17
Moderate pain	28	32
Severe pain	39	46
Unbearable pain	3	0

It is interesting to note that 15% of patients in group A often experienced a peak of moderate to severe pain and 16% had to wait for a long time (> 15 min) for medications, while in group B only 2% often experienced such pain and 6% felt that they had waited a long time (Tables 5 and 6). Furthermore, 39% patients in group A and 64% of patients in group B answered they had never experienced moderate to severe pain.

Table 5. Quality of analgesia

	Group A	Group B
1. Have you been informed to ask for medications in case of pain?		
Yes	84%	94%
No	16%	6%
2. When you asked for pain medication, did you have to wait a long time (more than 15 minutes) for it?		
Yes	16%	6%
No	84%	94%
3. Did you have itch?		
Yes	1%	5%
No	99%	95%
4. Did you have numbness in the legs?		
Yes	6%	11%
No	94%	89%
5. Were you too sedated?		
Yes	11%	22%
No	89%	78%
6. Did you have nausea or vomiting?		
Yes	11%	19%
No	89%	81%

Table 6. Intensity and frequency of pain

	Group A	Group B
1. On this scale, please circle the number that describes the worst pain you have had since the surgical procedure? 0 1 2 3 4 5 6 7 8 9 10 no pain the worst pain	Mean VAS: 3.73±2.68	Mean VAS: 5.27±2.04
2. On this scale, please circle the number that describes the lowest pain you have had since the surgical procedure? 0 1 2 3 4 5 6 7 8 9 10 no pain the worst pain	Mean VAS: 0.73±1.22	Mean VAS: 1.09±1.17
3. How many times have you had moderate to severe pain?		
Always	0%	0%
Nearly always	2%	0%
Often	15%	2%
Sometimes	44%	34%
Never	39%	64%
4. Prior to your surgery, how much postoperative pain did you expect?		
No pain	8%	24%
Mild pain	12%	6%
Moderate pain	31%	28%
Severe pain	41%	39%
Unbearable pain	8%	3%

VAS, Visual analogue scale

From a test of trends, a low correlation between preoperative expectation and postoperative pain experience was determined: Pearson product moment was 0.106 in group A and 0.132 in group B. It was found that the vast majority of group B patients was very satisfied with its postoperative pain treatment B (Fig. 1), despite

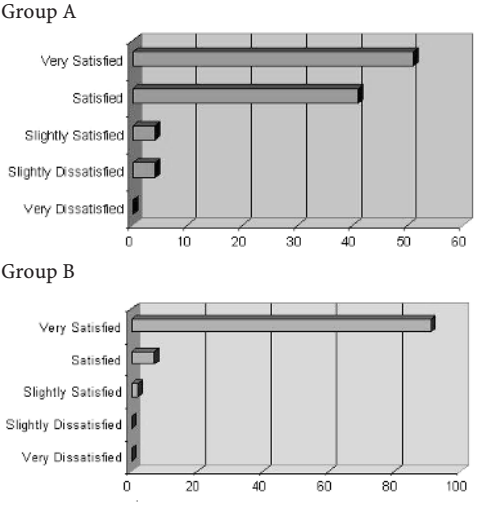


Fig. 1. Patient satisfaction with pain management

the fact that this group reported a mean postoperative pain intensity score that was higher than that of group A patients (mean worst pain of 5.27 ± 2.04 vs 3.73 ± 2.68).

The majority of patients, 93% in group A and 100% in group B, wanted to be treated in the same way if they were to undergo another procedure in the future. When asked how their postoperative pain management could be improved, 29% of patients in group B requested more information about the available analgesic methods, compared to only 9% in group A; 6% of group A patients requested better analgesia, compared to 5% in group B (Table 7).

Table 7. Satisfaction and suggestions

	Group A	**Group B**
1. Circle the phrase that indicates how satisfied you are with the way your nurses and doctors treated you pain:		
Very dissatisfied	0%	0%
Slightly dissatisfied	4%	0%
Slightly satisfied	4%	2%
Satisfied	41%	7%
Very satisfied	51%	91%
2. Would you like to have the same treatment if you should undergo another intervention in the future?		
Yes	93%	100%
No	7%	0%
3. Tell us please, how your postoperative pain should be improved?		
Improving information about available analgesic methods	9%	29%
Improving and increasing the doses of analgesic drugs	6%	5%
It's OK	80%	53%
Other	5%	13%

By hypergeometric distribution, used for problems with finite populations, in which each observation is either a success or a failure, the correlation between age, sex, expected pain intensity, information, and high level of satisfaction with the pain management was examined in patients of group A (Table 8).

Table 8. Multivariate influencing high satisfaction with postoperative pain management (group A)

Variable	***P***
Age (18–40 years)	0.1032
Age (60–84 years)	0.2235
Sex (females)	0.1435
Sex (males)	0.1762
Preoperative expectation of pain	
Severe to unbearable	0.0331*
Mild to moderate	0.4688
Information	0.0634

*$P < 0.05$

Discussion

It is usually considered that patient satisfaction is one of the most important endpoints in clinical practice and quality assurance [20]. A number of factors seem to influence satisfaction with hospital care. With difficulty, patients can assess the different factors involved in pain management; this becomes particularly evident by the provision of a questionnaire that allows patients to make suggestions or comments about the analgesia received. Several studies showed that female sex, high pre-operative pain intensity, high anxiety about postoperative risks and problems, relatively young age, and willingness to report pain correlated with low satisfaction; younger patients and females need different and more efficient pain management in order to achieve the same level of satisfaction with the therapy as experienced by elderly patients and males [21]. In the present study, age and sex were not significantly correlated with the patient's degree of satisfaction.

A question of clinical importance concerning the predictive relationship of pain expectancies in the experience of postoperative pain is: 'Does the manipulation of expectancies (by the provision of information regarding intensity, pattern, and duration of the pain and symptoms) reduce patients' experience of trauma, or does it sensitise them to the negative aspects of surgery?' According to De Groot et al. [22], patients who expect to feel pain will report greater pain intensity than patients who did not hold these expectations. The greater the discrepancy between expected and actual pain, the greater the experience of postoperative distress. Those patients who expect pain to be more intense than it actually is will report being less distressed [23]. The positive correlations between expected and reported pain and emotional variables suggest that manipulation of the patient's emotional responses may be as effective as manipulating pain expectancies in controlling the pain and the distress of surgery. Such a finding stresses the importance of pre-operative intervention strategies aimed at diminishing stress prior to surgical procedures.

A preliminary assessment by APS staff of the patient's capacity to cope, and how much analgesia is wanted would also be expected to lead to a greater satisfaction, as would a cognitive–behavioural reduction of anxiety. In the present study, expected severe to unbearable pain seemed to be significantly correlated to a high degree of satisfaction ($P = 0.0331$) in group A. The number of patients who experienced such pain was lower than the number of patients who expected it preoperatively; this may be the main determinant of high satisfaction in group A. In group B, an inverse correlation was observed, but, surprisingly, those patients who suffered from severe to unbearable pain were all very satisfied. Some studies have suggested that a more accurate picture of treatment can be built up if patients not only receive information about the procedure, but also sensory and temporal information about the physical impact of the procedure. This is supported by the finding that patients who receive accurate preparatory information about their surgery, compared to those who had no additional information, reported lower pain intensity but did not differ on expected pain intensity before the operation. Other authors showed that patients who received preparatory information reported lower pain intensity and lower expected pain

intensity, and that patients who expected more pain had less transient anxiety after surgery [24].

In our study, most patients expected to experience pain in the postoperative phase. No or only mild pain was expected by 20% in group A and by 30% in group B. The actual pain, however, was far less, i.e. no or only mild pain was experienced by 37% of patients in group A, but this was less the case (21%) in group B. The number of patients who expected moderate to unbearable pain in group A was higher (80%) than the number of patients who experienced it (63%), and in group B it was lower (Table 3 and 4). Paradoxically, patients who experienced higher pain than they had expected were more satisfied with their pain care than those who experienced less pain than expected. The observed discrepancy between actually experienced pain and patient satisfaction indicates that, from the patient's point of view, clinical pain management may not be as poor as pain intensity measurement suggests—and achieving satisfaction is not simply a matter of lots of analgesia and keeping pain levels low. It could also be that the pattern of relief [25], rather than the pain severity as such, may be a critical determinant in satisfaction. Our experience agrees with that of researchers who contend that high patient satisfaction commonly reflects both the low expectations of the patient and a positive interaction between patients and carers, and has a little relevance to successful relief of pain. Patients are commonly satisfied when they believe staff are caring and 'doing their best,' even if unsuccessfully. Conversely, most probably patients who were dissatisfied did not discriminate between pain management and problems with other aspects of their care, such as disagreement with a ward staff member or a dislike for hospital food.

In this study, the role of patient information was investigated as a determinant of high satisfaction. In group A, the number of 'very satisfied' was higher, but not statistically significant ($P = 0.0634$), in those who claimed to have received some information about postoperative pain management (46%), while all of the 'slightly satisfied' and 'slightly dissatisfied' patients belonged to the group who did not receive any information. A higher level of satisfaction (98% vs 92%) and a larger number of patients who were very satisfied with their pain management (91% vs 51%) was observed in group B. Several factors, not only improved information, may have contributed to this success, i.e. the lower incidence of side effects and a relatively short wait for medications. It was surprising to note that a degree of satisfaction as high as 98% was achieved in spite of the fact that most patients claimed to have experienced moderate or even severe pain in the postoperative period. One reason may be that the level of pain they experienced was acceptable to them, perhaps because the pattern of what they experienced matched their expectation or their previous experiences. Expectation about pain pattern, not about pain severity, may be the most important explanatory factor.

In the present study, the actual experience of inadequate postoperative pain relief was a significant factor influencing low satisfaction in group A (8%), as might have been expected. Many factors may have contributed to the lack of information (100%), a long waiting time for pain relief (50%), the incidence of side effects such as nausea and vomiting (100%), and actual pain intensity greater than expected

(50%). Unfortunately, none of the demographic variables were useful in predicting which persons were more prone to dissatisfaction: young age and female sex were not invariables in increasing the probability of being dissatisfied. Only 2% of patients were dissatisfied with their pain management in group B. These patients did not refer to long waits for pain relief, side effects, or frequent peaks of moderate to severe pain, nor did they expect severe and unbearable pain; they experienced pain that was less severe than expected and they received adequate information. These patients were probably dissatisfied with all aspects of their hospital care. However, they were asked to rate their satisfaction with postoperative pain care only and not to rate the entire hospitalisation episode. Despite their dissatisfaction, when questioned how to improve pain management they answered that it was fully adequate.

Finally, any patient satisfaction survey will be enhanced by directly questioning patients about how pain management might be improved at a given institution, and patients' responses to this open-ended question might provide new and innovative strategies. Surprisingly, in the present study, more informed patients requested greater information (29%), perhaps due to the patient's increased awareness about the possibilities to be accurately informed about postoperative pain management.

Another consideration that needs to be addressed when analysing data from a patient satisfaction survey on pain management is how an organisation determines the overall quality of the pain management services they provide. In reviewing our data, several deficiencies were noted, including moderate to severe postoperative pain intensity scores. Examining only the patient satisfaction scores from this survey, however, may lead one to draw the erroneous conclusion that there were no problems with pain management within our hospital.

Conclusions

There has been growing interest in the assessment of patient satisfaction with health care. Studies have shown that pain is a particularly important determinant of patient satisfaction. Therefore, an evaluation of patient satisfaction with pain management is one component of a total quality assurance program on pain management, as recommended by the American Pain Society.

Our experience suggests that a satisfaction questionnaire provides useful baseline data for evaluating the quality of an institution's overall pain management program. Furthermore it offers additional information that allows organisations to develop a plan to improve pain management practices more effectively. The survey is easy to conduct and can be repeated at regular intervals to determine the progress of its APS.

An awareness of the importance of controlling postoperative pain and about the presently available options for effective postoperative pain relief (due to accurate preoperative information) should have a positive influence on patient satisfaction, despite postoperative experience with pain severity.

A closer relationship between patients and hospital staff members seems essen-

tial for a more individualised approach to obtaining optimal pain relief. The presence of an APS in the hospital can improve both knowledge of pain treatment options and satisfaction, because patients are satisfied with the efforts that nurses and physicians make to manage pain, despite the fact that they experience high levels of pain. Consequently, while patient satisfaction is certainly important, it is too imprecise a measure to be used as a routine indicator of pain management. The results of this study raise a number of questions: To what extent do predisposing personality factors contribute to postoperative satisfaction? What are the best ways to predict patient dissatisfaction? To what extent does perceived satisfaction predict positive outcome of treatment?

Despite the limitations of this study, the results support the notion that adequate postoperative pain management supported by good information has a positive impact on patient satisfaction, but it remains unclear whether if evaluated in the absence of other data, satisfaction ratings could erroneously lead one to believe that pain management practices are optimal.

References

1. Cousins MJ, Power J, Smith G (2000) Labat lecture: pain-a persistent problem. Reg Anesth Pain Med 25:6–21
2. Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78:606–667
3. National Health & Medical Research Council of Australia (1999) Acute pain management scientific evidence. Canberra, Australia: Ausinfo
4. American Pain Society (1991) Quality assurance standards for relief of acute pain and cancer pain. In: Bond MR, Charlton JE, Woolf CJ (eds) Proceeding of the VIth World Congress on Pain. Elsevier, Amsterdam, pp 185–189
5. Ready LB, Edwards WTY (1992) Management of acute pain: a practical guide. Seattle: IASP Publications
6. US Department of Health and Human Services, Agency for Health Care Policy and Research (1992) Acute Pain management: operative or medical procedures and trauma. Publication n.92–0032. Rockville. MD: AHCP Publications
7. Anonymous (1995) Practice guidelines for acute pain management in the perioperative setting: a report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology 82:1071–1081
8. Wulf H, Neugebauer E, Maier C (1997) Die Behandlung akuter perioperative und pottraumatischer Shmerzen: Empfehlungen einer interdisziplinaeren Expertenkommission. G Thieme, New York
9. Joint Commission on Accreditation of Healthcare Organizations (2001) 2001 Hospital accreditation standards. Joint Commission Resources
10. Zimmerman DL, Stewart J (1993) Postoperative pain management and acute pain service activity in Canada. Can J Anaesth 40:568–575
11. Gouche CR, Owen H (1995) Acute pain management in Australia and New Zeeland. Anaesth Intensive Care 23:715–717
12. Rawal N, Allvin R (1998) Acute pain services in Europe: a 17-nation survey of 105 hospitals. The Euro Pain Acute Pain Working Party. Eur J Anaesthesiol 15:354–363

13. Rawal N (1994) Organization of acute pain services. Pain 57:117–123
14. Gould TH, Crosby DL, Harmer M (1992) Policy for controlling pain after surgery: effect of sequential changes in management. Brit Med J 305:1187–1193
15. Werner Mu, Soholm L, Rotholl-Nielsen P (2002) Does acute pain service improve postoperative outcome? Anesth Analg 95:1361–1372
16. Smith G (1991) Pain after surgery. Br J Anaesth 67:232–233
17. Donovan M, Dillon P, Mc Guire L (1983) Incidence and characteristics of pain in a sample of medical-surgical patients. Pain 30:69–78
18. Sjoling M, Nordahl G, Olofsson N (2003) The impact of preoperative information on state anxiety, postoperative pain and satisfaction with pain management. Patient Educ Couns 51(2):169–176
19. Lee A, Gin T (2005) Educating patients about anaesthesia: effect of various modes on patient's knowldg, anxiety and satifaction. Curr Opin Anaesthesiol 18(2):205–208
20. Miaskowski C, Nichols R, Brody R et al (1994) Assessment of patient satisfaction utilizing the American Pain Society's Quality Assurance Standards on acute and cancer-related pain. J Pain Symptom Manage 9:5–11
21. Svensson I, Sjostrom B, Haljamae H (2000) Assessment of pain experiences after elective surgery. J Pain Symptom Manage 20:193–201
22. De Groot KI, Boeke S, Passchier J (1999) Preoperative expectations of pain and recovery in relation to postoperative disappointment in patients undergoing lumbar surgery. Med Care 37:149–156
23. Jamison RN, Mitchell JR, Hoopman P et al (1997) Assessment of postoperative pain management: patient satisfaction and perceived helpfulness. Clin J Pain 13:229–236
24. Wallace LM (1998) Surgical patients' expectations of pain and discomfort: does accuracy of expectations minimise post-surgical pain and distress? Pain 75:177–185
25. Ward SE, Gordon DB (1996) Patient satisfaction and pain severity as outcomes in pain management: a longitudinal view of one setting's experience. J Pain Symptom Manage 11:242–251

QUALITY OF CARE

Chapter 75

Monitoring process quality in intensive care

M. Hiesmayr

Intensive care can be seen as a set of serial and parallel processes with the ultimate goal to reach an achievable outcome with the largest proportion of admitted patients. The intensity of the necessary processes can vary from intensive monitoring to support and replacement of organ function.

The aim of this investigation is to present and evaluate the difference between intermittent and continuous methods of process-quality monitoring. In this investigation we propose to adapt several methods commonly used in the manufacturing world to medical activities [1]. We think that the application of process-control methods in medicine should not be delayed further.

Process monitoring

Process monitoring is a concept from the industrial world to make manufacturing more efficient [2]. The first quality-control methods at the end of the 19th century were based on judgement inspection. Skilled craftsmen reworked the products at the end of the production line until they considered them suitable for use. H. Ford introduced gauge inspection, the comparison with a standard, because he noted that variability between products impeded a continuous production. This could be considered as an early form of benchmarking. In the 1930s, Shewhart developed statistical process control with control charts that allowed detecting by intermittent sampling whether a process was drifting out of control [3]. The control limits for a process at 3 standard deviations (SD) from the mean have been widely used. This method is a compromise between detecting drifts and avoiding unnecessary warnings. Because this method is not effective for small drifts, additional methods such as the cumulative sum chart (CUSUM) have been added.

Actually, very efficient industries have introduced 100% inspection instead of sampling, together with changing the focus from the result to the inputs and the mistakes in the process execution. This means that instead of observing nonconformities/deviations, their prevention is applied. Although this is no longer a monitoring technique, we have to keep in mind that there are further methods to improve quality that are available in case of failure of the previous methods. This alternative method of source inspection and mistake proofing is applicable to rare events, such as may occur in intensive care, e.g. medication errors [4], infections, failed extubations, death. This method is widely applied in medicine with checklists

that have greatly increased patient safety [5]. The evaluation of their efficiency has rarely been done in a formal way. This latter method has been reported to be most efficient in order to reduce non-conformity and necessitated relatively low investments in quality control. The major goal was prevention, not observation.

In the intensive care environment, a large amount of data is documented and collected continuously. Thus, intensive care is an attractive area in which to develop and refine the various methods of process monitoring. Special attention has to be given to the fact that events may be relatively infrequent and that it is highly desirable to detect deviations early [6]. A typical intensive care unit (ICU) has between 8 and 12 beds and admits 350–700 ICU patients a year.

Definition of a process

A process is a defined activity to transform a given input, typically in medicine the patient with his or her clinical condition, into a desired state. This desired state may be a better health status or a higher degree of knowledge about the current state. Thus a process can be defined by the task to perform, the various inputs such as patients, human resources and capital and the output of the process, including its side-effects (Fig. 1).

Any process has a goal and the degree of fulfillment of the expected goal by the result is traditionally considered to be quality. In this sense, quality is related to hitting the target. A more advanced view includes the resources needed and the waste produced in the concept of quality. Thus a more advanced view adds the observation of deviations/errors/mistakes. A simple image could be the number of

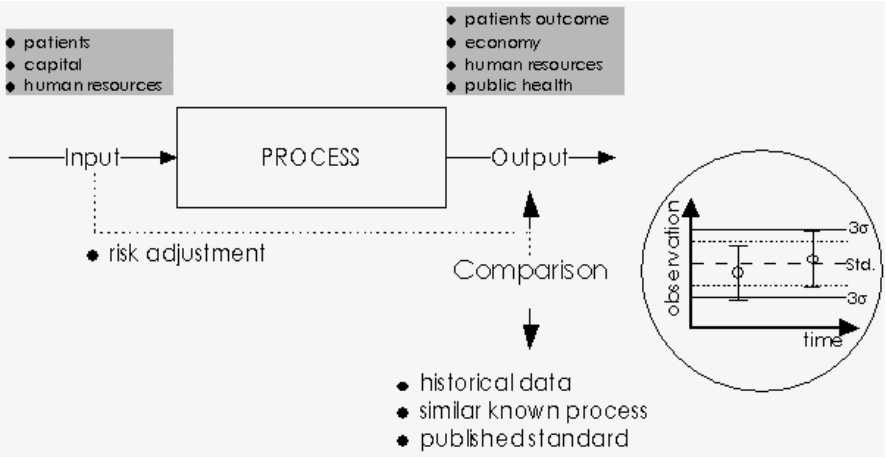


Fig. 1. Structure of a process and intermittent output monitoring . The *dashed line* represents the standard (*Std.*), the *dotted line* the 2 σ limits and the *continuous line* the 3 σ limits (*3 σ*). An optional important feature is to include risk adjustment in the comparison between output and standard. Risk adjustment helps to define input and to assess output

arrows needed to hit the target and the injuries caused by arrows outside of the target.

Typically, a process is mostly evaluated by comparison of the actual result with the expected result. In the field of intensive care, the inputs should also be monitored. It is not rare that a given performance can only be achieved with given inputs. A well-known example is the relation between accepted mortality and physiological derangement early after admission to an ICU as defined by several scoring systems (SAPS II, SAPS III, MPM). Some inputs cannot easily be controlled and thus a risk-adjusted evaluation of the process may be desirable.

Traditional quality assessment compares the result with the goal, a task called benchmarking, whereas a more advanced assessment would integrate the variability of the process over time in the assessment. Variability can be observed in output, resources and waste. In the advanced view, quality is inversely related to variability (Fig. 2). Thus quality is typically assessed by a minimum of two comparisons [7].

First, the actual result is compared with a standard or similar process in other

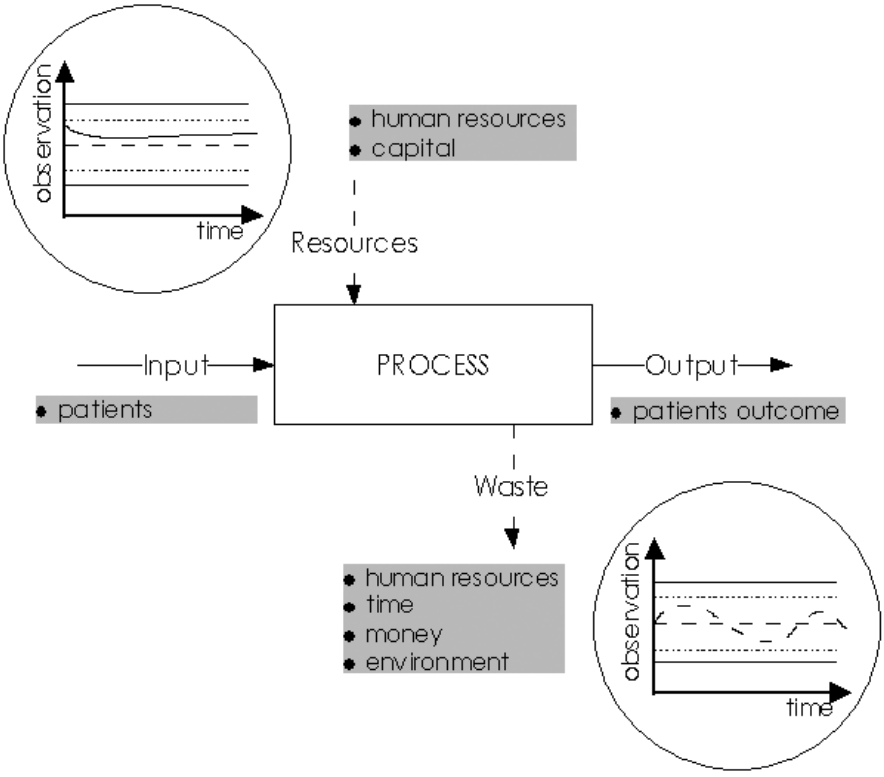


Fig. 2. Continuous and integrated process control

environments, a procedure called benchmarking, and second, the variability of the process about the target is determined, one of the tasks achieved by statistical quality control. In a competitive world, the actual target and thus the standard has to be challenged as well. In the more technical disciplines of medicine, technology may be introduced before systematic evaluation of its effectiveness.

Monitoring of process quality

Two elements define quality: the difference of the mean value from the target and the variability of this mean. With measurements, the variability can be assessed with the use of the SD, range or moving range, but for proportions a repeated determination is necessary (Fig. 3).

It has to be noted that deviations from the standard are not symmetrical in their effect on the process in many instances. An infection in the ICU necessitates a lot of resources that are not compensated by patients without infections. Losses have an irreversible character in medicine. In this sense many medical processes cannot be simply assimilated to stock exchange processes where losses can be compensated by gains.

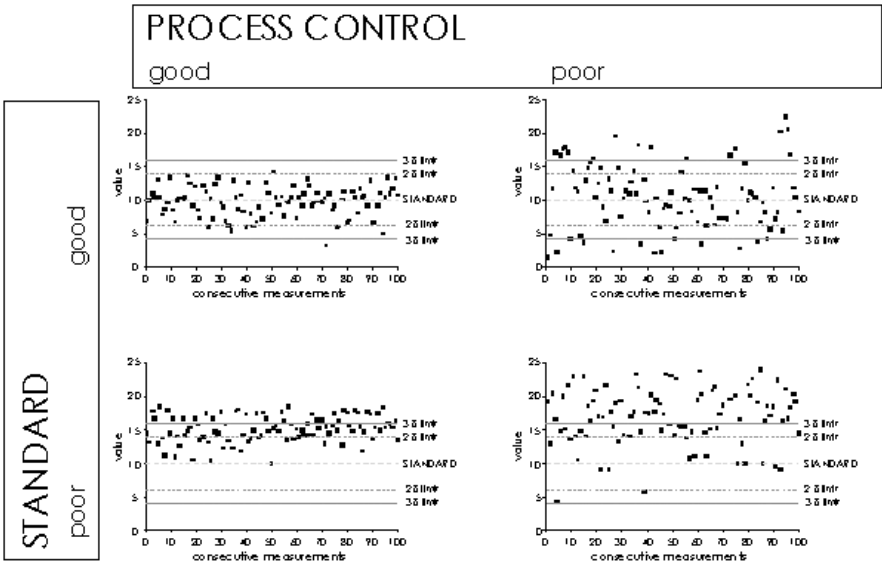


Fig. 3. Compliance with the standard and degree of process control as two dimensions of process monitoring

How to monitor a process

The information about a process is either a measurement or a count. Examples may be length of stay, duration of intubation, proportion of patients with nosocomial infections, proportion of patients with sufficient nutritional therapy, proportion of patients dying in hospital.

The process-quality monitoring is based on a comparison. The comparison can be either done with a given or known standard or a baseline determination obtained locally. A measurement or proportion in itself does not mean very much.

Intermittent method

Yearly intervals are the typical feature of many reports. An example is shown for the deep-wound infection rate (Fig. 4).

The different possible scenarios that are easily imagined for one identical infection rate points towards the need for more detailed insight into the process over time. This can only be done by analysis of time series continuously (Fig. 5).

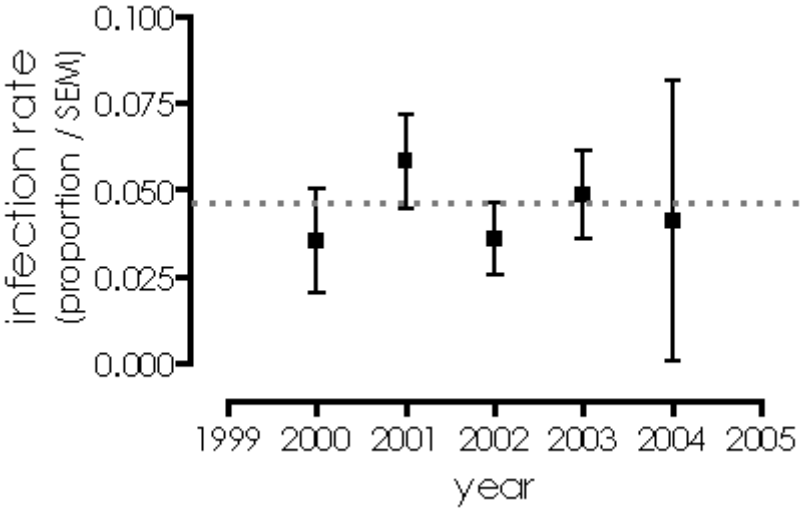


Fig. 4. Deep-wound infection rates from one institution. None of the samples deviated significantly from the mean rate over this 4-year period. SEM was calculated as √ (rate x (1–rate)/*n*)

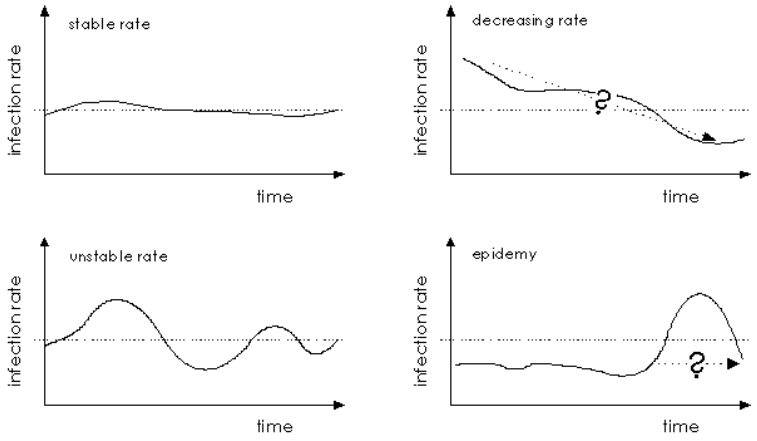


Fig. 5. Possible scenarios for the observed infection rate

Continuous method

Control chart

The control chart is constructed from the mean of a measurement or the observed proportion of events. Typically, confidence limits are added to the chart at 3 SD from the centre line. In certain cases it may be helpful to introduce an early-warning limit at 2 SD (Fig. 6) [3].

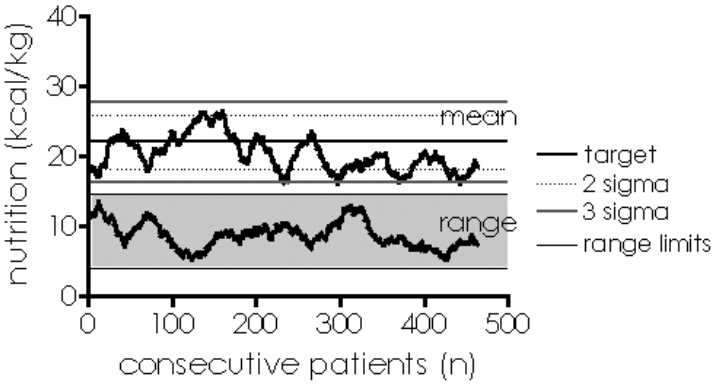


Fig. 6. Control chart for nutrition care in the ICU. The target for nutrition care was set at 22 kcal/kg/day on the 5th day post-admission in the ICU. The mean amount of nutrition given was derived from samples of 30 consecutive patients. The range was calculated as the mean absolute patient-to-patient difference for 30 consecutive patients. In four instances, the lower 3 sigma limit was reached, often in conjunction with a higher patient-to-patient moving range. Corrective measures would address the variability first

CUSUM + risk adjustment

The CUSUM is a sensitive instrument to detect small changes in process mean or proportions. For measurements, the CUSUM is able to detect shifts in performance that are smaller than 1 SD of a sample. For proportions, a cumulative number of events above 20 can be a clear sign of deviation from the original baseline. If a clear deviation is noted, a redefinition of the baseline should be considered.

Each CUSUM starts with an estimation of the baseline event rate. When the event of interest (death, infection) does not occur, the difference between the predicted event rate and the observed event rate is equal to the predicted event rate. This patient is assigned the event rate. When the event of interest occurs, the difference between predicted and observed rate is the predicted rate minus one event. Thus this patient will have assigned a negative value: (event rate –1). These values now cumulate from one patient to the next (Fig. 7).

The CUSUM also allows risk adjustment to be performed [8, 9]. In this case the risk derived from an individual score replaces the baseline score derived from local data. The application is shown in Fig. 8.

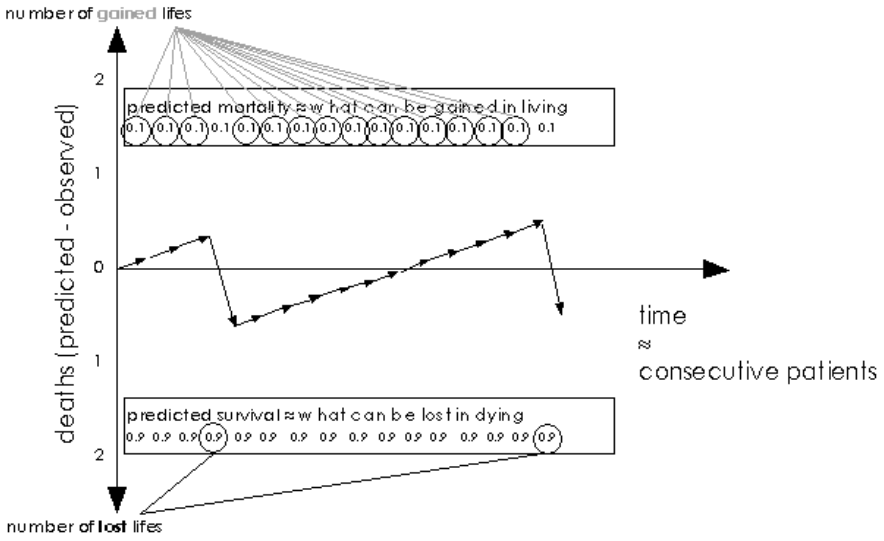


Fig. 7. CUSUM for mortality. The baseline mortality rate is set to 0.1. Predicted survival = 1–predicted mortality. Patients 4 and 16 died and thus lost their predicted survival

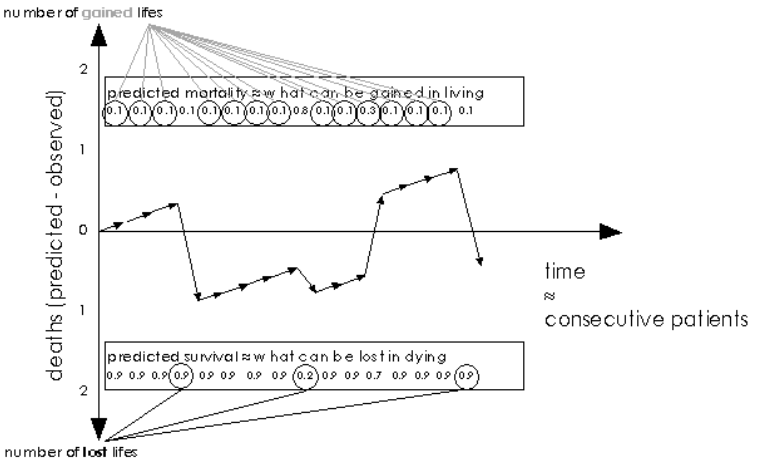


Fig. 8. Risk-adjusted CUSUM. The mortality rate is derived from a risk score. Predicted survival = 1–predicted mortality. Patients 4, 9 and 16 died and thus lost their predicted survival. Note that patient 9 with a high predicted mortality has less impact on the performance than the two other patients with a low predicted mortality

This methodology has been applied to follow surgical learning curves and performance in cardiac surgery [8, 9]. We applied this methodology to postoperative deep-wound infection and could identify a clear disadvantage of one of the drugs selected for antibiotic prophylaxis (Fig. 9).

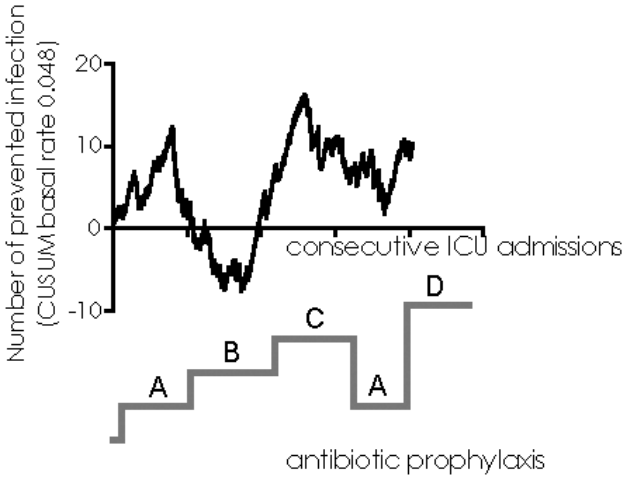


Fig. 9. CUSUM for deep-wound infection with the changes in antibiotic prophylaxis. The CUSUM is based on the difference between the predicted infection rate of 0.048 and the observed infections. The orange continuous line represents different choices for antibiotic prophylaxis over a period of 4 years. Antibiotic B was associated with an increase in observed infections

This example clearly demonstrates that continuous process evaluation increases knowledge and also has to be considered as a tool allowing learning from collected data.

Pitfalls and challenges

To define the correct starting points, I suggest starting from local data series. Select a series of sufficient length to be able to determine a local standard. Avoid false alarms and detect deviations early. Two deviations are of primary importance, deviations to the undesirable indicate poor control or changes that need investigation and thought, and desirable deviations may give an estimate of the possible performance of a process. At a first glance a deviation towards more undesired outcomes is not only a qualitative problem but also a quantitative decrease of the throughput because a decrease in quality needs 'reworking' and if resources are limited, the quantitative output will also decrease. As a clinical example, nosocomial infections increase suffering and length of stay at an individual level and decrease the availability of beds for other patients in need.

Conclusions

Continuous process evaluation is a key element to guide improvements in health care. Continuous process control has the advantage to allow early detection of deviations and to generate new information about the process, allowing learning from the actual activity.

The vision is that an evolution from the control of an isolated process to the integrated control of several processes is possible and that information will be presented as a common weighted risk-management display, as is used in manufacturing and service industries.

References

1. Berwick DM (1996) A primer on leading the improvement of systems. BMJ 312(7031):619–622
2. Hinckley CM (1997) Defining the best quality-control systems by design and inspection. Clin Chem 43(5):873–879
3. Montgomery DC (1997) Introduction to statistical quality control, 3rd ed. John Wiley & Sons, New York
4. Darchy B, Le Miere E, Figueredo B et al (1999) Iatrogenic diseases as a reason for admission to the intensive care unit: incidence, causes, and consequences. Arch Intern Med 159(1):71-78
5. Hinckley CM (2003) Make no mistake-errors can be controlled. Qual Saf Health Care 12(5):359–365

6. Harvey G, Wensing M (2003) Methods for evaluation of small scale quality improvement projects. Qual Saf Health Care 12(3):210-214
7. Frutiger A (1997) Process quality in the intensive care unit. Acta Anaesthesiol Scand 111(Suppl):14–16
8. Sherlaw-Johnson C, Lovegrove J, Treasure T, Gallivan S (2000) Likely variations in perioperative mortality associated with cardiac surgery: when does high mortality reflect bad practice? Heart 84(1):79–82
9. Lovegrove J, Valencia O, Treasure T et al (1997) Monitoring the results of cardiac surgery by variable life-adjusted display. Lancet 350(9085):1128-1130

Chapter 76

Evaluating quality of life after intensive care

M. Capuzzo, S. Bertacchini, C. Chiani

Survival after intensive care unit (ICU) admission was the outcome initially used to demonstrate the efficacy of that highly technological, and costly, environment [1]. However, mortality is an insufficient measure of ICU outcome, because the real aim of intensive care is that patients either return to their previous state of health, if suffering from an acute disease, or improve their state of health, if their illnesses were suitable for eradication.

With respect to a 'patient-centred outcome,' an evaluation of intensive care should incorporate an assessment of quality of life (QOL) [2]. This can be performed either focusing only on the patient's health status [3], or considering 'QOL as a uniquely personal perception' [4]. QOL has been defined as the 'holistic, self determined evaluation of satisfaction with issues important to the individual,' [5] and it needs to be distinguished from health-related QOL (HRQOL), which has been defined as the degree to which a patient's health status affects a patient's self determined evaluation of their satisfaction with their life [5]. Heyland et al. [6] describe a conceptual framework in which HRQOL results from the overlapping of health status with those non-medical aspects that influence well-being.

The meaning of the different measurements of outcome has been examined by Black et al. [7]. In a patient suffering chronic obstructive pulmonary disease, for example, the following different measurements of outcome can be applied: (1) impairment, which refers to the physiological aspects assessed objectively, such as FEV1; (2) disability, as measured according to symptoms associated with impairment, such as dyspnoea; (3) HRQOL, referred to the effect of disability, such as the inability to garden due to dyspnoea. Accordingly, HRQOL should describe the sum of patients' physiological and psychological functions, their capacity for meeting their social needs, and their own perception of their situation [8].

How to measure HRQOL

An instrument to measure HRQOL (questionnaire) has to be suitable for the purpose of the study to be performed, the patient population being evaluated, and the circumstance where it has to be applied. An instrument to be used in a general ICU setting should be generic, sensitive to changes [9], and simple [10]. Most of the HRQOL questionnaires are made up of several questions (items) in order to reflect the multidimensionality of QOL [10]. Investigators should select an instrument

suitable for their objectives and focusing on their patient population. Furthermore, the instruments should meet the following requisites.

Test-retest reliability

Any questionnaire must produce the same results on repeated use under the same conditions [7, 10, 11]. This means that an instrument needs a high signal-to-noise ratio: the variability within patients (noise) has to be lower than the variability between patients (signal) [12]. In other words, patients who answer the same questionnaire on two occasions separated by a few days should show more or less the same results.

Internal reliability

To examine the extent to which individual items in a domain seem to measure the same underlying concept, the internal reliability (or consistency) of the questionnaire is analysed using Cronbach's alpha coefficient [13].

Validity

To demonstrate that the instrument is appropriate for a particular application and that its measurements are meaningful and easily understood ('face validity'), the assessment should comprise different kinds of comparisons, according to the presence or absence of at least one 'gold standard' [6, 7, 11, 12]. When a 'gold standard' is not available, as in HRQOL evaluations, the construct validity approach is applied [12]. This involves comparisons between measures and examines the logical relations that should exist between the measure being used and the characteristics of the patient group under study [6, 7, 11, 12]. Taking as an example a study in which HRQOL questionnaires were administered to ICU patients, the validity of the instruments used was demonstrated by the relationship between the HRQOL scores and both the classification of functional limitation assigned by the interviewer and the presence of chronic disease [14].

Responsiveness

An instrument should be able to detect clinically meaningful or important changes (signal) of HRQOL within individuals over time [6, 7, 11, 12]. To validate an HRQOL questionnaire before application, we administered it to a group of elderly surgical patients before surgical intervention, and then 7 days after hospital discharge [15]. All the investigated domains changed significantly, with the global score (possible range 0–24) increasing from 4.3 ± 2.3 to 9.6 ± 2.6. Most of the patients reduced their best physical activity from 'going up one floor without trouble' to 'doing the housework' and their most complex social life from 'having leisure activities' to 'watching television.'

Available instruments

Hyland et al. [6] identified 19 studies including HRQOL measurements among 1073 articles published in three key ICU journals and found that only three articles met the methodological criteria predefined by the authors to assess the validity of HRQOL assessment. A more recent and wider systematic review devoted to outcome measures [7] identified 764 articles, 144 of which met the following inclusion criteria: performed in adults (age at least 16 years), including data on outcomes after ICU discharge, and studying at least 20 patients. Only the following nine generic HRQOL instruments were used on at least two occasions [7]: Sickness Impact Profile, Perceived Quality of Life Scale [17], Nottingham Health Profile [18], Medical Outcome Study Short Form 36, Rosser Disability and Distress Categories, Spitzer Quality of Life Index, Psychological General Well-being Schedule, Rivera-Fernandez Questionnaire [19], and Whiston Hospital Questionnaire. Surprisingly, that review of outcome measures [7] did not mention the EuroQol (EQ) [20], an instrument recently suggested as being one of the best-suited for measuring QOL in multicentre critical-care trials [2].

A personal search, performed in PubMed, based on the subject headings 'quality of life AND (intensive care OR critical care)' and restricted to adult (age 19 + years) patients, led to the identification of 72 articles in the period 1992–1995 and 157 in the period 2001–2004, testifying to the growing interest of intensivists in the field of HRQOL. The large number of papers published mirrors the large number of instruments used. However, the application of so many different tools adds variability to the variability of both the patient population and ICU practices, thereby preventing comparisons.

A similar PubMed search aimed at identifying the tools most frequently used in the last 10 years (1995–2004) showed that only three instruments were reported in at least ten articles: Medical Outcome Study Short Form 36 (SF-36) in 23, Nottingham Health Profile (NHP) in 13, and EuroQol (EQ) in 10.

Medical Outcome Study Short Form 36

The Medical Outcome Study produced a 36-item questionnaire for HRQOL evaluation. It assesses eight dimensions: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health. According to the most commonly used scoring system (SF-36), two scores can be computed: physical and mental component summary [21]. The higher the score, the better the HRQOL. A less frequently used scoring system (RAND-36) differs slightly in pain and general health dimensions [22]. SF-36 has been well validated in the UK [23, 24], and an Italian version is available with normative data [25].

Nottingham Health Profile

The Nottingham Health Profile, which was developed in the UK [18], consists of two parts. The first part measures subjective functional status by yes/no answers to 38 questions investigating six domains: physical mobility, pain, sleep, energy, emotional reactions, and social isolation. The lower the score, the better the HRQOL. The second part focuses on QOL in seven areas of daily life.

EuroQol

The EQ [20] evaluates the patient's present condition and consists of two parts. In the first part, the following five dimensions are considered: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is investigated by a question, which has three possible answers: no problems, some problems, extreme problems. In the second part, the EQ-VAS, the patient is asked to rate his/her health status on a scale ranging from 0 (the worst imaginable health status) to 100 (the best imaginable health status). An index (EQ index) based on the scoring of each dimension has been used [26]. The higher the score, the better the HRQOL. A comparison of EQ and RAND-36 in 1099 former ICU patients [27] showed that the scores correlated strongly, but the EQ was weaker than RAND-36 due to a ceiling effect. The Italian version of the questionnaire can be obtained electronically (www.euroqol.org).

How to administer the instrument

Any instrument can be administered by interviewer, face-to-face or by phone, or sent by mail (self-administered). In comparison with self-administered questionnaires, face-to-face and telephone modes of administration decrease errors of misunderstanding and do not allow missing items [12]. Different methods of administration of the instruments could influence the reliability of the results; good reproducibility for telephone/direct interview has been reported for the Rivera Fernandez questionnaire [19], and the EQ has been administered by telephone in some studies [28, 29].

Who to interview

Some patients admitted to the ICU cannot answer questions about their QOL, due to their critical condition. Usually, when the patient cannot co-operate, the intensivist interviews the next-of-kin about the patient's QOL before ICU admission. In patients admitted to the ICU, Rivera Fernandez et al. [19], validating their HRQOL questionnaire, and Badia et al. [30], using the EQ, concluded that the respective questionnaire could be reliably answered by proxies. Nevertheless, Diaz-Prieto et al. [31], using the EQ, observed a fair to moderate agreement between patient and proxy responses, while a study using the SF-36 [32] concluded that relatives are able

to give a good assessment only of functional aspects of QOL. In a study in which two HRQOL instruments were administered to 172 adult, co-operative ICU patients and their relatives [33], concordance was excellent in both questionnaires for the domains of physical activity and social life, but not in emotional aspects and perceived QOL. Gender, living together with the patient, and the degree of relationship of relatives did not influence the agreement.

When to measure HRQOL

In the scientific literature devoted to HRQOL, different tools administered to different patient populations admitted to different ICUs have been applied at different points in time after ICU discharge. As a consequence, the many differences preclude meaningful comparison between studies or pooling of the results.

A longitudinal study of 153 medical cardiovascular and pulmonary patients was carried out to assess HRQOL before, 1 month after, and 9 months after intensive care [34]. The results showed a worsening of the physical component of SF-36 at 1 month, but no impairment after 9 months. Kvale and Flaatten [35] studied 100 patients 6 months and 2 years after discharge from ICU. They found an improvement in six out of eight dimensions of SF-36 between the first and second assessment. An improvement between 1 and 2 years has been reported also in multiple trauma patients, whose HRQOL after 2 years appeared to be influenced by age, severity of illness, and previous QOL [36]. However, for comparative purposes, in a recent review considering 21 studies of HRQOL in ICU patients [37], the time of assessment was 6 months in most of the investigations, being lower (3 months) in three studies and higher (1 or 2 years) in five of the non-longitudinal studies.

Making a comparison

Ideally, discharge from the hospital can be regarded as the time when the acute illness has resolved and the patient has gradually returned to, or improved, his or her previous state of health. Based on this assumption, the HRQOL of ICU survivors discharged from the hospital should be compared with that of the normal population of the same gender and age.

Matched general population

Studies comparing the HRQOL of patients before their admission to the ICU with that of the matched general population [24, 34, 38] demonstrated worse baseline values in ICU patients. At follow-up, the HRQOL of former ICU patients was still worse than that of the matched general population [22, 24, 34, 38–40].

Individuals over time

The evaluation of any therapy should include a comparative study; thus, if intensive care is considered to be a treatment, the HRQOL of patients before and after ICU admission should be measured. When patients' pre-ICU HRQOL is rated retrospectively, a recall bias may be present [41]. However, it has been demonstrated that assessment of pre-hospitalisation health status during the 3 months following a hospital stay is similar [42].

What we know now

The results of the most recent systematic review of HRQOL studies in ICU patients [37], analysing 7320 survivors, can be summarised as follows: (1) the HRQOL before ICU admission was worse than that of the matched general population; (2) generally, the HRQOL after hospital discharge was worse with respect to the physical dimension than that of the matched general population, or, at best, clinically similar in some subgroups (i.e. elective surgical, less seriously ill); (3) the HRQOL 1 month after discharge from the ICU showed a clinically meaningful worsening of the physical component, followed by a clinically meaningful improvement over time (with final assessment between 6 and 12 months).

Older patients, compared with younger patients, did not show a significantly worse change in HRQOL [39]. Patients who suffered acute pathologies reported significant decreases in HRQOL whilst those with pre-existing illness reported significant improvement [3, 24]. Accordingly, compared with the pre-ICU level, trauma patients have worse HRQOL 1 year after hospitalisation, while scheduled surgical patients improve their HRQOL during that time [28]. Moreover, the perceived HRQOL did not appear to change compared with the pre-ICU level [15, 22].

A look into the future

While HRQOL is increasingly being taken into account by intensivists, other outcome measures should also be considered in order to obtain a complete picture of the other aspects comprising QOL. The development of post-traumatic stress disorder (PTSD) was reported in 27.5% of 80 German survivors of acute respiratory distress syndrome [43]. Jones et al. [44] recorded a high incidence of PTSD-related symptoms in 45 UK patients, and we found PTSD-related symptoms at 3 months follow-up in 5% of an Italian population of ICU patients [45]. Clearly, our understanding of the HRQOL of former ICU patients seems to be just beginning and certainly needs to be improved.

References

1. Keenen SP, Dodek P (2003) Survival as an outcome for ICU patients. In: Angus DC, Carlet J (ed) Surviving intensive care. Update in intensive care medicine. Springer, Berlin, pp 3–20
2. Angus DC, Carlet J (2003) Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med 29:368–377
3. Vazquez Mata G, Rivera Fernandez R, Gonzales Carmona A et al (1992) Factors related to quality of life 12 months after discharge from an intensive care unit. Crit Care Med 20:1257–1262
4. Gill TM, Feinstein AR (1994) A critical appraisal of the quality of quality of life measurements. JAMA 272:619–626
5. Curtis JR (2003) Measuring health status after critical illness: where are we and where do we go from here? In: Angus DC, Carlet J (ed) Surviving intensive care. Update in intensive care medicine. Springer, Berlin Heidelberg New York, pp 181–196
6. Heyland DK, Guyatt G, Cook DJ et al (1998) Frequency and methodologic rigor of quality-of-life assessments in the critical care literature. Crit Care Med 26:591–598
7. Black NA, Jenkinson C, Hayes JA et al (2001) Review of outcome measures used in adult critical care. Crit Care Med 29:2119–2124
8. Spanish Group for the Epidemiological Analysis of Critical Patients (1994) Quality of life: a tool for decision-making in the ICU. Intensive Care Med 20:251–252
9. Fletcher A, Gore S, Jones D et al (1992) Quality of life measures in health care. II: Design, analysis and interpretation. BMJ 305:1145–1148
10. Fitzpatrick R, Fletcher A, Gore S et al (1992) Quality of life measures in health care. I: Applications and issues in assessment. BMJ 305:1074–1077
11. Rowan KM, Jenkinson C, Black NA (2003) Health-related quality of life. In: Angus DC, Carlet J (ed) Surviving intensive care. Update in intensive care medicine. Springer, Berlin Heidelberg New York, pp 36–50
12. Guyatt GH, Feeny D, Patrick DL (1993) Measuring health-related quality of life. Ann Intern Med 118:622–629
13. Knapp TR (1991) Coefficient alpha: conceptualizations and anomalies. Research in Nursing & Health 14:457–460
14. Capuzzo M, Grasselli C, Carrer S et al (2000) Validation of two quality of life questionnaires suitable for intensive care patients. Intensive Care Med 26:1296–1303
15. Capuzzo M, Bianconi M, Contu P et al (1996) Survival and quality of life after intensive care. Intensive Care Med 22:947–953
16. McHugh LG, Milberg JA, Whitcomb ME et al (1994) Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med 150:90–94
17. Patrick DL, Danis M, Southerland LI et al (1988) Quality of life following intensive care. J Gen Intern Med 3:218–223
18. Hunt SM, McKenna SP, McEwen J et al (1981) The Nottingham Health Profile: subjective health status and medical consultations. Soc Sci Med 15A:221–229
19. Rivera Fernandez R, Sanchez Cruz JJ, Vazquez Mata GV (1996) Validation of a quality of life questionnaire for critically ill patients. Intensive Care Med 22:1034–1042
20. The EuroQol group (1990) EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 16:199–208
21. Heyland DK, Hopman W, Coo H et al (2000) Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. Crit Care Med 28:3599–3605

22. Kaarlola A, Pettila V, Kekki P (2003) Quality of life six years after intensive care. Intensive Care Med 29:1294–1299
23. Chrispin PS, Scotton H, Rogers J et al (1997) Short Form 36 in the intensive care unit: assessment of acceptability, reliability, and validity of the questionnaire. Anaesthesia 52:15–23
24. Ridley SA, Chrispin PS, Scotton H et al (1997) Changes in quality of life after intensive care: comparison with normal data. Anaesthesia 52:195–202
25. Apolone G, Mosconi P (1998) The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol 51:1025–1036
26. Granja C, Teixeira-Pinto A, Costa-Pereira A (2002) Quality of life after intensive care: evaluation with EQ-5D questionnaire Intensive Care Med 28:898–907
27. Kaarlola A, Pettila V, Kekki P (2004) Performance of two measures of general health-related quality of life, the EQ-5D and the RAND-36 among critically ill patients. Intensive Care Med 30:2245–2252
28. Badia X, Diaz-Prieto A, Gorriz MT et al (2001) Using EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. Intensive Care Med 27:1901–1907
29. Garcia Lizana F, Peres Bota D, De Cubber M et al (2003) Long-term outcome in ICU patients: What about quality of life? Intensive Care Med 29:1286–1293
30. Badia X, Diaz-Prieto A, Rué M et al (1996) Measuring health and health state preferences among critically ill patients. Intensive Care Med 22:1379–1384
31. Diaz-Prieto A, Gorriz MT, Badia X et al (1998) Proxy-perceived prior health status and hospital outcome among the critically ill: is there any relationship? Intensive Care Med 24:691–698
32. Rogers J, Ridley S, Chrispin P et al (1997) Reliability of the next of kins' estimates of critically ill patients' quality of life. Anaesthesia 52:1137–1143
33. Capuzzo M, Grasselli G, Carrer S et al (2000) Quality of life before intensive care admission: agreement between patient and relative assessment. Intensive Care Med 26:1288–1295
34. Graf J, Koch M, Dujardin R et al (2003) Health-related quality of life before, 1 month after, and 9 months after intensive care in medical cardiovascular and pulmonary patients. Crit Care Med 31:2163–2169
35. Kvale R, Flaatten H (2003) Changes in health-related quality of life from 6 months to 2 years after discharge from intensive care. Health Qual Life Outcomes 1:2–9
36. Vazquez Mata G, Rivera Fernandez R, Perez Aragon A et al (1996) Analysis of quality of life in polytraumatized patients two years after discharge from an intensive care unit. J Trauma 41:326–332
37. Dowdy DW, Eid MP, Sedrakyan A et al (2005) Quality of life in adult survivors of critical illness: A systematic review of the literature. Intensive Care Med 31:611–620
38. Pettila V, Kaarlola A, Makelainen A (2000) Health-related quality of life of multiple organ dysfunction patients one year after intensive care. Intensive Care Med 26:1473–1479
39. Wehler M, Geise A, Hadzionerovic D et al (2003) Health-related quality of life of patients with multiple organ dysfunction: individual changes and comparison with normative population. Crit Care Med 31:1094–1101
40. Kvale R, Flaatten H (2003) Follow-up after intensive care: a single center study. Intensive Care Med 29:2149–2156
41. Crosby RD, Kolotkin RL, Williams GR (2003) Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 56:395–407

42. Guadagnoli E, Cleary PD (1995) How consistent is patient-reported pre-admission health status when collected during and after hospital stay. Med Care 33:106–112
43. Schelling G, Stoll C, Haller M et al (1998) Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med 26:651–659
44. Jones C, Griffiths RD, Humphris G et al (2001) Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit Care Med 29:573–580
45. Capuzzo M, Valpondi V, Cingolani E et al (2005) Posttraumatic stress disorder-related symptoms after intensive care. Minerva Anestesiol 71:167–179

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