Topical Issues in Anesthesia and Intensive Care

Davide Chiumello
Editor

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Preface

This book describes the state of the art concerning some of the most hotly debated topics in anesthesia and intensive care and is at the same time intended to serve as a useful practical guide that will assist in improving outcomes. The topics covered are wide ranging and include, for example, the use of antibiotic during renal replacement therapy, the role of video laryngoscopy, the management of mechanical ventilation in the operating room, the use of high frequency ventilation in respiratory failure, the management of potential brain dead patient, the perioperative delirium, and the single lung ventilation and the use of lung imaging in critically ill patients.

Written by recognized experts in the field, this book will offer a comprehensive and easy to understand update for specialists and students of anesthesia and intensive care.

Milano, Italy — Davide Chiumello

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Antibiotic Dosing During Continuous Renal Replacement Therapy (CRRT)

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Giorgio Tulli

1.1 Introduction

In critically ill patients, antibiotic dosing is much more complex than other therapeutic classes such as sedatives, analgesics, vasoactive drugs, and other drugs commonly used in the ICU, because the so-called effect "end-of-needle" does not immediately manifest itself. This complicates a lot of attempts to titrate the antibiotic dosing on the basis of clinical evolution. Moreover, many critically ill patients develop severe sepsis and septic shock inward or in the ICU setting; many of them have acute kidney failure and need kidney care support: renal replacement therapy (RRT) or more often continuous renal replacement therapy (CRRT). Combination of sepsis and acute renal failure is common in critically ill patients [1, 2], and it is associated with a high mortality [3]. A suitable treatment is essential to optimize patient survival. Antibiotic underdosing may result to a decrease of the "killing" of bacteria and lead to a defeat in clinical resolution of infections and to an increased bacterial resistance; furthermore, antibiotic overdosing results in toxicity [4].

1.2 Pharmacokinetics and Pharmacodynamics of Antibiotics (Figs. 1.1, 1.2, and 1.3)

Study of drug effects in animals and humans includes *pharmacokinetics*, or processes by which the body absorbs, distributes, and disposes of a drug, and *pharmacodynamics* with reference to the processes by which the drug produces its desired effect. For critically ill patients with renal failure, the elimination of a drug may be altered compared to that observed in healthy volunteers, and the ability of a

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Antibiotic classification	Definition of PK/PD target	PK/PD target
Concentration dependent	Ratio of the peak antibiotic concentration to the MIC of the pathogen (Cmax/MIC)	Aminoglycoside: C_{max}/MIC 8–10 [14] Daptomycin: C_{max}/MIC 8–10,$AUC_{0\text{-}24}$/MIC 100[6,108]
Time dependent	Percentage of time during dosing interval for which the free plasma concentration of the antibiotic remains more than the MIC of the pathogen (%fT>MIC)	β-Lactams: 50–70 % fT>MIC [6] Carbapenems: ≥40 % fT>MIC [6] Linezolid: 40–80 % fT>MIC, 40–100 % of dosing interval > 5 times MIC [109, 110]
Concentration dependent with time dependent	Ratio of the area under the concentration-time curve (AUC) during a 24h period to the MIC of the pathogen ($AUC_{0\text{-}24}$/MIC)	Fluoroquinolones: C_{max}/MIC 10, $AUC_{0\text{-}24}$/MIC 125 ciprofloxacin (Gram negatives), 34 (Streptococcus pneumoniae) [111, 69, 112, 113] Glycopeptides: $AUC_{0\text{-}24}$/MIC > 400 vancomycin (Staphylococcus aureus) [114, 115] Colistin: $AUC_{0\text{-}24}$/MIC 53- 141 (Pseudomonas aeruginosa) [116]

Fig. 1.1 Antibiotic killing characteristics and pharmacokinetic/pharmacodynamic target (metronidazole, concentration dependent, pharmacokinetic target not established; macrolides, azalides, ketolides, concentration dependent, pharmacokinetic target, probably $AUC_{0\text{-}24}$/MIC (drug concentration at target site). Relevance of plasma concentrations doubtful given the fact that drugs are concentrated in the tissue) (Moore et al. [14], Craig [6, 109], Safdar et al. [108], Andes et al. [110], Blasier et al. [111], Forrest et al. [69], Ambrose et al. [112], Schentag [113], Ryback et al. [114], Rybak [115], and Dudhani et al. [116])

Class	Example	Mechanism of action	Microbial killing profile
Beta lactams	Penicillin, ceftriaxone, meropenem	Irreversible binding to enzymes necessary for peptidoglycan synthesis in the bacterial cell wall	Time dependent [117, 118]
Macrolides	Erythromycin	Bind 50S subunit of ribosome and block peptide chain elongation and protein synthesis	Time dependent [119]
Aminoglycosides	Gentamicin	Bind 30S ribosome and interfere with peptide chain elongation, but individual agents may have additional effects	Concentration dependent [120]
Fluoroquinolones	Ciprofloxacin	Inhibits DNA gyrase and blocks protein synthesis	Concentration dependent [121]
Tetracyclines	doxycycline	Bind 30S ribosome and prevent transfer RNA from binding, thus preventing peptide chain elongation and blocking protein synthesis	Not well studied Concentration dependent [122]
Glycopeptides	Vancomycin	Inhibits cell wall synthesis	Time dependent [115]
Lipopeptides	Daptomycin	Depolarizes cell membrane	Concentration dependent [123]
Polyenes	Nystatin, Amphotericin B	Binds to ergosterol component of fungal cell membrane and increases membrane permeability	Concentration dependent [124]
Triazoles	Fluconazole	Blocks synthesis of ergosterol component of fungal cell membrane	Time dependent [125, 126]
Echinocandins	Caspofungin	Inhibits B(1,3) glucan synthase and interrupts fungal cell wall synthesis	Concentration dependent

Fig. 1.2 Antimicrobial properties (Adapted and with permission from: Fissell [20], Sauermann et al. [117], Shea et al. [118], Van Bambeke and Tulkens [119], Decker et al. [120], Wright et al. [121], Agwuh and MacGowan [122], Rybak et al. [115], Begic et al. [123], Groll et al. [124], Baddley et al. [125], Andes et al. [126], and Antachopoulos et al. [127])

particular dosing to obtain the therapeutic goals in a patient may change substantially from what expected. The bacterial "killing" characteristics of antibiotics and the pharmacokinetics associated with optimal "killing" vary from antibiotic to antibiotic. The "killing" characteristics may be described as time dependent or concentration dependent. For drugs that exhibit a time-dependent "killing" of the bacteria (such as beta lactam), the "killing" is related to the time during which the blood concentration is over a threshold concentration. Appropriate values are controversial both for the threshold concentration and time, with recommended

Drug	PBC, %	Primary route of elimination[a]	Volume of distribution, L/kg	Half-life for normal renal function, h	Time-dependent or concentration-dependent killing	Target trough level, mg/L[b]
Acyclovir	15	Renal	0.6	2–4	Time	NA[c]
Ampicillin	28	Renal	0.29	1.2	Time	8
Aztreonam	56	Renal	0.2	1.7–2.9	Time	8
Cefepime	16	Renal	0.25	2.1	Time	8
Cefotaxime	27–38	Renal	0.15–0.55	1	Time	8
Ceftazidime	21	Renal	0.23	1.6	Time	8
Ceftriaxone	90	Hepatic	0.15	8	Time	8
Cilastatin	40	Renal	0.20	1	NA	NA
Ciprofloxacin	40	Renal	1.8	4.1	Concentration	1
Clavulanate	30	Hepatic	0.3	1	NA	NA
Clindamycin	60–95	Hepatic	0.6–1.2	3	Time	2
Colistin	55	Renal	0.34	2	Concentration	4
Daptomycin	92	Renal	0.13	8	Concentration	4
Fluconazole	12	Renal	0.65	30	Time	8–16[d]
Imipenem	20	Renal	0.23	1	Time	4
Itraconazole	99	Hepatic	10	21	Time	0.125–0.25[d]
Levofloxacin	24–38	Renal	1.09	7–8	Concentration	2
Linezolid	31	Hepatic	0.6	4.8–5.4	Time	4
Meropenem	2	Renal	0.25	1	Time	4
Moxifloxacin	50	Hepatic	1.7–2.7	12	Concentration	2
Piperacillin	16	Renal	0.18	1	Time	16
Tazobactam	20–23	Renal	0.18–0.33	1	NA	4
Ticarcillin	45–65	Renal	0.17	1.2	Time	16
Sulbactam	38	Renal	0.25–0.5	1	Time	1–4
Vancomycin	55	Renal	0.7	6	Time	10
Voriconazole[e]	58	Hepatic	4.6	12	Time	0.5

NOTE. NA, not applicable; PBC, protein-binding capacity.

[a] Data are for the parent compound.

[b] Denotes the highest MIC in the susceptible range for applicable pathogens, such as the β-lactam MIC for *Pseudomonas aeruginosa*.

[c] Trough concentrations of acyclovir are not routinely measured because this agent is phosphorylated into the active form acyclovir triphosphate.

[d] The higher level is the recommended target trough concentration for *Candida* species with an MIC in the dose-dependent, susceptible range (fluconazole MIC, 16–32 μg/mL; itraconazole MIC, 0.25–0.5 μg/mL).

[e] The oral bioavailability of voriconazole is estimated to be 96 %.

Fig. 1.3 Pharmacokinetic and pharmacodynamic parameters of drugs used for treatment of critically ill adult patients receiving continuous renal replacement therapy (Reprinted with permission from: Trotman et al. [84])

concentrations ranging from one to five times Minimal Ihibitory Concentration (MIC) [5], and time ranges from 40 to 100 % interval dosing [6]. The use of continuous infusion of time-dependent antibiotics may be higher in order to optimize the time above the threshold concentration without unnecessary high peak concentrations [7–12]. However, data showing the best outcomes are lacking as of today. For concentration-dependent drugs, the optimal "killing" of the bacteria is associated

with the relationship between plasma concentration peak post distribution (Cmax) and the MIC (e.g., aminoglycosides), with the ratio of the area under the plasma concentration-time curve in a period of 24 h (AUC 24) compared to MIC (e.g., AUC24:MIC, for linezolid) or both (e.g., the fluoroquinolones). For aminoglycosides, maintaining a fixed dosing with prolonged interval dosing not only increases the effectiveness of treatment but also minimizes drug toxicity [13, 14]. The pharmacokinetic profiles of drugs in critically ill patients are significantly different either in patients with chronic kidney disease or in healthy volunteers. Variables affecting excretion of drugs during hemofiltration for acute renal failure in critically ill patients can be broadly divided into three major categories.

A. *Patient-related variables*
B. *Hemofiltration-related variables*
C. *Drug-related variables*

1.3 Variables Affecting the Elimination of Antibiotics in the CRRT

The active amount of a drug is its free fraction to its site of action, determined by dosing, absorption, protein binding, volume of distribution, and clearance. Absorption of antimicrobials is rarely a problem in critical illness, as most of them will be intravenously administered. Protein binding of drugs with acid valence, as antimicrobials, is frequently altered in critical illness due to falling serum albumin. Protein binding may be also altered by a decrease of systemic pH and the presence of uremic toxins, bilirubin, and free fatty acids; each dysfunction may be present in renal failure and sepsis [15–17]. The volume of distribution (Vd) is an apparent volume correlated with the amount of drug which should be suspended to give the observed blood concentration. For many antimicrobials, the Vd significantly arises in sepsis, due to increased capillary permeability and penetration within tissues, and in kidney failure due to retention of water, and the Vd can exceed the total volume of body water. Many antimicrobials are eliminated through the kidney, and therefore, a significant reduction in creatinine clearance can result in a half-life extension of some agents such as cefotaxime and teicoplanin [18]. However, hepatic metabolism and biliary or gut excretion may substantially raise in the presence of renal failure; for example, fecal levels of ciprofloxacin considerably increase [19].

1.4 Principles of Pharmacokinetics [20]

1.4.1 Absorption

Enteric drug absorption in critically ill patient may be quite unpredictable for several reasons: proton pump inhibitors administered for ulcer prophylaxis may raise gastric pH enough to dissolve pH-dependent coatings on tablets; fluid overload and gut edema, as well as loss of enteric microarchitecture may impair absorption across

the enteric mucosa; cholestasis in the setting of shock or sepsis condition may alter the enterohepatic recirculation; disruption of epithelial "tight junctions," loss of enteric mucosa, or partial denudation of the enteric lumen may lead to increased absorption; and "first-pass" effects may be altered by portosystemic shunts. For these reasons, oral administration of pharmacologic agents is not even discussed in critical illness. Parenteral administration is in fact preferred in certain settings.

1.4.2 Distribution

After an agent is administered, either orally or parenterally, it will be transported to a greater or lesser extent, from its original location throughout the rest of the body. For this discussion, we will assume intravenous administration. As a result of this active and passive transport, the measured concentration of drug in the plasma will be less than just the administered dose divided by the estimated plasma volume. Dosage administrated divided by the final concentration yields a number with units of volume, called the volume of distribution (V_d). Once the drug has distributed throughout the body, it will have some final concentration that then gradually decreases as the body eliminates the drug. Drugs do not distribute into the entire body; there are certainly anatomical compartments in the body to which some antibiotics have poor access, such as abscesses, bone, and cerebrospinal fluid. Many antibiotics intravenously administered penetrate the blood-brain barrier slowly or not at all. This is a major challenge in therapeutic drug monitoring, as antibiotic concentrations for therapeutic drug monitoring are measured in blood samples that overestimate concentrations at the site of infection. Volumes of distribution in acute renal failure may be very different from published population estimates derived from healthy subjects.

1.5 Clearance Metabolism and Excretion

Clearance is a familiar concept to most nephrologists which needs a further discussion in the context of pharmacokinetics. Creatinine clearance, commonly used as an easily calculated surrogate for glomerular filtration rate, includes creatinine removed from blood by glomerular filtration and tubular secretion, although in individual patients the relative contributions of each are generally not known. The same is true for drugs which may be filtered and either reabsorbed or secreted by the tubule. In renal failure, filtration and secretion are reduced, and it is usually assumed that reduced renal drug clearance occurs in proportion to reductions in glomerular filtration rate. Uremia and/or azotemia can change hepatobiliary drug metabolism, possibly via product inhibition by accumulated metabolites. Hepatic cytochrome P450 expression is reduced in chronic uremia, and in vitro studies suggest that a dialyzable factor contributes to the suppression. Extracorporeal clearance by the dialysis circuit occurs in parallel with endogenous clearance. Only the unbound or free drug is removed by the dialysis circuit, as the plasma proteins (albumin) to which the drug is bound are too large to pass through the pores of the dialysis membrane. CRRT has dialysate/effluent flow-limited

small-solute clearance (blood flow "Q_b" ≫ dialysate flow "Q_d"), and CRRT urea clearance is generally close to the effluent flow rate, typically 2–3 L/h or 33–50 mL/min. Sustained low-efficiency dialysis (SLED) ($Q_d > Q_b$, Q_b 100 ~ mL/min) and hemodialysis ($Q_d > Q_b$; Q_b ~ 350–400 mL/min) have blood flow-limited small-solute clearance, and barring significant recirculation or clotting in the fiber bundle, urea clearance is close to the blood flow rate. In CRRT, SLED, and conventional hemodialysis, middle-molecule clearance is appreciably less than urea clearance and may be negligible. Typical antibiotic-dosing adjustments in CRRT involve estimating ongoing extracorporeal clearance (e.g., 15 mL/min) and dosing the antibiotic according to the guidelines for the equivalent creatinine clearance. Typical dose adjustments in intermittent dialysis involve estimating drug removal in the course of a single session, frequently from the published literature rather than individualized data, and then supplementing the regular antibiotic dosing schedule with additional doses after each dialysis session.

1.6 Pharmacodynamics [20]

Antimicrobial antibiotics fall into several broad classes of agent which exert their selective effect on microbes by targeting enzymes that are not shared with their host. Each class of agent is thought to have a particular preferred concentration-time profile that optimizes microbial killing while minimizing side effects. Drugs are usually classed as time dependent, meaning that time – or percentage of the dosing interval – above some threshold concentration influences kill rates to a greater extent than does the magnitude of the peak concentration observed; conversely, concentration-dependent agents show more dependence on the magnitude of the peak concentration than how long the concentration exceeded some multiple of the MIC. Several agents exhibit a potent post-antibiotic or post-antifungal effect caused by the irreversible binding of the drug to bacterial or fungal cellular machinery. The pharmacokinetic processes (distribution and clearance) described above cause the concentration-time profile at the site of infection to differ from the concentration-time curve in plasma, so that plasma concentrations may or may not be close to concentrations at the site of infection. Optimization of the plasma concentration profile to achieve a desired tissue concentration-time profile is an active area of research.

1.7 Hemofiltration-Related Variables

CVVH removes plasma water, thus producing an ultrafiltrate and a purification of molecules of various sizes by convection. This process of molecular clearance is influenced by:

1. *Sieving coefficient of molecules removed*
2. *Ultrafiltration rate*
3. *Proportion of replacement fluid given in pre-dilution or post-dilution*
4. *Membrane characteristics*

The "sieving coefficient" (concentration in ultrafiltrate divided by mean of concentrations in pre- and post-filter blood) of a drug reflects its capacity to pass through filter membranes, and ranges vary from 0 to 1, respectively, for drugs that do not pass membrane and drugs that freely pass through. Sieving coefficient for antibiotics is from 0.02 (oxacillin) to 0.9 (ceftazidime). Furthermore, drug clearance is directly proportional to ultrafiltration rate; a higher drug proportion is removed at higher filtration rates. With convective elimination, the transfer of drug across membrane filter even depends on drug concentration. A reduction in local concentration may decrease drug clearance, like in pre-dilution modes in which a proportion of fluid is infused before the filter. When total replacement fluid is infused after hemofilter (post-dilution), maximum ultrafiltration rate is limited to about 25–30 % of plasma flow rate, due to hemoconcentration within the filter. Drug-sieving coefficients are also reduced because of polarization of the molecules [21]. This is a dynamic process during hemofiltration, where protein plasma and drugs bind to filter membrane and thus reduce its permeability. By infusing the replacement fluid before the filter (pre-dilution), the filter lifetime is prolonged thanks to a reduction of hematocrit and an improvement of the flow. Sieving coefficient increases, whereas drug clearance decreases because of reduced drug concentration. Modern membranes for hemofiltration (e.g., those made in polysulfone) have large pores with functional "cutoff" points of ≥20 kDa [22], above antibiotic measurement used in intensive care. A solute-membrane interaction has been described leading to protein-layer formation on the same membrane [23]. Plasma proteins precipitate on membrane, reducing its permeability and convective transport of solutes. A substantial absorption of aminoglycosides [36] and quinolones [37] was observed in traditional membranes of polyacrylonitrile (PAN) causing a decreased removal of these antibiotics when these membranes are used for a prolonged and continuous hemofiltration. The use of a large membrane surface area and frequent changes of the filter membrane will also significantly increase the amount of drug removed.

1.8 Basic Principles of CRRT (Fig. 1.4)

Modern CRRT is performed as continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis (CVVHD) [24–26]. Since CRRT is relatively a slow and constant process, there is the risk that administered dose of CRRT can be substantially lower than the one prescribed in ICU, because of potential interruptions during treatment not registered in medical record (e.g., transport outside ICU for tests or surgery, or clotted filter and its replacement).

1.9 Hemofiltration

Hemofiltration uses convective removal. Plasma water passes across the filter membrane down a pressure gradient, dragging solutes. For the most commonly used antibiotics, which include large molecules such as vancomycin (1448 Da) and

Mode of CRRT	Clearance
CVVH(post-dilution)	$CL_{cvvh(post)} = Q_f \times S_c$
CVVH(pre-dilution)	$CL_{cvvh(pre)} = Q_f \times S_c \times (Q_b / (Q_b + Q_{rep})$
CVVHD	$CL_{cvvhd} = Q_d \times S_d$
CVVHDF	$CL_{cvvhdf} = (Q_f + Q_d) \times S_d$

Fig. 1.4 CRRT clearance equations (*CL cvvh(post)* clearance by CVVH (post-dilution), Q_f ultrafiltrate flow rate, S_c sieving coefficient, *CLccvh(pre)* clearance by CVVH (pre-dilution), Q_b blood flow rate, Q_{rep} replacement fluid flow rate, *CLcvvhd* clearance by CVVHD, Q_d dialysate flow rate, S_d saturation coefficient, *CLcvvhdf* clearance by CVVHDF)

teicoplanin (1878 Da), convective transport across the most commonly used modern membranes (pores sizes 10,000–30,000 Da) is independent on molecular weight [27, 28]. Drug's ability to pass through the membrane is expressed as the sieving coefficient (S_c): the relationship between drug concentration in filtrate and in plasma.

$$S_c = \frac{\text{Drug concentration in filtrate}}{\text{Drug concentration in plasma}}$$

In general, the sieving coefficient has a range that goes from 0 to 1. Drug binding to proteins is the main determinant of S_c, and the S_c can be estimated from published values of protein binding (P_b), so that $S_c = 1\text{-PB}$. S_c measured and S_c estimated by protein binding ($P_{b)}$ published values are correlated [29]. Nevertheless protein binding in critically ill patients is variable, and for some drugs (such as levofloxacin), the Sc widely varies [30–34]. Furthermore, the S_c can be altered by membrane-manufacturing material, drug-membrane interactions, and properties of the flow. Replacement fluid can be added to the circuit or before the filter (pre-dilution) or after the filter (post-dilution). In post-dilution, drug clearance depends on ultrafiltration rate and S_c:

$$\text{CI cvvh}\left(\text{post}\right) = Q_t \times S_c$$

In pre-dilution, plasma entering the hemofilter is diluted by the reinfusion fluid, so that drug clearance will be lowered by a correction factor ($C_{f)}$ determined by blood flow rate (Q_b) and pre-dilution replacement rate (Q_{rep}). Drug clearance in the pre-dilution can be calculated as

$$\text{CIcvvh}\left(\text{pre}\right) = Q_f \times S_c \times C_f^*$$

* $C_f = Q_b/(Q_b + Q_{rep})$

1.10 Hemodialysis

Hemodialysis is based on the *diffusion* of solutes across a filter membrane down a concentration gradient that exists between plasma and dialysate. Equilibrium through filter membrane is dependent on the relationship of molecular weight,

blood, and dialysate flows. As dialysate flow rate in CVVH and CVVHDF is relatively low in comparison to blood flow rate [35], neither blood flow rate nor molecular measurement are important factors in the clearance of the most commonly used antibiotics. Drug's ability to pass through the membrane is expressed as dialysate saturation (S_d):

$$S_d = \frac{[\text{Drug}]\text{dialysate}}{[\text{Drug}]\text{plasma}}$$

Protein binding (P_b) is the main determinant of S_d. Similar to the sieving coefficient, S_d is membrane specific, subject to drug membrane interactions and flow properties, with a range of values between 0 and 1. According to standard clinical practice, blood flow is so high compared to dialysate flow that completed saturation occurs and drug clearance is actually dependent on dialysate flow rate (Q_d) and S_d:

$$\text{Cl cvvhd} \sim Q_d \times S_d$$

1.11 Hemodiafiltration

Hemodiafiltration is based on both *convection* and *diffusion* to eliminate drugs. In general, drug clearance in CVVHDF can be estimated as

$$\text{Cl cvvhdf} = \left(Q_f + Q_d\right) \times S_d$$

However, during CVVHDF, the two processes interact decreasing the respective efficiency. As a result, simple addition of each component will result in an overestimate of total clearance, but the clinical relevance is unclear [36]. Nevertheless, it has been shown that CVVHDF ensures higher clearance than CVVH pre-dilution by equal effluent flow (ultrafiltrated and dialysate) [37].

1.12 Drug-Related Variables

Several drug factors play an important role in determining the final amount of drug removed by hemofiltration mainly:

1. *Molecular weight of drug*
2. *Protein binding*
3. *Degree of renal clearance*

Many antibiotics have a molecular weight less than 750 Da; the only exceptions are for vancomycin and teicoplanin with a molecular weight of 1448 Da and 2000 Da, respectively. The molecular weight influences clearance, as the contribution of convective transport relating to diffusion grows with the increasing of molecular weight medications. Molecules larger than 10 kDa are removed by convection alone. Protein-binding degree of drugs is important, because only free fraction is

available for clearance through hemofiltration. Protein binding can be altered in very serious illness, especially for changes in pH and low serum albumin levels. Many antimicrobials have limited protein binding, but some of them are extensively protein bound (oxacillin, teicoplanin, ceftriaxone), mainly albumin. Less than 70 % of protein binding does not seem to limit the availability of free drug to act on its site [38] and therefore its availability for elimination by hemofiltration. Hemofiltration will only have an effect on antimicrobial plasma levels or their metabolites if the drug is currently removed by hemofiltration. Extracorporeal clearance during CVVH can be substantial for some drugs with low molecular weight and low volume of distribution, although of importance is the contribution of extracorporeal clearance to total drug clearance.

1.13 CRRT and Various Classes of Antibiotics (Figs. 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, and 1.13)

1.13.1 Vancomycin

The half-life of vancomycin is significantly increased in patients with renal insufficiency. It is a large molecular weight antibiotic (MW 1448 Da), and although compounds of this size are poorly removed by intermittent hemodialysis, they are removed by CRRT [39–41]. Vancomycin has pharmacokinetic data comparable to other antimicrobials ($V_d = 0.38$ L/kg; protein binding = 30 %). About 70 % of the drug is filtered by kidneys in healthy volunteers. Nonrenal clearance of vancomycin is initially preserved in acute renal failure, but decreases exponentially and reaches values equal to those of patients with chronic kidney disease (about 12–15 % clearance in healthy volunteers) after 10–15 days [27]. CVVH, CVVHD, and CVHDF all effectively remove vancomycin [42, 43]. Because of the prolonged half-life, the time to reach steady state will also be prolonged. Therefore, a vancomycin-loading dose of 15–20 mg/kg is justified. Vancomycin maintenance dosing for patients receiving CVVH varies from 1000 mg q24h to 1500 mg q48h. For patients receiving CVVHD or CVVHDF, we recommend a vancomycin maintenance dosage o f 1–1.5 g q24h. Monitoring of plasma vancomycin concentrations and subsequent dose adjustments are recommended to achieve desired post-filter concentrations. A post-filter concentration of 5–10 mg/L is adequate for infections in which drug penetration is optimal, such as skin and soft-tissue infections or uncomplicated bacteremia. However, higher post-filter values (10–15 mg/L) are indicated for infections in which penetration is dependent on passive diffusion of drug into an avascular part of the body, such as osteomyelitis, endocarditis, or meningitis. Recent guidelines also recommend higher post-filter values (15–20 mg/L) in the treatment of care-associated pneumonia, because of suboptimal penetration of vancomycin into lung tissue.

Drug	Dosage, by type of renal replacement therapy	
	CVVH	CVVHD or CVVHDF
Amphotericin B formulation		
Deoxycholate	0.4–1.0 mg/kg q24h	0.4–1 mg/kg q24h
Lipid complex	3–5 mg/kg q24h	3–5 mg/kg q24h
Liposomal	3–5 mg/kg q24h	3–5 mg/kg q24h
Acyclovir	5–7.5 mg/kg q24h	5–7.5 mg/kg q24h
Ampicillin-sulbactam[a]	3 g q12h	3 g q8h
Aztreonam	1–2 g q12h	2 g q12h
Cefazolin	1–2 g q12h	2 g q12h
Cefepime	1–2 g q12h	2 g q12h
Cefotaxime	1–2 g q12h	2 g q12h
Ceftazidime	1–2 g q12h	2 g q12h
Ceftriaxone	2 g q12–24h	2 g q12–24h
Clindamycin	600–900 mg q8h	600–900 mg q8h
Ciprofloxacin[b]	200 mg q12h	200–400 mg q12h
Colistin	2.5 mg/kg q48h	2.5 mg/kg q48h
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
Fluconazole[b]	200–400 mg q24h	400–800 mg q24h[c]
Imipenem-cilastatin[d]	250 mg q6h or 500 mg q8h	250 mg q6h, 500 mg q8h, or 500 mg q6h
Levofloxacin[b]	250 mg q24h[e]	250 mg q24h[e]
Linezolid[b]	600 mg q12h	600 mg q12h
Meropenem	1 g q12h	1 g q12h
Moxifloxacin	400 mg q24h	400 mg q24h
Nafcillin or oxacillin	2 g q4–6h	2 g q4–6h
Piperacillin-tazobactam[f]	2.25 g q6h	2.25–3.375 g q6h
Ticarcillin-clavulanate[g]	2 g q6–8h	3.1 g q6h
Vancomycin	1 g q48h[e]	1 g q24h[e]
Voriconazole[h]	4 mg/kg po q12h	4 mg/kg po q12h

NOTE. All dosages are administered intravenously, unless otherwise indicated. The recommendations assume an ultrafiltration rate of 1 L/h, a dialysate flow rate of 1 L/h, and no residual renal function. CAVHD, continuous arteriovenous hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodialfiltration.

[a] Available commercially in a fixed ratio of 2 mg of ampicillin to 1 mg of sulbactam.

[b] The switch from the intravenous to the oral formulation is possible when appropriate.

[c] A dose of 800 mg is appropriate if the dialysate flow rate is 2 L/h and/or if treating fungal species with relative azole resistance, such as *Candida glabrata*.

[d] Available commercially in a fixed ratio of 1 mg to 1 mg.

[e] Recommended loading dose is 15–20 mg/kg of vancomycin and 500 mg of levofloxacin.

[f] Available commercially in a fixed ratio of 8 mg to 1 mg.

[g] Available commercially in a fixed ratio of 30 mg to 1 mg.

[h] The oral bioavailability of voriconazole is estimated to be 96%. Consider 2 loading doses of 6 mg/kg po q12h. See Antifungals for details on contraindications associated with the intravenous formulation in patients with renal failure.

Fig. 1.5 Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy (Reprinted with permission from: Trotman et al. [84])

Aminoglycoside	Gram-positive synergy, dosage	Infection with gram-negative bacteria	
		Loading dose	Maintenance dosage
Gentamicin	1 mg/kg q24–36h	3 mg/kg	2 mg/kg q24–48h
Tobramycin	Not applicable	3 mg/kg	2 mg/kg q24–48h
Amikacin	Not applicable	10 mg/kg	7.5 mg/kg q24–48h

NOTE. See Aminoglycosides for recommendations on monitoring drug levels. Target peak and trough levels vary depending on the type of infection. Use calculated dosing body weight for obese patients.

Fig. 1.6 Aminoglycoside-dosing recommendations for critically ill adults receiving continuous renal replacement therapy (Reprinted with permission from: Trotman et al. [84])

1.13.2 Linezolid

Fifty percent of a linezolid dose is metabolized in the liver to two inactive metabolites, and 30 % of the dose is excreted in the urine as unchanged drug. There is no adjustment recommended for patients with renal failure; however, linezolid clearance is increased by 80 % during intermittent hemodialysis. There are very few data on linezolid clearance during CRRT. On the basis of four studies [44–47], a linezolid dosage of 600 mg q12h provides a serum post-filter concentration of >4 mg/L which is the upper limit of the MIC range for drug-susceptible *Staphylococcus* species. Thus, no linezolid dosage adjustment is recommended for patients receiving any form of CRRT; however, in such patients, neither the disposition nor the clinical relevance of inactive linezolid metabolites is known.

1.13.3 Daptomycin

Daptomycin is a relatively large molecule that is excreted primarily through the kidneys and requires dose adjustment in patients with renal failure. There are no published pharmacokinetic studies of daptomycin in patients receiving CRRT.

1.14 Beta-Lactamase

1.14.1 Carbapenems

Imipenem is metabolized at the renal brush-border membrane by the enzyme dehydropeptidase-I, which is inhibited by cilastatin. Seventy percent of the imipenem dose is excreted unchanged in the urine when it is administered as a fixed-dose combination with cilastatin. Imipenem and cilastatin have similar pharmacokinetic properties in patients with normal renal function; however, both drugs accumulate in patients with renal insufficiency. To maintain an imipenem post-filter concentration of ~2 mg/L

	Loading dose	Maintenance dose
Cephalosporins		
Cefpirome	2.000 mg	1.000 mg q12h Consider higher dose for gram negative or intermediate sensibility (no post-antibiotic effect)
Cefepime	2.000 mg	No dose adjustment required
Piperacillin-tazobactam	4.500 mg	4.500 mg q8h Tazobactam may accumulate. Consider alternation with piperacillin alone.
Meropenem	1.000 mg	1.000 mg q12h –1.000 mg q8h (Consider higher dose if monotherapy, proved intermediate sensibility or neutropenic patient)
Aminoglicosydes	Preferred once daily dose (Once-Daily Aminoglycoside-ODA), strictly monitor plasmatic levels	
Levofloxacin	500 mg	500 mg once daily Depending on ultrafiltration rate (>3L/ora) and from sensibility of the microorganim, consider loading dose of 750 mg with maintenance dose of 500 mg q8h
Vancomycin	15 mg/kg	1.000–1.500 mg once daily It is mandatory to monitor plasmatic levels
Erytromicyn	Same dose of normal renal function	No further adjustment required
Metronidazole	Same dose of normal renal function	No further adjustment required

Fig. 1.7 Dosing regimes for ultrafiltration rate 30–35 mL/kg/h (Adapted from Glossop and Seidel [85])

Broad guidelines that can be used to assist antibiotic dosing adjustment for critically ill patients

	Suggested Dosing Adjustment for Critically Ill Patients	
Antibiotic Class	Normal Renal Function	Moderate to Severe Renal Dysfunction Comments
Aminoglycosides	Use high doses (e.g., gentamicin 7 mg/kg) where possible to target C_{max}:MIC ratio of 10; monitor C_{min} and aim for undetectable plasma concentrations[a]	Use high doses where possible and monitor C_{min} thereafter (36 to 48 hourly extended interval dosing acceptable); dosing can be guided by MIC data if available if dose reductions are essential
β-lactams Carbapenems	Consider extended or continuous infusion or more frequent dosing to ensure T > MIC; therapeutic drug monitoring may be useful if available	If intermitted dosing used, dosing can occur at reduced dose or frequency (not both); err toward larger doses as β-lactams have large therapeutic window
Glycopeptides	Dosing at 30–40 mg/kg/day (vancomycin), which can be increased according to C_{min} plasma concentrations (aim for 15–20 mg/L); continuous infusions should be used when difficulty obtaining therapeutic C_{min}	High dosing on day 1 may be required to ensure adequate distribution; dose adjustments should occur according to C_{min} concentrations
Fluoroquinolones	Doses that achieve high C_{max}:MIC ratio should be targeted (e.g. ciprofloxacin 1200 mg/day); levofloxacin may require 500 mg 12-hourly in some patients with high creatinine clearance; where high doses used, monitor for toxicity (seizures)	Dose adjustment is probably only required in renal impairment for levofloxacin, gatifloxacin, and ciprofloxacin; where possible reduce frequency and maintain dose
Tigecycline	Use 100 mg loading dose then 50 mg 12 hourly	No dose adjustment required in renal failure or dialysis[b]
Linezolid	Use 600 mg 12 hourly	No dosage adjustment required in renal failure or dialysis
Lincosamides	Use 600–900 mg 8 hourly	Decreased lincomycin dose or frequency in renal or hepatic dysfunction; decrease clindamycin dose or frequency in hepatic dysfunction
Colistin	Use 5 mg/kg/day of colistin base (75,000 international units/kg/day colistimethate sodium)[c] intravenously in 3 divided doses	Reduce dose or frequency (not both)

MIC, minimum inhibitory concentration; C_{max}, maximum concentration; C_{min}, minimum concentration.
[a]Aminoglycoside levels should be undetectable for no more than the post-antibiotic effect. We recommend a maximum of 4 hrs before redosing as any longer delay may enable bacterial regrowth; [b]if severe cholestasis present then tigecycline should be dosed with 50-mg loading dose, then 25 mg 12 hourly; [c]1 mg colistimethate sodium is equivalent to 12,500 international units (165).

Fig. 1.8 Broad guidelines that can be used to assist antibiotic-dosing adjustment for critically ill patients (Reprinted with permission from: Roberts et al. [128])

during CRRT, a dosage of 250 mg q6h or 500 mg q8h is recommended [48–50]. A higher dosage (500 mg q6h) may be warranted in cases of relative resistance to imipenem (MIC, ≥4 mg/L). Cilastatin also accumulates in patients with hepatic dysfunction, and increasing the dosing interval may be needed to avoid potential unknown adverse effects of cilastatin accumulation. This represents an appropriate post-filter concentration for critically ill patients, especially when the pathogen and MIC are not yet known [51, 52]. Many studies have analyzed the pharmacokinetics of meropenem in patients receiving CRRT [53–57]. There is significant variability in the data, owing to different equipment, flow rates, and treatment goals. However, a meropenem dosage of 1 g q12h will produce a post-filter concentration of ~4 mg/L in most patients, regardless of CRRT modality. If the organism is found to be highly susceptible to meropenem, a lower dosage (500 mg q12h) may be appropriate.

1.15 Beta Lactamase-Inhibitor Combinations

Of the three β-lactamase-inhibitor combinations available commercially, only piperacillin-tazobactam has been extensively studied in patients receiving CRRT. On the basis of published data, piperacillin is cleared by all modalities of CRRT [58–61].

Antifungal agent	Mechanism	Use	Adverse effects	Elimination	Dosage during CRRT
Lipid formulations of amphotericin B	Interacts with ergosterol in the fungal cell membrane	I.V.	Hepatic, renal and cardiovascular toxicity	Unaffected by CRRT	5 mg/kg/day
Fluconazole	Exhibits time-dependent activity	I.V. or ORAL	Hepatic toxicity	High elimination by CRRT	600 mg/12h
Voriconazole	Reduced ergosterol syntesis	I.V. or ORAL	Toxicity in AKI with I.V. use	Poor elimination of I.V. form with CRRT	Loading dose: 6 mg/kg Maintenance dose: 4 mg/kg/12h
Echinocandins	Inhibits β(1,3)-glucan synthesis	I.V.	Potential hepatic toxicity	Unaffected by CRRT	Anidulafungin: Loading dose: 200 mg Maintenance dose : 100 mg/day Caspofungin: Loading dose 70 mg Maintenance dose : 50 mg/day

Fig. 1.9 Characteristics of major antifungal agents including recommended dosages during CRRT (Adapted from Honorè et al. [129])

Antibiotic	Elimination	Dose adsorbed within 24 h	Current dose in CRRT	Class effect	Dose suggested during H-A-M CRRT*
Aminoglycosides (amikacin)	Mainly convection (S_c = 0.9) H.A.M CRRT adsorption might reach 50 %	As high as 1.000 mg No saturation Irreversible binding	30 mg/kg loading dose Monitoring serum levels	YES (tobramycin, netilmycin, arbekacin)	Initially 40 a 45 mg/kg/day
Colistin	Up to 90 % adsorption	Between 5 & 10 MIU No saturation	9 MIU loading dose, then 4,5 MIU bid	NO	9 MIU loading dose, then 4,5 MIU tid
Vancomycin	Mainly convection (S_c=0,75) Adsorption might reach 20 %	Up to 1/3 of loading dose (±350–400 mg) No saturation	20 mg/kg loading dose then 30 mg/kg/day Monitoring serum levels	YES(daptomycin)	25 mg/kg loading dose, then 40 mg/kg/day Monitoring serum levels
Teicoplanin	Limited convection (S_c = 0.15) Mainly adsorption (90–95 %)	Up to 25 % of loading dose (±200–250 mg) Saturation unknown	10 mg/kg loading dose bid, repeated 3 times, then 10 mg/kg/day Monitoring serum levels	NO	12 mg/kg loading dose bid repeated 3 times, then 12 mg/kg/day Monitoring serum levels
Levofloxacin	Mainly convection (S_c=0.8) Saturation present (SatC = 0.75)	Up to 30 % of loading dose (±250–300 mg) Saturation resent	750 mg loading dose then 500mg bid	Highly possible but not yet shown	1.000 mg loading dose, then 500 mg/day tid

Fig. 1.10 Impact on antibiotic dosing of elimination mechanism and degree of membrane adsorption during conventional and highly adsorptive membrane continuous renal replacement therapy (HAM CRRT) * Hypothetical dose, needs to be confirmed (Adapted from Honorè et al. [130])

Drug	Loading dose	Maintenance dose
Colistin	9 MIU	4.5 MIU tid
Amikacin		50–60 mg/kg ± every 24 h, according to MIC and optimal trough level (4–8 μg/ml; TDM : Therapeutic Drug Monitoring)
Gentamicin		20–25 mg/kg ± every 36 h, according to MIC and optimal trough level (5–10 μg/ml; TDM : Therapeutic Drug Monitoring)
Voriconazole	8 mg/kg q 12h	6 mg/kg q 12h

Fig. 1.11 Suggested loading and maintenance doses of colistin, aminoglycosides, and voriconazole for treatment of highly resistant Gram-negative and fungal infections under CRRT (Adapted from: Honorè et al. [131])

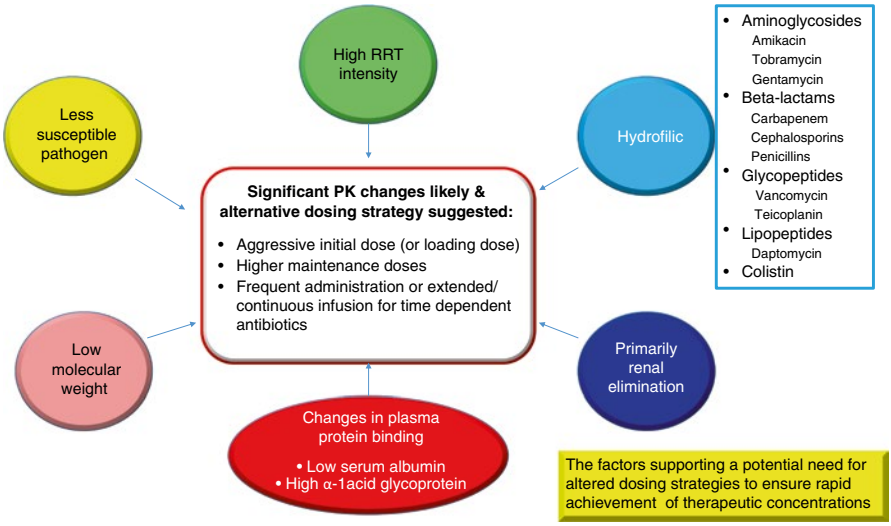

Fig. 1.12 The factors supporting a potential need for altered dosing strategies to ensure rapid achievement of therapeutic concentrations [132]

The tazobactam concentration has been shown to accumulate relative to the piperacillin concentration during CVVH. Thus, piperacillin is the limiting factor to consider when choosing an optimal dose. On the basis of results of four studies evaluating piperacillin or the fixed combination of piperacillin-tazobactam in patients receiving CRRT, a dosage of 2 g/0.25 g q6h piperacillin-tazobactam is expected to produce post-filter concentrations of these agents in excess of the MIC for most drug-susceptible bacteria during the majority of the dosing interval. For patients receiving CVVHD or CVVHDF, one should consider increasing the dose to 3 g/0.375 g piperacillin-tazobactam if treating a relatively drug-resistant pathogen, such as *Pseudomonas aeruginosa*. For patients with no residual renal function who

Antibiotic	Effluent flow rate	%CRRT clearance of Total Clearance	Sc	Antibiotic Dosing Loading dose	Antibiotic Dosing	Comment
Amikacin	40–68 ml/min	80 %	0.8	25 mg/kg (Cmax/MIC)	36–48 hourly	Postantibiotic effect
Gentamicin	40–68 ml/min	80 %	0.8			
Ceftazidime	20–50 ml/min	50 %	0.7–1		4–8 g/day(Cmin above susceptibility breakpoint 8mg/L)	Continuous Infusion
Cefepime	16–42 ml/min	20–50 %	0.7–0.9		2–6 g/day	Continuous Infusion
Piperacillin/tazobactam 30 %PB	27–57 ml/min	2–42 %	0.4–0.8		8/1–16/2 g/day (Cmin above susceptibility breakpoint 16 mg/L)	Continuous Infusion TDM
Meropenem	10–70 ml/min	>50 %			2–3 g/day(Cmin above susceptibility breakpoint 2mg/L	Continuous Infusion
Imipenem	20–37 ml/min	20–30 %			1–2 g/day	
Levofloxacin	20–37 ml/min	40 %			0.25–0.5 g/day(AUC/MIC>125-MIC1mg/L Gram negative)	TDM
Ciprofloxacin	19–60 ml/min	20 %			0.4–08 g/day (MICo.5 mg/L)	TDM
Vancomycin	20–50 ml/min		0.7–0.9	25 mg/kg for high volume CRRT (AUC/MIC>400)		TDM
Daptomycin High PB 90 %	33–45 ml/min	30 %	0.2	8 mg/kg	4–6 mg/kg/day(Cmax/MIC >8 AUC/MIC 100 – MIC 1 mg/L)	
Linezolid	17–40 ml/min	8–40 %			>1.2 g/day(AUC/MIC >50 not achieved – MIC 4 mg/L)	Higher doses for pathogens with higher MIC
Colistin				Higher loading doses and maintenance doses		Limited pharmakinetic studies

Fig. 1.13 How can we ensure effective antibiotic dosing in critically ill patients receiving different types of RRT? (Adapted and with permission from: Jamal et al. [132])

are undergoing CVVH and receiving prolonged therapy with piperacillin-tazobactam, it is not known whether tazobactam accumulates. Moreover, the toxicities of tazobactam are not known, and it has been recommended that alternating doses of piperacillin alone in these patients may avoid the potential toxicity associated with tazobactam accumulation. Although few data exist with ampicillin-sulbactam and ticarcillin-clavulanate [62], extrapolations are possible between piperacillin-tazobactam and ampicillin-sulbactam. Piperacillin, tazobactam, ampicillin, and sulbactam primarily are excreted by the kidneys, and all four drugs accumulate in persons with renal dysfunction. However, the ratio of β-lactam to β-lactamase inhibitor is preserved in persons with varying degrees of renal insufficiency, because each pair has similar pharmacokinetics. This is not true for ticarcillin-clavulanate. Although ticarcillin will also accumulate with renal dysfunction, clavulanate is not affected; it is metabolized by the liver. If the dosing interval is extended, only ticarcillin will remain in the plasma at the end of the interval [63]. For this reason, an interval >8 h is not recommended with ticarcillin-clavulanate during CRRT. Because CVVHD and CVVHDF are more efficient at removing beta lactams such as ticarcillin, the dosing interval with these CRRT modalities should not exceed 6 h for ticarcillin-clavulanate. Piperacillin is an acylamino penicillin (MW 539 Da, protein binding 16 %, V_d about 0,3 L/kg) that is predominantly (65–70 %) excreted via the renal route. Cappellier et al. studied removal of piperacillin at low CVVH flow rate and found limited removal of piperacillin with high peak levels [61]. Consequently, they recommended a dose reduction to 4.000 mg twice daily in view of a possible drug accumulation and increased risk of seizures.

1.16 Cephalosporins and Aztreonam

Cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, and aztreonam were investigated. With the exception of ceftriaxone, these beta lactams are renally excreted and accumulate in persons with renal dysfunction. Because the rate of elimination is directly proportional to renal function, patients requiring intermittent hemodialysis may receive doses much less often. In some instances, three times weekly dosing after hemodialysis is adequate. However, clearance by CRRT is greater for most of these agents, necessitating more-frequent dosing to maintain therapeutic concentrations greater than the MIC for an optimal proportion of the dosing interval. Ceftriaxone is the exception in this group of beta lactams, primarily because of its extensive protein-binding capacity, which prevents it from being filtered, and its hepatic metabolism and biliary excretion. Ceftriaxone clearance in patients receiving CVVH has been shown to be equivalent to clearance in subjects with normal renal function, and therefore, no dose adjustment is necessary for patients receiving CRRT [64, 65]. The other cephalosporins and aztreonam are cleared at a rate equivalent to a creatinine clearance rate of 30–50 mL/min during CVVHD or CVVHDF, whereas the rate of clearance by CVVH is lower. If the goal in critically ill patients is to maintain a therapeutic concentration for the entire dosing interval, a normal, unadjusted dose may be required. This is the case with

cefepime. On the basis of two well-done studies involving critically ill patients, a cefepime dosage of 1 g q12h is appropriate for most patients receiving CVVH, and up to 2 g q12h is appropriate for patients receiving CVVHD or CVVHDF [66, 67].

Cefepime and ceftazidime pharmacokinetics are almost identical, and similar doses are advocated. Older recommendations for CVVH dosing (1–2 g q24–48 h) are based on CAVH data [68]. As with cefepime and many other beta lactams, CVVHD removes ceftazidime more efficiently than does CVVH. A ceftazidime dosage of 2 g q12h is needed to maintain concentrations above the MIC for most nosocomial gram-negative bacteria in critically ill patients receiving CVVHD and CVVHDF. Ceftazidime 1 g q12h is appropriate during CVVH. Studies have not been performed with cefazolin, cefotaxime, or aztreonam during CRRT.

1.17 Fluoroquinolones

Few antibiotic classes have more data supporting the influence of pharmacodynamics on clinical outcomes than fluoroquinolones. The ratio of the area under the curve (AUC) to the MIC is a particularly predictive pharmacodynamic parameter [69], and most authorities recommend maximizing this ratio. This is best accomplished by optimizing the dose, which may be difficult in the critical care setting where fluoroquinolone disposition may be altered and fluoroquinolone elimination may be reduced. The additional influence of CRRT makes dosing even more complex. Many studies have documented minimal effects of CRRT on fluoroquinolone elimination [31, 32, 70–73]. However, evidence exists that manufacturer-recommended dosing for ciprofloxacin will not always achieve a target AUC/MIC ratio in critically ill patients, including those who are receiving CAVHD [74]. A ciprofloxacin dosage of 400 mg qd is recommended by the manufacturer for patients with a creatinine clearance rate of <=30 mL/min. In critically ill patients receiving CRRT, a dosage of 600–800 mg per day may be more likely to achieve an optimal AUC/MIC ratio, and for organisms with a ciprofloxacin MIC of >=1 μg/mL, standard doses are less likely to achieve a target ratio. In addition, dose escalation may be warranted if ciprofloxacin is the only anti-gram-negative bacteria antibiotic prescribed, especially if the pathogen is *Pseudomonas aeruginosa*.

Levofloxacin is excreted largely unchanged in the urine, and significant dosage adjustments are necessary for patients with renal failure. Intermittent hemodialysis does not effectively remove levofloxacin, and therefore, supplemental doses are not required after hemodialysis. Levofloxacin is eliminated by CVVH and CVVHDF. Some authors [32] found that a levofloxacin dosage of 250 mg q24h provided Cmx/MIC and AUC24/MIC values that were comparable to the values found in patients with normal renal function after a dosage of 500 mg per day. Levofloxacin dosages of 250 mg q24h, after a 500-mg loading dose, are appropriate for patients receiving CVVH, CVVHD, or CVVHDF. These data, as well as known pharmacokinetics data, indicate no need to adjust the moxifloxacin dosage for patients receiving CRRT. Ciprofloxacin and levofloxacin are two quinolones that have been in clinical use for many years. Their pharmaceutical data (MW 370 DA, Vd 1.2–1.8 L/kg, protein binding 25–50, and 50–70 % renal elimination) make them less liable to clearance by CVVH than beta lactams. Data on

single 500 mg infusion dose of levofloxacin in critically ill patients receiving CVVH come from three studies. Pharmacokinetic data from two of these studies are comparable; with ultrafiltrate rates of 840–1300 mL/h and 1300 mL/h, fractional extracorporeal clearance was 16–40% and 40%, respectively, with a polyacrylonitrile membrane (PAN). The study by Traunmuller et al. differ considerably using ultrafiltrate flows of 3300 mL/h with polyamide membrane. Malone recommended a dosing of 250 mg/d, but Traunmuller, despite demonstrating adequate AUC/MIC ratios for bacteria with a MIC <0.21, suggested that further multiple-dose studies during CVVH are needed. Hansen et al [32] followed up their initial levofloxacin bolus with a daily dose of 250 mg for a further 6 days. No drug accumulation after the initial loading dose was observed, and the mean elimination half time was measured at 21 h. AUC/MIC ratios were adequate (>125) for all bacteria except *Pseudomonas aeruginosa*. Based on this study, we recommend a 500 mg loading dose of levofloxacin, followed by a daily dose of 250 mg.

1.18 Colistin

Polymyxins have recently reemerged as therapeutic options for multidrug-resistant gram-negative organisms, such as *Pseudomonas aeruginosa*, *Acinetobacter*, and *Klebsiella*. Colistimethate sodium is the parenteral formulation of colistin and is the product for which dosing recommendations are made. Colistin is a large cationic molecule with a molecular weight of 1750 D, and it is tightly bound to membrane lipids of cells in tissues throughout the body [75]. These two properties suggest that the impact of CRRT on colistin elimination is minimal. Colistin dosing should be based on the following two patient-specific factors: underlying renal function and ideal body weight. No clinical data exist on colistin dosing for patients receiving CRRT. On the basis of clinical experience and the pharmacokinetic properties of colistin, we recommend using colistin at a dosage of 2.5 mg/kg q48h in patients undergoing CRRT.

1.19 Aminoglycosides

Two pharmacokinetic parameters are essential predictors of aminoglycoside dosing. The volume of distribution can be used to predict the drug dose, and the elimination rate can be used to predict the required dosing interval. The volume of distribution may be significantly larger in critically ill patients and may result in subtherapeutic concentrations after an initial loading dose. CRRT itself may contribute to a larger volume of distribution. However, CRRT offers some control in such a dynamic state, and if the variables of CRRT are held constant, aminoglycoside elimination is likely to be similarly constant. Current filters are capable of removing aminoglycosides at a rate equivalent to a creatinine clearance rate of 10–40 mL/min. This equates to an aminoglycoside half-life of 6–20 h. The typical dosing interval with aminoglycosides will be about 3 half-lives; therefore, the typical dosing interval during CRRT will be 18–60 h. Indeed, most patients undergoing CRRT will require an interval of 24, 36, or 48 h. The target peak concentration can also predict the dosing interval. If gentamicin is prescribed for

synergy in the treatment of infection with gram-positive organisms, the target peak is 3–4 μg/mL. Only 2 half-lives are required to reach a concentration of ≤1 μg/mL, a typical post-filter level. If the target peak concentration is 8 μg/mL, it will take an additional half-life to get to 1 μg/mL. Therefore, the higher the target peak concentration, the longer the required dosing interval. Monitoring aminoglycoside concentrations is essential to determine the most appropriate dose. Performing first-dose pharmacokinetics may be the quickest way to assure adequate and safe dosing. To determine the most appropriate dose, the volume of distribution and the elimination rate can be estimated by measuring the peak concentration and a 24-h concentration. Even if first-dose pharmacokinetics analysis is not performed, determination of the 24-h concentration is warranted to provide a measure of elimination and the ultimate dosing interval. Aminoglycosides show an antibacterial concentration-dependent activity versus gram-positive and gram-negative bacteria.

1.20 Final Considerations (Figs. 1.14, 1.15, and 1.16)

Dose adjustment of antibiotics in critically ill patients treated with RRT is a real challenge. Too-low serum levels may render the treatment ineffective, whereas too-high levels may cause toxicity. After intravenous administration, the serum level of a drug is mainly determined by its protein binding and volume of distribution. In critically ill patients, hypoalbuminemia may lead to an increased fraction of unbound drug; but decreased protein binding, fluid overload, and increased tissue binding may lead to an increase in volume of distribution and to a decrease in serum drug level [76]. Drug clearance in critically ill patients can be expressed by renal, extrarenal, and extracorporeal elimination. Most authors have underlined the importance of therapeutic drug monitoring (TDM) use to optimize dose adjustment of antibiotics. Although aminoglycosides and vancomycin are generally monitored, commercial assays to perform such monitoring are not available for most antibiotics. They are available for most of the other antibiotics [77]. Therefore, the possibility of predicting serum levels of antibiotics by means of an algorithm including dose, protein binding, volume of distribution, and renal, extrarenal, and extracorporeal clearance might be a practical support for the prescription of antibiotics to critically ill patients treated with RRT [78]. It is important to know the impact of variation in RRT settings on the antibiotic clearance [79]. The study of these impact antibiotics, such as meropenem, piperacillin, and vancomycin, has found effluent flow rate as a good predictor of antibiotic clearance, although it altered pharmacokinetics; in the presence of high rate of effluent flow and/or in the presence of slightly sensitive pathogens to antibiotics, it may be needed regimen with highest dosages in critically ill patients undergoing RRT. In critically ill patients, both renal and extrarenal clearance of drugs can be altered. Renal function usually changes dynamically during the patient's clinical course, making it difficult to predict the renal clearance on a daily basis. In addition, the metabolic enzyme activity may be disturbed, causing a decrease in extrarenal clearance. Extracorporeal clearance is determined by several factors related to both the drug and the technique used. The fact that a drug can be eliminated by extracorporeal

Elements	Critical notes
Pharmacokinetics elements	
Residual renal elimination	
Non renal elimination	May be increased in Acute Kidney Injury but may be decreased by concomitant hepatic failure
Volume of distribution (VD)	Increased VD results in need for larger loading dose and reduces efficacy of removal by CRRT
Protein binding (PB)	Only the unbound fraction is removed by CRRT
CRRT elements	
Mode of CRRT	
Dose of CRRT delivered	In clinical practice Effluent Volume is the most important CRRT variable in determining drug elimination. Effluent Volume is dependent on both effluent flow and duration of CRRT
Blood flow rate	Within usual clinical limits varying blood flow rate has little effect on elimination
Filter material	Sieving Coefficient may vary between different filter materials for some antibiotics
Surface area	This has no direct effect on elimination

Fig. 1.14 Antibiotic elimination in patients receiving CRRT. *The most important elements*

Drug data		
Antibiotic assayed	Specified target concentration	Dose recommendation

Patient demographics					
Age	Weight	Severity of illness	Number of patients in study	Residual renal function	Hepatic function

Basic pharmacokinetics		
Volume of distribution (V_d)	Total, CRRT and non-CRRT clearance	Protein binding/serum albumin

CRRT clearance			
Membrane type/surface area			
CVVH		CVVHD	CVVHDF
Pre-dilution	Post-dilution		
S_c Ultrafiltration rate (Q_f) Blood flow (Q_d) Haematocrit (HCT) Predilution replacement rate (Q_{rep})	S_c Ultrafiltration rate (Q_f)	S_d Dialysate rate (Q_d)	S_c/S_d Ultrafiltration rate (Q_f) and Dialysate rate (Q_d) or Effluent rate ($Q_f + Q_d$)

Fig. 1.15 Pharmacokinetic parameters required for antibiotic dosage modification in patients receiving CRRT (Reprinted with permission from: Li et al. [78])

techniques is determined by its molecular weight, protein binding, and volume of distribution [80]. Extracorporeal clearance is determined by the technique used, composition and surface area of the filter membrane, as well as by effluent blood and dialysate flow. In diffusive techniques such as hemodialysis, clearance depends on blood flow and rate of diffusion. In convective techniques, water and solutes pass through the filter membrane down a pressure gradient, and replacement fluid is added either before (pre-dilution) or after the filter (post-dilution). The ability of drugs to pass through the membrane is characterized by the "sieving coefficient," which is determined by protein binding [81]. In post-dilution mode, clearance equals the

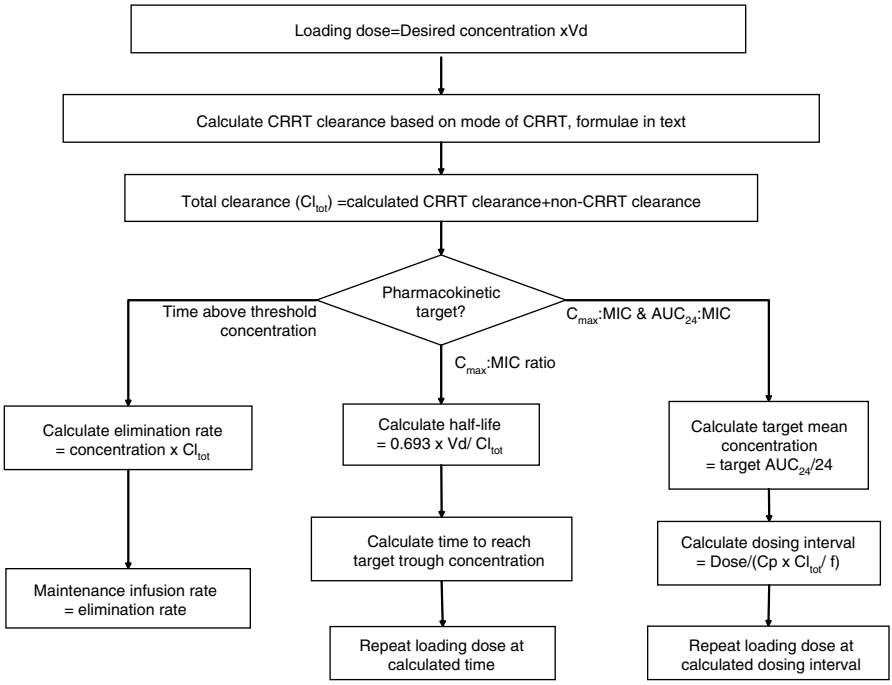

Fig. 1.16 Calculation of intravenous antibacterial doses based on first principles. Noncontinuous renal replacement therapy clearance is the sum of nonrenal clearance plus residual renal clearance. *Cltot* total clearance, C_{max} maximum postdistribution plasma concentration, *MIC* minimum inhibitory concentration, *AUC24* area under concentration-time curve over 24 h, *Vd* volume of distribution, C_p target plasma concentration (Reprinted with permission from: Li et al. [78])

effluent flow multiplied by "sieving coefficient," obtaining a maximum of 3 l/h or 50 mL/min. Since clearance is limited by the blood flow in diffusive techniques and by the effluent flow in convective techniques, much higher small-solute clearances can be reached with diffusive techniques. Even in SLED, small solute clearance is higher than in convective techniques as CVVH [82]. If an antibiotic is effective, it depends on the type of action. For time-dependent antibiotics, the optimal "killing" of bacteria is achieved by maximum amount of time over the MIC. As the volume of distribution in critically ill patients is often increased, it is recommended an increased loading dose. In order to keep the serum level above the MIC, continuous infusion is recommended for beta lactams such as meropenem and piperacillin and for glycopeptides such as vancomycin [83]. For vancomycin, an area under the concentration over time curve that exceeds 400 times the MIC or post-filter levels that exceed 10–15 mg/L is recommended. Dosing of antibiotics in critically ill patients treated with RRT remains difficult because of the great number of variables that influence the pharmacokinetics, and it should be individualized [84, 85] The clinical effectiveness of treatment with beta lactams and glycopeptides can be improved by using a normal or elevated loading dose followed by continuous infusion. CRRT has been

universally considered as a preferred treatment for AKI and for fluid overload, since it was first described [86]. CRRT has been studied from many angles and its usage has become routine. Generally, it has done a good job of designing an effective system to control azotemia, balancing electrolytes and removing fluids. In treating critically ill patients with CRRT and other RRT, clinicians are cautious in antibiotic dosing. Most antibiotics are filtered by the kidney, and dosage reduction is required in renal disease to prevent drug and metabolite accumulation. Many of these agents are nephrotoxic and the possibility that AKI could worsen should be considered. The combination of very efficient RRT and concerns about giving excessive doses led to an unintended side effect of antibiotic underdosing in many patients receiving CRRT. Sepsis is a common cause of AKI in critically ill patients, with 70 % of those requiring RRT [87]. Adequate antibiotic dosing is essential to minimize the morbidity and mortality of sepsis, but is very challenging due to the complexity associated with underlying diseases and their unpredictable impact on pharmacokinetic properties of drugs. Variance in RRT modalities and regimens and a discrepancy between prescribed and delivered RRT regimens complicate the issue. No prospectively validated guidelines exist to aid antibiotic dosing. Clinicians frequently consult renal dosing references or software programs for help. However, these recommended doses are often based on in vitro studies, case reports, or very small clinical pharmacokinetic trials often using obsolete CRRT technologies or techniques.

The degree or characteristics of pharmacokinetic alteration in critically ill patients with AKI are not the same as those with ESRD. Patients with AKI may exhibit relatively higher nonrenal clearance which can significantly remove several antibiotics including imipenem, meropenem, and vancomycin [55, 88, 89]. Patients with AKI may require a higher antibiotic dosage than those with ESRD.

The usage of "one-size-fit-all" dosing strategy, regardless of body mass, carry "bias" due to lack of integration of the variability in body sizes and body fluid compositions of patients. Patients with AKI often exhibit a larger drug volume of distribution due to sepsis, fluid overload, and obesity. Increased body mass index is reported as a significant risk factor of antibiotic therapy failure [90]. It may be prudent to use weight-based dosing regimens in cases where a patient's body size and fluid composition vary from the normal ranges. Evidence of an association between initially low serum antibiotic concentrations and suboptimal antibiotic therapy and a decrease in pathogen susceptibility suggest the necessity of early attainment of pharmacodynamic goals [91, 92]. In contrast to our current relatively cautious antibiotic dosing practices in patients with AKI, higher antibiotic dosing may be necessary to reduce the incidence of antibiotic resistance. Regarding constant extracorporeal drug removal via CRRT and altered pharmacokinetics, very large initial doses may be needed to maximize therapeutic efficacy. Utilization of a loading dose may be beneficial not only in antibiotics with concentration-dependent killing to achieve a higher initial peak but also those with time-dependent killing to allow target serum concentration to be reached as early as possible.

Adequate concentrations in the serum should not be interpreted as an equivalent concentration at the actual sites of infection which mostly occurs in tissues. Impaired tissue penetration caused by altered pathophysiology and transporter activity in this

population may result in a subtherapeutic infection site concentration despite a therapeutic serum concentration [93–96]. The influence of RRT dose intensity must be taken into account when designing an antibiotic dosing regimen. In the past ten years, the most common CRRT debate has been about CRRT dose intensity. It was suggested that high volume CVVH was superior to lower doses [97]. Very large trials [98–100] found that patient outcomes did not differ between more aggressive and less aggressive CRRT. The nephrology and critical care community appear to have embraced this view, and guidelines have been published that recommend relatively low-intensity CRRT [101]. However, the study designs of the trials comparing high- and low-intensity CRRT had one common flaw: patients in both CRRT groups received the same antibiotic doses [102]. If appropriate antibiotic dosing and antibiotic exposure is important in septic patient outcomes [103], it should suggest that patient outcomes with high-intensity CRRT were not inferior to low-intensity CRR, if antibiotic serum concentrations/antibiotic exposure was kept equal between the two groups.

In summary, for antibiotic therapy in critically ill patients receiving CRRT, clinicians have to start from concepts regarding pharmacokinetic differences between different antibiotics and pathophysiologic changes in the course of critical illness and their mutual interactions. For antibiotics that have multiple elimination pathways, the presence of acute renal failure appears to cause an increased of nonrenal excretion pathways leading to a lower antibiotic concentration than that expected. Knowledge of the pharmacokinetic characteristics of an antibiotic may help predict changes in antibiotic concentration in different clinical scenarios. CRRT enhances the elimination of antibiotics, and so this effect must be considered and the dosing regimen adjusted in order to ensure proper antibiotic effect. Key points that should always be considered [104–106]:

1. CRRT different types and technical setting (in particular effluent production rate) and CRRT duration (on time-off time).
2. CRRT prescribed dosing: important predictor of antibiotic clearance. In critically ill patients undergoing CRRT, effluent flow rate correlates with extracorporeal clearance for beta lactam antibiotics, piperacillin, and vancomycin.
3. Antibiotic-loading dose closely related to volume of distribution measurement and concentration desired, linked to the killing characteristics of different antibiotics and pharmacokinetic goals associated with the optimal killing of bacteria.
4. Antibiotic maintenance dosing linked to antibiotic clearance (non-CRRT and CRRT).
5. Patient's morphological characteristics (due to obesity).
6. Site infections (deep site infections).
7. Sensitivity degree of bacteria.
8. Overdosing risks (costs and toxicity problems) [107].
9. Underdosing risks which showed to be prevalent in ill critical patients.

While waiting for more robust guidelines which take into account variation of each parameters, as well as CRRT setting and different types generated by large

multicenter studies, clinicians may use flowchart dosing, such as those proposed by Choi's group, or, if possible, by measuring antibiotic concentrations using therapeutic drug monitoring (TDM). The feasible TDM is harder for some antibiotics than others (beta-lactam), but it remains the only way to know for sure if a patient has therapeutic exposures to prescribed antibiotic, and if intervention is required to optimize treatment of critically ill patients with a severe infection, severe sepsis, or septic shock.

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Video Laryngoscope: A Review of the Literature

2

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2.1 Introduction

Orotracheal intubation is the gold standard technique to secure the airways during general anesthesia, in the intensive care unit and in the often hostile prehospital setting. Major complications during airway management are mainly due to inability to secure or maintain the airways, because of an unexpected difficult tracheal intubation, an esophageal intubation, gastric aspiration, and/or iatrogenic trauma of the upper airways [1]. According to one of the most recent observational studies, difficult endotracheal intubation or problematic airway management may be not infrequent. Severe complications are reported to be close to 1/22,000, while death or brain damage occurs in 1:150,000 [2]; these complications are the main cause of anesthesia-related injury, possibly leading to major morbidity and mortality [3]. Large part of the perioperative adverse events associated with a problematic airway management occur to healthy individuals undergoing elective surgery under general anesthesia. Obesity and upper airway obstruction are since long-recognized risk factors for difficult airways, accounting by themselves for approximately 80 % of major complications. In "cannot ventilate and cannot intubate" situations, reiterations of attempts before changing strategy or considering alternative devices are associated with poor outcomes such as death and brain damage [2, 3]. Prediction of a difficult airway management is sometimes unreliable, being at best an inexact science, with poor sensitivity and specificity. Bedside predictors of difficulty are thyromental distance, sternomental distance, mouth opening, or a combination of tests and the laryngeal view obtained. Mallampati and more recently and perhaps more precisely El Ganzouri classifications can be used to predict difficult intubation [4]. Difficult glottic vision during intubation attempts is more

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frequent in emergency situations and in the critical care setting than during general anesthesia (grade III Cormack & Lehane: 13 % in emergency vs 5 % in general anesthesia; grade IV Cormack–Lehane 7 % vs 1 %, respectively) [2]. After the introduction in the early 1940s of Miller (1941) and Macintosh (1943), straight and curved laryngoscope blades to ease direct laryngoscopy, laryngoscopes (LA) remained largely unchanged for more than 50 years. With the development of rigid fiber-optic laryngoscopes – the first generation of video laryngoscopes – clinicians benefited from advances such as eyepieces that could be attached to optional video cameras. Rigid fiber-optic laryngoscopes placed the observer's eye close to but above the glottis, allowing a controlled insertion and advancement of an endotracheal tube between the vocal cords. Flexible bronchoscopic intubation in case of intrahospital difficult airway management is today the standard method; this technique, however, requires adequate training and a routine use to be effective. In recent years the development of digital photographic and video techniques has led to video laryngoscopes (VDLs). These devices offer an improved (and shared) indirect view of the glottis on a remote or built-in video screen. A handle and a blade are the components of both LA and VDL, the latter having a fiber-optic or microvideo camera encased close to the end of the blade. The particular shape of the curve blade allows a wider viewing angle, making oral pharyngeal and tracheal axes alignment unnecessary, optical alignment being achieved by the video camera. According to Donati et al., VDLs are generally classified in three groups: (1) standard or Macintosh blade type, (2) angulated blade type, and (3) anatomically shaped with a guide channel [5]. The majority of these devices use a digital camera on the tip of a standard Macintosh or Miller laryngoscope blade providing the indirect visualization of the glottis on a video display (C-MAC, GlideScope, McGrath, Pentax Airway Scope). Less frequent is the use of fiber-optic cables connected to a display (Airtraq). Video laryngoscopes lack the versatility of flexible bronchoscopic intubation (FBI), but are more easy to use, less fragile, and provide a supraglottic vantage point. Learning curve, however, is not as short as proposed by someone.

2.2 Video Laryngoscopes

Among the current devices available on the market, the most widely (but not only!!) used options for video laryngoscopy are:

- GlideScope (GVL, Verathon)
- Video laryngoscope McGrath (Aircraft Medical) (Series 5 e MAC)
- Video laryngoscopes Storz (C-MAC, V- MAC and Storz D-Blade)
- Pentax Airway Scope
- Airtraq optical laryngoscope

VDL *GlideScope*, *McGrath Series 5*, and *Storz C-MAC D-Blade* have more angulated blades, characterized by a sharper upward curve, approximating 60° degrees upward. This angle is wider when compared with the traditional Macintosh

blade, allowing better glottic view with less cervical manipulation. With these devices, direct visualization is usually not possible. In case of reduced mouth opening or ogival palate, despite a good glottic view, tube delivery to the glottis might be, in spite of the good laryngeal exposure, the most difficult part of the manipulation. As a matter of fact, the orotracheal tube might be pushed downward and posteriorly, making esophageal intubation more than probable: in these cases the tube, mounted on a preshaped 60° (or more) angled stylet, has to be introduced following the particular angulated curved shape of the blade; the stylet, shaped to match the blade's curvature, has a pivotal role in reducing this potential inconvenience [6]. Frova stylet has been successfully used by one of the authors, and some case reports support this practice. Sometimes rotation of the tube is required.

The blades of the *Storz C*, *C-MAC*, *V-MAC*, *and McGrath MAC* are similar to the conventional Macintosh blades, the difference being a video camera mounted at the end of the blade. The glottis can be visualized directly or on the video and therefore is often possible to intubate without a stylet. The reduced upward deflection makes the glottic view more dependent on the wide-angle camera than its upward orientation, and often external laryngeal pressure may be required.

Finally, the VDL *Pentax* AWS and *Airtraq*, which use an optical system to provide the glottic view, have a guide channel in the blade to direct the tube toward the glottis and within the vocal cords. These devices have the video embedded in their handle. The endotracheal tube is lubricated and loaded into the tube channel on the side of the blade. The tube should be positioned in order to have the tip of the tube out of view of the camera. The blade is inserted into the mouth in the midline and advanced over the tongue and along the palatal wall until the epiglottis is visualized. The tip of the blade is used to elevate the epiglottis to visualize the vocal cords: the glottis should be placed in the center of the video to ease the insertion of the tube via the side channel.

2.2.1 GlideScope Verathon

The VDL GlideScope has been designed by Pacey in Canada in 1997. The original GlideScope is reusable and has nondetachable curved blade, a handle, LCD monitor, and a camera. On the tip of the blade is embedded a video camera connected to a separated monitor through an external cable. Energy support is guaranteed by a rechargeable battery. It has a curved blade with a 60° angulation up from the horizontal line. The camera is located in the midline at the bottom of the blade. The GlideScope camera incorporates an integrated antifog system. The curved blade is introduced from the middle rather than the angle of the mouth without a tongue sweep. Once inserted completely, the blade tip is placed in the vallecula, and an optimized view places the laryngeal inlet lying centrally in the upper third of the display. The endotracheal tube stylet requires a 90° bend just proximal to the cuff in order to follow the shape of the airway. In a randomized study on surgical patients intubated with GlideScope in operating room (OR), a 90° angle resulted in the best time to intubation and an easier intubation as compared with 60°. The caliber of the endotracheal tube did not affect the time of intubation [7]. Once inserted through the

vocal cords, the stylet has to be partially withdrawn to allow the endotracheal tube to be advanced into the trachea. The tubes sometimes have to be gently rotated. This step can be challenging, and the manufacturer provides a custom-made rigid stylet to facilitate this action. According to a retrospective study of 473 emergency department intubations, the use of the custom-made rigid stylet is associated with higher rates of successful intubation, both at the first attempt and overall [8]. This is in contrast to an operating room report in which the GlideScope stylet and a standard malleable stylet were found to be equally effective when used by experienced anesthesiologists [9]. We suggest the use of rigid stylet in case of difficult airways, particularly in case of reduced mouth opening: maximal attention has to be always paid in order to avoid soft tissue damage and airway injuries. GlideScope is currently available in three models. The original GlideScope has a reusable video laryngoscope and separate mounted video screen.

- The GlideScope Cobalt system provides a single-use option. The Cobalt system relies upon a small video baton that fits into a disposable plastic laryngoscope blade. This eliminated the need for sterilization and minimizes the risk of equipment damage or loss.
- GlideScope Ranger and Ranger Single Use are a handheld version, with the video laryngoscope connected by a short wire to a durable (90 min) battery-operated screen. The system has been ideated for the prehospital use and incorporates a 3.4-in. antireflective screen, designed for outdoor use in daylight conditions. The device has storage capacity of 60 min of video.

Reusable blades for use with the original GlideScope are available in sizes 2, 3, 4, and 5, with a maximum height of 14.5 mm. The newer GlideScope Cobalt comprises a video baton (available in two sizes) with disposable blades called "stats." These "stats" range in size from 0 to 4 and are bulkier than the reusable blades with a maximum height of 16 mm at the mouth, comparing favorably to the height of a Macintosh laryngoscope, which is approximately 25 mm thick. Pediatric blades require a smaller video baton. Anesthesia literature suggests the GlideScope and Storz C-MAC D-Blade provide a better view of the glottis than direct laryngoscopy, require less time to intubation, and lead to higher rates of successful intubation.

2.2.2 McGrath Aircraft Medical, UK

Introduced into clinical practice in 2008, the McGrath Series 5 consists of three basic components: handle, camera stick, and single-use angulated blade (60°). Blades are available in sizes equivalent to Macintosh sizes 3, 4, and 5. The length of the camera stick and the docked blade can be further adjusted by disarticulating the camera and inserting it inside the blade to three different positions. The maximum height of the blade is 13 mm, allowing the insertion in case of reduced mouth opening. The video display is mounted on the handle and can be rotated through 90° in both the horizontal and vertical planes, allowing the operator to simultaneously focus on the video display and the patient. In the last version (MAC), on the handle

is mounted a clock to count the time left to the battery expiration. There is no antifog system, and the manufacturer recommends separate application of antifog solution prior to use, which may be disadvantageous when used in an emergency situation. The device lacks the ability to record or store images.

McGrath Series 5 can be used in children weighing more than 15 kg. Due to the small size and the light weight, this device is very easy to be handled and to be transported. The blade can be inserted in the mouth before the handle connection; this operation can ease the intubation in obese and obstetric patients. Stylet use is strongly suggested; Truflex stylet has also been successfully used. One of the authors used Frova and the custom-made GlideScope rigid stylet. McGrath MAC is similar to Series 5 (although the performance is lower) and is connected to Macintosh standard blades, allowing direct laryngoscopy together with video laryngoscopy. In a randomized simulated study on manikins, McGrath Series 5 had a better performance compared to flexible fiber optic endoscopy in terms of time to intubation. The authors suggested the introduction of video laryngoscopy in difficult intubation algorithms [10].

2.2.3 C-MAC: Storz

Introduced into clinical practice in 2009, the Storz C-MAC has three Macintosh-style blade options (sizes 2–4) and more recently a Miller-style blade, usable with either a video display or a video screen mounted on the laryngoscope handle. The reusable blades are only 14 mm thick and useful for patients with limited mouth opening. The 80° angle allows a very wide view, enhanced by an integrated white balance and antifogging system. There is also the possibility to record static images or 60 min of video onto a digital card. Rechargeable lithium-ion batteries allow a recording time of approximately 2 h. The compact, ergonomically designed monitor can be used in a protective bag, without the need to be removed. Due to its compact size, light weight, and simple handling, the CcC- MAC could be considered for prehospital use as it fits in all ambulances and rescue helicopters. Interestingly, C-MAC video laryngoscope uses standard Macintosh or Miller blades, allowing two approaches to visualize the glottis: first, the direct view of the glottis and, second, an indirect view by means of a miniature camera on the screen of the monitoring unit. The C-MAC Macintosh-style blade is inserted into the mouth similar to a conventional laryngoscope. The new component for the C-MAC system – the D-Blade – has an elliptically tapered blade shape rising to distal with a 60° angle. The lateral guide on the D-Blade for large suction catheters emphasizes its application in emergency medical care and trauma management.

2.2.4 Airway Scope Pentax

The device comprises a handle (housing a built-in charge-coupled device camera and a light-emitting diode attached to the tip of the scope) and a disposable blade. Powered by two batteries lasting 1 h, the image is displayed on a monitor built into the top of the handgrip. A single-use rigid blade (P-blade) protects the video system

from oral contamination and has two side grooves where the tracheal tube (inside diameter between 6.0 and 8.5 mm) and suction catheter (<12 French) are preloaded. The P-blade has only one size, which accommodates endotracheal tubes up to size 8 and can be therefore use for pediatric patients. The Pentax AWS is slightly bulkier than other video laryngoscopes being 18 mm at its maximum height, necessitating adequate patient mouth opening for this device to be useful.

To prepare the Pentax, the P-blade is attached, and the endotracheal tube is loaded into the tube channel on the side of the blade. The blade is inserted into the mouth in the midline and advanced over the tongue and along the palatal wall until the epiglottis is visualized. The target symbol on the video display should be aligned with the glottis and the tube advanced through the vocal cords before being detached from the blade laterally.

2.2.5 King Vision Ambu

The King Vision video laryngoscope has been studied to be a less expensive alternative to the other devices. The King Vision is a two-piece design. It has a reusable monitor that attaches to disposable blades. The blades are all Macintosh nr 3 size, and compared to a normal Macintosh nr 3-bladed laryngoscope, the King Vision blades appear wider and shorter. There are blades with a guiding channel and standard blades without.

2.2.6 Optical Laryngoscope Airtraq Airtraq

Airtraq is a single-use laryngoscope. At the tip of the blade, there is a light source that incorporates an antifog system. The device has a battery lasting 90 min. The blade has two channels: one allows preloading the endotracheal tube; the other one is the optical system composed of lenses and prisms. The optical system produces an image that can be visualized in the eyepiece or connected to an external video display. The Airtraq is available in different versions, blades are only of two sizes (a small and a regular), allowing 6.0–7.5 and 7.0–8.5 mm endotracheal tubes. The endotracheal tube should be lubricated before being loaded in the channel. The blade is inserted in the mouth in the midline over the tongue and the tip of the Airtraq should be placed in the vallecula. The tube is then advanced in the trachea and the Airtraq disconnected from the endotracheal tube with a lateral movement. The optical system is reusable, the blades disposable.

2.3 The Video Laryngoscope in Emergency Medicine and Prehospital Setting

Successful and rapid airway management is relevant in the emergency setting and in life-threatening situations. According to a prospective study dealing with prehospital airway management, there was significantly higher incidence of Cormack–Lehane

grade III and IV laryngeal views and multiple and failed tracheal intubation attempts compared to elective anesthesia. Causes included suboptimal patient positioning and difficult laryngoscopy. An appropriate and favorable positioning of the patient for direct laryngoscopy appears to be an important issue in prehospital management [11]. Moreover, emergency intubation (in and out of hospital) is associated with higher rate of complications such as gastric aspiration, secretions, and esophageal intubation as compared with elective anesthesia. In one study on patients with major trauma, esophageal intubation or inability to correctly intubate the patient was not associated with higher mortality: this could support the use of bag-valve-mask as an adequate method of airway management for critically ill trauma patients in whom intubation cannot be achieved promptly in the prehospital setting [12]. Emergency intubation has in any case, an extremely high success rate (above 97 %) and a very low rate of delayed complications [13–15]. In a systematic retrospective review on more than 30 studies, the overall incidence of difficult intubation was 5.8 % and a Cormack–Lehane grade >2 ranged between 1 and 9 % of the intubation attempts [16, 17]. In a very recent randomized study on 692 patients, difficult intubation in prehospital emergency was 3.2 % [15]. Few rigorous randomized trials have been performed to assess the performance of VDLs in emergency airway management. Nevertheless, based upon our clinical experience and available data, we believe these devices are highly effective and can help emergency clinicians and other emergency airway managers maximize first-pass intubation success in both routine and difficult airway scenarios. Sackels et al. in 2012 demonstrated that the C-MAC was associated with a greater proportion of successful intubations and a greater proportion of Cormack–Lehane grade I or II views compared with direct laryngoscopy [18]. In this study, performed on 750 patients in emergency department, the use of video laryngoscope was associated with lower rate of immediately recognized esophageal intubation. Kory et al. [19] compared video laryngoscopy with direct laryngoscopy during emergency intubation performed by less experienced operators, demonstrating higher rate of first-attempt success using video laryngoscopy (91 % vs 68 %) and a lower rate of intubations requiring ≥3 attempts (4 % vs 20 %). The use of video laryngoscopy (Airtraq, GlideScope, McGrath) during simulated difficult airway (tongue edema, pharyngeal obstruction, cervical spine immobilization) provides better glottic view and higher intubation rates when compared with direct laryngoscopy [20]. Multiple controlled and prospective observational studies report that VDLs as a class provide superior views of the glottis compared with direct laryngoscopy [21–25]. In the prehospital setting, C-MAC video laryngoscope had a good performance in 80 patients: this device allowed to perform direct laryngoscopy and video laryngoscopy at the same time, option that seems to be a useful opportunity during extrahospital intubation [26]. According to a meta-analysis of nine trials involving 2133 patients requiring tracheal intubation in the intensive care unit, video laryngoscopy reduced the rate of difficult intubation, Cormack–Lehane grade III–IV, while increased the rate of first-attempt success, a factor associated with reduced complication rate compared to standard direct laryngoscopy [27]. Nevertheless, no statistically significant difference was found for severe hypoxemia, severe cardiovascular collapse, or airway injury. In one study Silverberg et al. reported a first-attempt success of 74 % using GlideScope video laryngoscopy compared with 40 % using direct laryngoscopy [28].

There was no significant difference in rates of complications (esophageal intubations, aspiration events, desaturation, and hypotension) between direct laryngoscopy and GlideScope video laryngoscopy. Goldman et al. reported that the use of video laryngoscopy during rapid sequence induction did not affect the time of intubation and improve the glottis visualization [29]. A meta-analysis of 12 small randomized trials (1061 patients) comparing the Airtraq with a standard Macintosh laryngoscope found a reduced time required for intubation (15 s less) in the Airtraq group, increased first-pass intubation success rates among novice airway managers, and a reduced incidence of esophageal intubation [29, 30]. Individual studies noted that the use of Airtraq led to reduced cervical spine motion and less change in heart rate compared with direct laryngoscopy [31]. The use of video laryngoscopes for ICU patients requiring tube exchange has recently been described [32]. Tracheal tube exchange via an airway exchange catheter is commonly combined with conventional laryngoscopy to assist intubation of the trachea. Video laryngoscopes were used in conjunction with an airway exchange catheter if high-grade Cormack–Lehane was evident with conventional direct laryngoscopy. The use of the video laryngoscope in these situations improved glottic exposition in the majority of cases. Video laryngoscopes have been also used during extubation, in case of problematic intubation or extubation. The main advantage appears to be the better visualization of the larynx even with the cervical spine fully extended. More, it allows tube positioning view on the screen to both the tutor and the operator [33].

2.4 Video Laryngoscopy in Patients with Unsecured Cervical Spine

Several studies investigated the potential benefits of video laryngoscopy to minimize cervical spine motion during intubation [31, 34–38]. Two studies compared the GlideScope with traditional direct laryngoscopy using fluoroscopic video. GlideScope did not reduce significantly segmental C-spine motion but provided a better glottis visualization during in-line stabilization [31, 35]. In one study on 22 patients, orotracheal intubation with McGrath provided less C3–C4 cervical spine motion and improved visualization of the vocal cords, without causing adverse consequences as compared with Macintosh laryngoscope [36]. In patients requiring cervical spine immobilization, the use of Pentax Airway Scope has been shown to improve laryngeal view, time to intubation, and success rate [37, 38]. Individual studies noted that the use of the Airtraq led to reduced cervical spine motion and less change in heart rate compared with DL using a Macintosh laryngoscope [39–42].

2.5 Video Laryngoscopy in Anesthesia

According to the American Society of Anesthesiology (ASA), anesthesia-related injury is often caused by difficult tracheal intubation and difficult mask ventilation [1]. Incidence of difficult intubation ranges between 1.15 and 3.8 % during elective

anesthesia. In Europe, unanticipated difficult airways occur in 1.9 % of the intubations [43]. Unanticipated difficult airways are dreaded among anesthesiologists, and difficult tracheal intubation and difficult mask ventilation can cause serious patient complications. Better prediction of difficult airways may reduce morbidity and mortality by allocating in advance experienced personnel and an appropriate equipment. The use of video laryngoscopy during general anesthesia has been investigated by several studies. However it should be emphasize that although the glottic visualization is improved using indirect laryngoscopy, the time for intubation is often longer, and the intubation success rate is not always and automatically improved. For this reason, the routine use of video laryngoscopy in patients without predictable difficult laryngoscopy is not recommended as yet. This item is, however, under an ongoing hot debate. There is no agreement in the literature on glottis visualization. Video laryngoscopy usually implies a very good to excellent visualization of the glottis: in one study on 867 patients, Kaplan et al. showed an improved view of the larynx using video laryngoscopy compared with direct visualization [44]. In several studies GlideScope was superior to Macintosh blade, improving the glottic view by one or two Cormack–Lehane grades [45, 46]. In one study comparing McGrath video laryngoscope with direct laryngoscopy, no differences were reported in the visualization of the glottis, confirming no advantages for the use of the McGrath laryngoscope for uncomplicated tracheal intubation [47]. In contrast, recently Laosuwan et al. were able to document a better glottis visualization using McGrath video laryngoscope [36]. The Pentax Airway Scope (AWS-S100) offers an excellent glottic exposure and less potential for dental trauma than the conventional Macintosh blade [48–52]. Studies reported a superior glottic view (Cormack–Lehane grade I or II) as compared with conventional laryngoscopy (Cormack–Lehane grade III or IV) [49, 52]. Observational and randomized trials suggest that during general anesthesia Storz V-Mac provides better glottic views and higher first-pass success rates for intubation when compared with direct laryngoscopy [53, 54]. With respect to direct laryngoscopy, the time to intubation is often prolonged using video laryngoscopy [51, 55]. Recently, Yao et al. reported that the use of McGrath Series 5 video laryngoscope provided more Cormack–Lehane grade I views but a longer mean intubation time [56]. In this trial the authors described a better glottic view using video laryngoscopy when Cormack–Lehane was IIb or higher under direct laryngoscopy. In these cases intubation success rate was almost 95 %, thus confirming the indication of VDL for the more difficult conditions. In another randomized trial which enrolled 130 patients undergoing elective surgery with anticipated difficult airways (Mallampati score $\geq$3), intubation using the Storz C-MAC was faster and with a first-attempt higher success rates compared with intubation performed with the McGrath video laryngoscope [57]. Remarkably, there was no correlation between the first-pass success and the glottic view, improved by the use of McGrath. Nevertheless, we believe that the use of an appropriate stylet (and perhaps correct manipulations of the tube) may play a role in such a setting. In fact, in a randomized trial in surgical patients with anticipated difficult airway, the use of flexible fibroscopy or McGrath Series 5 did not change the intubation time and the first-attempt success rate [58]. Randomized and observational studies explored the use of video

laryngoscopy as "rescue" device in unpredicted difficult airways. In one study in 270 patients with difficult direct laryngoscopy, Asai et al. could successfully intubate 268 patients using Pentax AWS video laryngoscope [49]. Similarly using C-MAC video laryngoscope, Piepho et al. intubated 49 of 52 patients with Cormack–Lehane grade III under conventional laryngoscopy [59]. In difficult airway scenarios, GlideScope, Airtraq, and McGrath Series 5 were demonstrated to be superior to direct laryngoscopy in securing the airway [60–64]. Video-assisted laryngoscopy (VAL) has been considered in the most recent edition of ASA practice guidelines for the management of the difficult airway [1]. According to the results coming from meta-analysis of RCTs, in patients with predicted (or simulated) difficult airways, VAL, when compared with conventional direct laryngoscopy, showed improved laryngeal views, higher frequency of successful intubations, and higher frequency of first-attempt intubations (A1-B evidence). Among the recommended strategies for intubation, VAL is considered as a possible initial approach. At variance of other reports, no differences in time to intubation, airway, dental, or soft tissue trauma were reported (A1-E evidence). Evidence exists, however, of possible airway injuries during intubation with video-assisted laryngoscopy (B3/B4-H evidence). *Our conclusion is that both in anticipated and unpredicted difficult airway scenarios, the need and relevance of video laryngoscopy are now supported by the literature (and, as we will see, by the 2015 new guidelines). Under hot debate is instead the use of VAL as an alternative to DL in routine practice with normal (or reputed normal) airways.*

2.6 Video Laryngoscope in the Obstetric Patient

Mortality following cesarean delivery is reported to be 12/1,000,000 patients: 80 % is attributable to difficult airway management [65]. The incidence of failed intubation did not decrease in the last 20 years despite advances in airway techniques. Age, body mass index, and Mallampati score are independent predictors of failed tracheal intubation [66]. The use of video laryngoscopy in obstetrics is limited. Schonfeld et al. reported good performance of the video laryngoscope C-MAC in 27 patients [67]. In 80 obstetric patients undergoing planned cesarean section, the use of McGrath video laryngoscope, while prolonging the time to intubation, provided a higher rate of good glottic view. Remarkably, however, a better glottic view did not influence the rate of successful intubation [68]. When used in the obstetric patient with anticipated difficult airway, three case reports support the use of video laryngoscopy as a first choice [69–71]. In November 2015 the most recent guideline on difficult and failed intubation in obstetrics was released [106]: the availability of video laryngoscope in the obstetric setting is more than advised. Even if no comparative studies are available, VDLs (as an alternative to direct laryngoscopy) and supraglottic devices are considered in case of second attempt, failed intubation, and poor glottic view. Risk of trauma has always to be considered, when stylets or bougie is used. Failed intubation is declared in case of three failed attempts (the third by the more experienced anesthetist available). The master algorithm reported in the

guideline includes steps in case of failed intubation and in case of CICO (the acronym for "cannot intubate/cannot oxygenate"). However in the editorial following the guidelines (GLs), the role of VDLs in problematic airways during cesarean section is, in our opinion, still in a gray zone [105]. In our opinion, a video laryngoscope should always be available in the obstetric area.

2.7 Video Laryngoscopy and the Obese Patients

The several physiological and anatomical changes present in obese patients are to be known for an appropriate airway management. Morbidly obese patients have increased airway resistance, reduced chest wall elasticity, and abnormally elevated diaphragm. Obesity alters upper airway anatomy. Increased fat deposition in pharyngeal tissues increases the likelihood of pharyngeal wall collapse, which can complicate the performance of intubation. Such patients may have a poor view of the glottis despite optimal laryngoscopic technique due to reduced neck mobility and augmented thoracic circumference. In addition, short, thick necks may limit mobility and make it difficult to place the patient in the optimal sniffing position (ramping position is advised). Morbidly obese patients often have a large neck circumference that necessitates special positioning for intubation and reduced posterior airway space that could lead to improper mask ventilation. Body mass index (BMI) is correlated with the incidence of difficult intubation, being 1.24 times higher with BMI between 25 and 35 kg/m^2 and 1.42 times if BMI exceeds 35 kg/m^2 [72]. In 86 morbidly patients, the use of C-MAC Storz video laryngoscope improved the glottic view when compared with direct laryngoscopy [73]. Maassen et al. randomly selected 150 consecutive adult morbidly obese patients (body mass index >35 kg/m^2) for intubation with GlideScope, Storz V-Mac, and McGrath video laryngoscope: the patient who underwent intubation using Storz V-Mac had lower intubation time, lower number of intubation attempts, and lower necessity of extra adjuncts [74]. In 2012, a pilot study in 50 morbidly obese (BMI $\geq$40 kg m^{-2}) did not find any statistically significant differences in time to optimal view of the glottis, time of intubation, or number of attempts comparing C-MAC with C-MAC D-Blade [75]. Airtraq optical laryngoscope had a good performance in obese patients [76, 77]. In 2010 Pelosi and Gregoretti recommended the routine use of video laryngoscopic technique in morbidly obese patients [78].

2.8 Video Laryngoscopy in Awake Intubation

Awake intubation is the gold standard for anticipated difficult airway [1]. Rosenstock et al. compared the use of flexible fibroscopy with video laryngoscopy for endotracheal intubation in awake patients with anticipated difficult airway [58]. The authors did not find any difference between the two devices in time to tracheal intubation and intubation success at the first attempt. Abdellatif et al. investigated GlideScope performance in obese patients with anticipated difficult airway as compared with

fiber-optic intubation reporting 75 % first-attempt success and 81 %, respectively [79]. According to a 2014 Cochrane Review, the best intubation technique in obese patients (BMI >30) has yet to be defined. In the small and very heterogeneous studies analyzed in the Cochrane, no differences were found between fiber-optic and video laryngoscopic techniques [80].

2.9 Video Laryngoscopy in the Pediatric Patient

Compared to adults, children have a more cephalad larynx, a relatively larger tongue, and a more limited mouth opening. Furthermore, the oxygen consumption in children is much higher than in adults, making shorter the time allowed for the intubation, if an oxygen source is not available during the procedure. For these reasons the unanticipated difficult airway management is a mandatory skill for pediatric anesthetists. In the setting of general anesthesia, difficult airways (Cormack–Lehane III or IV) occur in 1.35 % of intubations and in patients less than 1 year old; the incidence is higher than in older age (4.7 % vs 0.7 %) [81]. The use of VDL in pediatric patients, although attractive, remains controversial, and rigorous trials are scarce. Different VDL manufacturers (Airtraq, GlideScopepe, GlidesSope, Storz, McGrath) promote research in this field, and pediatric blades are now available. Few case reports described successful intubations using GlideScope [82, 83], Airtraq [84], or Storz [85] in pediatric patients. Nevertheless, in simulated scenarios using advanced infant simulator GlideScope did not improve intubation performance when compared with the standard laryngoscopy in normal and difficult airways [86, 87]. In one study on 134 children, glottic view GlideScope did not improve or worsen attempts when compared to direct laryngoscopy [88]. Su et al. in 2011 reviewed this topic in a meta-analysis on randomized trials in over thousand patients: VDL provided a better glottic view when compared with direct laryngoscopy with no differences in success intubation rate. In a subgroup of patients with anticipated difficult airways, VDL was associated with shorter time to secure a definitive airway [22]. A more recent meta-analysis reviewing 14 randomized trials reported different results [89]. Quite surprisingly, VDL improved the glottic view but prolonged time to intubation when compared with direct laryngoscopy, particularly if GlideScope and Storz were used. Although the success rate of the first attempt and associated complications were similar in both groups, VDLs were associated with a higher incidence of failure. In this analysis, only one study focused on patients with simulated difficult airway [90]: in 40 pediatric patients, direct laryngoscopy provided a higher performance (time to intubation and success rate) than VDL. Time to intubation is an important issue in children (20 s or less, as recommended), and the outcome of glottis visualization is less important than the outcome of time to intubation: good glottis visualization does not guarantee a rapid intubation. For these reasons *the use of video laryngoscope in pediatric patients is not recommended as yet. Very recently, guidelines for the difficult unanticipated airway in pediatric patients were made available* [93].

Finally, in the infant cardiac arrest scenario, the ability to intubate the trachea during uninterrupted chest compressions was not improved by the use of video

laryngoscopy, and the time to intubation was significantly longer with GlideScope than with the Miller laryngoscope [91]. Donoghue et al. reported similar findings [92]. On the other hand, in a recent study, paramedic performance and time to intubation during pediatric cardiopulmonary resuscitation was improved using GlideScope, McGrath, and Airtraq video laryngoscopes if compared to direct laryngoscopy [94]. A very recent Cochrane Review analyzing the use of video laryngoscope during neonatal resuscitation concludes that there is insufficient evidence to recommend or refute the use of video laryngoscopy for endotracheal intubation [95].

2.10 Discussion and Conclusions

According to the available experience, video laryngoscopy improves visualization of the glottis with a greater proportion of Cormack–Lehane grade I or II scores if compared with the traditional direct laryngoscopy using a conventional Macintosh blade. Although a better view of the glottis is obviously desirable, it does not necessarily imply that intubation will be completed at the first attempt in a timely manner. Indeed, the improvement in Cormack–Lehane grade does not necessarily translate into an overall reduction in the time to intubation and, more importantly, in a successful intubation. Despite an improved glottic view, endotracheal tube insertion may be problematic and may require longer intubation time, especially with angulated blade video laryngoscopes. For these reasons it is important to consider the following:

1. Each device has his specifications, user interfaces, efficacy, and safety aspects.
2. Video laryngoscopes expose to possible complications.
3. Each device has manufacturer recommendations, to be mandatorily known by the operator.
4. Each device has dedicated accessories such as custom-made rigid stylets that are not optional.

Video laryngoscopes do not seem to have advantages when used in patients with normal airway and good laryngeal view (Cormack–Lehane I and II), even if a debate has been recently opened on their use in normal airway [96]. In patients considered at high risk of difficult laryngoscopy, VDLs may have greater benefits. Evidence exists on the utility of video laryngoscopy as a rescue technique in anticipated/unanticipated problematic direct laryngoscopy, since “blind intubations” can be changed into intubations under glottic view. As proposed by Cooper, the best methods should be offered to all the patients and not only in case of predicted problematic intubation [97]. Video laryngoscopy allows the view of the maneuver and the glottis to other members of the anesthetic team: for didactic purposes, VAL enables the trainer to help the junior anesthetist while performing the intubation, easing the recognition of the anatomical structures, and directing every single maneuver, exactly knowing when the learner needs help and how the learner should be helped. The importance

of a better glottic view shared with other members of the anesthesia team was investigated by Loughnan et al. during rapid sequence induction with cricoid pressure and/or laryngeal manipulation. They showed that 41 % of views were improved when the assistant applying cricoid pressure could see the screen: 45 % were unchanged and 14 % were initially worse. Better tracheal manipulation by the assistant might be another positive result [98]. VAL can also offer the chance to record the intubation technique and store the video in an electronic file, as recently proposed by Zaouert et al. [99]. To make tracheal intubation even safer is a relevant issue: Zaouert et al. stated that no other anesthetic gesture is so important, as failure to intubate might lead to a life-threatening situation [99]. Whether or not video laryngoscopes will become the new standard for intubation is still a matter of hot debate (see letters, discussing the editorial of Zaouert et al.) [99]. Although video laryngoscopes can ease the approach to a difficult airway, an adequate mouth opening is still mandatory (at least 2.5 cm; in some cases successful intubation has been reported with mouth opening of 2 cm, using pediatric blades); good vocal cords view does not translate into intubation ("I see the aditus, but I can't pass the tube"; "I see but I fail to intubate"). The presence of blood or secretions in the airway can alter/obscure the view. Last but not least, the learning curve of the VDLs, by some advocated to be "smoother" than with the "old" laryngoscopes, could be even steeper [96]. This is a good reason in favor of maintaining, once acquired, the necessary knowledge and skill in the use of the new device(s). A recent review on the use of video laryngoscopes concluded that "the most convincing literature to date supports the use of video laryngoscopes in unanticipated, difficult or failed laryngoscopy. Several of these devices have a high intubation success rate in this clinical scenario" [99, 100]. The scenario, however, is rapidly changing. In November 2015, Difficult Airway Society (DAS) published in advance in British Journal of Anesthesia the new GL to manage unanticipated difficult intubation in adults, updating 2004 GL [102]. In NAP4, main contributors to poor outcome while managing unanticipated difficult intubation were deficiencies in preoperative assessment, communication, planning, equipment, and training [103]. An accurate preoperative airway assessment makes possible the identification of possible problems and the adoption of strategies and alternative plans: the aim is the reduction of risk of complications. Four alternative algorithms are proposed (Plan A to D). In Plan A of the matrix algorithm, the aim is to maximize the chance of successful intubation at the first attempt. No more than three attempts are suggested (the forth, if to be done, only by the most experienced anesthetist available, see algorithm and suggestions). Among the key features of Plan A is the recognized role of video laryngoscopy in difficult intubation and the privilege for all the anesthetists of a skilled use of the VDL [101]. To conclude, the role of video laryngoscopes in securing patients' airways is increasingly supported by evidence. However, according to the available literature, direct laryngoscopy remains the technique of reference in the OR and in the intrahospital and prehospital emergencies. This is why, at least up to now, skill and experience in direct laryngoscopy with "traditional" laryngoscopes are to be maintained. According to Kleine-Brueggeney and Theiler, "videolaringoscopes are to be considered additions, not replacements to our airway tool library" [104] (Table 2.1).

Table 2.1 Advantages and disadvantages of video laryngoscopy

Advantages	Disadvantages
Improvement in Cormack and Lehane grade I–II views	Many different models, with different characteristics and requirements for positioning blade and optimization maneuvers
Improved success of intubation at first attempt in predicted difficult airways	No comparative studies are available of which video laryngoscope is most appropriate in specific situations
Evidence of utility as a rescue technique in difficult direct laryngoscopy	Time to intubation may be longer
Usefulness as a teaching tool	Adequate mouth opening required
Advantageous in cervical spine pathology	Trauma to mucosa from styleted tubes
Reduced risk of dental trauma	Lack of knowledge of all factors making video laryngoscopy difficult or contraindicated

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Lung Ultrasound in the Critically Ill Patient

3

Davide Chiumello, Sara Froio, Andrea Colombo, and Silvia Coppola

3.1 Introduction

Lung ultrasound provides the opportunity of a whole-body approach for the evaluation of the critically ill patient, based on a combination of simple protocols. Therefore, it is a basic application, allowing assessment of urgent diagnoses in combination with immediate therapeutic decisions [1].

Many patients in the intensive care unit (ICU) can develop day-by-day lung and pleural diseases, such as interstitial syndrome, pneumonia, pleural effusion, and pneumothorax. Although computed tomography (CT) is useful to identify the most of pulmonary abnormalities, it requires transport of critically ill patients outside the ICU.

For many years, clinical examination and chest X-ray have been used at bedside to diagnose common clinical problems. However, mechanical ventilation and supine or semirecumbent positions represent limitations for the application of both clinical and radiological evaluations. Instead, lung ultrasound allows a bedside,

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noninvasive, and dynamic examination without the drawbacks of the radiological diagnostics, such as irradiation, low information content for radiography, and need for transportation [2].

Because lung ultrasound is not only a diagnostic tool but it can be also considered as a part of the physical exam, it has the potential to become the stethoscope of the twenty-first century [1].

3.2 Principles of Lung Ultrasound

Lung ultrasound has been underestimated for many years because the ribs, sternum, and aerated lungs have been considered obstacles for the ultrasound waves. For these reasons, the main opinion was that echography was not the appropriate instrument to study the lungs and pleurae. Actually, according to the laws of physics, sonographic evaluation of the chest is limited by significant changes in impendence and several artifacts [3–5].

However, many diseases affecting thoracic structures, such as pleurae and lungs, result in deep alterations in tissue composition, allowing an improved acoustic transmission and an adequate sonographic assessment.

The chest wall and the peripheral lungs can be examined by linear probe's higher frequencies (5–17 MHz). For the lung evaluation according to an intercostal, under costal, or parasternal approach, convex probes with frequencies of 3.5–5 MHz should be used to ensure an appropriate depth of penetration [3]. Obviously, in this context, multifrequency probes are more suitable for the evaluation of pleural and peripheral pulmonary lesions and of practical value.

Depending on what you want to assess, the patient lies in supine position to investigate the ventral chest, or he/she is asked to sit to study the posterior and lateral chest. The arm lifted above the head allows the narrow intercostal spaces to expand and a best evaluation of subscapular region. Bedridden ICU patients, the topic for this discussion, can be examined in oblique position.

Lung ultrasound in the critically ill patient is based on seven principles:

1. Lung (and critical) ultrasound is performed at best using simple equipment.
2. In the thorax, gas and fluids have opposite locations, or are mingled by pathologic processes, generating artifacts.
3. The lung is the most voluminous organ. Standardized areas can be defined [6].
4. All dynamic signs and artifacts arise from the pleural line, the most important reference point.
5. Static signs are mainly artifactual, and although they could be considered as drawbacks, they can have a specific interest [7, 8].
6. The lung is a vital organ. The signs arising from the pleural line are foremost dynamic.
7. Almost all acute life-threatening disorders are localized about the pleural line, explaining the potential of lung ultrasound [9].

3.3 The BLUE Protocol

Acute respiratory failure is a life-threatening condition whose cause is sometimes difficult to recognize immediately. Initial mistakes have deleterious consequences. The patient's extreme suffering requires the use of any tool to expedite relief and to administer the therapy. The BLUE protocol allows the application of lung ultrasound in the critically ill patient and provides the instruments for a correct differential diagnosis of the acute respiratory failure [10].

It is based on the seventh principle of lung ultrasound that places all the pulmonary life-threatening disorders superficially, at the pleural level, to identify the six most common acute respiratory diseases by using eight ultrasonographic profiles.

In the BLUE protocol, three standardized points are investigated:

1. The upper BLUE point
2. The lower BLUE point
3. The PLAPS point

Two hands placed next to each other on the thorax with the upper hand touching the clavicle, thumbs excluded, correspond to the location of the lung.

The upper BLUE point is at the middle of the upper hand between the third and the fourth finger; the lower BLUE point is at the middle of the lower palm. The PLAPS point is defined by the intersection of a horizontal line at the level of the lower BLUE point and a vertical line at the posterior axillary line [1].

The pleural line is a hyperechoic horizontal line 0.5 cm below the rib line and indicates the parietal pleura. The ribs produce two underlying shadows. The combination of the ribs and pleural line generates the *bat sign* (Fig. 3.1).

Below the pleural line, the horizontal artifactual repetition of the pleural line is called A-line. A-lines, thus, are artifacts characterized by horizontal not moving lines, parallel to the pleural line at regular intervals. They are the specular representation of the pleural line itself both when air is intra-alveolar and when air is free in the pleural cavity (pneumothorax).

The M-mode reveals the *seashore sign*, representing the lung movement ("lung sliding") linked to the more superficial structures of the chest wall. The *seashore sign* is a grainy image that represents the movement of the visceral and parietal pleura. The seashore sign indicates that the pleural line also contains the visceral pleura. In M-mode above the pleural line, the not moving chest wall appears as a stratified pattern, while below the pleural line displays a sandy pattern. The lung sliding and the A-lines form together the A-profile of the BLUE protocol. "A-profile" represents dry lungs. It indicates the gas movement and the sliding of the parietal and visceral pleura.

The B-lines are a comet-tail artifact produced by reverberation, characterized by hyperechoic vertical lines, arising from the pleural line (Fig. 3.2) and always moving in concert with lung sliding. B-lines arise when an ultrasound wave interacts with a small air-fluid interface, for example, when there is fluid or thickening of the

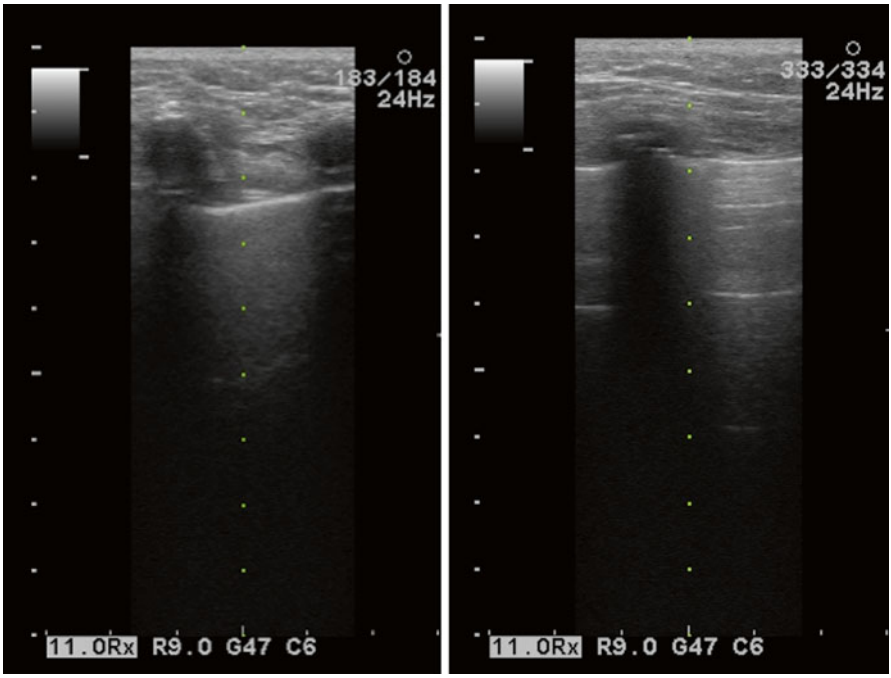

Fig. 3.1 Bat sign. Hyperechogenic and horizontal pleural line is visible under the rib line. In the *left panel*, the ribs with vertical shadows are shown; in the *right panel*, a rib with respective shadow is visualized (Reprinted with permission from Medical Evidence Percorso Formativo 2015, year. 8, n. 104, www.ati14.it)

interstitium. These lines have a clinical relevance if they are two or more for each space between two ribs. If they are four or five and spaced from each other at least 7 mm, they are suggestive for interstitial edema (*lung rockets*). If instead they are twice as many, multiple, and widespread, they are suggestive for pulmonary edema with 100 % sensibility and 93 % specificity [11].

At the PLAPS point, under the pleural line, a regular hyperechogenic line may be visible parallel to the pleural line: the visceral pleura. The visceral and the parietal pleural lines, together with rib shadows, form the "*quad sign*" when pleural effusion is present. In M-mode during inspiration, the lung line, or visceral pleura, (white arrows) moves toward the horizontal pleural line, or parietal pleura, with a sinusoidal movement (*sinusoid sign*) that is indicative of pleural effusion [6].

The BLUE protocol identifies eight profiles, related to six diseases observed in 97 % of patients hospitalized in the ICU [6, 10]. These eight profiles (A, A', B, B', A/B, C, PLAPS, and nude) should allow a rapid diagnosis using standard points of analysis. They are identified on the patient's anterior chest wall in supine position and using the sonographic findings described above.

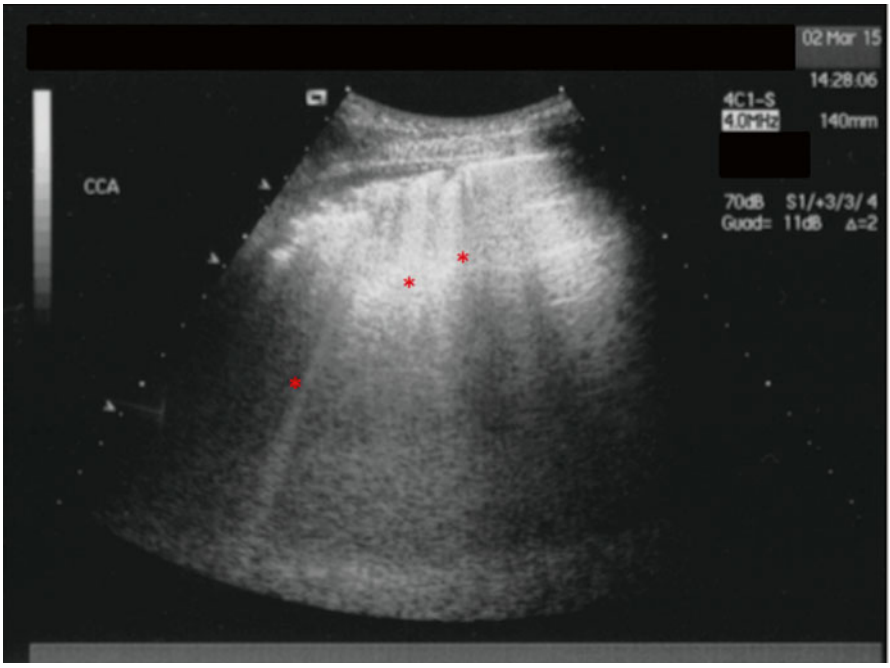

Fig. 3.2 B-lines. *Red asterisks* identify some B-lines: comet-tail artifacts, characterized by hyperechogenic vertical lines arising from pleural line (Reprinted with permission from Medical Evidence Percorso Formativo 2015, year. 8, n. 104, www.ati14.it)

The A-profile (A-lines associated with lung sliding) identifies normal lung surface. If deep venous thrombosis is present, this profile allows the diagnosis of pulmonary embolism with 99 % specificity.

The A'-profile is an A-profile with abolished lung sliding and is suggestive of pneumothorax. It requires the identification of the lung point as specific hallmark of pneumothorax that corresponds to the sudden transition from an A'-profile to an A- or B-profile.

The B-profile is characterized by the presence of anterior lung sliding and lung rocket B-lines and identifies the acute pulmonary edema with 95 % specificity.

The B'-profile is a B-profile with lung rockets but without lung sliding and is highly related to pneumonia with 100 % specificity.

The A/B-profile is an A-profile at one lung and a B-profile at the other one. It is also related to pneumonia.

The PLAPS (posterolateral alveolar and/or pleural syndrome) profile is characterized by the presence of an A-profile that can be suggestive for an acute respiratory failure due to pulmonary embolism but without the signs of deep venous thrombosis signs (making the diagnosis of pulmonary embolism less likely) and by the presence of a posterolateral alveolar and/or pleural syndrome. This profile is highly suggestive for pneumonia.

The nude profile is an A-profile without deep venous thrombosis signs and PLAPS profile. It relates to asthma or chronic obstructive pulmonary disease (COPD).

The C-profile is featured by a thickened, irregular pleural line and suggests pneumonia [9].

The B'-profile, A/B-profile, PLAPS profile, and C-profile indicate pneumonia. The BLUE protocol, therefore, represents a systematic approach for the sonographic diagnosis of respiratory failure [6].

3.4 Lung and Pleural Diseases

3.4.1 Pleural Effusion

The ultrasound diagnosis of a pleural effusion is quite easy (Fig. 3.3). The level of diagnostic accuracy of this method is comparable to the CT scan, and obviously is much better compared to chest X-ray [11, 12].

The probe is directly applied at the PLAPS point where it is possible, in supine patients, to visualize all free effusions regardless of their volume. This approach identifies the quad sign and sinusoid sign, both already described above. The sinusoid sign in M-mode, characterized by the movement of the lung line toward the parietal pleura during inspiration according to sinusoidal movement, allows to decide where to insert a needle for drainage, if necessary.

The ultrasound characteristics of pleural effusions may vary according to their nature: transudates are anechogenic, while exudates present echoes moving with breaths. Because of the different geometric features and the breath-related movements, a precise quantification of the volume of pleural effusion may be difficult. Several techniques have been developed, but all of them provide estimation rather than an exact quantification. In ICU supine patients, the volume of effusion may be estimated by a simplified formula: volume is equal to 20 for the maximal separation (mm) between the parietal pleura and visceral pleura ($V = 20 \times$ maximal separation) [13].

3.4.2 Hemothorax

The presence of blood in the pleural cavity (hemothorax) is common both in blunt and in penetrating trauma; however, it could be also due to inflammations (e.g., tuberculosis) or malignancy. Hemothorax with or without pneumothorax may be reliably identified by ultrasound evaluation. The collection of fresh blood is poorly echogenic, while the clotted blood is always more echogenic [3]. Lung ultrasound should be used during the first minute of trauma assessment to evaluate the severity of thoracic trauma and decide on the necessity for placement an urgent thoracic drainage. Currently, ultrasound is considered essential in the algorithm for the primary assessment of polytrauma. The sensibility of sonography in the diagnosis of posttraumatic hemothorax was found equivalent to the chest X-ray, but echography

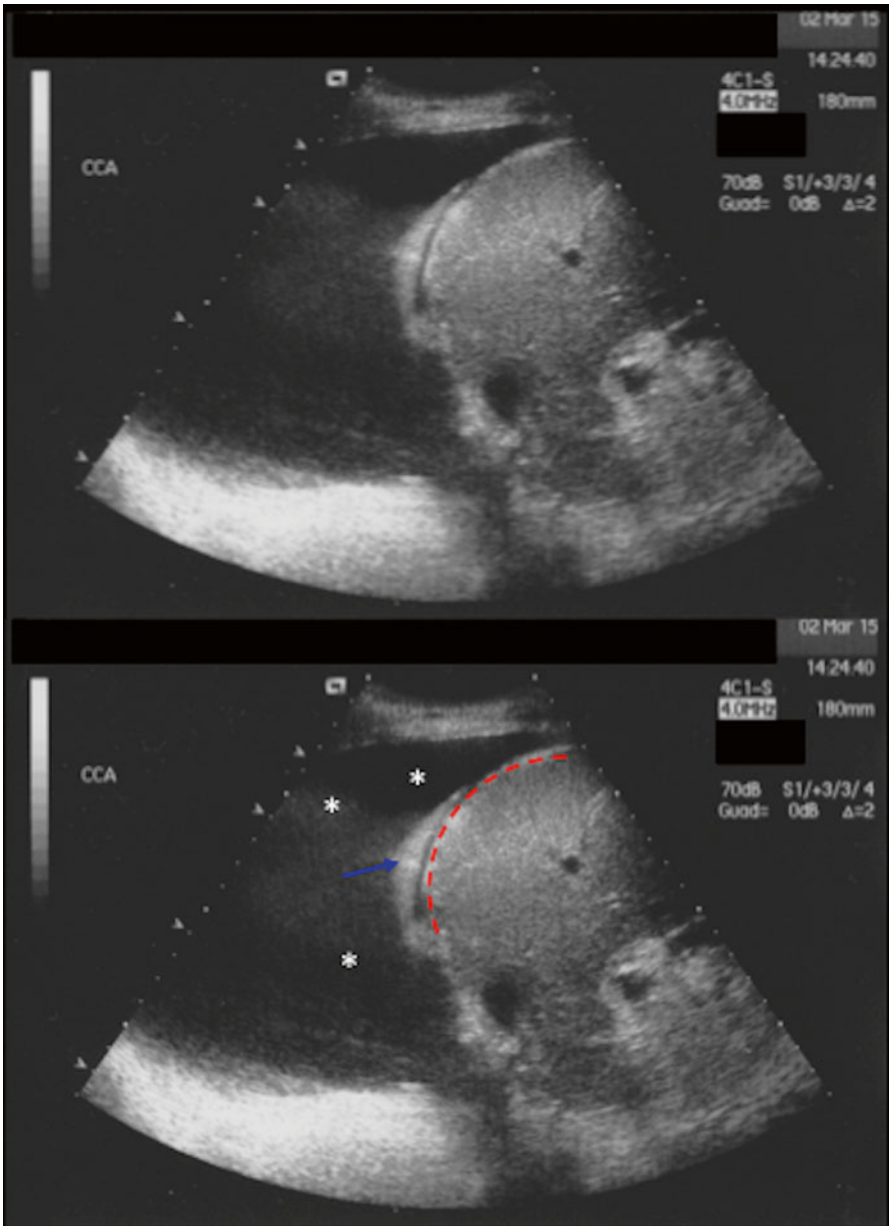

Fig. 3.3 Effusion. The *red line* identifies the diaphragm that separates hepatic parenchyma and thoracic cavity. *White asterisks* are placed in the cavity occupied by the pleural effusion (hypo-/anechogenic). *Blue arrow* indicates the portion of lung parenchyma visible in this sonographic exam (Reprinted with permission from Medical Evidence Percorso Formativo 2015, year. 8, n. 104, www.ati14.it)

has been shown faster, requiring about 1 min against 15 min necessary for chest X-ray. However, the ultrasound evaluation of the deeper structures of the rib cage is much more reduced if subcutaneous emphysema is present [3, 14, 15].

3.4.3 Pneumothorax

Chest X-ray still remains the gold standard for the diagnosis of pneumothorax. The use of ultrasound for the assessment of pneumothorax is a relatively new concept and requires more experience than the diagnosis of pleural effusion. In particular, it is useful to compare the echographic image of one lung with its contralateral hemithorax.

Specific sonographic hallmarks of pneumothorax are:

- The absence of lung sliding
- The absence of B-lines
- The presence of the lung point

The combination of the first two signs on the anterior thoracic wall describes the A'-profile of the BLUE protocol, as stated above. When B-lines and the lung sliding are not present, we should slide the probe in the lateral-cranial direction, because when B-lines and lung sliding reappear, we can recognize the third pathognomonic sonographic sign of pneumothorax (the *lung point*). In M-mode, the absence of lung sliding is characterized by the "stratosphere sign" that replaces the seashore sign. Moreover, in M-mode the lung point is identified where the lung sliding (where the visceral pleura appears just before the parietal pleura) disappears and the visceral pleura is no longer beside the parietal pleura. Soldati and colleagues reported that lung ultrasound is superior to chest X-ray for the diagnosis of pneumothorax in blunt chest trauma [16]. In their prospective study, the ultrasound, performed by an expert operator, has a 92 % sensibility (using CT scan as gold standard), while only 52 % of pneumothorax is diagnosed with chest X-ray. Chest ultrasound was found very useful in ICU and in out-of-hospital settings, where radiographic tools may not be immediately available and diagnosis of pneumothorax is primary, as it may be responsible for a sudden clinical worsening.

3.4.4 Pneumonia

Alveolar consolidations contain little air and lot of water; therefore, they are easily penetrable by ultrasound. Alveolar consolidations affect the lung periphery in 98 % of cases and are located at the PLAPS point in most cases (90 %) [17]. They have a liver-like echostructure (hepatized) [3]. Superficial outlines may be regular, and they are given by the pleural line or the contours of a pleural effusion, if present. On the contrary, deeper outlines are irregular because they are in contact with the aerated parenchyma. Only if the whole lobe is consolidated, the deeper outlines are regular.

In the critically ill patient, pneumonic infiltrations are classified as translobar and non-translobar, each with a distinct ultrasound hallmark. Non-translobar consolidation that does not affect the entire lobe is characterized by the *shred sign*, whereby the border between aerated and nonaerated lung parenchyma is irregular as a shredded profile, opposed to the regular lung line or visceral pleura. An anterior consolidation that is reaching the pleura, with these characteristics, identifies the C-profile of the BLUE protocol.

The translobar consolidation, which affects a whole lung lobe, presents a more dense echostructure similar to a parenchymatous organ; it looks like the liver or spleen [9].

From a dynamic point of view, the consolidated area appears fixed and the lung sliding is often abolished or reduced. In M-mode, the sinusoidal movement is absent allowing to distinguish the lung consolidations from the corpuscular effusions subjected to the breath-related movements. B-lines without lung sliding identify the B'-profile; likewise, the presence of B-lines at one lung and A-lines at the other one identifies the A/B-profile. Both profiles are suggestive for pneumonia and have 100 % specificity but low sensibility [9]. Similarly, the C-profile and the A-V PLAPS profile, suggestive for pneumonia, are characterized by high specificity and low sensibility.

Furthermore, in the pneumonic infiltrations, we can find the "dynamic bronchogram," represented by air that moves according to breathing movement, and the "static bronchogram" marked by anechoic or hypoechoic branched tubular structures full of liquid. The detection of the dynamic bronchogram allows to distinguish pneumonia from atelectasis [3].

3.4.5 Alveolar Interstitial Syndrome

Pulmonary diseases with the interstitial involvement, such as fibrosis, interstitial pulmonary infections, congestive cardiac failure, and acute respiratory distress syndrome (ARDS), have an ultrasound pattern similar to that described as the interstitial syndrome [18]. The interstitial syndrome is characterized by the increase in fluid in the interstitium resulting in the impairment of the alveolar gas diffusion. The sonographic pattern is based on the presence of several B-lines or comet-tail artifacts that are the consequence of the high impedance discontinuity due to close proximity between alveolar air and interstitial fluid.

The B-lines, as already described, if spaced by more than 7 mm, are suggestive for mild forms of interstitial edema, while if they converge, hiding the A-lines, indicate a greater interstitial fluid overloading.

In the assessment of patients with acute respiratory failure, the presence of B-lines allows to differentiate between cardiac and pulmonary etiology, because forms of acute exacerbation of COPD, pulmonary embolism, pneumonia, or pneumothorax, produce a "non-interstitial" sonographic pattern [9].

In the cardiogenic edema, interstitial syndrome is usually bilateral and symmetrical, with few pleural abnormalities, and B-lines are homogenously and bilaterally

spread. Differently, ARDS presents a nonhomogeneous distribution of B-lines associated with subpleuric consolidations, spared areas of normal parenchyma, and abnormalities of the pleural line. Likewise, lung fibrosis also presents an irregular distribution of B-lines together, but with a fragmentation and thickening of the pleural line [19, 20].

3.4.6 COPD and Asthma

Asthma and COPD are mainly bronchial diseases and the lung surface is generally normal. For these reasons, the echography can distinguish them from pulmonary edema, although by a diagnosis of exclusion. The presence of A-lines together with lung sliding, which is typical of a sonographically normal profile, identifies in case of respiratory failure an asthmatic syndrome or COPD with 89 % sensibility and 97 % specificity.

In the BLUE protocol, A-profile, without signs of deep venous thrombosis and PLAPS profile, identifies the nude profile allowing the diagnosis of asthma and COPD [6].

3.4.7 Pulmonary Embolism

Pulmonary embolism does not involve the interstitium or pleura, resulting in a normal sonographic profile, characterized by A-lines bilaterally. However, if signs of deep venous thrombosis are detected in a dyspneic patient with a normal lung ultrasound pattern, diagnosis of a pulmonary embolism can be suspected with 81 % sensibility and 99 % specificity. Clearly, this approach requires the presence of signs of thrombosis, and if they are not detected, we should be very cautious to avoid errors. In fact, the CT scan with contrast still remains the gold standard for the diagnostic confirmation of pulmonary embolism. However, the BLUE protocol provides an effective bedside tool to gain time in the differential diagnosis of patient with acute respiratory failure [6].

3.5 Assessment of Diaphragmatic Motion

The diaphragm is the principal respiratory muscle susceptible to different injuries such as hypotension, hypoxia, and sepsis, all common in ICU patients. Moreover, mechanical ventilation per se may cause diaphragmatic dysfunction, reducing its contraction capacity (ventilator-induced diaphragmatic dysfunction). This can result in several respiratory complications. The sonographic evaluation has allowed to study the prevalence of diaphragmatic dysfunction and clinical relevance. Ultrasound assessment of the diaphragmatic dysfunction does not require fluoroscopy maneuvers, the unpleasant phrenic nerve conduction study, and the

transportation of critically ill patients outside the ICU. In addition to these well-known advantages, it can give functional information and can be repeated whenever the follow-up is required [21].

Different ultrasound techniques have been used to assess diaphragmatic motion including the M-mode technique and the measurement of the diaphragmatic thickness. Among these, the M-mode ultrasound was demonstrated as the easiest technique with a correlation coefficient between and within observers [22].

The probe for the study of the diaphragm (microconvex 3.5–5 MHz) should be placed immediately below the right or left costal margin in the midclavicular line, or in the right or left anterior axillary line [23]. The 2D mode is initially used to find the line to investigate; the M-mode is used to show the motion of the anatomical structures along the selected line [23].

The normal inspiratory diaphragmatic movement is caudal; in fact, the diaphragm moves toward the probe, while the normal expiratory excursion is cranial, and the diaphragm moves away from the probe. In M-mode, the diaphragmatic excursion (translation, cm), the speed of contraction (slope, cm/s), the inspiratory time (Tinsp, s), and the length of the cycle (Ttot, s) can be measured [23].

In mechanically ventilated patients, the diaphragmatic assessment can sometimes require a short disconnection of the patient from the ventilator to better display the spontaneous respiratory efforts. Values of diaphragmatic excursion in healthy patients have been computed: 1.8 ± 0.3, 7.0 ± 0.6, and 2.9 ± 0.6 cm for males and 1.6 ± 0.3, 5.7 ± 1.0, and 2.6 ± 0.5 cm for females, during quiet, deep, and voluntary breathing, respectively [22].

Ultrasound evaluation allows to assess the diaphragmatic thickness (TDI, mm) in the point of apposition of the diaphragm to the thoracic wall that is the lower point of the thoracic wall where the abdominal contents reach the rib cage. In this area, the diaphragm is visualized as a structure formed by three different layers: a central non-echogenic layer among two echogenic layers, the peritoneum and diaphragmatic pleura. The linear probe (10 MHz) is used to measure the diaphragmatic thickness during quiet breathing and during a maximal inspiratory and expiratory effort. Normal values of diaphragmatic thickness in healthy subjects at functional residual capacity (FRC) range from 1.8 to 3 mm.

The increase of the lung volume from residual volume (RV) to total lung capacity (TLC) results in a mean TDI increase of 54 % (range 42–78 %).

However, the measurements of thickness depend on the active contraction and the lung volume according a nonlinear relationship [23].

Diaphragmatic ultrasound has been shown to be very useful during the respiratory weaning from mechanical ventilation. Jiang et al [24] realized a sonographic assessment of diaphragmatic motion by measuring the liver/spleen displacement during spontaneous breathing. This exam provides a good predictor of extubation outcome. The mean cutoff value of 1.1 cm for the liver/spleen displacement represents a predictor of successful extubation with a sensibility and specificity of 84.4 % and 82.6 %, respectively, better than traditional weaning parameters used in this trial [24]. Patients with an adequate spontaneous tidal volume, but with an inadequate diaphragmatic

excursion, failed more frequently the spontaneous breathing trail compared to patients with adequate spontaneous tidal volume and a good diaphragmatic movement. This can be explained as follows: the spontaneous tidal volume is the result of the activation of all respiratory muscles without the specific measure of the diaphragm contribution, while the diaphragmatic movement represents the final result of diaphragmatic strength and intrathoracic and intra-abdominal pressures. The authors suggested that diaphragmatic excursion is a more sensible and specific parameter compared to weaning parameters referring to volume in predicting extubation outcome. In fact, patients that need to use respiratory accessory muscles to keep adequate tidal volumes may run into failed extubation [24]. However, the role of diaphragmatic excursion as predictor of the respiratory weaning remains to be evaluated.

Conclusions

Currently, in the critically ill patients, both for pulmonary and pleural diseases, the ultrasound proves to be a useful tool for the differential diagnosis of acute respiratory failure, for the assessment of the respiratory complications suddenly arising, for the daily follow-up, and for the process of weaning from mechanical ventilation. Therefore, the intensivist should know the basic concepts of this diagnostic tool and apply it to the management of critical ill patient.

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Does High-Frequency Ventilation Have Still a Role Among the Current Ventilatory Strategies?

4

Rosa Di Mussi and Salvatore Grasso

4.1 Introduction

After the decline of the "iron lung," mechanical ventilation is currently based on intermittent positive pressure (IPPV). Accordingly, a "positive" pressure (i.e., greater than the atmospheric pressure) inflates the tidal volume (VT), while expiration is passive, due to the elastic return of the respiratory system. During IPPV, the mean airway opening pressure ($P_{AO,\,MEAN}$) depends on the pressure applied to supply the VT, on the eventual level of positive end-expiratory pressure (PEEP), and, on a lesser extent, on respiratory rate (RR) and inspiratory time (T_{INSP}). High-frequency oscillation ventilation (HFOV) is an alternative technique that applies a constant lung-distending pressure with superimposed small pressure oscillations (±2–4 cmH_2O) delivered at very high rate (between 180 and 900 cycles per minute) [1, 2]. The resulting VTs are smaller than the anatomic dead space (between 1 and 3 ml/kg) and therefore the CO_2 is not cleared by alveolar ventilation as happens with IPPV, but through "unconventional" mechanisms (see below).

The main determinants of ventilator-induced lung injury (VILI) are hyperinflation and/or opening and closing of lungs units (atelectrauma) [3, 4]. In patients with acute respiratory distress syndrome (ARDS), both these phenomena may occur at each respiratory cycle. According to a lucky definition by Luciano Gattinoni and Antonio Pesenti [5], the ARDS lung may be thought as a "baby lung." Ventilating the "baby lung" with an "adult" VT prompts VILI: *first*, the smaller the "baby" aerated lung the greater will be its end-inspiratory hyperinflation [6]; *second*, the atelectatic but not consolidated (unstable) lung areas will open up during the inspiratory phase and close again at end expiration [7]. Lung protective ventilation aims to minimize hyperinflation and atelectrauma [4]. A low VT, i.e., adequate to the "baby" lung size, is used in

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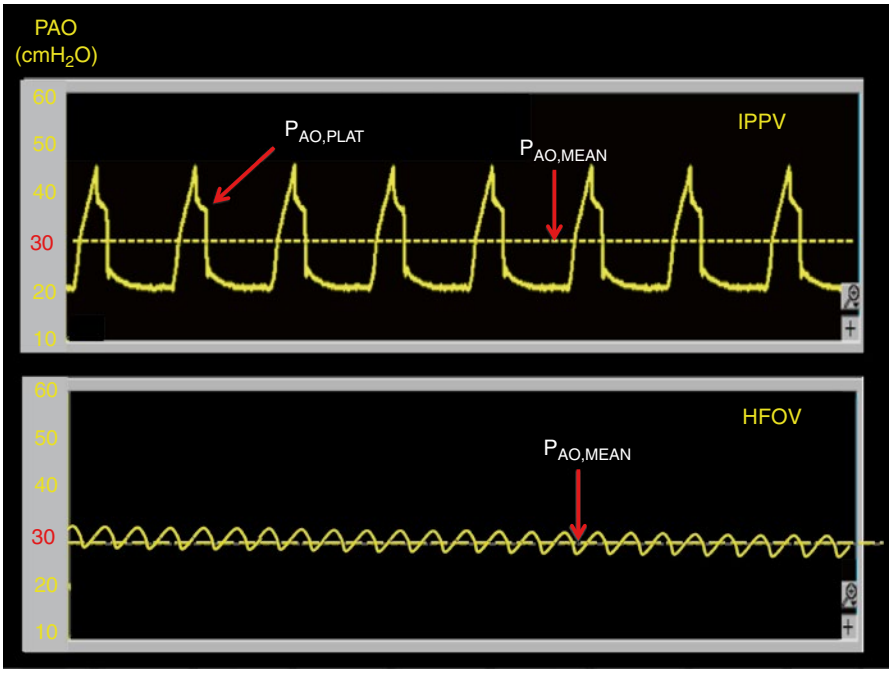

Fig. 4.1 Comparison of intermittent positive-pressure ventilation (*IPPV*) and high-frequency oscillation ventilation (*HFOV*) in terms of inspiratory pressures. At the same level of mean airway opening pressure ($P_{AO,MEAN}$, *dotted line*), the end-inspiratory plateau airway opening plateau pressure ($P_{AO,PLAT}$) generated by IPPV is higher than the one generated by the HFOV positive-pressure spikes

conjunction with an "adequate" PEEP level. The latter is doubly important: (a) improves oxygenation by opening lung areas that collapse at functional residual capacity (alveolar recruitment) and (b) keeps constantly open those unstable lung units that would otherwise undergo to tidal opening and collapse. The reference ARDS Network protocol limits VT to 4–6 ml/kg predicted body weight (PBW) and static end-inspiratory plateau pressure (P_{PLAT}) to 30 cmH_2O. In additions, it prescribes a stepwise PEEP setting: PEEP and FiO_2 (inspiratory oxygen fraction) are increased to match a "minimal" oxygenation target (i.e., PaO_2 between 55 and 80 mmHg) [8].

In the first period of its clinical application, the focus on HFOV pointed on its ability to improve oxygenation. In the following years, after the introduction of the VILI concept, the focus shifted on VILI prevention [2]. Indeed, at any $P_{AO,MEAN}$ level, HFOV applies a lower end-inspiratory pressure as compared to IPPV (Fig. 4.1). Thus, from a theoretical point of view, HFOV should prevent both hyperinflation and atelectrauma. In synthesis, HFOV promises optimal recruitment without VILI. Nevertheless, two recent phase III trials have not validated HFOV for standard ARDS treatment [9, 10]. In this chapter, we would talk about the most important characteristics of HFOV to stress the idea that HFOV remains an effective "rescue" approach in the algorithm of the "difficult to ventilate" ARDS patient [11, 12].

4.2 The HFOV Technique

In order to understand the HFOV basics, it is worth to consider the main components of any HFOV apparatus (Fig. 4.2):

- A fresh gas source that generates a bias air/oxygen flow (20–60 l/min)
- A low-pass expiratory valve that pressurizes the HFOV circuit
- A large membrane "loudspeaker" oscillator that generates pressure waves into the HFOV circuit

Briefly, a continuous lung-distending pressure (CDP) is generated into the HFOV circuit by a continuous fresh gas flow passing through an adjustable expiratory valve. The CDP can be compared with the $P_{AO,MEAN}$ delivered during conventional IPPV. The "loudspeaker" membrane generates pressure oscillations in the circuit air column, moving at a very high rate (180–900 cycles per minute, or 3–15 Hz). When the membrane moves toward the patient side, the pressure increases above the CDP and vice versa. The resulting sinusoidal pressure waveform, which alternates positive and negative spikes, is superimposed to CDP (Fig. 4.3). Close to the oscillator, the spike amplitude is high (±30–90 cmH_2O), but, of note, at the airway opening it significantly decreases up to ±2–4 cmH_2O due to the circuit resistance and the quick passage from the positive to the negative phase. Each positive-pressure spike supplies to the patient a small VT, of about 1–2 ml/kg, and the following negative spike actively removes it. Thus, another difference between IPPV and HFOV is that during HFOV the expiratory phase is active.

The most important feature of HFOV is its ability to clear CO_2 virtually without ventilating the alveolar space. Indeed, HFOV was initially born to measure respiratory

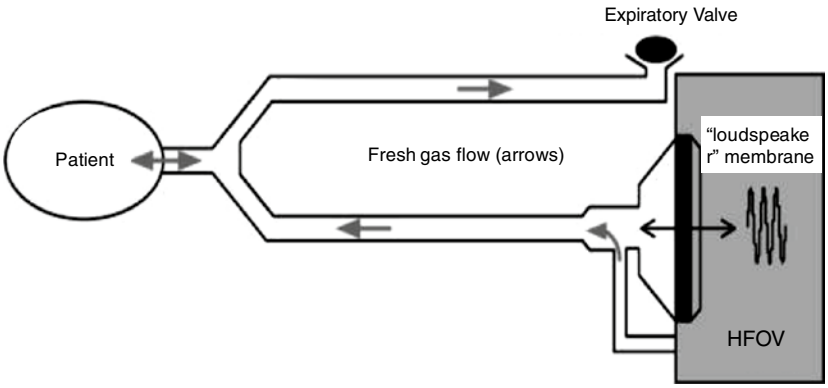

Fig. 4.2 Schematic representation of a basic HFOV apparatus. A continuous lung-distending pressure (CDP) is generated into the circuit by a continuous fresh gas flow passing through an adjustable expiratory valve. A large "loudspeaker" membrane generates pressure oscillations in the circuit air column, at a very high rate (180–900 cycles per minute, or 3–15 Hz). When the membrane moves to the patient side, the pressure increases above the CDP and vice versa

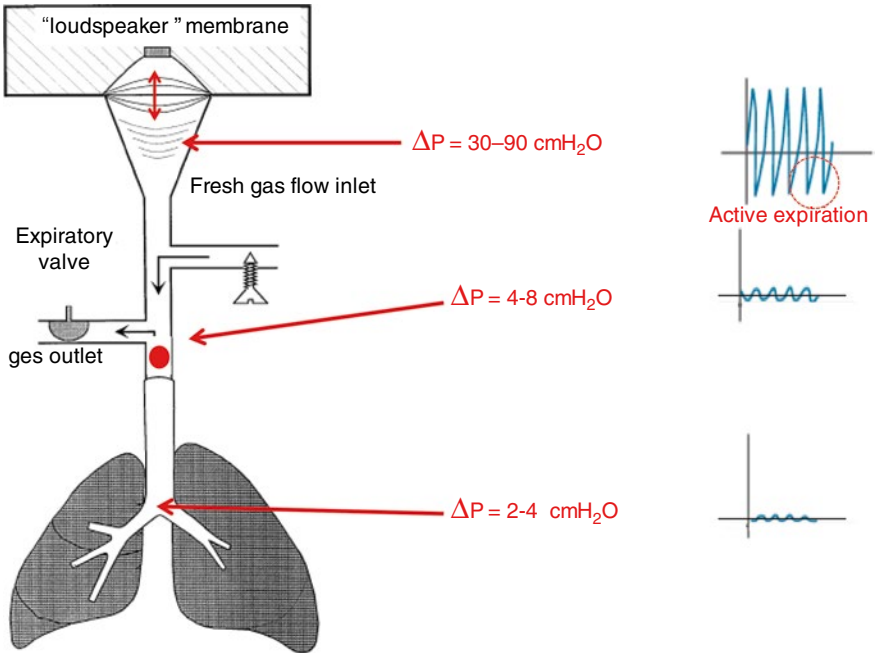

Fig. 4.3 Basic functioning of an HFOV circuit. ΔP (the delta pressure generated by the oscillator) is the difference between positive and negative peak pressure. Close to the oscillator, the spikes amplitude is high but it significantly decreases at the airway opening due to the tube resistance and the quick passage from the positive to the negative phase at each oscillatory cycle. Please note that during HFOV the expiratory phase is active

system impedance in paralyzed animals; it became a ventilation technique thanks to the serendipitous evidence that, during the measurements, the animals remained normocapnic. Various mechanisms have been proposed to explain how HFOV can clear CO_2. In its excellent review on this topic [13], Chang quotes: (a) direct ventilation of the proximal alveoli, (b) "molecular" diffusion of CO_2, and (c) convective and dispersion phenomena. The small VT delivered by the HFOV into the anatomical dead space scavenges alveolar CO_2 and brings it to the airway opening. Here, the continuous fresh gas flow washes it toward the expiratory valve (Figs. 4.1 and 4.2).

In general, the CO_2 removal during HFOV is directly proportional to the oscillation amplitude and to the fresh gas flow and inversely proportional to the oscillation frequency [14]. In most patients, adjusting HFOV effectively keeps $PaCO_2$ and pH within clinically acceptable ranges. Rarely, CO_2 removal is insufficient. In this case, an interesting approach could be combining HFOV and extracorporeal CO_2 removal ($ECCO_2R$) [15]. Regarding oxygenation, it simply depends on the ability of the CDP to recruit atelectatic lung areas and on the FiO_2 in the fresh gas flow. In order to fully recruit the lung, before applying the HFOV it could be worth to perform a lung-recruiting maneuver (LRM) [16, 17]. Of note, during HFOV, a simple LRM can be realized temporarily blocking the oscillations while increasing the CDP.

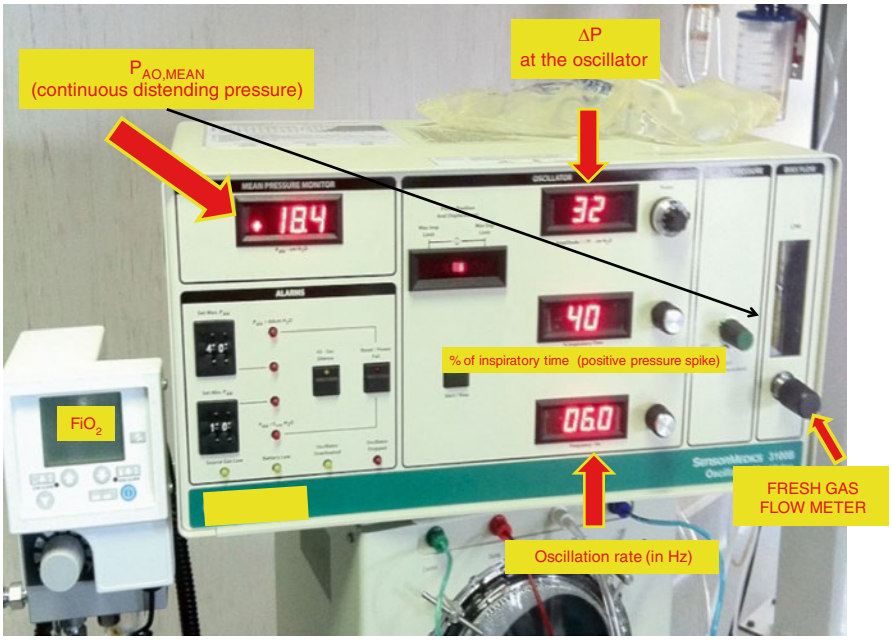

Fig. 4.4 Main HFOV parameters setting in a commercial ventilator

An important premise for the clinical use of the HFOV in adults with ARDS is that the patient must be deeply sedated and/or paralyzed. A recent consensus conference proposed the following initial settings for HFOV in ARDS patients (Fig. 4.4) [18]:

1. Fresh gas flow = 40 L/min
2. I:E ratio (positive-oscillation/negative-oscillation ratio) 1:2
3. CDP = 30–35 cmH_2O
4. $FiO_2 = 1$
5. Oscillation amplitude close to the membrane (delta P) = 90 cmH_2O.
6. Oscillation frequency (based on the previous $PaCO_2$ determination) = 4 Hz for pH < 7.10; 5 Hz for pH between 7.10 and 7.19; 6 Hz for pH between 7.20 and 7.35; 7 Hz for pH > 7.35.

In other protocols, the CDP is initially fixed at the same $P_{AO,MEAN}$ value registered during IPPV and then increased up to 30–35 cmH_2O.

4.3 HFOV: Recent Studies

In 2010, a meta-analysis sustained that HFOV, as compared to IPPV, could reduce the mortality rate in ARDS [19]. However, that meta-analysis mixed very different studies. In some, the control group was ventilated with a nonprotective strategy,

raising the hypothesis that the advantage of the HFOV was just due to an excess of VILI in the controls. Those considerations prompted two large phase III studies, the OSCAR (oscillation in ARDS) [10] and the OSCILLATE (oscillation for ARDS treated early) trials [9], published on the New England Journal of Medicine in the 2013. Both these studies compared lung-protective IPPV with HFOV in moderate-severe ARDS. Whereas the OSCAR trial did not show differences between HFOV and IPPV in terms of mortality, adverse events, and need for non-ventilatory "rescue" therapies for refractory hypoxemia, in the OSCILLATE trial in-hospital mortality was 47 % in the HFOV group versus 35 % in the control group $P = 0.005$. In both the studies, there was a larger use of sedative and paralytic drugs in the HFOV group. In the OSCILLATE trial, vasopressors were more used in the HFOV group as compared with the control group.

The OSCAR trial took the ARDS network protocol as the control strategy. As known, this protocol minimizes alveolar hyperinflation, whereas it targets the lower PEEP level compatible with an acceptable oxygenation, without allowing the use of LRMs. The HFOV setting also adopted a "minimal lung distension" strategy, with rather low CDPs (26.9 cmH_2O in the first day, 25 cmH_2O in the third day) and without LRMs. The OSCILLATE trial, on the other hand, aimed at maximal alveolar recruitment in both the study arms (the so-called open-lung approach). Maximal LRMs were performed before PEEP and CPD setting in the control and HFOV groups, respectively. The mean CDP was 31 cmH_2O in the HFOV group. One intriguing explanation of the negative results of the OSCILLATE trial is that the high CDP deteriorated the right ventricle function because of an "afterload effect." In fact, HFOV likely carries a higher risk of RV "afterload" effect as compared to IPPV. Experts suggest that echocardiography should be routinely performed in patients ventilated with HFOV [20–22].

Did the OSCAR and the OSCILLATE trials penalize the HFOV technique? This is difficult to say and, unfortunately, other clinical trials would be difficult to realize on the basis the OSCILLATE trial results. In terms of evidence-based medicine, HFOV should not be used as "first choice" in moderate-severe ARDS. Anyway, the experts' opinion is that HFOV remains a valuable "rescue" therapy in the "difficult to ventilate" patient [11, 12, 17]. We will focus on this in the remaining part of this chapter by briefly assessing the concept of "difficult ventilation" in ARDS and the clinical algorithm to the "difficult to ventilate" patient.

4.4 The "Difficult to Ventilate" Patient with ARDS (Fig. 4.5)

The "difficult to ventilate" concept compares the mean positive pressure and FiO_2 with the resulting arterial partial oxygen pressure (PaO_2) [23, 24]. In other words, it expresses "the price" to pay, in terms of VILI, to maintain oxygenation. The oxygenation index (OI) is a suitable index to quantify this concept:

$$\mathrm{OI} = \left(P_{\mathrm{AO,\ MEAN}} * \mathrm{FiO_2} * 100\right) / \mathrm{PaO_2}$$

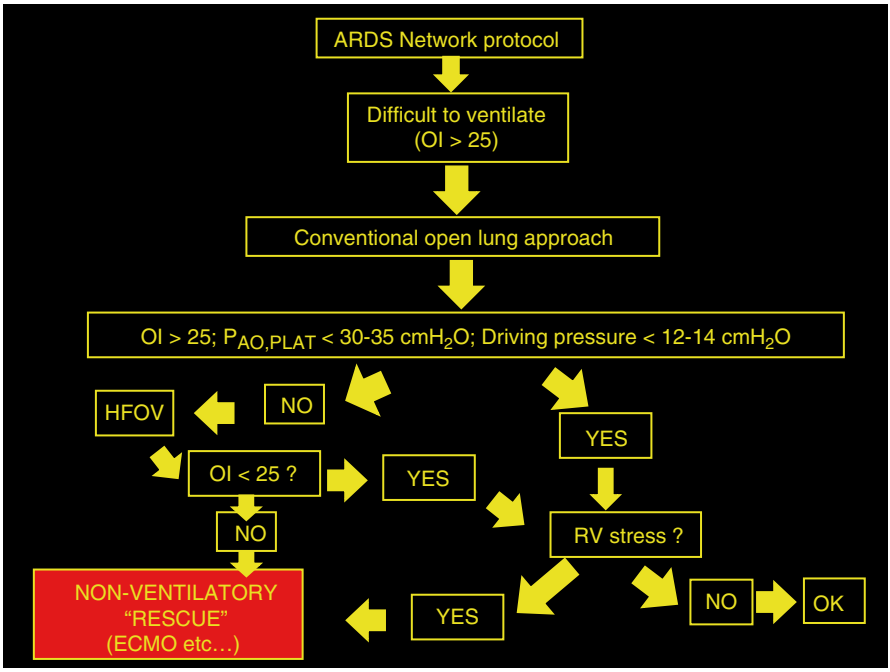

Fig. 4.5 Therapeutic algorithm of the "difficult to ventilate" patient with ARDS. *OI* oxygenation index, $P_{AO,PLAT}$ plateau airway opening plateau pressure, *RV* right ventricle, *ECMO* extracorporeal membrane oxygenation

Of note, the $P_{AO,\,MEAN}$ is a figure that incorporates PEEP, peak and plateau pressure, respiratory rate, and inspiratory to expiratory ratio.

A patient with an OI higher than 25 when submitted to a "conventional" lung-protective protocol, prone position [25], and neuromuscular blockade [26] is "difficult to ventilate" because of an excess of VILI and/or a severe deficit in oxygenation. This is the ideal candidate to "rescue" ventilatory and non-ventilatory strategies.

Physiological studies have shown that at least half of the patients ventilated according to the ARDS network protocol have a high potential for recruitment [27]. The "open-lung" approach may potentially improve oxygenation and, contemporarily, minimize VILI. The critical issue for the success of any open-lung strategy is the potential for alveolar recruitment, which is extremely variable and difficult to estimate a priori [28]. The simplest approach is to consider the effects of the recruitment strategy on one or more key parameters: oxygenation, respiratory system or lung compliance, electrical impedance tomography, or CT scan. Different approaches to maximal lung recruitment as well as to the open-lung ventilation have been proposed. Their description is beyond the scope of this chapter [29, 30, 31].

If the potential for recruitment is high, the OI will likely decrease below the critical threshold with a "conventional" (i.e., IPPV based) open-lung strategy [31, 32]. However, some "difficult to ventilate" patients may need uncommonly high PEEP

levels (20–25 cmH_2O) to stay "recruited" and their lung remains "stiff" lung despite optimal recruitment [33]. In those patients, when a VT is inflated by IPPV, the $P_{AO,PLAT}$ may easily increase over the "safe" threshold (30–35 cmH_2O) [34]. Most important, the driving pressure, i.e., the difference between $P_{AO,PLAT}$ and PEEP, could reach excessively high levels, well beyond the 14 cmH_2O threshold. Strong physiological and clinical data suggest that the driving pressure is the most important determinant of alveolar stress and strain and correlates with mortality [35, 36]. Of note, the driving pressure delivered by the ventilator to inflate the respiratory system may be split in two components: one to drive the lung, the transpulmonary pressure, and one to drive the chest wall, the pleural pressure. The transpulmonary pressure applied to the lung parenchyma for a given total driving pressure depends hence on the ratio between the elastance of the lung and the chest wall, independently on their absolute values [37–39].

When the conventional recruitment strategy fails, HFOV could be a suitable alternative. As discussed above in this chapter, the HFOV technique is unique in keeping the lung well recruited without the need of superimposed pressure (Fig. 4.1). Accordingly, the HFOV may be precious in patients with high potential of alveolar recruitment developing excessive $P_{AO,PLAT}$ and/or driving pressures.

Obviously, in patients with low or nil potential for recruitment or in patients that develop severe right ventricular failure in response to the open-lung approach, the focus shifts on non-ventilatory approaches. In this chapter, we just remember that veno-venous extracorporeal membrane oxygenation (ECMO) is at present the most important non-ventilatory rescue therapy for refractory hypoxemia [40, 41].

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Noninvasive Assessment of Respiratory Function: Capnometry, Lung Ultrasound, and Electrical Impedance Tomography

5

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The monitoring of vital functions, based on technologically advanced instruments, is pivotal in intensive care unit.

The progress in industrial and military technology (ultrasound, radiation, fiber optic, electronics, and informatics) has given very important tools to physicians.

In the last 30 years, the medical world, and in particular the surgical and the intensive care one, has undergone a revolution, thanks to the improvement in therapeutic and diagnostic techniques.

When we talk about monitoring, we refer to continuous signal analysis derived from parameters that give us information about body functions: in particular, circulation and respiratory function monitoring is essential in the operating room and intensive care unit.

Besides the costs, the operator dependence, and the reliability degree compared to the gold standard, we must always take into account the invasiveness and its potential role in causing injury to the patient.

The aim of this paper is to emphasize three noninvasive approaches, which permit to obtain information about lung function, especially in patients undergoing mechanical ventilation: capnometry, lung and diaphragm ultrasound, and electrical impedance tomography.

5.1 Capnometry

Carbon dioxide (CO_2) is a waste product of aerobic metabolism. It dissolves into the blood and reaches the pulmonary alveoli through diffusion. Since pulmonary alveoli are connected to the mouth through the bronchial tree, carbon dioxide concentration in exhaled air can easily be measured.

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Capnometry gives information about three biological functions that have a pivotal role in human pathophysiology: systemic metabolism, circulation, and alveolar ventilation. This is the reason why it represents an important tool in the hands of the anesthesiologists and intensive care physicians [1].

Therefore, if expired CO_2 measurement aims to be a useful monitoring instrument for patient's respiratory status, his hemodynamic condition, pH, and metabolism, would not undergo sudden variations in the meantime.

In order to define CO_2 concentration, infrared technology (IR) is the most widely used method in clinical practice. The sensor emits IR light, across a gas sample that needs to be examined, to a photodetector. Carbon dioxide (CO_2) keenly and specifically adsorbs IR light at 4.3 μm: the higher the carbon dioxide concentration is, the lower the IR intensity detected. At these wavelengths the presence of other gases (i.e., oxygen, nitrogen, water vapor, and anesthetic gases) barely interferes with the measurement.

In case the photodetector gets dirty, i.e., with secretions or water vapor, the measurement can be invalidated. That happens mostly using *mainstream* capnometers that are located in line with the respiratory gas stream and measure carbon dioxide directly at the sample site that reflects carbon dioxide partial pressure in real time within the airway. On the other hand, *sidestream* devices aspirate a sample of gas from the breathing circuit, and the measurement occurs at a sensor distant from the sample site. Using a site located further results in a delay time but rarely gets dirty; moreover, these are particularly suitable for non-intubated patients.

The measurement of CO_2 in expired gas is given by *capnometry*, which defines the end-tidal partial pressure of carbon dioxide, or *capnography*, that displays a graph of expiratory CO_2 plotted against time or expired volume. The latter provides more information, if compared to the former.

The level of carbon dioxide released at the end of a quite exhaled breath (expiration), expressed in mmHg, represents the *end-tidal CO2 (ETCO2).* It depends from the P_{aCO_2} (arterial carbon dioxide partial pressure), the V_D/V_T (V_D is the dead space volume and V_T is the tidal volume), and the resistance of the respiratory tract to airflow during expiration [2].

Dead space requires a more detailed definition:

- *Anatomical dead space* is the portion of the airways that conducts gas to the alveoli. Here, no gas exchange can occur.
- *Alveolar dead space* is the volume of gas within alveoli that have ventilation-perfusion mismatch.
- *Physiological dead space* is the sum of the anatomical dead space and the alveolar dead space.

In 1950 Riley designed a three-compartment model [3] in which the lungs are described as consisting of three functional areas: the first one is completely ventilated but not perfused (dead space), the second one is both ventilated and perfused ("ideal alveoli"), and the third one is unventilated but perfused (shunt zone).

Due to physical and chemical properties, the shunt effect on the P_{aCO_2} is negligible, if compared to the one on the PaO_2. Thus, except for particular cases in which

the shunt area is dramatically increased, the shunt effect can be overlooked if the interest is on the PCO_2 value. The two other areas define the $ETCO_2$ value.

Since the ventilation/perfusion ratio (V/Q) is optimal into the ideal alveoli, the balance between gases into the alveoli and those in the pulmonary capillary blood flow (that has roughly the same PCO_2 as the arterial blood) is equal. Here, the ventilation is due to the fraction of tidal volume not directed to the physiological dead space.

$$VT_A = V_T * \left(1 - \left(V_D / V_T\right)\right)$$

VT_A = alveolar tidal volume, V_T = tidal volume, and V_D = dead space.

In the dead space area, by contrast, gas exchange doesn't occur. Thus, this area represents a lung zone lacking of carbon dioxide. Therefore, the volume released from this area, during a quite expiration, is accountable for the "ideal gas" (the gas coming from the ideal alveoli) dilution. The latter one is directly proportional to V_D/V_T ratio (V_D is the alveolar dead space, V_T is the tidal volume). Even if in human there are no strictly topographic lung regions, the Riley three-compartment model is clinically useful in the critical patients.

In the supine posture, under normal conditions, the alveolar dead space is that small that we can't even measure it. It becomes significant during some pathological circumstances in which the ventilation/perfusion ratio (V/Q) is impaired, i.e., low cardiac output (in which the perfusion is lower at the top of the lung – in west zone 1), pulmonary embolism (in which there's a lack of perfusion in some areas of the lung), and sedated patient during mechanical ventilation in lateral decubitus (in which the ventilation is higher at the superior lung but the perfusion is higher at the inferior one).

The idea of measuring the partial pressure of carbon dioxide at the end of a quite expiration is aimed to obtain a gas sample representative of the alveolar air composition. In case the expiratory flow is higher and/or in case of auto-PEEP presence (i.e., in patient with obstructive airway disease or undergoing mechanical ventilation with an impaired circuit), the expiratory phase is longer, and the moment in which the $ETCO_2$ value approaches the alveolar one is delayed.

In fact, the typical low flow of these circumstances lets the gas that is coming from the airway dead space and that is usually exhaled early during the expiratory phase (phase 0 on the capnogram) mix more with the gases coming from the pulmonary alveoli.

Usually, during these pathological conditions, higher respiratory rate and shorter expiratory phase also occur that can cause an impaired $ETCO_2$ that is badly correlated to the alveolar PCO_2.

Whereas this mechanism barely affects the interpretation of capnography (they are easily recognizable, for example by a rise during phase III of the capnography (Fig. 5.1)), they can cause underestimation of the alveolar PCO_2 (and, as a consequence, overestimation of the alveolar ventilation), if just capnometry is used. Therefore, the isolated $ETCO_2$ interpretation, as a P_{aCO_2} substitute, is misleading and should always be matched with P_{aCO_2} and respiratory status assessment.

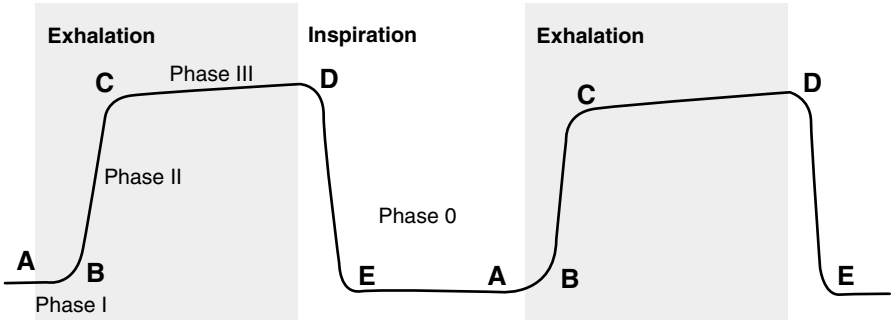

Fig. 5.1 Normal capnogram. Phase I: since it represents the gas mixture coming from the anatomical dead space, exhaled CO_2 is essentially zero. Phase II: since the alveolar CO_2 replaces the gases coming from the dead space, the PCO_2 increases quickly. Phase III: it is also known as "alveolar plateau"; it records the gas flow containing CO_2. It usually rises slowly, but, in case of longer expiratory phase, it can increase (i.e., COPD). D, end-tidal CO_2 ($ETCO_2$). Phase 0, inspiration, it is marked by a rapid CO_2 downward

5.2 Practical Utility

Monitoring of Ventilation Capnometry is increasingly used to assess the adequacy of patient ventilation [4]. When used in the correct setting, in fact, it allows to early recognize alveolar hypoventilation or hyperventilation. As previously said, when the presence of an increased physiological death space or an increased expiratory load is not expected, $ETCO_2$ precisely approaches PCO_2.

In conditions of hemodynamic and metabolic stability (i.e., in conditions in which CO_2 production is constant), this value depends on the alveolar ventilation according to the following formula:

$$P_{aCO_2} = K * V_{CO_2} / V_A$$

K is a constant; V_{CO_2} stands for CO_2 production; and V_A is the alveolar ventilation.

In such circumstances, the continuous $ETCO_2$ measurement can effectively reduce the need for multiple blood samples. Moreover, most of the capnometers provide real-time accurate interpretations of respiratory rate, instead of the 30–60 s intervals that are usually necessary for a manual evaluation. This feature is not to be underestimated in an emergency setting.

The ventilation monitoring through capnometry is particularly useful in situations in which the risk of hypoventilation is high. This is especially true when supplemental oxygen is provided to patients, because it can delay the onset of hypoxia, even if hypoventilation (and hypocapnia) is already present.

Some examples in which a capnometric continuous measurement is useful are:

- The difficult weaning of long-term mechanical ventilation patients
- Intra- or interhospital transport, when orotracheal tube obstructions and tube disconnection from ventilator are frequent
- Deep sedation in non-intubated patients during endoscopic procedures, during interventional radiology, electric cardioversion, etc.
- According to the fact that it is not possible to predict how a patient will react to a sedative dose and according to the fact that capnography could permit early therapeutic interventions which can prevent relevant O_2 desaturations, some important anesthesia societies such as ASA (American Society of Anesthesiology) and AAGBI (The Association of Anaesthetists of Great Britain and Ireland) included capnographic monitoring during sedations in the standards of care.

Moreover, the *British NAP4 study group* shows that in a typical ICU patient, 74 % of deaths or neurological impairments due to a bad airway management in ICU are avoidable using a capnometric continuous measurement [5].

Death Space Measuring Since $ETCO_2$ value is influenced by the presence of alveolar death space, it is possible to use capnometry in order to measure it. Such measuring finds several applications in daily clinical practice: COPD, pulmonary emboli, and low cardiac output [2].

The physiological death space (the sum between alveolar death space and anatomic death space) is commonly calculated using Bohr's equation, modified by Enghoff:

$$V_D / V_T = \left(P_{aCO_2} - P_{\bar{E}CO_2}\right) / P_{aCO_2}$$

V_D is the physiological death space, V_T is tidal volume, P_{aCO_2} is CO_2 arterial partial pressure, and P_{CO_2} is mean CO_2 expiratory partial pressure.

Moreover, the same equation allows, through small adjustments, to isolate anatomic death space (by substituting P_{aCO_2} with P_{ETCO_2}) or alveolar death space (by subtracting the anatomic component from the physiological death space).

Even though reliable methods with direct measurements cannot be easily implemented into the clinical practice.

The measuring of P_{ETCO_2}, in fact, involves the collection of expirated air during quite expiration in big bags.

The physiological death space, with every single component, is measured almost exclusively through a capnometric curve plotted against the expired air volume (Fig. 5.2). However, as we said before, it is not affordable in most hospitals. Although the simple capnometry and/or time capnography measure only the

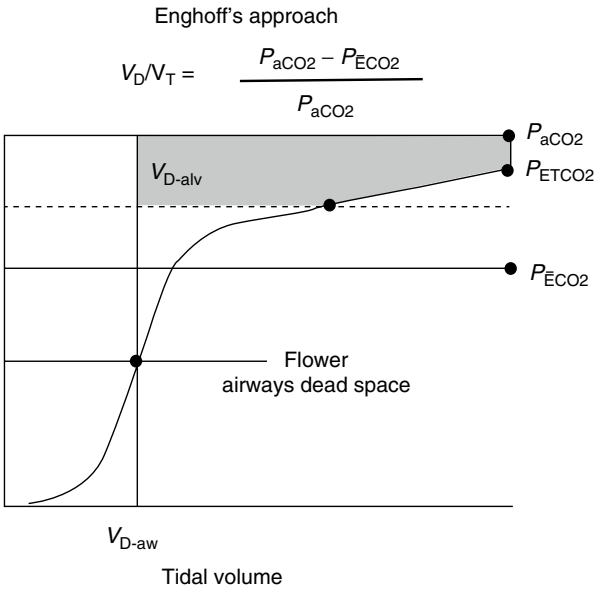

Fig. 5.2 Volumetric capnography. Notice the opportunity to measure the single components of physiological death space: airways death space ($V_{D\text{-}aw}$) and alveolar one ($V_{D\text{-}alv}$)

alveolar component of death space, they are readily available tools. As previously explained, the existence of alveolar-arterial PCO_2 increased gradient, in the absence of enormous arteriovenous shunts or important expiratory resistances, is an indicator of "wasted ventilation."

The normal value of alveolar-arterial PCO_2 is lower than 5 mmHg. A sudden increase of such gradient can be useful when a pulmonary embolism is suspected.

The so-called alveolar death space fraction, described by Nunn and coll. provides a similar information, where the cutoff is 0.2, and it is mathematically described by the following formula:

$$\left(P_{aCO_2} - ETCO_2\right) / P_{aCO_2}$$

$P_{aCO_2} = CO_2$ partial pressure; $ETCO_2$ = end-tidal CO_2.

Many studies demonstrate a sensibility of about 85 % for the diagnosis of pulmonary thromboembolism and a NPV (negative predictive value) of about 95 %. These values rise when this finding is concordant with negative d-dimers.

In addition to the numerical values, the capnogram evaluation (and specifically the study of the α-angle and the phase III slope) can provide important clues about the pathology that withstands the death space modification.

Repeated evaluations of alveolar death space can be used to monitor the progressive resolution of a reversible pathologic process, as it happens in the case of pulmonary thromboembolism.

Orotracheal Intubation Confirmation There is a broad consensus among anesthesia and critical care scientific societies in considering capnometry as an essential tool for orotracheal intubation confirmation [6].

Although its systematic and routine use is not considered yet unanimously a standard of care in ICU and emergency department (as it happens for a long time in surgery rooms), it is increasingly recommended.

A stable $ETCO_2$ for few consecutive respiratory acts or, even better, the identification of valid capnographic curves at the monitor provides a reliable confirmation of a correct positioning of the tube in few seconds. This allows to earn time in adopting early corrections in case of esophageal intubation.

The increasingly availability of portable instruments, for example, colorimetric capnographs, has extended the use of capnometry for the confirmation of tracheal intubation also in extra-hospital emergency.

Optimization of Ventilatory Setting During ARDS [7] A V_T/V_D measurement is precious for the study and management of acute respiratory distress syndrome (ARDS).

- A sustained elevation of V_D/V_T ratio (>59 %) in early and intermediate phases of an ARDS is significantly related to an increase in mortality [8]. The rationale behind is yet under discussion: an augmented V_D/V_T can represent both an early sign of alveolar overdistention caused by an inaccurate ventilation and a severity index of ARDS-related pulmonary vasculopathy.
- Changes in V_D/V_T ratio are early and affordable indicators of alveolar recruitment (or derecruitment). In the presence of an important venoarterial shunt (for instance, more than 50 %), there is a loss of correspondence between P_{aCO_2} and alveolar PCO_2. This leads to an overestimation of V_D/V_T (usually calculated through the P_{aCO_2} in Enghoff-Bohr's equation) that is proportional to the extent of the shunt. Such relationship can be favorably used for clinical evaluation of alveolar recruitment of a ventilated patient.
- Following on from a Gattinoni's experiment [9], Charon et al. [10] demonstrated in their study that measurement of V_D/V_T can represent a particularly convenient method to early assess the reaction to a pronation.
- Modifications of V_D/V_T ratio are useful in the titration of best PEEP value. They are able, as previously stated, to reveal both a recruitment and an alveolar overdistention.
- V_D/V_T ratio can be useful to set the inspiratory pattern of an ARDS-affected patient, in order to achieve an optimal elimination of carbon dioxide.

5.3 Lung Ultrasound in ICU

The possibility of exploring the lung using ultrasound, at the bedside and noninvasively, is gaining popularity among intensivists. Traditionally the lung was thought to be amenable to ultrasound due to its high air content and acoustic impedance;

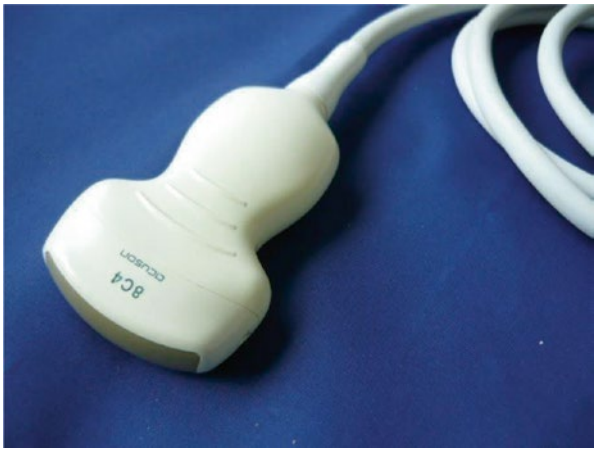

Fig. 5.3 Convex probe

however, the description of common artifacts by Lichtenstein [9] and their pathological correlates on CT scan has led to an expansion in the use of bedside thoracic ultrasound, culminating in evidence-based consensus guidelines. The advantages of correct use of bedside lung ultrasound in the emergency setting are striking, particularly in terms of saving from radiation exposure, delaying or even avoiding transportation to the radiology suite, and guiding lifesaving therapies in extreme emergency [10, 11].

Ultrasound is performed with microconvex or convex probe (Fig. 5.3). Patients are investigated in a semi-recumbent position or supine if intubated. The area of investigation includes three regions: frontal (zone 1), lateral (zone 2), and posterior-lateral (zone 3); each of these regions can be divided in a superior area and an inferior area.

5.3.1 Ultrasound Approach

Lung ultrasound provides a representation of the lung and is based both on images and artifacts. The generation of ultrasound artifacts by aerated lung tissue is the result of sound wave reflection and reverberation. Both these phenomena originate from the high-acoustic impedance interface between pre-pleural "watery" tissues and the aerated lung. The physical site of this interface is represented by the point of contact of the parietal and the visceral pleural layers. It appears ultrasonographically as a hyperechoic transverse line called "pleural line," located between and deep to the ribs. The pleural line generates the "bat sign," a landmark that indicates the parietal pleura. The normal lung surface associates lung sliding with horizontal repetitions of the pleural line, called A-lines. Lung sliding is a to-and-fro movement at the pleural line, spreading below. The M-mode helps to understand that this movement is relative to superficial tissues ("seashore sign"). In the absence of ventilation, pleural sliding is substituted by heartbeat-synced pleural motion called lung

pulse. The B-line, on the contrary, is the name given to a comet-tail artifact, arising from the pleural line, hyperechoic, well-defined, erasing A-lines and moving with lung sliding when lung sliding is present [12, 13]. It reflects the coexistence of elements with a major acoustic impedance gradient, such as fluid and air. Three or more B-lines in a single view are called B + lines. B + lines indicate an interstitial syndrome [12]. B-lines can be well spaced, crowded, or coalescent ("white lung" pattern). Four or five B-lines well spaced indicate an interstitial (edema, fibrosis) or an alveolar (pneumonia, atelectasis) disease; crowded B-lines are the same of ground-glass areas on CT [17]. Finally, "white lung" pattern is the sign of complete deaeration on CT [17].

Lung consolidations are fluid disorders and, therefore, are easily traversed by ultrasound. In the critically ill, consolidations are non-translobar or translobar, an important distinction because this generates different signs, each quite specific. The sign of non-translobar consolidation (most cases) is the shred sign: the border between consolidated and aerated lung is irregular, drawing the fractal line, fully opposed to the lung line. The sign of translobar consolidation is the tissue-like sign: it looks like the liver. The presence in consolidation of white dots/lines reinforced at inspiration ("dynamic air bronchograms") suggests a patent airway, whereas their absence equates to atelectasis.

Posterior and/or lateral examination on the contrary is useful for the analysis of pleural effusions. The application of a probe at the PLAPS-point, a posterior area accessible in supine patients, locating all free effusions, regardless their volume. This direct approach generates standardized signs: the quad and the sinusoid sign. The deep boundary of the collection is regular, roughly parallel to the pleural line, and is called the lung line (visceral pleura). This draws the quad sign. The lung line moves toward the pleural line on inspiration. This draws the sinusoid sign. Traditionally the effusions are anechoic; the most severe cases (empyema, hemothorax), on the contrary, are echoic. Valuation of effusion size is often difficult; in critically ill (supine patients) patients, the volume of the effusion can be calculated as the product of 20 for the maximum distance between pleural line and lung line.

5.3.2 BLUE Protocol

BLUE Protocol (Bedside Lung Ultrasound in Emergency) is an algorithm based on lung ultrasound that provides a direct approach to acute respiratory failure. This protocol is based on rapidity. Lung ultrasound immediately provided diagnosis of acute respiratory failure in 90.5 % of cases. Each cause of respiratory failure has a specific ultrasound profile that can be rapidly identified. The six profiles are:

A-Profile It associates anterior lung sliding with A-lines. It is a pattern compatible with pulmonary embolism. This pattern is associated with a condition of deep venous thrombosis and dyspnea provides a diagnosis of pulmonary embolism with 81 % sensitivity and 99 % specificity. However, CT scan remains the gold standard for the diagnosis of pulmonary embolism.

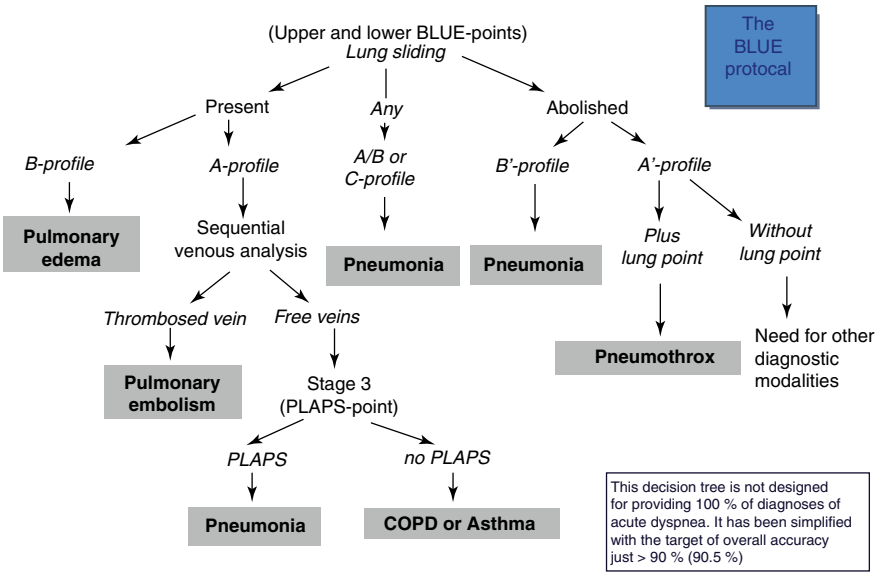

Fig. 5.4 BLUE protocol

A'-Profile It is an A-profile with abolished lung sliding and suggests a pneumothorax. The lung point in M-mode represents the pathognomonic sign of pneumothorax.

B-Profile It associates anterior lung sliding with lung-rockets B-pattern and provides a diagnosis of cardiogenic pulmonary edema with 100 % specificity.

B'-Profile It is a B-profile with abolished lung sliding and provides a diagnosis of pneumonia with 100 % specificity.

A/B Profile It is characterized by a half A-profile at one lung and a half B-profile at another; it is correlated with a pneumonia.

C-Profile Indicates anterior lung consolidation, regardless of size and number. It is characterized by a thickened, irregular pleural line.

BLUE protocol algorithm starts from valuation of lung sliding. If lung sliding is abolished, B'-profile is indicative of pneumonia, whereas A'-profile is indicative of a pneumothorax. If lung sliding is present, on the contrary, the B-profile is associated to a cardiogenic pulmonary edema, A-profile associated to a history of deep venous thrombosis indicates a pulmonary embolism, and finally both A/B profile and C-profile indicate a pneumonia (Fig. 5.4).

5.4 Diaphragm Ultrasound

The diaphragm is the main muscle that powers breathing, and, for this reason, an impaired function of this muscle can lead to respiratory complications and often prolong the duration of mechanical ventilation [19, 20]. Several conditions can lead to alterations in diaphragmatic function: nerve damages, neuromuscular disorders, cardiac and abdominal surgery, polyneuropathy, and mechanical ventilation [21–24]. Bedside ultrasonography, which is already crucial in several aspects of critical illness, has been recently proposed as a simple, noninvasive method of quantification of diaphragmatic contractile activity. For the valuation the convex probe is placed below the right or the left costal margin along the midclavicular line. M-mode is used to display diaphragm excursion.

5.4.1 Assessment

Physiologically the diaphragm moves toward the probe during inspiration and away from it during expiration. Ultrasound may be used to measure diaphragmatic excursion, the thickening of the diaphragm, and the speed of diaphragmatic contraction. The values of diaphragm excursion in healthy individuals were reported to be 1.8 ± 0.3, 7.0 ± 0.6, and 2.9 ± 0.6 for men and 1.6 ± 0.3, 5.7 ± 1.0, and 2.6 ± 0.5 for women, respectively, during quiet, deep, and voluntary breathing [25]. In mechanically ventilated patients, evaluation of diaphragmatic motion sometimes necessitates to briefly disconnect the patient from the ventilator to better visualize spontaneous breathing efforts. The slope (speed) of diaphragmatic contraction, during quiet breathing, has been measured at 1.3 ± 0.4 cm/s in forty healthy individuals without any significant differences between males and females [26].

The diaphragmatic thickness (tdi) can be measured during quiet spontaneous breathing and during a maximal inspiratory and expiratory effort. To obtain adequate images of diaphragmatic thickness in M-mode and 2D mode, a linear high-frequency probe (>10 Mhz) is necessary. The diaphragmatic thickness is evaluated in the zone of apposition, the area of the chest wall where the abdominal contents reach the lower rib cage. In this area, the diaphragm is observed as a structure made of three distinct layers: a non-echogenic central layer bordered by two echogenic layers, the peritoneum, and the diaphragmatic pleura [27]. In normal individuals, there is a wide range of tdi at functional residual capacity (FRC), ranging between 1.8 and 3 mm. As lung volume increase from the residual volume (RV) to total lung capacity (TLC), there is a mean tdi increase of 54 % (range, 42–78 %).

Measurement of tdi alone, however, may lead to false-negative results in the setting of acute paralysis where atrophy has not yet occurred or to false-positive results

in small individuals, since tdi varies with weight and height. Due to the above limitation, to safely diagnose diaphragmatic paralysis, diaphragmatic thickening (Δtdi) or thickening fraction (TF) should be calculated during inspiration according to the formula:

$$\mathrm{TF} = \left[\mathrm{tdi}\left(\mathrm{TLC}\right) - \mathrm{tdi}\left(\mathrm{FRC}\right)\right] / \mathrm{tdi}\left(\mathrm{FRC}\right).$$

The change in Δtdi strongly correlates with changes in vital capacity and the maximal inspiratory pressure reflecting inspiratory muscle strength [28].

5.4.2 Diaphragmatic Sonography in ICU

Sonography is a simple, noninvasive alternative method of diaphragmatic imaging, ideal for repeated or prolonged examinations, such as those required for the diagnosis and follow-up of uni- or bilateral diaphragmatic paralysis. Traditionally, methods to diagnose diaphragmatic weakness and paralysis examine the thoracic and abdominal pressures generated during spontaneous inspiration. Measurement of transdiaphragmatic pressure (Pdi) remains the gold standard for diagnosing bilateral diaphragmatic paralysis. However, Pdi is poorly sensitive and thus ineffective to diagnose unilateral diaphragmatic paralysis. In this context, chest radiographs have a sensitivity of 90 % and a specificity of only 44 % in detecting unilateral diaphragmatic paralysis [29]. Ultrasound has been used to assess the motion of the diaphragmatic dome. In unilateral or bilateral diaphragmatic paralysis, the negative pressure generated by the other respiratory muscles during inspiration causes the diaphragm to passively move cranially instead of its normal caudal movement [25]. The M-mode trace of the paralyzed side shows the absence of active or a paradoxical movement. Moreover, the M-mode tracing of the diaphragmatic movement direction (cranial vs caudal) allows distinguish diaphragmatic weakness from paralysis. During inspiration, in patients with diaphragmatic weakness, one observes a reduced diaphragmatic caudal movement and in patients with diaphragmatic paralysis, a paradoxical motion.

Sonography may also be of help during weaning from mechanical ventilation. Patients with adequate spontaneous tidal volume but poor diaphragmatic excursion were more likely to fail a breathing trial compared to patients with adequate spontaneous tidal volume and good diaphragmatic movements; this can be explained by the fact that spontaneous tidal volume represents the result of the combined activation of all respiratory muscles used without specifically measuring the contribution of the diaphragm, whereas diaphragmatic excursion represents the final result of combined diaphragmatic strength, intrathoracic and intra-abdominal pressures. Patients who recruit accessory respiratory muscles to maintain adequate tidal volumes may therefore experience more difficulties to sustain spontaneous breathing and fail extubation more often [22].

Overall, lung ultrasound represents a valid help for the intensivists for approach to acute respiratory failure, evaluation of respiratory complications, daily follow-up, and weaning from mechanical ventilation.

5.5 Electrical Impedance Tomography

Computed tomography (CT) has increasingly gained importance during the past 25 years as a diagnostic tool in the clinical assessment of pulmonary diseases. This represents a means of primary importance for both diagnostic and research purposes.

CT makes possible to correctly evaluate almost every pneumatological disease through a biplane view of the thorax. This is clearly in contrast with the traditional monoplane images provided by common radiographies. The densitometric evaluation of each constituent of the thorax (expressed in Hounsfield) is also feasible trough CT.

Moreover, the appliance of CT to adult respiratory distress syndrome (ARDS) gave a great drive to our knowledge. In particular it allowed shedding light on both the physiopathology of ARDS and the morphological and functional consequences of common maneuvers used during its treatment (i.e., prone position).

Despite that CT is not feasible for a bedside application, with the single exception being represented by some niche devices employed in neurointensive care units, it requires the transfer of a patient to the department of radiology, it produces static images (therefore not being serviceable as a monitoring tool), and, most importantly, it entails a significant risk for the patient to be exposed to radiation and, in some cases, to contrast agents.

Electrical impedance tomography (EIT) is a potentially revolutionary technique within the framework of mechanical ventilation. Albeit it is rapidly moving from research laboratories to clinical practice, it is still waiting for a thorough validation for clinical purposes.

Generally speaking, EIT features a technique that provides an image of the electrical conductivity of a body part through the measurement of surface electrical currents. Usually, some conductive electrodes are placed on the skin of the patient, and a slight alternating current is applied to some or all of them. Resulting electrical potentials are measured, thereby providing a map of the electrical conductivity of the analyzed area. The reported process might be repeated with different configurations of applied currents.

The potential availment of EIT for medical imaging purposes is attributed to a scientific paper published in 1978 by John G. Webster et al. Nevertheless, the first realization of an EIT in human healthcare dates back to 1984 being documented in a work by David C. Barber and Brian H. Brown.

Barber and Brown developed the first EIT device, namely, the Sheffield Mark 1, in the early 1980s. Henceforward, prototypes were used for disparate purposes, among the others the evaluation of gastric emptying, the screening of breast cancer, and the study of pulmonary perfusion and that of myocardial or cerebral function. It is noteworthy that a few decades earlier Kubicek developed the "tissue impedance technology" for NASA in order to monitor circulatory performance during spaceflights.

From the middle of the 1990s, the EIT group from Gottingen, directed by G. Hellige and G. Hahn, produced the first digital prototype (the GOE MF II), and in 2001 the same group started a research partnership aimed to bring the

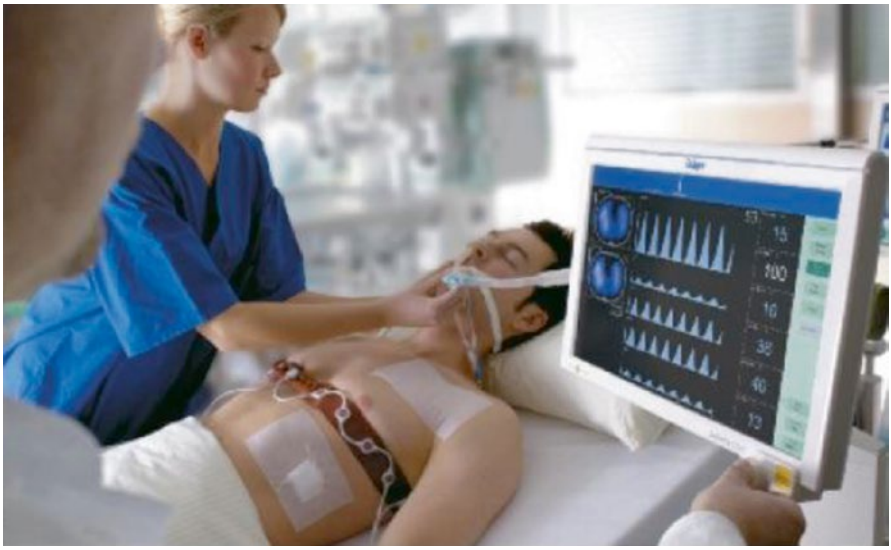

Fig. 5.5 Electrical impedance tomography: the instrument

prototypical production to the bedside. They succeeded in their purpose in the early 2010 with the production of a currently available device suitable for clinical practice: the Drager PulmoVista 500 (Fig. 5.5).

5.5.1 Theory

The electrical conductance (the physical dimension which expresses the ratio between the intensity of an electric current and that of an electric field) and the permittivity (the physical dimension which describes the behavior of a dielectric material in the presence of an electric field, i.e., the tendency of the material to counteract the intensity of the electric field present in it) of a biological tissue vary with the change of the tissue's characteristics, principally depending from temperature and physiologic factors. As an example lungs are less conductive when alveoli are filled with air.

EIT involves the use of relatively slight current which is below the threshold for nerve stimulation. Moreover, frequency is high enough to avoid causing electrolytic effects in the body. Lastly, the ohmic power is low and scattered enough on the body surface that the corporeal thermoregulatory system easily counteracts for its effect.

The application of the stimulus requires a power source, which is interposed among couples of electrodes, a converter (from potential to current), and a controlled input obtained through a converter (from digital to analogic). The measurement may employ a single voltage assessment or the use of coupled electrodes. Recent systems can directly convert the alternating signal thereby realizing the demodulation digitally.

In EIT some adhesive electrodes are placed on the patient's skin, and an alternating electrical current is applied among two or more of them. The current is usually few milliampére (mA) in intensity and is characterized by a frequency ranging from 10 to 100 kilohertz (kHz).

The reported sequences are repeated through several "stimulation patterns," e.g., through the consecutive stimulation and interrogation of subsequent couples of electrodes.

5.5.2 How Thoraco-Pulmonary Application Works

The EIT principle is based on electrical voltages measurement on the thorax surface. The impedance is measured between two electrodes (injector and detector) applying a known current and then determining the resulting voltage.

Since electrodes are placed in circle around the thorax, if we apply this rule to pairs of adjacent electrodes (13 pairs overall), we obtain 208 measured values, which represent an image of a transversal section composed of multiple points.

Thanks to a complex elaboration of the obtained data and their disposal on a pixel matrix (pixels are the punctiform elements which build the digital image represented on a screen), the regional distribution of pulmonary impedance is graphically represented. Obviously, sequences may continuously follow one another as time goes, giving a moving representation of impedance variations in a "bidimensional way": during time and in different areas of the lung.

EIT data are therefore processed into bidimensional images, which represent the distribution of thoraco-pulmonary electric impedance.

Lungs own peculiar electrical properties which, besides, periodically change during ventilation. This distinctive feature makes EIT scans particularly suitable in studying the pulmonary function.

In fact, the pulmonary impedance varies as pulmonary air content changes. An inspiration from residual volume (RV) to total lung capacity (TLC) amplifies the regional bioimpedance of the thorax up to 300 % (notably, the heart only accounts for a 3 % variation moving from systole to tele-diastole).

Throughout each breath, the air content of the lungs increases or decreases in relation to functional residual capacity (FRC) during inspiratory or expiratory phases, respectively.

Every point change in the pulmonary air content is corresponded by a variation in the thoracic electrical impedance. This occurs either relative to an immediately preceding or following value as well as to a basal value assumed as a reference (e.g., the measured end-expiratory bioimpedance).

It follows, intuitively, that a relation becomes established between the instantaneous pulmonary volume and the corresponding thoracic impedance on one hand, and between the pulmonary volume variation and the corresponding variation of the thoracic impedance on the other. The graphic representation of pulmonary aeration that results, introduces a list of measurable parameters, equations and computations, which makes EIT resemble the better-known parameters of respiratory mechanic.

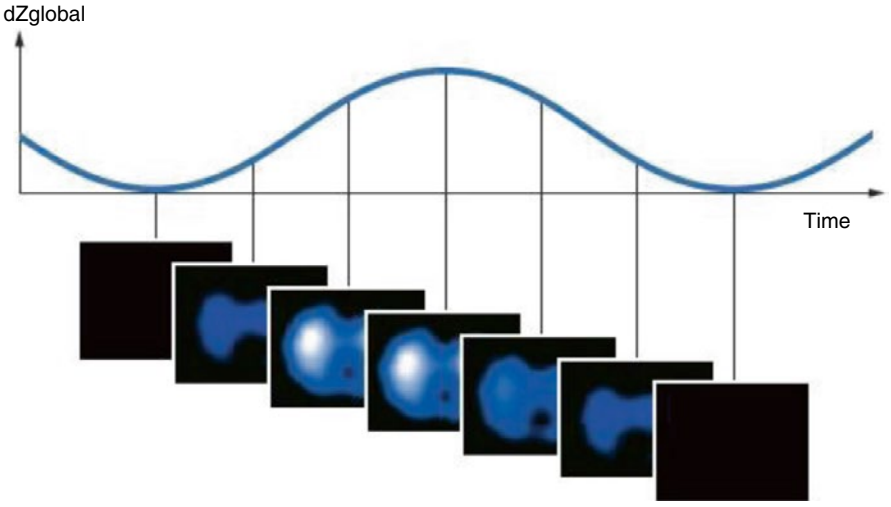

Fig. 5.6 Impedance waveform

EIT data are therefore processed into bidimensional images, which represent the distribution of thoraco-pulmonary electric impedance. Lungs own peculiar electrical properties witch, besides, periodically change during ventilation. This distinctive feature makes EIT scans particularly suitable in studying the pulmonary function. In fact, the pulmonary impedance varies as pulmonary air content changes. An inspiration from residual volume (RV) to total lung capacity (TLC) amplifies the regional bioimpedance of the thorax up to 300 % (notably, heart only accounts for a 3 % variation moving from systole to tele-diastole). Throughout each breath, the air content of the lungs increases or decreases in relation to functional residual capacity (FRC) during inspiratory or expiratory phases, respectively. Every point change in the pulmonary air content is corresponded by a variation in the thoracic electrical impedance. This occurs either relative to an immediately preceding or following value as well as to a basal value assumed as a reference (e.g., the measured end-expiratory bioimpedance). It follows, intuitively, that a relation becomes established between the instantaneous pulmonary volume and the corresponding thoracic impedance on one hand and between the pulmonary volume variation and the corresponding variation of the thoracic impedance on the other. The graphic representation of pulmonary aeration that results introduces a list of measurable parameters, equations, and computations, which makes EIT resemble the better-known parameters of respiratory mechanic.

A "static" image can quantify the distribution of regional ventilation taking as landmark of the beginning and the end of the inspiration. In EIT the chest representation is similar to CT scan. As in CT scan, in fact, the chest can be divided in three or four regions (ROI, regions of interest), and it is possible to independently evaluate aeration and impedance in each of these regions. The analysis of impedance

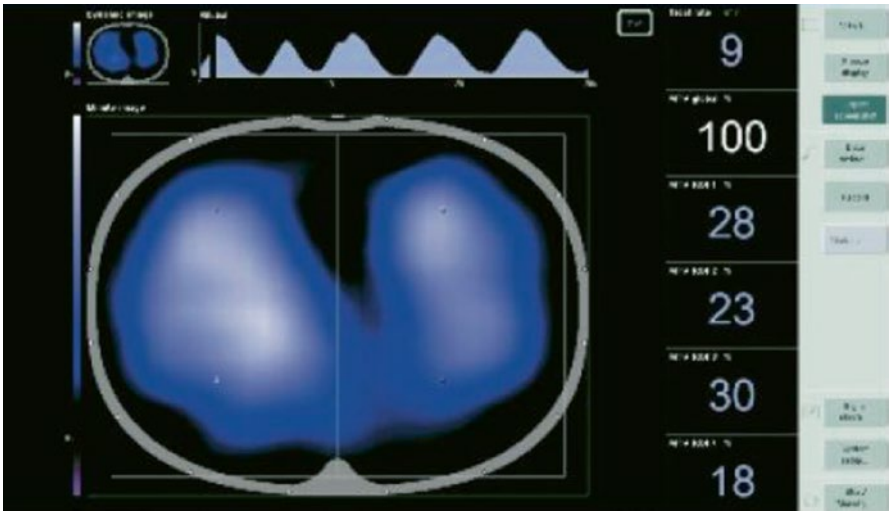

Fig. 5.7 Screen view

waveform (Fig. 5.6) shows, globally or in the different ROI, impedance changes caused by ventilation.

The global waveform relates well with the volume curve represented on the ventilator (timing and events), and it is shown on the EIT display in analogy to pressure, volume, and flow morphologies. The four different morphologies of lung regions are used for comparison of impedance variations: if there is lung heterogeneity, the morphology and the time delay between tracks give information about areas in delayed alveolar filling.

The EIT has been shown to correlate well with computed tomography (CT scan) to evaluate changes in the volume of gas and intrapulmonary tidal volume [35]. This technique gives the possibility to assign numerical values to impedance variations: there are parameters that describe the distribution of ventilation, giving the possibility to optimize settings of ventilation.

In a recent paper, Blankman studied the utility of different parameters derived from EIT in defining the "best PEEP" during a decremental PEEP trial in ventilated patients [36] (Fig. 5.7).

After filtration of impendentiometric signal, the change in recorded impedance represents the inspiratory and expiratory phases by total impedance variation (TIV):

$$\text{TIV} = \text{max impedance} - \text{Minimum impedance}$$

Regional compliance is based on the possibility of EIT to be computed and represented in different regions of the chest, even just in dependent and nondependent segments. In analogy to dynamic compliance, the regional compliance can be calculated by dividing the regional TIV for the pressure differential.

$$\text{Regional compliance} = \text{Regional TIV} / \text{Over PEEP pressure}$$

When regional compliance decreases with PEEP incrementation, it is likely lung hyperinflation; on the contrary, regional compliance reduction with PEEP decrease indicates alveolar collapse.

An image of regional impedance is constituted by pixels, and these can be identified as being representative of aeration (ventilated pixels) or absence of aeration (unventilated pixels). Therefore, it is possible to assign a value to the ventilation surface area (VSA): if this value increases with PEEP increase, there is a recruitment; if this value increase (or remains constant) with PEEP decrement, there is a hyperinflation. More complex calculations give the possibility to calculate the regional ventilation delay (RVD), that is, the time required to reach the 40 % of the regional variation of impedance. Large differences in RVD in different areas of the lung indicate irregular ventilation. The inspiratory part of TIV, appropriately divided in eight equal segments, gives the possibility to calculate the percentage contribution to the inspiratory phase in dependent and nondependent regions. It is also possible to calculate the intratidal gas distribution index (ITV), a measure of the lung in homogeneity.

The center of ventilation (VOC) reflects the distribution of tidal volume in ventral-dorsal direction. It is calculated dividing the TIV of dependent regions for the total TIV:

$$\text{VOC} = \text{TIV dorsal} / \text{TIV total}$$

In a model of ventilation where the ventilation is distributed above all in nondependent regions, VOC is high. During recruitment or PEEP, trial is possible at VOCs movement.

To quantify the distribution of ventilation in lungs, Zhao has developed the global inhomogeneity index (GI index) [37], which computes the change in pixel impedance compared with the overall change for each image. The smaller is the GI index, the more homogeneous is the ventilation.

Blankman has shown how, using EIT parameters in a number of cardiac surgical patients in the postoperative phase, one can view the "best PEEP" (considered as the minimum alveolar collapse and the minimum overdistention) in the aim to minimize the damage from ventilation (VILI, ventilator-induced lung injury).

Since in a "PEEP trial," the maintenance of a reduced tidal volume and a pressure less than 30 cmH_2O does not protect the totality of patients by overdistention (and therefore from alveolar damage), ITV assumes a great importance because it is able to recognize the start of overdistention in dependent areas and the recruitment in dependent areas. EIT gives the possibility to represent the geography of spontaneous breathing effects on the distribution of ventilation.

In a case report [38], this technique showed the disappearance of ventilation in dorsal regions when spontaneous breathing was discontinued in a patient in APRV ventilation for ARDS. The dominance of distribution of controlled ventilation in ventral regions is well known, but it is remarkable to show it during sedation or introduction of controlled ventilation. As is well known, especially in patients with ARDS, the common and frequent maneuvers of endotracheal suction may induce alveolar derecruitment which often heavily penalize gas exchanges.

In two subsequent papers, Lindgren measured variations in lung volume and compliance with EIT and demonstrates the validity of this technique in showing rapid changes resulting from the operations of suction and, later, he monitors the quick alveolar derecruitment and the slow alveolar re-recruitment that is induced by the same maneuvers [39, 40]. EIT is an interesting application also in monitoring variations in regional ventilation in patients placed on the side or pronated. For example, the visual identification of "responder" to pronation in patients with acute lung injury is important [41]. EIT is probably a revolutionary method in monitoring of mechanical ventilation. Already available in clinical practice, EIT represents a step forward in the rapidly changing, perhaps the "Holy Grail" of technique in monitoring mechanical ventilation [32]. The same Marini [41], in a recent review, analyzing the lessons learned from 50 years of mechanical ventilation, puts the EIT in emerging technologies, as a tool for monitoring regional dynamic inhomogeneous lung.

Conclusions

The monitoring of vital function and physiological parameters has grown exponentially since the technology gave it a great support. Electronics, electromagnetic waves, and optics are so important in this context that biophysics have become an essential component in critical care. It is mandatory not to give discomfort to the patient, by trying to avoid invasiveness when possible, but at the same time to give the physicians precise parameter's assessment in order to guide the diagnostic and therapeutic management. In accord with these considerations, the techniques described in this chapter represent useful bedside tools in approaching respiratory disease pathophysiology.

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Protective Mechanical Ventilation in Brain Dead Organ Donors

6

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6.1 Introduction

Mechanical ventilation is the procedure to assist or replace spontaneous breathing in all clinical conditions where the function of the lungs to remove carbon dioxide and supply oxygen is compromised. Originally developed to manage the respiratory consequences of anesthesia [1], the use of mechanical ventilation to manage patients with acute respiratory failure during the 1952 epidemic of poliomyelitis in Copenhagen decreased mortality from 80 to 40 % [2]. Since then mechanical ventilation became a mainstay for patients with acute respiratory failure, including patients with severe brain injury and brain dead subjects who may become potential organ donors.

The main indication for ventilatory support in patients with severe brain injury is to treat the respiratory dysfunction consequent to cerebral damage since adequate control of blood gas exchange prevents secondary brain insults.

In this prospective, optimization of ventilatory management for potential lung donors may represent an effective intervention to increase the number of lung transplants decreasing the time spent on the waiting list and mortality rate of lung recipients.

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6.2 Epidemiology

Almost 10 % of patients with severe brain injury evolve into brain death: often the clinician, once made the diagnosis of brain death, matches the required criteria for organ donation, but at the end of the period required for death diagnosis (6 h according to Italian law) has to face with signs of organ dysfunction of the lung. That may preclude donation of the organ itself [3]. While the percentage of dysfunction of other organs (heart, liver, and kidneys) is between 30 and 40 %, the rapid deterioration in pulmonary function causes a reduction of 75–80 % of the lungs eligible for transplantation: therefore, only 15–20 % of the lungs can be used for transplantation [4]. Recent experimental and clinical data suggest that this phenomenon may also be due to iatrogenic injury caused by mechanical ventilation [4]. In this perspective, the optimization of ventilatory management of potential donor would be a real tool to increase the number of lung transplants, reducing waiting times and mortality of patients listed for lung transplantation.

6.3 Pathophysiology of Lung Damage Following Acute Brain Injury Evolving to Brain Death

Brain death results from damage to the brain stem with complete irreversible loss of its function. After this devastating event, a series of systemic consequences may occur with a negative effect on the peripheral organs.

A massive and immediate activation of the sympathetic system follows the primary injury to the brain [5]. The initial period of arterial hypertension is followed by a progressive decrease of arterial pressure until severe hypotension is reached due to systemic vasodilation [6, 7]. The acute increase in intracranial pressure induces a transient increase in systemic intravascular pressure that damages the endothelium enabling protein-rich plasma to escape into the interstitial and alveolar space [8].

The so-called “blast injury” theory may explain the coexistence of hydrostatic and high permeability mechanisms of edema: the degree of capillary hypertension determines whether unbalanced Starling forces increase water flux across the endothelium or whether structural damage of the capillary wall allows plasma to escape into the interstitium and alveolar space [9].

Later on Fisher and coworkers found higher level of IL-8 in the bronchoalveolar lavage of brain dead donors compared to ventilated non-brain dead patients. These data led to the hypothesis that upregulation of the inflammatory reaction also plays a role in the development of peripheral organ failure associated with brain damage [10].

Several data support this hypothesis: an increased intracranial production of proinflammatory cytokines resulting in secondary cerebral insults and the alteration of blood–brain barrier occurring after traumatic brain injury causes release of inflammatory mediators into the systemic circulation leading to peripheral organ damage [11–15].

6.3.1 The Double-Hit Model

To explain the development of organ failure associated with severe brain injury evolving to brain death, a "double-hit" model has been proposed integrating the above-described experimental and clinical evidence [16, 17].

The first hit is represented by the systemic consequences of the sympathetic storm and the pro-inflammatory environment caused by brain injury eventually evolving to brain death. Once "primed" the respiratory system is then vulnerable to further inflammatory insults caused by mechanical stress induced by mechanical ventilation. A vicious circle may therefore be activated: the deterioration of the respiratory function may worsen damage of the central nervous system that will result in distal organ failure. In this prospective, the lungs represent an organ particularly susceptible to receive further insults if mechanical ventilation is not applied with a protective modality [17].

In a model of traumatic brain injury, membrane lipid peroxidation, nuclear chromatin degeneration, vacuolar degeneration of subcellular organelles, and downregulation of antiapoptotic genes have been demonstrated in type II alveolar cells [18, 19]. In a rat model of intracerebral hemorrhage, Wu and coworkers showed increased expression of inflammatory mediators and neutrophil infiltration both in the brain and lung [20]. In an experimental model of ischemic stroke, lung water content was significantly increased compared to control [21]. Kalsotra et al. in an experimental model of cortical impact injury found altered lung permeability, marked migration of neutrophils, and activated macrophages in the alveolar space [22].

All these data led to the conclusion that the acute brain injury should induce cellular changes and function in the lungs. Another line of research has instead focused the attention on the role of mechanical ventilation after acute brain injury. Quilez and coworkers demonstrated that an injurious mechanical ventilation may induce neuronal activation in the amygdala, thalamus, and paraventricular hypothalamic nuclei in intact animals [23]. Heuer and coworkers showed neuronal shrinkage in the hippocampus region of previously healthy animals with acid aspiration-induced lung injury.

In addition to these experimental studies on animal models, there are clinical data that demonstrate the susceptibility of the respiratory system after acute brain injury. In patients with cerebral hemorrhage, evidence of acute lung edema has been demonstrated by extravascular lung water accumulation [24], while in patients dying at the scene and within 96 h of acute brain injury, evidence of elevations in lung weights has been shown [25]. More recently, Mascia and coworkers demonstrated that patients with acute brain injury are more susceptible to develop respiratory failure (47 %) than a general population of critically ill patients (38 %) [26].

6.3.2 The Role of Mechanical Ventilation

The main indication for ventilatory support in patients with severe brain injury is to treat the respiratory dysfunction consequent to cerebral damage. Under these circumstances, an adequate ventilatory setting to guarantee tight control of blood gas

exchange helps in preventing secondary brain insults. However, in patients with a diagnosis of brain death, mechanical ventilation is used to maintain gas exchange that ensures homeostasis of the peripheral organs.

There has been increasing evidence that the mechanical forces necessary to inflate the lung during ventilatory support can cause damage – so-called ventilator-induced lung injury (VILI) – and this damage may worsen outcomes [27]. This phenomenon is more evident in pulmonary conditions characterized by a nonhomogeneous distribution of lung damage such as ARDS. In these patients it is well established that a ventilatory strategy designed to minimize VILI by applying a tidal volume of 6 ml/kg of predicted body weight (PBW) and plateau pressure <30 cmH_2O improves outcome [28]. Later on, the hypothesis that VILI may occur also in "normal" lungs has been made. This hypothesis has generated some studies on the effects of protective mechanical ventilation during general anesthesia. The major goal was to apply the theories "of open lung approach" derived from mechanical ventilation of patients with ARDS to organ donor lungs ventilated for a short period of time.

To date, all these studies demonstrated that in patients who underwent mechanical ventilation for elective surgery or in the ICU, protective ventilation strategy with low tidal volume significantly reduced mortality, pulmonary infection, and atelectasis [29]. On the contrary, the level of optimal PEEP is still controversial.

Regarding the relationship of mechanical ventilation with brain damage, recent experimental studies showed that VILI may also impact brain structure and function. Lung stretch-induced hippocampal apoptosis has been demonstrated in mechanically ventilated animals with high pressure. Models of coexisting lung and brain acute injuries show that lung damage is worsened by the copresence of brain injury. Lopez-Aguilar and coworkers demonstrated that massive brain injury might increase lung vulnerability to subsequent injurious mechanical or ischemia–reperfusion injuries increasing the risk of posttransplant primary graft failure [30]. Heuer and coworkers demonstrated that acute intracranial hypertension damaged previously normal lungs and exacerbated the damage in lungs with preexisting lesions [31]. Krebs and coworkers demonstrated that protective ventilation minimized lung morpho-functional changes and inflammation in the presence of massive brain injury compared to conventional ventilation [32].

Traumatic brain injury has been definitively identified as a predisposing factor for ARDS [33]. Recently, Rincon et al. reported that the occurrence of this complication carried a higher risk of in-hospital death after brain injury [34]. In a prospective observational study in patients with severe brain injury, Mascia and coworkers demonstrated that injurious mechanical ventilation was a contributing factor to the development of ARDS and that patients with this complication were more dependent from ventilatory support and spent more days in the ICU [35]. Similar results were also demonstrated in potential organ donors. In an observational study conducted in 15 Italian ICUs, after diagnosis of brain death, cardiovascular management was modified to preserve peripheral organ perfusion, while ventilatory management was not modified from a "cerebral protective" to a "lung protective" strategy, and no maneuvers for recruiting the lung and preventing mechanical stretch

were performed. Consequently during the 6 h period required by the Italian law for brain death confirmation, 50 % of potential lung donors became ineligible for lung donation due to deterioration in oxygenation [16]. These data strongly support the notion that activation of the innate immune system after brain injury causes distal organ injury through the release of inflammatory mediators even without macroscopic evidence of organ damage and suggest that mechanical ventilation may affect lung function of potential organ donors predisposing to posttransplant primary graft failure. Therefore, the lungs primed by an inflammatory response elicited by brain injury could be further injured by sequential noxious stimuli leading to lung failure and ARDS.

6.4 Ventilatory Management of Potential Organ Donors

As the number of patients waiting for lung transplantation exceeds the number of organs available, recently several approaches have been proposed to increase them. These are protective mechanical ventilation, expansion of donors including patients who died after cardiac arrest, and pulmonary reconditioning techniques (EVLP) using marginal lungs [36].

The technique called EVLP (ex vivo lung perfusion) uses a chamber in which the lung of the donor to be reconditioned for 4 h during the treatment of perfusion and ventilation is placed. Also in this case protective mechanical ventilation is proposed (7 ml/kg PBW of the donor, FiO2 of 0.2, and respiratory rate of 7 breaths/min) with a recruitment maneuver per hour. The lungs are considered eligible for transplantation if at the end of four hours the lungs have a $P/F \geq 350$ with a tidal volume of 10 ml/kg.

Protective ventilation applied to the donor after brain dead diagnosis is at the moment the approach proposed mainly to the ideal donors to preserve their function.

The standards for donor lung transplantation are represented by a person with age <55 years, the PaO_2/FiO_2 ratio >300, nonsmoker or former smoker for at least 20 years, a negative chest X-ray for pulmonary condensations, absence of purulent pulmonary secretions, and negative microbiological tests [37, 38].

In donors who meet these criteria at the beginning of the observational period required for brain death diagnosis, clinicians should avoid the deterioration of lung function, adopting a protective mechanical ventilation.

Often in potential donors, some conditions of hypoxemic lung injury can be observed, identified by chest X-ray: pulmonary infiltrates, atelectasis, and pulmonary edema. A recent study has highlighted the potential reversibility of two of the three types of lung injury. Indeed, if handled properly, edema and atelectasis can not only be limited in their evolution, but also potentially corrected by appropriate therapeutic interventions.

To understand the ventilatory approach used in the past for organ donors, it is useful to briefly recall that mechanical ventilation for patients with severe brain injury is oriented to a "cerebral protective" strategy in order to avoid hypoxemia and hypercapnia, thus limiting secondary insults to the brain. According to available guidelines [39], a $PaCO_2$ between 35 and 40 mmHg is usually obtained with high

tidal volumes and low respiratory rates, while a $PaO_2 > 90$ mmHg should be obtained with high FiO_2 and low level of PEEP to avoid interference with cerebral venous drainage. If patients with severe brain injury evolve to brain death, critical care management of the potential organ donors suggests that the priority should be shifted from a "cerebral protective" strategy to an "organ protective" strategy able to optimize organ donation. In this prospective, the lungs of potential organ donors may play a double role: the lungs are responsible for maintaining systemic homeostasis (optimal oxygenation and optimal acid–base balance), but the lungs act also as potential organs to be donated and such as they should be protected by further "hits" that can impair their function.

Traditionally only the maintenance of systemic homeostasis has been considered as a therapeutic target; indeed clinical management of potential organ donors is oriented to guarantee optimal oxygenation and perfusion rather than to primarily protect the cardiothoracic organs.

Following this approach, the report of Crystal City meeting recommended the following ventilatory strategy [40]: tidal volume between 8 and 15 mL/kg to maintain $PaCO_2$ between 35 and 40 mmHg and peak pressure lower than 30 cmH_2O and PEEP levels equal to 5 cmH_2O and elevated fraction of inspired oxygen (FiO_2) in order to guarantee O_2 saturation higher than 95 %. Apnea test for brain death declaration is performed disconnecting the patient from the ventilator with high-flow oxygen, and besides bronchoscopy, frequent suctioning and aspiration precautions are also recommended. These guidelines are not substantially different from the above-quoted Brain Trauma Foundation guidelines for management of traumatic brain injury patients. Although after brain death declaration the ventilatory strategy is no more oriented to cerebral protection, the shift proposed is mainly oriented to guarantee systemic homeostasis. The adherence to the international guidelines for organ donor management has been verified in a multicenter observational study which confirmed that the ventilatory and hemodynamic management of potential organ donors was coherent with published recommendations and might have been suboptimal in preserving lung function. Therefore a potential conflict of interest may exist between the priority to maintain systemic homeostasis (optimal gas exchange and acid–base balance) and the priority to protect the lungs based on the robust evidence that VILI may occur also in "normal" lungs at risk to develop ARDS predisposing to posttransplant primary graft failure.

Recently a multicenter randomized controlled trial compared the use of a protective ventilatory strategy to the conventional strategy proposed by the international guidelines in potential organ donors [41]. The protective strategy included low tidal volume (6–8 mL/kg of predicted body weight), PEEP equal to 8–10 cm H_2O, the use of closed circuit for tracheal suction, alveolar recruitment maneuvers after any disconnection, and the use of continuous positive airway pressure during apnea test. The application of this strategy increased the number of eligible and transplanted lungs, while the number of transplanted hearts, livers, and kidneys was similar in both groups [41].

In the same prospective, several studies have proposed to extend lung donor criteria and to apply protocols to fully recruit the lungs. Angel and coworkers proposed the San Antonio Lung Transplant (SALT) protocol applying levels of PEEP up to

15 cmH_2O, limiting inspiratory pressure to 25 cmH_2O with neutral fluid balance, head elevation at 30°, and inflation of the endotracheal cuff at pressure of 25 cmH_2O; this approach compared with the 4-year period before the implementation of the protocol increased the rate of lung procurement from 12 to 26 % [42]. Noiseux and coworkers demonstrated that lung recruitment maneuvers (two deep inflations at pressure of 30 cmH_2O for 30 s followed by 1 h of mechanical ventilation with peak pressure <30 cmH_2O and PEEP of 10 cmH_2O) resulted in a significant increase in rate of transplanted lungs from 20 to 33 % without affecting the homeostasis of other organs [43].

Paries and coworkers in a case–control study demonstrated that the application of one-lung recruitment maneuver performed just after apnea test (35 $cmH_2O \times 40$ s) improved oxygenation with transient side effects on systemic hemodynamics. Compared to the historical control, this maneuver improved the rate of lungs that met eligibility criteria for transplantation.

Minambres and coworkers in a cohort study with historical control demonstrated that a protocol with tidal volume of 8 ml/kg, PEEP of 8–10 cmH_2O, apnea test performed with continuous positive airways pressure, recruitment maneuvers performed every 2 h and after disconnection from the ventilator, negative fluid balance, and hormonal replacement therapy increased the rate of the lungs eligible for transplant without adverse effect on kidney graft survival [44].

Bernard and colleagues proposed the use of beta 2 agonists, assuming that they could reduce the incidence of edema and could therefore increase the values of *P*/*F* of donor's lungs, but one randomized study showed no improvement in oxygenation, without any increase of the number of transplantable lungs [45].

A recent review of Ruchi Bansal and colleagues proposed a ventilation of the potential donor to prevent overdistension using low tidal volumes and a plateau pressure <30 cm H_2O. The other objectives were the maintenance of an adequate alveolar recruitment with PEEP between 8 and 10 cm H_2O and the reduction of the potential toxic effects of oxygen by the use of low values of FiO_2 while maintaining the oxygen saturation between 92 and 95 % [46]. The most interesting aspect of the study was that the protocol was applied to ideal and marginal lungs for oxygenation.

This approach is coherent with the meta-analysis of Rech et al. which showed that in the management of the donor organ, protective mechanical ventilation is supported by the strongest level of evidence, while other strategies, such as hormone replacement therapy, currently have a less strong evidence [41, 47].

Conclusion

In conclusion, the low availability of transplantable lungs in relation to the number of patients waiting for transplantation has led to solutions to increase organ availability.

The main goal of ventilatory management of the potential organ donor, as pointed out by Slutsky and Ranieri [27], is the lung protection by the application of a low tidal volume equal to 6–8 ml/kg PBW associated with a PEEP of 8–10 cm H_2O to maintain *P*/*F* ratio >300, $PaCO_2$ between 35 and 40 mmHg, and a pH of

between 7.35 and 7.45. Bronchoscopy is necessary during the period of observation to investigate the anatomy of the lung, for the aspiration of secretions, and for the execution of microbiological tests. In order to prevent atelectasis, the use of a closed circuit for the tracheal aspiration, the execution of recruitment maneuvers after each disconnection from the ventilator, and the application of a continuous positive airway pressure during the apnea test are recommended. The hemodynamic management should be restrictive and appropriate to maintain hemodynamic values of CVP between 6 and 8 mmHg and PCWP between 8 and 12 mmHg. Indications for protective mechanical ventilation are supported by strong scientific evidence that recognizes the evolving brain damage in brain death as the predisposing factor for the development of ARDS. Moreover, an inappropriate mechanical ventilation may increase the risk of VILI in potential organ donor. Finally, the application of a protective mechanical ventilation should increase the number of transplantable lungs significantly, without affecting the number of other transplanted organs. This approach is based on a strong level of evidence and has gradually been adopted in recent guidelines.

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Management of Perioperative Arrhythmias

7

Fabio Guarracino and Rubia Baldassarri

7.1 Introduction

The perioperative period is defined as the length of time between the preoperative assessment and 36–48 h after surgery. Perioperative arrhythmias are one of the most common cardiac complications in noncardiac surgery. In addition, the arrhythmic events are a major cause of perioperative morbidity and mortality.

Although most of the perioperative arrhythmic events occur in patients undergoing lung surgery with more or less extensive resection of the parenchyma (lobectomy, pneumonectomy), disturbances of the heart rhythm can occur in any surgical setting.

Early detection of perioperative cardiac arrhythmias is fundamental. In fact, although the majority of the arrhythmic events are either self-limited or well tolerated in critically ill patients, malignant arrhythmias may cause severe cardiac dysfunction in some cases and can even lead to cardiac arrest (Table 7.1).

The arrhythmic events can also lead to severe haemodynamic alteration and increase the perioperative risk of the patients scheduled for noncardiac surgery.

The availability of systems for the continuous monitoring of the electrocardiogram (EKG) has allowed for real-time evaluation of any arrhythmic event occurring in either the operating room or the postoperative care units.

Prior to this, the true incidence of perioperative cardiac arrhythmias has long been underestimated. It should be considered that the evaluation of the heart rhythm was based on periodic EKGs recorded at more or less regular intervals of time [1].

In addition, the application of the Holter technique, which provides continuous recording of the heart rhythm, has allowed for the detection of arrhythmic events that occur outside of both the operating room and the intensive care units where the

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Table 7.1 Cardiac arrhythmias: classification

Site	*Supraventricular:* origin above the AV node (atrial or nodal)
	Supraventricular premature beats
	Paroxysmal supraventricular tachycardia (PSVT)
	Atrial fibrillation (AF)
	Atrial flutter
	Wolff-Parkinson-White (WPW)
	Ventricular: origin under the AV node
	Ventricular premature beats (VBPs)
	Ventricular tachycardia (VT)
	Ventricular fibrillation (VF)
Heart rate	Tachyarrhythmia (>100 b/min)
	Bradyarrhythmia (<50 b/min)

Table 7.2 Incidence of intraoperative arrhythmias

Bradyarrhythmias	Tachyarrhythmias	
Complete AV block	Supraventricular 90 %	Ventricular 10 %
AV block	AF 45 %	VT
	TR AV 35 %	VF
	Atrial flutter 8 % TA 1 %	
	TS 1 %	

AV atrioventricular, *BAV* atrioventricular block, *AF* atrial fibrillation

patients are under EKG monitoring. The data emerging from the recent literature report an incidence of perioperative arrhythmias of 10–30 % in cardiothoracic surgery versus 4–20 % in noncardiac surgery [2] (Table 7.2). Although cardiac arrhythmias can occur in healthy patients under stress conditions, such as surgery, temporary haemodynamic impairment and electrolyte disturbance, in most cases, the arrhythmic event is the expression of an underlying cardiac disease that may also be undiagnosed. For example, the majority of the hyperkinetic arrhythmias, such as atrial fibrillation (AF) and ventricular tachycardia (VT), are associated with a pre-existing cardiopulmonary disease. In the recent guidelines [2] for the perioperative management of cardiac patients undergoing noncardiac surgery, continuous EKG monitoring is highly recommended in all patients undergoing surgery (class IC). Still, according to the mentioned guidelines, EKG monitoring should start before either the induction of general anaesthesia or the performance of a peripheral block [3]. The early detection of arrhythmic events should be aimed at the evaluation of both the severity of the arrhythmia and the associated haemodynamic implications. The early detection and treatment of malignant, life-threatening arrhythmias are mandatory in surgical patients, especially those at high risk. An adequate haemodynamic support is required in cases of arrhythmias inducing severe cardiovascular dysfunction. The identification of the aetiological

Table 7.3 Diagnostic tools for the detection of arrhythmias

Electrocardiogram (ECG)
Echocardiography
Holter (dynamic ECG)
Event monitor (prolonged monitoring)
Tilt table test
Electrophysiological studies (EPSs)

mechanisms of malignant arrhythmias is aimed at correcting any electrolyte or metabolic imbalances as well as at the introduction of a specific antiarrhythmic therapy.

7.2 Diagnosis

The diagnosis of malignant arrhythmia is not always easy or immediate. In case of complex arrhythmias, the patients should be referred to the cardiologist for a careful evaluation of either the patient's clinical conditions or the ECG alterations. Adjunctive diagnostic tests could be necessary to achieve the diagnosis.

In this context, an accurate preoperative assessment of either a history of preexisting arrhythmias or clinical symptoms suggestive for alteration of the heart rhythm is mandatory in the patients enrolled for noncardiac surgery.

Intraoperative arrhythmias can lead to severe cardiovascular alteration that will require immediate diagnosis and treatment to restore haemodynamic stability. In the operative setting, diagnostic tests are not available. Therefore, the diagnosis of arrhythmia is based on the analysis of the ECG alterations, and, in selected cases, echocardiography can help to achieve the diagnosis.

Postoperative arrhythmias can be evaluated either by the direct analysis of ECG monitoring or by the performance of specific cardiac tests (Table 7.3).

It should be considered that the severity of either the cardiac arrhythmias or the associated cardiovascular impairments depends on several factors including the origin and type of arrhythmic event, the patient's clinical conditions and the type of surgery. Potentially harmful arrhythmias such as ventricular fibrillation (VF) and asystole induce severe cardiac dysfunction and can lead to cardiac arrest.

7.3 Ventricular Arrhythmias

In approximately 10 % of the patients with ventricular arrhythmias, an organic cardiomyopathy is not evident. The ECG pattern and the most common diagnostic tests (echocardiography, coronary angiography) are generally normal. In these cases, more advanced investigation with NMR can identify structural myocardial defects responsible for the arrhythmia.

Nevertheless, in the majority of the patients, the cause of the ventricular arrhythmia is underlying cardiac disease, including organic cardiomyopathy (dilated or

hypertrophic), myocardial scar and myocardial structural alterations [5, 6]. The most common ventricular arrhythmias are the ventricular premature beats (VPBs) and the VT.

VT can be classified according to:

- *The site of origin*: from the right ventricle (RV) or the left ventricle (LV). The VT arising from the RV outflow tract (RVOT) is the most common idiopathic VT [7].
- *The structural characteristics*: monomorphic, polymorphic, sustained and non-sustained.
- *The response to pharmacologic agents and catecholamines.*

Ventricular arrhythmias include clinical syndromes such as Brugada syndrome, Torsades de pointes (TdP) and long QT syndrome that are characterized by diagnostic altered ECG patterns [8].

7.3.1 Diagnosis

The preoperative detection of new-onset ventricular arrhythmias (VPBs, VT) requires a proper patient evaluation to identify acute or chronic myocardial ischaemia. Diagnostic evaluation with echocardiography and invasive tests such as coronary angiography with eventual myocardial revascularization are recommended in these cases. More specific electrophysiological tests are required in select patients.

7.3.2 Treatment

The management of ventricular arrhythmias depends primarily on the associated cardiovascular dysfunction.

- Isolated VPBs and non-sustained monomorphic VTs do not generally require any suppressive therapy because they are not associated with a worsening of the clinical outcome. The removal of the underlying trigger is generally sufficient to terminate the arrhythmias.
- In patients with a history of ventricular arrhythmias, the preoperative antiarrhythmic therapy should not be discontinued before surgery (class IC).

The American College of Cardiology/American Heart Association/ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend that:

- Sustained, monomorphic VTs with haemodynamic instability should be treated with *electric cardioversion*; *amiodarone* is indicated in haemodynamically stable patients.
- Immediate defibrillation is recommended to terminate VF and sustained polymorphic VT.

- In the case of recurrent episodes of sustained polymorphic VT, especially when myocardial ischaemia is either suspected or cannot be excluded, *beta-blockers* are recommended; *amiodarone* can be reasonably helpful when long QT syndrome is not present.
- In haemodynamically stable monomorphic VT, the use of amiodarone to prevent recurrences is indicated.

In cases of TdP, the following is recommended:

- Withdrawal of the underlying triggers (drugs, electrolyte disturbances) that is generally sufficient to terminate the arrhythmias.
- Intravenous *magnesium sulphate* is indicated in the presence of long QT syndrome.
- Recurrent pause-dependent TdP without long QT syndrome can be treated with *isoproterenol*.
- Patients with TdP and sinus bradycardia can receive *beta-blockers* and *temporary pacing*.

VT should always be suspected in the presence of wide QRS tachycardia of uncertain diagnosis. In these cases, the use of calcium channel blockers is contraindicated to terminate the arrhythmia, especially in patients with a history of myocardial ischaemia.

Electric storm (ES) can occur in patients who are refractory to medical therapy. ES is characterized by recurrent and very frequent (more than 3 in the 24 h) episodes of either polymorphic VT with haemodynamic impairment or VF requiring continuous defibrillation [9–11].

The causes of the ES are different, and they include myocardial ischaemia, myocardial scarring generating recruitment circuits and genetic predisposition to develop ventricular arrhythmias under stress conditions, which occurs in catecholaminergic polymorphic ventricular tachycardia (CPTV).

One of the causes of the ES occurring under stress conditions, such as surgical stress, is the increase in blood levels of catecholamines due to the activation of the sympathetic nervous system.

The use of an implantable defibrillator is the gold standard therapy for patients with ES. Because of the procedure-related complications, left cardiac sympathetic denervation (LCSD) has been proposed as a valid therapeutic option for those patients, especially young patients, who do not tolerate ICD [12–15].

In particular, thoracoscopic LCSD, which has been available since 1971, has been progressively improved in the last decades. This surgical technique consists of ablation.

7.4 Supraventricular Arrhythmias

Perioperative supraventricular arrhythmias are quite common and are more frequent than ventricular arrhythmias in patients undergoing noncardiac surgery. In most cases, the withdrawal of the trigger (perioperative respiratory failure, electrolyte alterations) is sufficient to terminate the arrhythmic event.

The association between perioperative neurologic events such as stroke and supraventricular tachyarrhythmias (ST) has been well documented [16]. Despite the increasing number of patients undergoing noncardiac surgery, studies of the incidence and complications of perioperative AF (POAF) in a large surgical population are still lacking [17]. POAF is the most common perioperative arrhythmia in noncardiac surgery patients [18, 19]. The cardiac arrhythmias occurring in noncardiac surgery strictly depend on the patients' clinical conditions and the type of surgery [1]. Approximately 10–20% of the patients who undergo noncardiac thoracic surgery experience POAF, and this is dependent on the type of surgery and the patients' characteristics (age, therapy with beta-blockers, cardiac valve disease and heart failure) [20–23].

New-onset POAF in noncardiac surgery patients has been associated with an increased risk of perioperative neurologic complications leading to an increased perioperative risk [24, 25].

7.4.1 Treatment

According to the current guidelines, the treatment of POAF should be aimed at the control of the ventricular heart rate. The use of *beta-blockers* and *calcium channels blockers* is recommended as the treatment of choice by the ESC guidelines on AF management [26].

The use of *amiodarone* is recommended in patients with heart failure, while *digoxin* is not helpful in surgical patients because of the increased perioperative adrenergic stress.

When surgery can be delayed, select patients with paroxysmal supraventricular tachycardia (PST) and AF can benefit from *transcatheter radiofrequency ablation* to remove the aetiological pattern of the arrhythmia.

According to the guidelines, supraventricular PBs do not require any therapy, and STs generally respond to vagal manoeuvres. In these cases, *adenosine* is effective to terminate the ST. The prophylactic use of *beta-blockers*, *amiodarone* and *calcium channel blockers* should be used in patients with recurrent ST.

AF with haemodynamic instability requires immediate electrical cardioversion. In the case of new-onset AF in patients undergoing noncardiac surgery, the use of beta-blockers appears to be associated with a high incidence of cardioversion to sinus rhythm [27].

7.5 Bradyarrhythmias

Perioperative bradyarrhythmias do not commonly require the implantation of a temporary or permanent cardiac pacing because they respond well to medical therapy. Cardiac pacing is recommended in the case of either complete heart block or episodes of symptomatic asystole. In asymptomatic patients with bifascicular blocks, with or without first-degree atrioventricular block, the prophylactic use of cardiac pacing is generally not recommended. In these cases, the use of external pacing for transcutaneous pacing is indicated before surgery.

7.6 Pacemaker and ICD

Patients with definitive cardiac pacing and/or ICD can safely undergo surgery, but require a careful management of the devices.

It is well known that the electrical stimulation induced by the use of the unipolar electrocautery can alter the function of the PM either suppressing or reprogramming the intracardiac device.

Some precautions can be taken to reduce the interferences with the PM/ICD function during surgery:

- Using bipolar electrocautery far from the site of the intracardiac device; employing brief bursts at the lowest amplitude possible.
- Setting the PM in the asynchronous or non-sensing mode in those patients who are PM dependent; in the operating setting, this can easily be done by positioning a magnet on the skin over the PM.

The same precautions should be taken in patients with ICD: the device should be deactivated before surgery and immediately switched on in the postoperative period. Additionally, an external defibrillator should always be available in the operating room when patients with ICD are submitted to noncardiac surgery.

In the case of elective surgery, the identification of the type of the device implanted and the evaluation of its effective functioning should always be performed before surgery.

In addition, the patients' clinical history should be investigated to understand why and when the device has been implanted.

7.7 Arrhythmogenic Syndromes of Anaesthesiological Interest (Brugada Syndrome, Long QT Syndrome)

As previously reported, although not all perioperative arrhythmias are severe or potentially life-threatening, some arrhythmogenic syndromes that occur during general anaesthesia can be critical. These syndromes represent a real challenge for the anaesthetists and require careful management because of their haemodynamic implications. The arrhythmic event can be triggered or worsened by either the most common drugs used during general anaesthesia or by the conditions typically associated with general anaesthesia, such as hypothermia, haemodynamic alteration and electrolyte disturbance. In addition, emotional and ambient perioperative stress can also initiate or worsen the cardiac arrhythmia.

In this context, the anaesthesiologist should know the pathophysiological pattern of the arrhythmic event to avoid any situation that can initiate or worsen it. Moreover, the proper management of the eventual emergency is mandatory.

These are generally inherited arrhythmias characterized by the malfunction of cardiac ion channels resulting in the alteration of intracellular homeostasis potentially leading to ES. Although these arrhythmias are genetically determined, they can be secondary to paraphysiological conditions or to the use of some drugs.

7.7.1 Brugada Syndrome

Brugada syndrome (BS) is a genetic disorder characterized by the alteration of cardiac ion channels, in particular those of sodium that can lead to life-threatening ventricular arrhythmias [28]. It has been recognized as the most common cause of sudden death with an incidence of 4 % in the world population and of 20 % in people without cardiac structural defects [29, 30].

BS is characterized by a typical ECG pattern with complete or incomplete right bundle branch block (RBBB) and ST-segment elevation detected in the right precordial leads (V1–V3). Three types of ECG patterns are recognized in BS: type 1 with coved ST-segment elevation ≥2 mm, type 2 with saddleback ST-segment elevation ≥2 mm and type 3 with ST-segment elevation <1 mm [30, 31].

In patients with BS, the ECG is generally normal, while the typical ECG alterations can be caused by the administration of sodium channel blockers or by the exposure to particular stress conditions, such as fever or the consumption of cocaine [32, 33]. BS typically occurs in patients without underlying cardiac disease, cardiac structural alterations, myocardial ischaemia or electrolyte disturbances [30].

Most patients with the genetic pattern of BS are asymptomatic, and the first symptom can be sudden death for TdP. In some cases, BS can be suspected in patients with unexplained syncope or symptomatic ventricular tachyarrhythmias. Due to the severity of the disease, the early diagnosis of this potentially lethal heart rhythm disturbance should be mandatory in patients suspected of having BS.

The diagnosis of BS is actually achieved by the intravenous administration of sodium channel blockers. The differential diagnosis is also very important because an ECG pattern mimicking the typical ECG pattern of BS (Brugada-like ECG) can be observed either in some cardiac diseases or under particular stress conditions such as extreme exercise [34, 35].

7.7.1.1 Anaesthesiological Considerations

BS can either occur or worsen during anaesthesia. The cardiac arrhythmia can be induced by changes in the body temperature, the electrolyte balance and the haemodynamic state occurring in patients under anaesthesia. The administration of some local anaesthetics (lidocaine, bupivacaine) and ipnotics (propofol, ketamine) has been correlated with the manifestation of BS.

The proarrhythmic effects of propofol are still not well documented. Although data on its effects on the sodium channels of neuromuscular cells have been reported in the literature, its role as a sodium channel blocker in cardiomyocytes is still unclear [36, 37].

Although Brugada-like ECG patterns have been reported in patients undergoing prolonged propofol infusion, the data on the proarrhythmic action of propofol in patients at risk of BS are still unclear.

In this context, careful management of the anaesthetic drugs in patients at risk for BS should be performed.

7.7.2 Long QT Syndrome

Long QT syndrome (LQTS) is a familial disease characterized by an abnormal prolongation of the QT interval on the ECG secondary to the genetic alteration of the ion channels of the cardiomyocyte. Acquired LQTS can be caused by drugs prolonging the QT period or by electrolyte disturbances [38–40].

Although several drugs induce QT prolongation, the occurrence of TdP after their administration is not frequent. Predisposing trigger factors seem to play a key role in the onset of TdP with long QT ECG patterns; therefore, the aetiological mechanism of TdP is likely multifactorial. In this context, research regarding ECG findings with adjunctive predictive value for TdP in the presence of drug-induced long QT has recently been emphasized [41].

Among the various drugs (cardiologic and non-cardiologic agents) that are able to induce long QT, no anaesthetic agent has been described, although the proarrhythmic effects of anaesthetic drugs have been known since the origin of anaesthesia [38].

Although the data reported in the literature are controversial, the anaesthesiological management of patients with certain or suspected LQTS should be aimed at either the prevention of the life-threatening arrhythmia or the avoidance of any potential arrhythmic trigger.

7.7.2.1 Anaesthesiological Management

Preoperative evaluation of symptoms, signs and patient history that are suggestive for LQTS should be adequately investigated to perform perioperative risk stratification. The close interaction between the anaesthesiologist and the cardiologist should be aimed at the optimization of the preoperative therapy.

Patients who are symptomatic despite treatment with beta-blockers are at high risk to develop malignant arrhythmias [42]; nevertheless, beta-blocker therapy should be continued throughout the perioperative period [3, 4, 38].

Basal preoperative 12-lead ECG can be absolutely normal in patients at risk for LQTS. It can be useful when compared with new-onset ECG changes, such as the duration of the QT interval and the morphology of the T wave, which can indicate a major adverse arrhythmic event.

The management of patients with ICD is based on the guidelines or recommendations [3, 4].

The maintenance of the correct electrolyte balance and the correction of eventual electrolite imbalance are fundamental to reduce the perioperative risk of malignant arrhythmias. The values of calcium, sodium and magnesium ions should be tightly monitored and maintained within the normal ranges [38].

It should be considered that the mean age of the surgical population has been progressively increasing over the last few decades. For this reason, most of the patients scheduled for noncardiac surgery have been administered cardiologic and non-cardiologic chronic therapy that may include drugs that can potentially increase QT time. The administration of anaesthetic agents can enhance the arrhythmic effects of these medications. In this context, any proarrhythmic medication taken by the patient should be suspended before surgery if possible. When

the potentially arrhythmic medication cannot be suspended, careful monitoring and anaesthesiological management are mandatory.

7.7.3 Preoperative

It should be considered that either the perioperative stress or the administration of anaesthetic agents can increase sympathetic tone leading to malignant arrhythmia in patients with LQTS.

The effects of sympathetic tone on the prolongation of the QT interval are well known. During general anaesthesia, regardless of the use of anaesthetic drugs, several events are potentially arrhythmogenic because an increase of sympathetic tone can occur. Among them, endotracheal intubation is one of the most important [43, 44]. The anaesthesiological management of patients with certain or suspected LQTS should be aimed at the reduction of perioperative stress and sympathetic tone. A calm environment and adequate preoperative medication can help to reduce the sympathetic activity. Midazolam can safely be used in premedication [38, 45].

7.7.4 Intraoperative Period

Most anaesthetic agents can be safely used in patients with LQTS. Propofol can be safely used either for the induction or maintenance of general anaesthesia because it has minimal effects on the QT interval. It should be considered that all of the volatile agents affect ventricular repolarization. Among them, isoflurane can be safely used for the maintenance of general anaesthesia [38, 45, 46]. Muscle relaxation can be safely induced by rocuronium, vecuronium and atracurium, and the opioids remifentanil and fentanyl are safe [38, 45, 47]. The use of anticholinesterase is not recommended. Ketamine and thiopental sodium should not be used because of sympathomimetic activity and the effect on the QT interval, respectively [46].

Regardless of the anaesthetic agent used, the aim of anaesthesiological management should be the achievement of an adequate anaesthesiological plan, especially prior to endotracheal intubation. The association between an adequate preoperative sedation and deep anaesthesia, the use of intraoperative opioids and the topic administration of local anaesthetics on the laryngeal mucosa should minimize the risk of arrhythmogenic events induced by endotracheal intubation.

During general anaesthesia, electrolyte disturbances and hypothermia should be avoided.

Continuous ECG monitoring should be performed during general anaesthesia and prolonged until the first postoperative hours. Patients at high risk for TdP should receive intravenous administration of short half-life beta-blockers (esmolol) under ECG monitoring [48]. An external defibrillator for transcutaneous pacing/defibrillation should be available for high-risk patients, and everything should be ready for the emergency insertion of a temporary pacemaker.

Another important recommendation concerns the use of high peak pressures and a long inspiratory/expiratory ratio during mechanical ventilation that, mimicking a Valsalva manoeuvre, can prolong the QT interval.

7.7.5 Postoperative Period

Recovery from general anaesthesia should take place in a calm environment, and ECG monitoring should be continued in the postoperative hours, especially in patients without ICD.

Postoperative analgesia can be achieved with opioids such as morphine. Ondansetron seems to be the drug of choice for the prevention and treatment of postoperative nausea and vomiting [38, 45, 46].

7.7.5.1 Regional Anaesthesia

Most local anaesthetics do not affect the QT interval duration and, therefore, can be safely used to perform regional anaesthesia as long as epinephrine is not added to the anaesthetic solution. As reported in the literature, the effects of the local anaesthetic on heart conduction seem to depend more on the site and type of the peripheral block rather than on the dose used.

Regional anaesthesia is indicated in women undergoing caesarean delivery because it reduces either the perioperative stress or the postoperative pain. Spinal anaesthesia is safe in these patients, while epidural anaesthesia can induce hypotension and consequent activation of sympathetic tone.

Conclusion

The management of perioperative arrhythmias is a challenge for anaesthesiologists. The preoperative patient evaluation is aimed at the performance of perioperative risk stratification. The detection of pre-existing cardiac diseases, of a history of receiving therapy for arrhythmias and of new-onset arrhythmias, as well as the early detection of intraoperative adverse arrhythmic events with continuous ECG monitoring, should be aimed at the selection of patients at high risk of developing severe perioperative arrhythmias who will require postoperative intensive care.

Although most of the perioperative arrhythmias are benignant and self-limiting, the anaesthesiologist should know the recommendations for the management of the perioperative arrhythmias in patients undergoing noncardiac surgery. Because of the increasing number of patients with intracardiac devices who are enrolled for noncardiac surgery, the implementation of the previously reported precautions is fundamental to avoid perioperative arrhythmic adverse events.

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Obstructive Sleep Apnoea Syndrome: What the Anesthesiologist Should Know

8

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8.1 Introduction

Obstructive sleep apnoea syndrome (OSAS) is a rather common sleep disorder and constitutes a risk or an aggravating factor for various underlying diseases. OSAS is characterised by repeated upper airway collapse during sleep causing fragmented sleep, hypoxemia and hypercapnia. It may also cause considerable changes in intrathoracic pressure and an increase in sympathetic nervous activity, which represent the basis of associated pathologies such as arterial hypertension, ischaemic heart disease, diabetes mellitus, stroke and sudden death [1]. Moreover, there is a well-established association between OSAS and postoperative complications [2, 3]. Nevertheless, a significant proportion of patients affected by OSAS undergo surgery without diagnosis and, consequently, without therapy [4]. Therefore, it is crucial for the anaesthesiologist to identify patients at risk of OSAS before surgery for a correct definition of a perioperative strategy to reduce the risk of perioperative complication. This process should be done independently and regardless of whether the patient undergoes general or locoregional anaesthesia.

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8.2 OSAS Diagnosis

OSAS recognition, diagnosis and management require specific skills in the field of sleep medicine and the need for special equipment. Diagnosis is based on clinical presentation, physical examination and objective data obtained from sleep monitoring. Polysomnography (PSG) represents the "gold standard" in OSAS diagnosis and provides necessary elements for the management of continuous positive airway pressure (CPAP) and/or intermittent positive pressure ventilation (IPPV) values required in the treatment. PSG entails the recording of parameters that enable the analysis of sleep in accordance with standard criteria (EEG; EOG; submental EMG) for the staging of sleep. It also allows the evaluation of microstructural events as well as respiratory noise, oral–nasal airflow, thoracic–abdominal movements, cardiac frequency and oximetry. Apnoea is defined as the total absence of airflow through the nose and mouth for more than 10 s. There are three types of apnoea: (1) central apnoea in sleep where the interruption in respiration is caused by changes in the central nervous system's ventilation control system and is not associated with respiratory efforts during the event; (2) obstructive sleep apnoea (OSA) where ventilation control is normal but an obstruction, usually pharyngeal, interrupts airflow despite vigorous inspiratory efforts generated by the patient (with the presence of paradoxical chest wall movements). A typical OSA patient experiences 30 or more apnoeic episodes during sleep, usually lasting less than 10 s with a severe reduction in oxygen saturation; (3) mixed-type sleep apnoea, namely, a combination of the aforementioned types of apnoea. OSAS is by far the most common pathology. In addition to apnoea, episodes characterised by a considerable reduction (up to 50 %) of current volume in the absence of a total interruption of respiratory flow may also occur. Such events are defined as "hypopnoea". Obstructive sleep hypopnoea is characterised by at least a 30 % reduction in airflow for no less than 10 s and is associated with a 4 % reduction in oxygen saturation. The Apnoea–Hypopnoea Index (AHI) is calculated by dividing the number of apnoea and hypopnoea episodes by the number of hours of sleep and is used to stage the seriousness of OSA. RERA (respiratory effort-related arousal) is a sequence of respiratory attempts characterised by increasing effort, which leads to awakening but does not satisfy the criteria for apnoea or hypopnoea. RDI (Respiratory Distress Index) is a parameter, which includes apnoea, hypopnoea and RERAs. Normal individuals generally have an Apnoea–Hypopnoea Index (AHI) of less than 5 [5, 6]. The American Academy of Sleep Medicine defines a light OSA as AHI = 5–15, moderate OSA as AHI = 15–30 and severe OSA as AHI > 30 [7].

Over the last decade, improvements in the instrumental diagnosis of OSAS have provided alternative methods to traditional laboratory PSG, with the introduction of portable monitoring instruments (PMs). Such methods are different from PSG, and each of them may differ in terms of sensitivity, specificity and costs and to date cannot be considered a substitute for PSG [8].

Table 8.1 Risk factors for OSAS

Heart failure
Arrhythmia
Non-controlled hypertension
Cerebrovascular pathology
Pulmonary hypertension
Metabolic syndrome
BMI >35 kg/m^2
Neck circumference >40 cm
Observed apnoea
Pregnancy

8.3 Prevalence in the Population

Although obesity is considered a risk factor for OSAS, the disorder also affects individuals of normal weight [9], in 44.4 % of cases. Young et al. [10] recorded a 2 % prevalence of symptomatic OSAS in women and 4 % in middle-aged men. Nonetheless, the prevalence of sleep disorders in the 30–60 age group was estimated as 9 % in women and 24 % in men. To date, no exhaustive explanations have been found regarding the greater prevalence in men. Chronic diseases, environment and work and behavioural risk factors may contribute to OSA [11], whereas hormones in premenstrual age may have a protective effect. Progesterone may contribute to respiratory system control, whereas testosterone contributes to adipose cervical deposits [12]. Such factors render OSAS a more common pathology than asthma. The risk of OSA increases with age; indeed 24 % of people over the age of 65 have OSAS, and over 50 % of elderly individuals in the home care setting suffer from clinically significant OSA [11]. Table 8.1 summarises risk factors for OSAS.

8.4 OSA and the Surgical Population

In most cases, OSAS frequency is substantially higher compared to the general population and varies according to type of surgery [13–16]. Data published on pathologically obese patients undergoing bariatric surgery indicates a 70 % prevalence of OSA, probably due to the accumulation of adipose tissue in the cervical region [17]. It is important to note that in spite of this prevalence, in most cases, patients undergo surgery without diagnosis [18]. Finkel et al. [19] studied 2,877 patients who underwent elective surgery and identified 661 (23.7 %) at a high risk of OSA. Out of these patients, 534 (81 %) had never been diagnosed. Portable postoperative PSG identified OSAS in 170 out of 207 (82 %) of patients. Twenty-six standard PSGs confirmed OSA in 19 of such patients. According to a study on the elective surgical population, the use of the Berlin Questionnaire identified 24 % of patients as being at high risk from OSA [4]. Lastly, in a Canadian study, Singh et al. demonstrated that surgeons

and anaesthetists were unable to recognise patients affected by OSA, even those with a pre-existing diagnosis, in over 60 % of cases [20].

8.4.1 Why Is OSA a Risk Factor in Perioperative Complication?

Although the main cause of OSA remains unknown, the pathophysiological mechanism of the syndrome has been described and consists of an upper airway collapse during sleep. In humans, the upper airways may be described as a flexible pipe (pharynx) located between two rigid structures (nose and larynx). Upper airway patency is determined by a balance between pharyngeal muscle activity (pharyngeal dilator muscles), negative pressure generated in the airways, upper airway compliance and size at the end of inspiration. Compliance is influenced by craniofacial structures, soft tissues and sleep stage [21]. The greater the patient's inspiratory effort and upper airway compliance, the greater the probability of airway obstruction.

During sleep, muscle relaxation causes the gradual closure of upper airways, with total (apnoea) or partial (hypopnoea) obstruction. Hypercapnia and acidosis caused by hypoventilation stimulate reawakening centres in the central nervous system with a subsequent increase in respiratory activity and the activation of pharyngeal dilator muscles in order to re-establish upper airway patency. Therefore, there are cycles where the patient repeatedly awakens and falls asleep. In severe cases, this cycle repeats itself hundreds of times every night. These apnoea–hypopnoea cycles lead to the development over time of arterial hypertension, chronic ischaemic heart disease, pulmonary hypertension and right heart failure [22]. Perioperative complications are caused by the interaction between anaesthetic agents and the anatomical characteristics of patients affected by OSAS. Hypnotics, opioids and volatile anaesthetic agents may induce respiratory depression in a dose-dependent manner, even in normal subjects [23–25]. Anaesthetic drugs abolish or attenuate mechanisms responsible for the re-establishment of airway patency in normal individuals, in a predictable dose-dependent fashion. OSAS patients prone to upper airway collapse in natural sleep are more sensitive to the effects of anaesthetics and sedatives and may develop respiratory complications in the postoperative period [26]. At an early stage, complications are mainly due to the negative effects of sedatives, anaesthetics and analgesics on pharyngeal muscular tone and to the lack of a reawakening response to hypoxia, hypercapnia and airway obstruction. Most of these complications occur during the first 24–48 h in the postoperative phase. At a later stage (even after a week), complications are mainly due to REM phase sleep rebound caused by high doses of opioids in the postoperative phase, which suppress REM phase, causing sleep deprivation [27, 28].

8.5 OSA and Perioperative Complications

OSAS increases the rate of postoperative complications, admission to the intensive care unit (ICU) and hospital length of stay. In one of the first studies defining postoperative risk, the authors retrospectively evaluated 101 patients with OSA who had

undergone hip or knee replacement surgery no later than 3 years before ($n=36$) or at any time after ($n=65$) OSA diagnosis [29]. The outcomes were compared to a control group of 101 patients without OSA who underwent the same surgical operations. Only half of patients with OSA diagnosis before surgery received CPAP at home before hospitalisation. Complications occurred in 39 % of OSA patients compared to 18 % of those in the control group. Severe complications requiring ICU admission, including ischaemic heart disease or respiratory failure, were recorded in 24 % of OSA patients compared to 9 % of the control group ($p=0.004$). Hospitalisation was longer in subjects with OSA ($p<0.007$). Most of the complications occurred in the first day after surgery, whereas a small number occurred at a later stage, 4 or 5 days later. Similarly, Liao et al. compared 240 patients with OSA to 240 non-OSA patients who underwent elective surgery. The authors recorded a complication rate of 44 % in OSA patients compared to 28 % in the control group ($p<0.05$). The most frequent difference between both groups was the detection of oxygen saturation below 90 % (17 % among OSA vs. 8 % in the control group). The highest rate of complication occurred in OSA patients who did not receive CPAP at home but requested the treatment in the postoperative phase. These data indicate that preoperative CPAP can be an effective tool even in the hospital setting. A few other retrospective studies have been conducted on the postoperative outcome of OSA in patients who have undergone nasal deformity surgery [30]. In these studies, respiratory complications and, in particular, oxygen desaturation episodes were the most common adverse events [31–33]. A retrospective study on OSA patients who underwent heart surgery also showed a higher incidence of postoperative complications and prolonged ICU length of stay [34].

OSA has been associated with a significantly higher risk of developing pulmonary complications and the need for intubation/mechanical ventilation after orthopaedic and general surgery. In a recent study, Memtsoudis et al. [35] evaluated postoperative pulmonary complications in orthopaedics and general surgery. The authors conclude that OSA patients develop more pulmonary complications than controls, both after orthopaedic surgery and general surgery. They found that “ab ingestis” pneumonia, acute respiratory distress syndrome (ARDS) and the rate of intubation and mechanical ventilation were significantly higher in patients with OSA compared to those without OSA in both orthopaedic and general surgery. Pulmonary embolism was shown to be more frequent in patients with OSA after orthopaedic surgery but not after general surgical procedures. Flink et al. [36] found a rate of 53 % for postoperative delirium compared to 20 % in non-OSA patients. A recent meta-analysis concluded that OSA patients who undergo non-cardiac surgery have a higher rate of desaturation in the postoperative phase, respiratory failure, cardiac events and unplanned transferrals to the ICU compared to patients unaffected by OSA [37]. However, a recent study failed to find an association between OSA and mortality after 1 year [38]. Other studies have also demonstrated a higher frequency of postoperative complications but failed to find an increase in mortality [39, 40]. Independently from these results on mortality rate, the association between OSAS and perioperative complications requires the implementation of strategies to guarantee the safety of these patients. Several authors have suggested therapeutic

clinical actions or have drafted recommendations to this aim [41–43] such as the 2012 recommendations of the SIAARTI (Italian Society of Anaesthesiology and Intensive Care Medicine)/AIMS (Italian Society of Sleep Medicine) [44].

8.6 Preoperative Evaluation

All patients scheduled for surgery should undergo targeted screening, given the prevalence and significant number of non-diagnosed individuals with OSA. Although PSG and PMs provide a complete evaluation, their routine use is limited by various factors including the drawback of postponing surgical schedules and the need for a dedicated specialised sleep laboratory with high additional costs. Other tools can be used as support in preoperative evaluation for the identification of an appropriate strategy. Among these tools, the fastest and easiest to use is the STOP (snoring-tired-observed-blood pressure) questionnaire which has been recently modified to include questions regarding additional risk factors for OSA, such as body mass index (BMI, B), age (age, A), neck circumference (neck, N) and gender (gender, G); the modified questionnaire has been named STOP-BANG (Fig. 8.1) [45]. Patients with a score of 0–2 are considered at low risk, 3–4 at medium risk and 5–8 at high risk [46, 47] of OSAS. Corso et al. [48] demonstrated that there is a higher incidence of postoperative complications among surgical patients identified by the STOP-BANG as at high risk from OSA (score > 5), confirming the usefulness of this questionnaire as a triage tool for patients in the perioperative phase. The approach for patients with OSA diagnosis or with high risk for OSA (HRO) is outlined Fig. 8.2.

8.7 Intraoperative Management

There is evidence in literature that locoregional anaesthesia is preferable to general anaesthesia [49] due to its minimal effects on airway patency and the maintenance of spontaneous breathing. Locoregional anaesthesia also avoids the negative effects of anaesthetics on sleep structure and the massive use of opioids avoiding postoperative REM sleep rebound with its negative consequences on airway obstruction.

8.7.1 Airway Management

Several studies have demonstrated a high incidence of difficult tracheal intubation in OSA patients [50–52]. The main limitation of these studies is their retrospective nature. In a multicentre prospective study, Corso et al. [48] showed an incidence of difficult intubation in 20 % of patients at high risk for OSA compared to 9 % in the low-risk population. This confirms the hypothesis that patients identifiable as high risk for OSA by the STOP-BANG questionnaire are also at a higher risk of difficult intubation. The link between OSA and difficult mask ventilation (DMV) is strong

S. **Snoring** (during sleep)

Do you Snore Loudly (loud enough to be heard through closed doors)?

Yes No

T. **Tiredness** (during the day)

Do you often feel Tired, Fatigued, or Sleepy during the day? Yes No

O. **Observed apnea**

Has anyone Observed you experiencing an apnoeic episode during your sleep

Yes No

P. **Blood Pressure**

Do you have or are being treated for High Blood Pressure ? Yes No

B. **Body Mass Index**

BMI higher than 35 kg/m^2? Yes No

A. **Age**

Are you over 50? Yes No

N. **Neck circumference**

Is your neck circumferance > 40 cm? Yes No

G. **Gender**

Are you male? Yes No

Fig. 8.1 The STOP-BANG questionnaire. A score of ≥3 identifies patients at high risk from OSA. A score of <3 identifies patients at low risk

and has been demonstrated in several studies. Kheterpal et al. [53] reported an incidence of impossible mask ventilation of 0.15 % in an observational study of 50000 anaesthetisations. A history of OSA is the only predictive factor for impossible ventilation. In a retrospective study, Cattano et al. [54] confirmed that OSA is a risk factor for DMV. However, the opposite is also true. In a prospective study, Plunkett et al. [55] found that OSAS was responsible of DMV in nine out of ten patients. It is important to emphasise that difficulties in ventilation (DMV) in these patients may be greater than those arising from intubation. In accordance with the SIAARTI

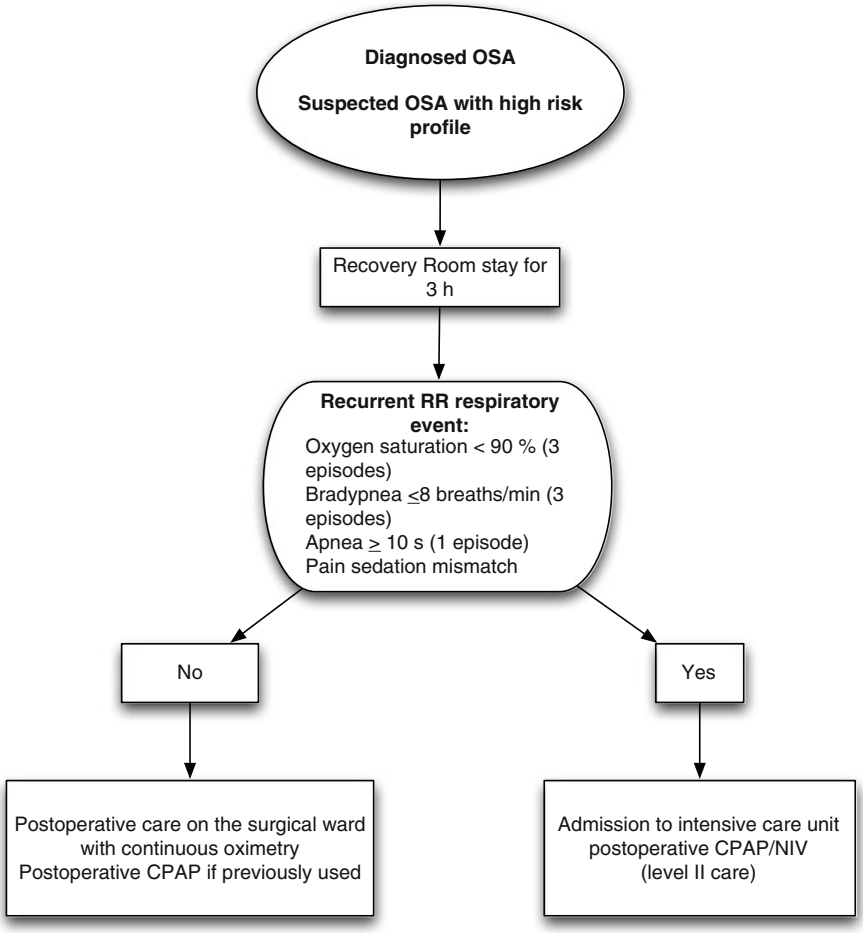

Fig. 8.2 Algorithm for post-operative management of patients with diagnosed OSA or Suspected OSA with high risk profile

algorithm and recommendations for difficult airway management [56], it is mandatory to have readily available equipment for difficult upper airway management before the induction of general anaesthesia.

8.7.2 Intraoperative Monitoring

There is no evidence to support recommendations for more aggressive or invasive intraoperative management in OSA patients. The intensity of monitoring should be established according to the nature of the scheduled surgical operation and the presence of other comorbidities. Patients undergoing surgical operations under anaesthesia with non-protected airways or under locoregional anaesthesia with sedation

should be monitored with capnography [57]. If neuromuscular blocking agents are used, the risk of postoperative residual paralysis should be prevented with adequate monitoring [58].

8.7.3 Extubation

Patients who remain intubated in the postoperative phase should be extubated after taking into account the type of surgical procedure, patients' characteristics and the suspicion or certainty of airway lesion caused by airway manipulation. Moreover, extubation should be performed when the patient is fully awake, regardless of whether this occurs in the operating room, recovery room or intensive care unit. The complete recovery from neuromuscular block should be verified through instrumental monitoring. Extubation in the anti-Trendelenburg or semi-orthopnoeic position minimises the compression of the abdomen on the diaphragm [59]. In case of difficult airway, it is important to have readily available advanced technologies, such as tube exchangers, to make reintubation easier if needed [60]. In cases of regional analgesic block, analgesia planning should be adjusted accordingly to the time of extubation.

8.8 Postoperative Management

Postoperative management should be aimed at:

- Correct planning of analgesic therapy
- Guaranteeing optimal oxygenation
- Defining of patient position
- Activation of a proper monitoring

8.8.1 Postoperative Analgesia

The management of postoperative analgesia in OSA patients is a major challenge for anaesthetists. In a retrospective study on 1600 patients who had received postoperative patient-controlled analgesia (PCA) with IV opioids, severe respiratory depression was recorded in eight cases. Identified causal factors were the basal infusion of opioids, old age, the concomitant administration of sedatives or hypnotics and positive history for OSAS [61]. The use of major opioids (e.g. morphine, buprenorphine, oxycodone) should be avoided or reduced, regardless of the method of administration (including neuraxial) [62]. When the administration of morphine is mandatory, additive/synergic (e.g. ketamine, ketorolac) drugs should be used to reduce overall dosage (multimodal analgesia). PCA administration of morphine is also recommended rather than continuous infusion [63]. The use of minor opioids, such as tramadol, is also advisable. The administration of NSAIDs (nonsteroidal anti-inflammatory drugs) and paracetamol should be optimised through their

prescription at pre-established times rather than according to patient's need. Lastly, locoregional analgesia techniques should be used both in intraoperative and postoperative phases (e.g. continuous infiltration of surgical wound via catheter or continuous peripheral nerve blocks).

The safe use of opioids in OSA patients foresees:

- The identification of doses and their adjustment based on effect
- Avoidance of continuous infusion
- Reduction of doses through multimodal analgesia
- Monitoring of analgesia and sedation (e.g. using visual analogue scale (VAS) and POSS)
- Correct patient's positioning (at least at 30° or lateral position)
- Continuous monitoring of oxygenation using a pulse oximeter
- Capnography whenever required

8.8.2 Patient Position

The importance of the patient's position should not be underestimated. In the postoperative phase, Loadsman et al. suggest placing the patient in the lateral position, given the tendency of airway collapse in the supine position [64]. Indeed placing the patient in a 30° position in the recovery room and/or in the ward may increase upper airway stability [65]. It is suggested that patient positioning should be specified in postoperative instructions for nurses.

8.8.3 Oxygenation and CPAP

Data provided by literature provides insufficient grounding for precise indications concerning supplemental O_2 in patients with OSA. The authors agree on the need to administer oxygen to maintain preoperative saturation levels in patients who were previously receiving O_2 therapy. Oxygen therapy should be administered continuously until the patient is able to maintain preoperative saturation values in room air. On the other hand, the administration of O_2 should not be undertaken when the patient is still able to maintain preoperative saturation levels in room air.

CPAP remains the most effective therapy for OSA as it pneumatically guarantees the maintenance of upper airway patency. Rennotte et al. demonstrated that beginning CPAP before surgery and resuming it immediately after extubation enable the safe management of numerous surgical procedures in OSA patients regardless of the analgesic drugs used. Thus, the authors recommend that all efforts should be made to identify patients with OSA and to undertake CPAP therapy before surgery [66]. Gupta et al. demonstrated that patients who had used CPAP in the preoperative period were affected by a lower incidence of postoperative complications and had a shorter length of hospital stay [29]. Recently, in a cohort study, Mutter et al.

demonstrated that in patients already diagnosed with OSA, the use of preoperative CPAP ensured a significant reduction in the number of postoperative cardiovascular complications [67]. As a consequence, the use of CPAP before and after surgical operation seems to be the best strategy for the reduction of complications in the postoperative phase. However, compliance with CPAP treatment still represents a limit to this technique. Of note, in a study by Liao et al. [68], only 26–48 % of patients used CPAP for more than 4 h. Furthermore, CPAP is unable to guarantee patient safety in case of apnoea caused by the administration of opioids. Although no studies have been conducted to this aim, the use of non-invasive ventilation with back-up respiratory frequency (e.g. assisted/controlled ventilation, pressure assist–control ventilation) may be advisable.

8.9 Ambulatory Surgery in OSA Patients

Few studies have investigated postoperative complications in OSA patients who undergo ambulatory surgery. A recent, systematic revision of SAMBA (Society for Ambulatory Anaesthesia) [69] concluded that it is possible for OSA patients to undergo ambulatory surgery provided that they are carefully selected and correctly managed. In order to establish patient eligibility for ambulatory surgery, a global evaluation of perioperative risk must be carried out, taking into consideration the severity of OSA, surgical invasiveness and the need for opioids in the postoperative phase. This evaluation must also encompass considerations about postoperative organisation and surgical needs, which should be adapted to fit OSA patients' requirements. OSA patients deemed eligible for ambulatory surgery should be programmed at the beginning of the surgical session to enable correct postoperative monitoring. It is recommended that after ambulatory surgery, OSA patients be observed and monitored for at least 3 h before being discharged. If a significant airway obstruction or apnoeic event occurs during this period, postoperative monitoring should be continued for more hours, and the patient must be hospitalised. Patients who undergo operations under locoregional anaesthesia must be monitored for at least 3 h in the recovery room even if no sedatives have been administered. The administration of postoperative analgesia in OSA patients who undergo ambulatory surgery is a major concern. Although it is possible to perform single shots or continuous regional blocks that are always highly recommended, the postoperative analgesic strategy at home always requires careful evaluation.

8.9.1 What to Do After Surgery: General Ward or Intensive Care?

It is important that OSA patients are managed in an appropriate postoperative environment. Although OSA patients require adequate monitoring and surveillance, especially during the first 24 postoperative hours, there is a lack of evidence on the

most appropriate duration of postoperative respiratory monitoring. Late complications, namely, those within the first week after surgical operation (REM sleep phase rebound), have been recorded following the use of high doses of opioids [70]. Recently, Ramachandran et al. identified OSA as an independent risk factor for critical respiratory events during postoperative antalgic therapy [28]. Ideally, the decision to send patients to intensive care (level II care), to the ward or to discharge them should be made before the surgical operation. Nevertheless, the decision can be also made in the RR. Moreover, the decision of sending the patient to the ICU should also be correlated with the need for analgesics. Admission to intensive care may not be necessary in case of upper airway surgery when opioids have not been used. Factors which should be taken into consideration when identifying the most appropriate environment are BMI, severity of OSA, severity of associated cardiovascular diseases, pregnancy, intraoperative complications and then as mentioned above the request for opioids in the postoperative period. If all of these variables are absent, patients can be transferred to a low-intensity care environment. If one of these factors is present, patients must be transferred to intensive care. The grey area between both scenarios is wide and requires accurate evaluation. The decision must also take into account whether the hospital has a RR. There is evidence to suggest that the occurrence of respiratory events in the RR or in the post-anaesthesia care unit (PACU) may predict the possibility of adverse events in the postoperative phase. The observation of recurrent respiratory events in the RR may be used as an indicator to determine whether a patient with OSA or at high risk of having OSA requires continuous postoperative monitoring [71]. A "recurring respiratory event" in the RR during a 30-min observational period is defined by one of the following events:

(a) Apnoea $\geq 10''$ (an episode is necessary to indicate yes)
(b) Bradypnoea ≤ 8 breaths/min (three episodes are necessary to indicate yes)
(c) Desaturation $<90\,\%$ (three episodes are necessary to indicate yes)
(d) Pain/analgesic administration mismatch, as defined by a mismatch between pain and analgesic characterised by a high pain score even after analgesic administration (e.g. need for high dose of opioids)

A "recurring respiratory event" in the RR should be defined as the presence of one of the mentioned above respiratory events (not necessarily the same type of event) in less than a 30-min interval.

Figure 8.3 shows the algorithm of SIAARTI/AIMS recommendations.

Conclusion

Patients affected by OSA syndrome are at high risk of developing adverse events in the perioperative period. Only the implementation of a well-defined clinical pathway throughout this critical period can decrease the onset of complications.

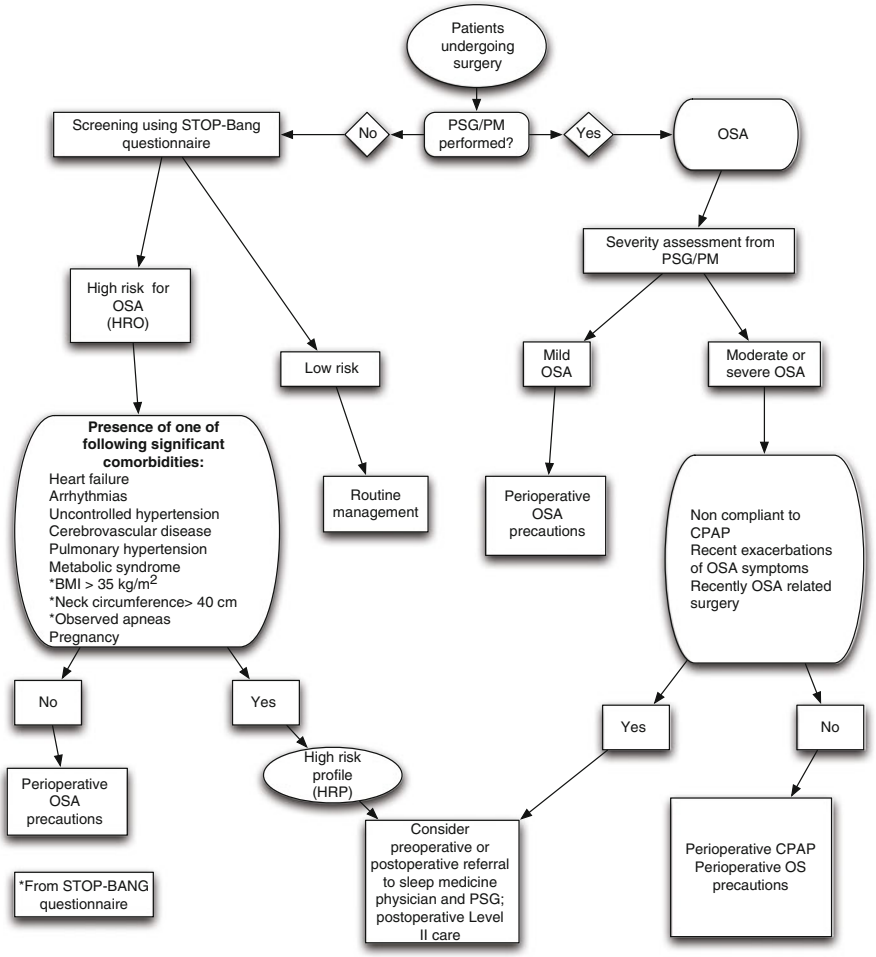

Fig. 8.3 Algorithm for SIAARTI/AIMS recommendations

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Postsurgical Liver Failure

9

Gianni Biancofiore

9.1 Introduction

The liver is unique due to its well-known capability of regeneration and functional recovery after parenchymal injury. However, when the number of the functioning liver cells is too small to satisfy metabolic demands, such a particular ability is lost resulting in a severe dysfunction which can lead to very serious complications, multi-organ failure, and significant mortality [26].

Although major liver surgery has become safer as a result of advances in surgical techniques and perioperative management, it remains particularly challenging because of unique anatomic architecture and vital functions. Liver resection provides the chance for cure in patients with early-stage primary liver tumors and metastatic colorectal cancer confined to the liver, but despite high experience, liver resection is still burdened by relatively high rates of postoperative morbidity (4.09–47.7 %) and mortality (0.24–9.7 %) [27]. In fact, in order to achieve the goal of a radical resection with tumor-free margins, liver resection up to the limit of the functional liver reserve is justified. Unfortunately, regenerative capacity is not fixed, but depends on various factors including hemodynamics, parenchymal integrity, and the functional reserve of the future liver remnant. Therefore, although in the majority of patients large liver resections can be performed safely with low morbidity and mortality, in a subgroup of patients, the risk of post-resection liver failure (PLF) is significant. Moreover, it can be expected that a growing number of patients with liver disease, both known and yet undiagnosed and asymptomatic, will undergo non-hepatic surgery with possible postoperative liver dysfunction from the decompensation of the primary liver disease. In fact, the number of patients with cirrhosis who require surgery is on the rise. Despite advances in antiviral therapeutics, the

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prevalence of cirrhosis secondary to hepatitis C continues to increase, as does the prevalence of cirrhosis due to chronic alcoholic liver disease. Additionally, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are gaining more attention, especially in association with metabolic syndrome and obesity. At the same time, the amount of medications and treatments aimed at improving survival among patients with cirrhosis has been increasing.

The aim of this review is to highlight the perioperative management of PLF by addressing two main questions: what is it and what can we do to prevent and treat it.

9.2 What Is PLF? Definition, Incidence, and Risk Factors

Many different definitions of PLF have been proposed in the literature through the years depending on local data, experiences, and practices, and up to a few years ago, there was no standardized definition or classification [13, 27]. However, in 2011, the members of the International Study Group of Liver Surgery (ISGLS) suggested a simple, clinical definition of PLF as a "postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5" [22]. From the clinical point of view, PLF was differentiated in three grades of severity (A, B, C) according to whether changes in clinical management of the patient or invasive treatments are needed (Table 9.1).

Unfortunately, due to the fact that a consensus definition of PLF was introduced only recently, the range of its incidence is still quite wide (1.2–32%) due to the different definitions used before its introduction. However, it is interesting to observe that, in the more recently reported experiences, the incidence of PLF is lower. This can be explained by the improvement in surgical techniques and in postoperative

Table 9.1 Consensus definition and severity grading of posthepatectomy liver failure by the ISGLS [22]

Grade	
A	PLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient
B	PLF resulting in a deviation from the regular clinical management but manageable without invasive treatment
C	PLF resulting in a deviation from the regular clinical management and requiring invasive treatment

Definition: A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying function, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cutoff levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, PLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out

INR international normalized ratio

Table 9.2 Risk factors for PLF

Patient related	Parenchymal disease: cirrhosis, nonalcoholic fatty liver disease, chemotherapy-induced liver injury (steatohepatitis and sinusoidal injury), cholestasis
	Age >65 years
	Excessive blood loss
	Diabetes mellitus
	Nutrition
	Male sex
Surgery related	Extent of resection (>4 segments)
	Use of vascular occlusive techniques
	Ex vivo hepatic resection
	Excessive blood loss and transfusion
	Vascular or biliary reconstruction
Miscellaneous	Hepatic parenchymal congestion
	Ischemia–reperfusion injury
	Infection

management in the intensive care unit (ICU). However, also an improved patient selection and management of risk factors seem to have a significant influence on the occurrence of PLF [13, 27]. The identification of the surgical risk is imperative in the care of any patient, especially as patients develop an increasing number of chronic comorbid medical conditions. In resective liver surgery, three groups of risk factors can be differentiated: patient, surgery, and miscellaneous (Table 9.2).

9.2.1 Patient-Related Risk Factors

Patients with a preexisting liver disease are at particularly high risk for an increased morbidity and mortality in the postoperative period of liver resections due to both the "generic" stress normally associated to any major surgery and specific conditions referable to the peculiarities of liver surgery itself. In a study comparing 135 patients with cirrhosis to 86 patients without cirrhosis, all undergoing non-hepatic general surgery, 1 month mortality rates were 16.3 % in the cirrhotic and 3.5 % in the control group [9]. Even steatosis of the liver seems to be associated with a higher perioperative rate of complications and increased incidence of PLF [4], whereas preoperative cholestasis was not shown to be associated with an increased risk for PLF [13, 27]. Besides "primary" liver diseases for various reasons, preoperative chemotherapy resulting in chemotherapy-associated steatohepatitis or sinusoidal obstruction is another important defined risk factor for PLF as well. Chemotherapy-induced liver injury is increasingly prevalent as more patients receive chemotherapy for colorectal liver metastases before liver resection. The liver injury varies according to the chemotherapeutic agents, duration of treatment, and presence of preexisting parenchymal disease. The two major patterns of liver injury are sinusoidal injury and chemotherapy-associated steatosis and steatohepatitis (CASH) [13, 27].

In summary, there is no doubt that patients suffering from any form of liver disease have an increased risk for PLF that depends on the functional reserve of the liver preoperatively. What is further evident in the literature is that decompensated liver disease increases the risk of postoperative complications (e.g., infections including sepsis, bleeding, poor wound healing, and renal dysfunction).

9.2.2 Surgical-Related Risk Factors

With regard to the surgical-related risk factors, the extent of resection correlates closely with the rate of PLF as failure to regenerate occurs when the remnant liver volume is below a certain threshold. It has been reported that the incidence of PLF increases with the number of segments resected and that death from PLF can be as high as 80 % after resection of more than 50 % of the native parenchyma. On the other side, PLF is less than 1 % in patients with no underlying parenchymal disease when one or two segments are resected, around 10 % when four segments are resected, and 30 % when five or more segments are resected [13]. It has been also estimated that a minimal functional liver remnant volume (FLRV) of 20–25 % will be needed for an adequate liver function after surgery in patients with a normal liver parenchyma, whereas patients with abnormal parenchyma (steatosis, fibrosis, or cirrhosis) will need an FLRV up to the 40 % of the native liver [28, 30]. Therefore, assessing how much functioning liver will be left after surgery is a cornerstone phase during the preoperative workout of candidates to liver resection. To this end, preoperative radiological assessment and volumetry using computed tomography (CT) or magnetic resonance imaging are used to enable prediction of FLRV and identification of underlying parenchymal disease, whereas CT-guided three-dimensional reconstructions allow visualization of the hepatic venous outflow and improve tumor localization, thus facilitating operation planning [8]. The sensitivity of volumetric assessment can be further enhanced by combining it with a body surface area or bodyweight calculation.

Other surgery-specific risk factors for PLF are related to the use of techniques temporarily occluding the liver vascular pedicle (Pringle maneuver) in the aim to limit bleeding due to the parenchyma resection. In fact, intraoperative vascular occlusive techniques can exacerbate the severity of postoperative hepatic dysfunction by inducing ischemia in the remnant liver. When vascular exclusion is total (inflow + outflow occlusion), the effect is the greatest, but liver cell injury can also occur after prolonged intermittent inflow occlusion [13, 27]. Another significant and equally severe risk factor results from the amount of intraoperative bleeding, and blood losses >1 L with the consequent need for a considerable amount of transfusions can significantly increase the risk of PLF [13, 14, 27]. Finally, a prolonged operation time can also play a role in increasing the risk for PLF [27].

9.2.3 Miscellaneous

Age (the regenerative capacity of liver tissue decreases with it), malnutrition (which is associated with an altered immune response and a reduction in hepatocyte regenerative capacity possibly due to disordered mitochondrial function), diabetes

mellitus (possibly due to immune dysfunction or because insulin absence or resistance reduces regenerative capacity), male sex (testosterone may have immune-inhibitory effects, predisposing to septic complications), and cholestasis can play a role in influencing the severity of PLF. In particular, cholestasis, such as from malignant hilar obstruction, reduces hepatic metabolic and regenerative capacity. Although preoperative biliary drainage (PBD) improves the remnant function, its routine use in jaundiced patients is debated as it does not confer a survival benefit and increases morbidity [15, 17]. Therefore PBD may be limited to those requiring major resection with a predicted FLRV of less than 40 %, who require volume manipulation or have cholangitis [15].

9.3 What Can We Do to Prevent PLF?

Because the therapeutic options for PLF are poor and scarce, great efforts should be made to prevent its occurrence. However, some of the risk factors cannot be influenced (age, gender, existence of cirrhosis or fibrosis, and diagnosis of the patient). Furthermore, patients in poor general condition have "per se" an overall higher risk for perioperative complications. Therefore, meticulous preoperative selection and optimization strategies, optimal intraoperative surgical and anesthetic techniques, and cautious postoperative care should be used to prevent PLF occurrence.

9.3.1 Preoperative Optimization

Candidates to liver surgery should fulfill the criteria for general operational capability. Comorbid conditions should be optimized before surgery as much as possible. To decrease the risk of general complications, diabetes mellitus should be screened for and treated before surgery. The optimization of nutritional status especially in patients with cirrhosis may be helpful, but no relationship between malnutrition and PLF has been demonstrated [27]. In particular, there is no evidence to support delaying liver resection for a period of nutritional preoptimization, unless the patient is severely malnourished [24].

9.3.2 Preoperative Care

Determining the functional reserve of the liver and predicting the volume of the remnant liver is a cornerstone in the patient preparation before liver surgery. Routine preoperative biochemical measurements (albumin, PT, bilirubin, aminotransferases, γ-glutamyl transferase, and alkaline phosphatase) can provide indicators of hepatic dysfunction and may reflect ongoing parenchymal damage or cholestasis but do not independently predict PLF [13]. Some scores have proved to be useful tools for assessing the functional capacity of the liver in view of a surgical intervention. The Child–Pugh classification is one of the more used to this end (Table 9.3). There is general consensus that liver surgery should only be conducted in patients with "stable" cirrhosis (classified as Child A) and in some very well selected Child B patients.

Table 9.3 Child–Pugh classification

Parameter	1 point	2 points	3 points
Total bilirubin, μmol/l (mg/dl)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8–3.5	<2.8
INR	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

The MELD (Model for End-Stage Liver Disease) score also reflects hepatocellular function. It is based on the formula that combines bilirubinemia, creatinine, and INR.

$$\text{MELD score} = (0.957 \cdot \ln(\text{serum creatinine}))\ 0{,}378 \cdot \ln(\text{serum bilirubin})\ 1{,}120 \cdot \ln(\text{INR} + 0{,}643) \cdot 10$$

This score, initially developed to predict death within 3 months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt procedure, was subsequently found to be useful in determining prognosis and prioritizing for receipt of a liver transplant and can be used for patients with hepatic malignancy undergoing liver resection to assess their perioperative morbidity and mortality [29]. A MELD score >10, when compared with a score of <9, was associated with a significant increased risk of PLF after hepatectomy for hepatocellular carcinoma in cirrhotic patient [5].

Beyond deductive methods, hepatic reserve can be assessed through more objective tests. The most commonly used method is based on the use of indocyanine green. After a bolus injection of indocyanine green, the dye binds to plasma proteins and is removed exclusively by the liver through a carrier-mediated mechanism; the dye is ultimately excreted unchanged into the bile. It is not metabolized and does not undergo enterohepatic circulation. The disappearance curve of ICG has two components, a distribution and an elimination phase, and the turning point of these two phases is 20–30 min. ICG has a relatively high intrinsic clearance; therefore, ICG retention at 15 min (ICG R15) represents hepatic perfusion. When hepatic function is impaired, ICGR15 increases. If ICGR15 is less than 14 % in patients with cirrhosis, major hepatectomy is well tolerated; when ICGR15 exceeds 20 %, major hepatectomy should be avoided. Patients with a rate between 14 and 20 % benefit from volume manipulation [6, 7]. Finally, there is recent evidence that intraoperative ICG clearance measurements might allow real-time monitoring of intraoperative liver function during surgery. In fact, trial clamping of arterial and portovenous inflow predicted, in 20 patients undergoing anatomic liver resection, immediate post-resection liver function, thus possibly helping to avoid PLF [31].

Another means for preventing or reducing the severity of PLF is improving size and function of the FLRV. Strategies available for volume manipulation include portal vein occlusion (PVO) and two-stage resection. PVO is usually performed

percutaneously by transhepatic portal vein embolization. This technique induces apoptosis in the ipsilateral lobe and proliferation of the contralateral lobe, thus increasing the functional capacity of the remnant liver and predicting the regenerative response in the future remnant. With portal vein embolization, a volume increase from 28 up to 46 % is obtainable depending on preexisting liver disease, but a concern exists: an increase in tumor growth. This possible threat can be treated with adjuvant (systemic or locoregional) chemotherapeutic strategies in combination with PVO before resection. In patients with a resectable bilobar tumor distribution, two-stage resection in combination with PVO and/or chemotherapeutic modalities can be considered [13, 27].

9.3.3 Intraoperative Care

One issue of significant clinical importance during the surgical phase of major liver resections is blood loss. Liver resections may result in significant hemorrhage and subsequent transfusions in about 25–30 % of patients [32]. The two main sources of bleeding during a liver resection are the inflow system (hepatic artery and portal vein) and the outflow system (backflow bleeding from the hepatic veins), but bleeding may also occur during liver mobilization, hepatic transection, and dissection of biliary structures. As excessive intraoperative blood loss is a risk factor for PLF, both surgeons and anesthetists need to seriously address this issue. Indeed, improvement in dissection technologies has led to a decrease in the volume of blood loss during liver resections and improved postoperative outcome. However, although vascular occlusion techniques have minimized hepatic bleeding, the risk for postoperative liver and/or renal failure remains high for patients of advanced age and those with steatosis and cirrhosis, on preoperative chemotherapy and with small remnant liver volumes [25]. The most common method to lower blood loss is clamping the portal vein. Systematic studies have shown that portal clamping is associated with a significant reduction in intraoperative bleeding [21]. However, vascular occlusion techniques can be associated with liver ischemia–reperfusion injury. Therefore, if resection without vascular occlusion is not possible, inflow occlusion is preferable to total vascular exclusion. Intermittent portal clamping with intervals allowed for reperfusion is preferred to continuous clamping, usually applying a 15-min clamp and 5-min release regimen [13, 19]. Vascular control techniques during hepatectomy require optimization of the cardiac and pulmonary function [20]. This is particularly important in patients with end-stage liver disease because they are characterized by an increased cardiac output with blunted response to painful stimuli, splanchnic vasodilatation, and central hypovolemia. As a result, silent moderate-to-severe coronary artery disease cannot be easily recognized. Preoperative invasive assessment of preexisting cardiovascular dysfunction is indicated only for high-risk patients, provided that any coagulopathy is corrected. In the noninvasive assessment of coronary artery disease in patients with cirrhosis, dobutamine stress echocardiography has failed as a screening tool. Furthermore, beta blockade discontinuation in order to permit adequate cardiac function assessment may be hazardous in this class

of patients as beta blockers reduce portal hypertension and decrease cardiac workload. Thus their use seems to be beneficial to both the liver and the heart in the setting of hepatectomy. In general, the preoperative assessment needs to be adapted to the individual patient to minimize the perioperative liver insults of hepatic vascular control [32].

From a strict anesthesiological point of view, a low CVP (2–5 mmHg), while aiming at euvolemia, reduces blood loss during liver surgery and improves survival [32]. A low CVP can be achieved by limitation of intravenous fluid administration both before and during surgery. A blood pressure >90 mmHg has been proposed as a target during parenchymal resection also in the view to ensure diuresis of at least 0.5 mL/kg/h. If fluid restriction is ineffective to keep a low CVP, vasoactive agents can be used. The advantages of a low CVP must be weighed against inadequate perfusion of the vital organs and loss of volemic reserve in case of bleeding and/or air embolism. Nonetheless, it should be remembered that a recent Cochrane meta-analysis showed that a reduced CVP may decrease the hepatic venous pressure, resulting in a decrease in the blood loss. However, this has not translated into a reduction in the red cell transfusion requirement [12]. Finally, it must be remembered that air embolism may be observed during parenchymal transection under low CVP anesthesia or during reperfusion (due to mobilization of air bubbles trapped in opened veins). Clinical signs of vascular air embolism during anesthesia with respiratory monitoring are a decrease in end-tidal carbon dioxide and decreases in both arterial oxygen saturation and tension along with hypercapnia. From the cardiovascular system monitoring, tachyarrhythmias, electromechanical dissociation, pulseless electrical activity, as well as ST-T changes can be noted. Major hemodynamic manifestations such as sudden hypotension may occur before hypoxemia becomes present. Vascular air embolism is a potentially hazardous complication particularly in severe cirrhotic patients undergoing hepatectomy because they can have pulmonary abnormalities including intrapulmonary shunting, pulmonary vascular dilatation, and arteriovenous communications. In these patients, air can pass into the systemic circulation (paradoxical air embolism), even if cardiac abnormalities (patent foramen ovale) are not present, thus evoking fatal consequences. Currently, the most sensitive monitoring device for vascular air embolism is transesophageal echocardiography detecting as little as 0.02 mL/kg [32]. It has been proposed that the consequences of air embolism can be minimized by placing the patient in a 15° Trendelenburg position. However, opinions on the efficacy of this maneuver on improving hemodynamics are not univocal [16]. Finally, the anesthetist should also provide normothermic conditions to the patient undergoing liver resection, because hypothermia reduces blood coagulation, especially platelet function, and increases intraoperative blood loss.

Ischemia and reperfusion (I/R) *injury* is a major cause of morbidity and mortality following liver surgery and transplantation. Iatrogenic occlusion of the supplying blood vessels, with the aim of reducing blood loss in hepatic trauma or resection, induces warm ischemia, similar to hemorrhagic, cardiogenic, or septic shock [13, 19, 32]. Liver tolerance for ischemia is poor and the safe ischemia time is not known. In addition to the direct ischemic insult, hepatic injury occurs during

reperfusion. The exact mechanisms, such as the activation of local macrophages and the production of reactive oxygen intermediates and proinflammatory cytokines, are still being investigated. The oxidative stress related to hepatic reperfusion injury has long been recognized, but is beyond the scope of this review. Hepatic I/R injury affects patient recovery after major surgery and bears a risk of poor postoperative outcome. In liver surgery, ischemic preconditioning (IP, defined as defined as a process in which a short period of ischemia, separated by intermittent reperfusion, renders an organ more tolerant to subsequent episodes of ischemia) has been proposed as a method to provide protection against tissue damage due to ischemia during inflow occlusion, particularly in steatotic livers. Promising scientific data of a potentially protective effect of ischemic preconditioning have led to several clinical trials, unfortunately with so far disappointing results [19]. In a current Cochrane review of four clinical trials comparing the effect of ischemic preconditioning with that of no preconditioning in a total of 271 patients, it was not possible to identify any beneficial effect of ischemic preconditioning on important clinical endpoints such as mortality, liver failure, other perioperative morbidities, or duration of hospital stay; the authors conclude that there is currently no evidence suggesting a protective effect of ischemic preconditioning; merely a reduction in the perioperative transfusion requirements could be achieved [11]. Of note, patients with liver cirrhosis were excluded from the reviewed trials, and no conclusion on the effect of preconditioning in a compromised hepatic condition can be drawn from these trials [3]. Preconditioning with sevoflurane has been shown to significantly limit the postoperative increase of serum transaminases and the rate of postoperative complications [2]. Finally, an experimental model has suggested that pretreatment with remifentanil can attenuate liver injury both in vivo and in vitro. These effects were thought to be mediated through inducible nitric oxide synthase by exhausting reactive oxygen species and attenuating the inflammatory response [35]. These novel pharmacological approaches have generated a new interest in the choice of anesthetic agents, which might influence the postoperative outcome.

9.3.4 Postoperative Care

Adequate postoperative monitoring is essential to predict postoperative complications early enough. Postoperative liver enzymes, albumin, creatinine, and blood coagulation should be monitored, and patients should be clinically reevaluated on a regular basis. Patients that develop complications like encephalopathy, altered coagulation, or jaundice should be placed in intermediate care or in the ICU for better monitoring and should be checked for PLF development. It is normal for serum bilirubin and INR levels to increase in the first 48–72 h after surgery. However, bilirubin above 50 μmol/l (3 mg/dl) or INR greater than 1.7 in the first 5 postoperative days usually predict liver dysfunction [1]. PT can also be a sensitive predictor of PLF, but its interpretation may be compromised if the patient has received clotting factors. Serum albumin, an indicator of hepatic synthetic capability, may vary in response to inflammation and the administration of intravenous fluids. Increased

levels of serum lactate are also used to monitor postoperative liver function and represent a valuable and sensitive indicator of liver dysfunction [13, 19, 27]. Ascites and hepatic encephalopathy are important markers for liver failure but may be of difficult assessment particularly in the immediate postoperative period. In fact, ascites can occur as a result of surgery, whereas an altered mental state may occur in response to drugs such as opiates. Finally, several studies have examined the role of postoperative functional assessment of the liver. The ICGR15 predicts PLF, but its value diminishes once liver failure is established because changes in hepatic blood flow also influence ICGR15 [7]. However, although numerous studies have demonstrated that indocyanine green elimination measurements in these patient populations can provide diagnostic or prognostic information to the clinician, hard evidence, i.e., high-quality prospective randomized controlled trials, is lacking with regard to this method [34].

9.4 What Can We Do to Treat PLF

Although surgical and anesthesiological techniques have improved in the last years, treatment of PLF still remains difficult. This is due also to the fact that large, randomized trials concerning the treatment of PLF are lacking. Therefore, recommendations for treatment modalities are difficult to make. Management principles resemble those applied to patients with acute liver failure, acute-on-chronic liver failure, or sepsis and focus on support of liver and end-organ function.

PLF should be recognized as early as possible. This is crucial for triggering early treatments. Grade A PLF will normally not need specific treatments but just clinical and laboratory monitoring. In case of grade B PLF, it is up to the clinicians to evaluate if the patient should be placed in the step-down unit or the ICU. Finally, patients with PLF grade C need invasive treatments and have to be admitted in the ICU. As controlled trials for PLF are lacking, management relies on data from experience with acute liver failure [13]. Nevertheless, vascular complications such as portal thrombosis or suprahepatic abnormalities responsible for venous liver congestion should be ruled out first by ultrasonography and Doppler or CT scan. Whether early postoperative portal thrombosis should be surgically managed by desobstruction or treated with anticoagulants is debated. Liver outflow obstruction can be surgically cured when caused by the rotation of the remnant liver. Improvement of the venous outflow could also be achieved with endovascular treatment using a metallic stent [13]. Avoiding postoperative sepsis is of paramount importance. To this end, C-reactive protein levels might not be accurate after major hepatic resection because they can be decreased probably due to the decrease in functional liver mass [23]. The use of prophylactic antibiotics after hepatectomy for the prevention of infectious complications is not supported by evidence from the literature [33]. The pattern of organ dysfunction that occurs as a result of PLF is similar to that in sepsis. Cardiovascular failure is characterized by reduced systemic vascular resistance and capillary leak. Lung injury up to acute respiratory distress syndrome may ensue. Acute kidney injury can progress rapidly and fluid balance should be managed with

avoidance of water overload. Coagulopathy may occur after major liver resection. In the absence of bleeding, usually it is not necessary to correct clotting abnormalities except for invasive procedures or when coagulopathy is severe. Vitamin K may be given but there is no support by clinical trials. Thrombocytopenia may complicate liver failure. Indications for platelet transfusion in acute liver failure include bleeding, severe ($<20\times10^6$/L) thrombocytopenia, or when an invasive procedure is planned. A platelet count $>70\times10^6$/L is deemed safe for interventional procedures. Nutrition is important and supplementation should be established early in patients with liver failure. Enteral nutrition is the preferred route as it improves gut function and restores normal intestinal flora. Cerebral edema and intracranial hypertension may occur as a result of PLF. Cerebral edema is unlikely in patients with grade 1 or 2 encephalopathy. With progression to grade 3 encephalopathy, a head CT should be performed to exclude intracranial hemorrhage or other causes of declining mental status [13, 19, 27].

Extrahepatic assistance devices have been developed in the last years. They fall into two categories: artificial and bioartificial systems. Artificial devices use combinations of hemodialysis and adsorption over charcoal or albumin to detoxify plasma. Bioartificial devices use human or xenogeneic hepatocytes maintained within a bioreactor to detoxify and provide synthetic function.

These systems have not been evaluated extensively in patients with PLF. Outcomes for the use of these different devices in the management of acute liver failure are also unclear [10]. Therefore, currently, their role in PLF is undefined.

Liver transplantation is the only radical treatment in patients with end-stage liver disease. However, patients with PLF are rarely eligible for it because of tumor or the severity of their comorbid conditions. Moreover, liver transplantation for PLF is associated with significant morbidity. Therefore, the use of a rescue hepatectomy and subsequent liver transplantation in patients suffering from PLF may be of value in desperate situations where conventional measures fail. It is based on the concept that the "necrotic liver" is the source of unknown humoral substances that contribute to the systemic inflammatory response syndrome [33]. The use of salvage hepatectomy and orthotopic liver transplantation for PLF has been reported in a case series of seven patients who underwent liver resection for cancer with an overall 1-year (88 %) and 5-year (40 %) survival promising rates [18]. However, it has been suggested to limit liver transplantation to patients below the age of 70 years, with HCC and no macrovascular invasion, and, possibly, a small cholangiocarcinoma (less than 3 cm) without lymph node invasion. There is no indication for transplantation in patients with liver metastasis, except those with neuroendocrine tumors [13].

Conclusion

PLF is a serious and life-threatening complication in patients undergoing major liver resections or limited functional reserve due to preexisting liver disease. Adequate preoperative risk assessment of liver function and general condition, parenchyma-sparing surgery, and optimal intra- and postoperative management and treatment are essential for preventing PLF. Early diagnosis of this

complication can help initiate early treatment in the ICU aiming at optimizing and recovering both hepatic and extrahepatic organ function. Extracorporeal liver devices are still experimental in this particular clinical setting. The anesthetists, in their quality of leaders of the perioperative process of patients undergoing complicated surgery, play a key role in the management of this class of patients and are called to address the *knowledge gap* that still characterizes this particular clinical setting.

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Postoperative Delirium

10

Franco Cavaliere

10.1 What Is Delirium?

Delirium or acute confusional state is a syndrome characterized by the depression of the highest mental functions and by a typical time course [2, 17]. Symptoms occur acutely, manifest a fluctuating trend, especially in relation to night and day alternation, and in most cases resolve without leaving sequelae. Condition for diagnosis is that such symptoms cannot be explained with a state of preexisting dementia, in accordance with the definition given by the Diagnostic and Statistical Manual of Mental Disorders (DMS-IV): "The essential feature of a delirium is a disturbance in consciousness that is accompanied by a change in cognition that cannot be better accounted for by a pre-existing or evolving dementia."

Alterations of consciousness do not reach the severity of stupor or coma; rather, patients do not pay attention to the surrounding environment and in certain phases may have a more or less marked drowsiness. The attention span is reduced, and they are easily distracted during the interaction with doctors and family members. Among cognitive processes, memory of recent events and orientation in space and time are particularly compromised. Often, patients do not know where they are (in the hospital, in the orthopedic ward, etc.) nor have the correct time references (which day and time are now, it is day or night, how old they are, etc.). There may also be language disorders, such as an inability to speak or write object names. Disorders of emotions manifest themselves from time to time with anxiety, fear, depression, irritability, anger, or euphoria. Diagnosis is often suspected when the patient reports altered perceptions, spontaneously or at the request of the doctor. Altered perceptions are classified into misinterpretations, delusions, and hallucinations. An example of misinterpretation of a real situation is to believe that the

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administration of a drug is an attempt to poison or that hospitalization is a kidnapping. An illusion is an erroneous perception of a sensation, often visual; for example, an infusion line or a fold of the sheet may look like a snake or a worm. A hallucination is a perception that does not match any real sense; particularly frequent is watching insects on the walls or persons in the vicinity of the bed.

Psychomotor activity is also affected by delirium. There are two distinct forms, the overactive one, characterized by hyperactivity, restlessness, and insomnia, and the underactive one, characterized by hypoactivity, drowsiness, and detachment from the environment. Mixed forms are also possible, alternating hypo- and hyperactive phases. Hyperactive forms are often easier to diagnose because patient management becomes problematic. Delirium is classified as prevalent when it is already present at the admission to the hospital, incident when it occurs during hospital stay, and subsyndromic when it does not match all the criteria needed for diagnosis [7]. Finally, delirium may overlap to a preexisting dementia [10].

10.2 Incidence of Delirium in the Perioperative Period

Postoperative delirium typically occurs in the first 48 h after surgery. It must be distinguished from the transient phenomena of agitation that may be observed during recovery from anesthesia and from postoperative cognitive dysfunction which, likewise delirium, affects superior brain functions, first of all the memory, but has different characteristics (Table 10.1).

Incidence of delirium varies in different series, but is anyway high, especially in the elderly. After elective surgery, delirium affects between 10 and 75 % of patients older than 65 years [6]. This percentage is heavily influenced by the type of surgery. For example, delirium occurs more frequently after vascular surgery and oral surgery of long duration (36 and 42 %, respectively) than after ophthalmologic procedures, such as extraction of the lens (4.4 %). Hip surgery is also characterized by a high incidence of postoperative delirium (5–30 %), which increases if the intervention is associated with prolonged bed rest as in traumatic fractures.

Influence of surgery can be explained in part by the characteristics of interventions (duration, amount of postoperative pain, risk of hypotension, hypoxia, and anemia) and in part by patient features. For example, vascular surgery is often

Table 10.1 Differential diagnosis between delirium and postoperative cognitive dysfunction (POCD)

Clinical features	Delirium	POCD
Delay after surgery	Hours/days	Weeks/months
Onset	Acute	Insidious
Duration	Days/week	Weeks/months
Attention	Altered	Altered
Consciousness	Altered	Normal
Recover	Yes	Sometimes after months

Modified from Krenk and Rasmussen [5]

performed on elderly patients, affected by arterial hypertension and suffering from an advanced degree of atherosclerosis. Of note, the incidence of postoperative delirium is positively correlated with the number of hypotensive episodes, of arterial desaturations, and of blood transfusions that occur during the surgical procedure.

10.3 Etiology and Pathogenesis

The etiology of postoperative delirium is complex and multifactorial. Causes and contributing factors can be divided in five groups:

(a) Factors that alter brain metabolism. These include hypoperfusion, hypoxia, anemia, hyperthermia, fluid and electrolyte abnormalities, liver and kidney failure, some endocrine disorders, and deficiency of vitamin B_1 and B_{12}.
(b) Abnormal and annoying stimuli and, in general, all that can alter perceptions. Pain caused by inadequate analgesia facilitates the onset of delirium (although opioid administration can be a facilitating factor). This is particularly relevant for the elderly or for patients suffering from dementia who are very susceptible to the onset of delirium and often receive inadequate doses of analgesics. Endogenous stimuli, e.g., relating to constipation or bladder distension, may also induce the occurrence of delirium. Finally, inadequate ambient lighting or removal of hearing aids or glasses may alter patient perceptions, favoring the isolation of the patient himself and the appearance of altered perceptions.
(c) Some drugs, often having anticholinergic activity. They include some analgesics (codeine, meperidine, morphine), antibiotics, antifungals and antivirals (acyclovir, amphotericin B, cephalosporins, ciprofloxacin, imipenem-cilastatin, ketoconazole, metronidazole, penicillin, rifampin, trimethoprim-sulfamethoxazole), antiepileptic drugs (phenobarbital, phenytoin), cardioactive drugs (captopril, clonidine, digoxin, dopamine, labetalol, lidocaine, nifedipine, nitroprusside, procainamide, propanolol), drugs of abuse (alcohol, sedatives, hypnotics, hallucinogens, amphetamine, cannabis, cocaine, phencyclidine), and others (hydroxyzine, ketamine, metoclopramide, theophylline, atropine, scopolamine, nonsteroidal anti-inflammatory agents).
(d) Acute suspension of certain drugs and substances that are active on the nervous system, such as sedatives, opioids, alcohol, and nicotine.
(e) Environmental factors. Sometimes, delirium occurrence is simply caused by partying from home and relatives, admission to the hospital, and prolonged bedding. In intensive care units, environmental noise and night lighting worsen the quality of sleep and alter circadian rhythm. Absence of time references, such as calendars and clocks, and the lack of information and entertainment tools, such as books, newspapers, radio, and television, favor patient disorientation in time and space and, ultimately, cause delirium occurrence.

The pathogenesis of delirium is also complex and still not fully cleared. It has been hypothesized that a role is played by an imbalance in the brain

cholinergic and dopaminergic systems in favor of the latter. Indeed, in clinical practice, drugs with anticholinergic activity, such as atropine, scopolamine, and opioids, facilitate delirium onset, while neuroleptics, which have an antidopaminergic action, are therapeutic. Other possible factors affecting the brain are inflammation, vascular endothelial dysfunction, altered oxidative metabolism, and alterations of some synaptic mediators such as GABA and serotonin. From the topographical point of view, the involvement of the reticular substance, the cortex, and the hippocampus may explain the particular complexity of the symptomatology.

10.4 Diagnostics

The diagnosis of delirium is essentially clinical. Medical history is important to recognize predisposing factors and to point out preexistent dementia. Other key elements are the acute onset, the fluctuating character of symptoms, and patient's inability to concentrate. Talking with the patient allows pointing out confusion, disorientation in space and time, and often the occurrence of altered perceptions. Daily drowsiness and nightly agitation should also lead to suspect delirium occurrence. A few instruments have been proposed to monitor patients at risk. Some of them, such as the CAM (Confusion Assessment Method), are effective in most patients, but are difficult to apply in critically ill patients, unable to speak because of the presence of an endotracheal tube. The CAM-ICU was designed to evaluate patients unable to speak, who respond to the operator's questioning by squeezing his/her hand. This test has high sensitivity and specificity (both >90 %), has a good interobserver correlation, and is performed in less than 4 min by an experienced operator. Likewise CAM-ICU, the Intensive Care Delirium Screening Checklist (ICDSC), has been designed to evaluate patients who cannot speak. Contrary to CAM-ICU, which is purely qualitative, this test provides a score and then a quantitative evaluation. Both tests can be downloaded from the website www.icudelirium.org/.

Once the presence of delirium is known, physical examination and laboratory tests can provide elements to assess causes and plan treatment. For instance, electroencephalogram usually shows slow rhythms, but is characterized by the presence of fast rhythms in delirium caused by abstinence from benzodiazepines or alcohol.

10.5 Course

As a rule, delirium is a temporary condition, which typically occurs 48–72 h after surgery and resolves in a few days (on average 10–12). However, there is a wide individual variability and it can last weeks or more, particularly in elderly patients. Sometimes, delirium occurs preoperatively, just after the admission to the hospital.

The occurrence of delirium is associated with an increase in perioperative mortality and length of stay in the intensive care and in the hospital, with the related costs. Even long-term survival and functional recovery are adversely affected. It is unclear whether this is a causal relationship or an association linked to causes common to both processes. Similarly, no conclusive evidence has been gathered on the possible role of delirium in the etiology of postoperative cognitive dysfunction or in worsening preexisting dementia.

10.6 Prevention

Prevention of postoperative delirium is complicated by the multiplicity of factors involved. There is a wide literature on this topic, but many studies had inadequate power; as a consequence, there are presently only few evidence-based interventions. According to a recent meta-analysis, the only ones significantly effective (possibly because tested with a suitable experimental design) are (a) performing preoperative evaluations by geriatricians in order to implement positive conditioning of the patient and (b) maintaining a relatively superficial level of anesthesia (characterized by BIS values between 40 and 60) (Table 10.2). The meta-analysis also suggested the possible effect of exposure to bright light for at least 2 h a day in order to restore the sleep-wake cycle and the prophylactic administration of haloperidol; both interventions, however, did not reach statistical significance. Haloperidol was administered in different doses and ways: 5 mg intravenously per day for 5 days or 1.5 mg orally before surgery and then for 3 days postoperatively. Interestingly, in comparison with regional anesthesia, general anesthesia was not associated with a higher incidence of delirium and the anesthetic technique (whether inhalation or intravenous) did not affect incidence either [6, 16]. A second meta-analysis that was focused on cardiac surgery showed the moderate effectiveness of pharmacological prophylaxis with several drugs, including dexamethasone, rivastigmine, risperidone, ketamine, dexmedetomidine, propofol, and clonidine [9].

Table 10.2 Some perioperative interventions investigated in order to decrease postoperative delirium in noncardiac surgery

Perioperative geriatric consultations with multicomponent interventions[a]
Lighter general anesthesia[a]
Diurnal bright light therapy (2 h or more) postoperatively[b]
Prophylactic haloperidol[b]
General anesthesia vs. regional anesthesia[c]
Intravenous anesthesia vs. inhalation anesthesia[c]
Donepezil vs. placebo[c]

From Moyce et al. [8]
[a]Statistically significant
[b]Just below statistical significance (possibly due to from RCT inadequate power)
[c]Not significant

Table 10.3 Interventions proposed by NICE guidelines for prevention of postoperative delirium [11]

1. Ensure that people at risk of delirium are cared for by a team of healthcare professionals who are familiar to the person at risk. Avoid moving people within and between wards or rooms unless absolutely necessary
2. Within 24 h of admission, assess people at risk for clinical factors contributing to delirium and, based on the results of this assessment, provide a multicomponent intervention
3. Address cognitive impairment and/or disorientation by:
(a) Providing appropriate lighting and clear signage; a clock (consider providing a 24-h clock in critical care) and a calendar should also be easily visible to the person at risk
(b) Talking to the person to reorientate them by explaining where they are, who they are, and what your role is
(c) Introducing cognitively stimulating activities (e.g., reminiscence)
(d) Facilitating regular visits from family and friends
4. Address dehydration and/or constipation
5. Avoid hypoxia
6. Prevent infection
7. Avoid immobility by encouraging people to mobilize soon after surgery
8. Provide adequate analgesia
9. Carefully evaluate drug therapy
10. Provide adequate nutritional intake
11. Avoid sensory impairment by resolving any reversible cause and ensuring patient hearing and visual aids are available and in good working order
12. Promote good sleep patterns

As a matter of fact, other interventions are quite reasonable even if not supported by statistical evidences. They are often inexpensive and effective to prevent perioperative complications other than delirium. For instance, since the incidence of postoperative delirium is positively correlated to the number of hypotensive episodes, arterial desaturations, and blood transfusions, intraoperative prevention of delirium should be based on the maintenance of clinical and laboratory parameters as close to the range of normality as possible. Particularly, anesthesiologists should avoid severe arterial hypotension, hypoxia, and excessive anemization, PONV, as well as excessive depth of anesthesia [3, 12, 14, 15, 18]. Postoperatively, adequate analgesia should be provided as well as other interventions. On this regard, the recent guidelines on delirium, sedation, and analgesia produced by the American College of Critical Care Medicine underline that preoperative identification of patients at risk of delirium (dementia, addiction to alcohol and drugs, disturbances of consciousness, use of benzodiazepines, severity of the disease) helps to implement adequate preventive measures, such as the suspension of the administration of benzodiazepines, the implementation of programs of physiotherapy and early mobilization, and measures to improve the quality of sleep [1]. The resumption of any preoperative therapy with antipsychotics is also recommended as soon as possible. The National Institute of Health and Care Excellence (NICE) has produced a list of interventions for prevention of postoperative delirium (Table 10.3).

10.7 Treatment

Environmental interventions are substantially the same as those recommended for the prevention of delirium. They were subject to a limited number of studies, hence evidence of their effectiveness is poor, but rationale is sound, and application is cheap.

In intensive care units, patients often develop a state of disorientation in space and time for the lack of windows open on the outside and of clocks, calendars, radio, and television. This condition can predispose to delirium development. Also excessively noisy alarms or nurse activity that continue even at night can alter sleep patterns. Actions to prevent these issues are hospitalization in environments that have windows and then daylight, switching off artificial lighting at night, and the presence in the room of a wall clock and a calendar. Radio and especially television punctuate with their transmissions the passing of the hours and days, keeping the patient in touch with the outside world. Health personnel can play a valuable asset to reorient the patient to the correct time and date, the place where it is, and its current issues. On this purpose, relatives can play a very important role, so that access policy to intensive care units and wards should be as liberal as possible.

Modulation of sensory stimulation is also important. On one hand, it is necessary to avoid annoying stimuli, such as noise from the alarms of monitors and other medical equipment; on the other hand, it is important to optimize patient perceptions. Hearing aids and glasses should be worn in hospital and in intensive care. The room lighting should be adequate to facilitate the interaction of the patient with the staff and with the families and to prevent delusions and hallucinations as much as possible. It should also be avoided or limited the use of coercive means, which may lead to the development of paranoid attitudes and misinterpretations.

Pharmacological interventions for the control of postoperative delirium include in the first place an adequate analgesic therapy, in which the use of opioids is limited in favor of the use of non-opioid analgesics (NSAIDs, paracetamol) and multimodal analgesia. Benzodiazepine administration should be discontinued, except in delirium caused by withdrawal from alcohol or benzodiazepines themselves. Any preoperative therapy for psychiatric disorders should be resumed as soon as possible.

Haloperidol and atypical antipsychotics are the drugs most commonly used in the treatment of postoperative delirium, but should only be considered when environmental measures alone are ineffective. In 2009, a survey of over 1,300 US health workers showed that the drug most widely used for the treatment of delirium in ICUs was haloperidol; in fact, it was used by 90 % of respondents, while atypical antipsychotics by less than 40 % [13]. However, studies that have evaluated haloperidol and atypical antipsychotic effectiveness have provided ambiguous results and suggest that these drugs are more effective in attenuating the severity of symptoms, particularly agitation and altered sensory perceptions, rather than in

shortening the duration of delirium. The dose of haloperidol is variable depending on the severity of the clinical picture. In mild forms, oral doses of 2.5-5 mg every 8 h are given. In severe cases, the drug is used intravenously, with doses of 5 mg to be repeated after lapses of time variable according to the control of symptoms (from 1 to 8 h). In the elderly, it is prudent to reduce the dosage.

Haloperidol, as all neuroleptics, reduces the initiative and interaction with the environment, as well as the emotions. Initially, it can slow responses to stimuli and induce drowsiness, but the patient can easily be awakened, answers questions, and preserves the intellectual functions [4]. The therapeutic effect manifests in particular with a reduction of the agitation and of alterations of sensory perceptions. The drug does not induce respiratory depression. Among the side effects, the possible appearance of extrapyramidal symptoms, of neuroleptic malignant syndrome (hyperthermia and extrapyramidal signs, associated with altered consciousness, impairment of the autonomic nervous system, leukocytosis, and elevated CK), and of ventricular arrhythmias (torsades de pointes, the occurrence of which is favored by the possible lengthening of the QT interval on the electrocardiogram, to be monitored during the treatment) should be mentioned.

Compared to haloperidol, atypical antipsychotics may have greater efficacy in some patients, partly because of their timoleptic properties (resulting in a feeling of well-being) and because the occurrence of extrapyramidal disorders may be less frequent. Atypical antipsychotics employed to control postoperative delirium are olanzapine, risperidone, ziprasidone, and quetiapine.

The National Institute of Health and Care Excellence (NICE) has recently developed a scheme of treatment of patients affected by delirium (which can be downloaded from the website: http://pathways.nice.org.uk/pathways/delirium). The initial approach includes (a) research and treat the causes of the onset of delirium; (b) seek to ensure effective communication with the patient, reassuring and explaining where he/she is, who is his/her audience, and what is their professional role; (c) assess whether relatives or friends can be involved in this guidance activities; (d) involve any doctors or staff that the patient knows from time; and (e) finally try to avoid moving the patient from one department to another unless absolutely necessary. If delirium does not improve after this first set of measures, it is recommended to (f) use de-escalation techniques to control conditions of aggression and/or violence; (g) assess the possibility of a short course of therapy (1 week) with haloperidol or olanzapine, starting from lower doses and then increasing dosage based on clinical effects (these drugs should be avoided in patients with Parkinson's disease or dementia with Lewy bodies). If despite this the delirium does not improve, you need to re-evaluate the diagnosis, specifically excluding dementia.

Conclusions

Delirium is a common postoperative complication, especially in certain groups of patients, and after certain types of surgery. To diagnose its occurrence, you need to know about its existence and apply diagnostic tests. For prevention and treatment, environmental interventions are more important than drug therapy.

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Perioperative Protection of Myocardial Function

11

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11.1 Introduction

The concept of cardiac protection, in the usual way, corresponds to any strategy of the mechanical, pharmacological, or physical types adapted to reduce or avoid the onset of cardiac permanent and disabling damage, so as to compromise the outcome. The goal is to mitigate the extent of the injury induced by the mechanism of ischemia-reperfusion and the early and late harmful effects, such as acute myocardial infarction (AMI), arrhythmias, ventricular dysfunction, cardiogenic shock, and the increase in fatal perioperative mortality.

Despite advances in the understanding of what determines coronary blood flow, the relationship between demand and supply of oxygen, and the cellular mechanisms triggered by ischemia, there is still a high incidence of perioperative AMI, which varies from 3 to 30 %, in different studies [1].

11.2 Ischemia and Reperfusion

Myocardial ischemia triggers a series of cellular events that occur earlier and become deleterious in the process of time. Although reperfusion is the final stage of the ischemic process and is essential to restore normal function and cell survival, this may paradoxically amplify the damage secondary to ischemia.

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During ischemia, the oxygen supply is subject to regional metabolic needs, resulting in exhaustion of the reserve of cellular adenosine triphosphate (ATP). There is a decrease of the efficiency of the sodium (Na^+)/potassium (K^+) ATP-dependent pump with increased levels of intracellular sodium.

Neutrophil and platelet aggregation determines microvascular obstruction, contributing to alter the supply/demand ratio of O_2 [2].

A recent evidence suggests that the overload of intracellular calcium can activate selective proteolytic enzymes, the system of calpains, resulting in selective myofibrillar proteolysis, and the time required for the synthesis of damaged proteins would explain the time required for the recovery of myocardial function after ischemia-reperfusion [3, 4]. In association with elevated levels of intracellular calcium, the increase of free radicals due to reperfusion with oxygenated blood is very important. The clinical consequences can range from myocardial reversible dysfunction after reperfusion, known as myocardial stunning, to myocardial infarction [5, 6].

11.3 Techniques of Myocardial Protection in Cardiac Surgery

11.3.1 Cardioplegia

The cardioplegic solutions rich in potassium have been virtually abandoned in the mid-1970s, when it was found that myocardial necrosis was linked to their high concentration of K^+ and hyperosmolarity [7]. Until 1980, the hypothermic crystalloid cardioplegic solutions have been the main technique of myocardial protection during cardiac surgery. Since 1980, studies have shown that the cardioplegic solutions with blood potassium determined more effective myocardial protection compared to crystalloid solutions, demonstrated by the decrease in the release of CK-MB and incidence of perioperative myocardial infarction [8].

11.3.2 Hypothermia

Therapeutic hypothermia is a different strategy to reduce myocardial damage secondary to ischemia. The classic explanation focuses on the decreased of the oxygen consumption induced by the decrease in metabolic activity of cellular enzymatic reactions, which could limit the areas at risk in the regions of ischemic myocardium. In humans cooled to 32 °C, the total consumption of oxygen is reduced by 45 % and is not related to the changes in the arterial oxygen saturation [9]. When the temperature decreases, also the oxygen consumption of the myocardium is reduced to below 1 % at 12 °C [10].

The deep hypothermia for very long periods may exacerbate intracellular calcium overload and induce the formation of peroxides and reactive oxygen species [11, 12].

11.3.3 Myocardial Preconditioning

In 1986, Murry and colleagues showed that the four successive cycles, each including a short ischemic episode, obtained by ligation of the circumflex artery in the canine myocardium, followed by a reperfusion period lasting 5 min, were able to reduce the extent of the infarct size by up to 30 % [13].

This mechanism inherent protection was called "ischemic preconditioning" and constitutes the most effective form of protection in vivo against ischemic infarction in addition to early reperfusion. The ischemic preconditioning determines a protection that is expressed early 2 h after the preconditioning stimulus, followed after about 24 h from a second window of protection (SWOP) [14] that persists for a period longer than 72 h.

11.4 Mechanisms of "Classic" Ischemic Preconditioning

The ischemic insult is the primary cause of the preconditioning mechanism, promoting the synthesis and release of a number of endogenous mediators, such as adenosine, acetylcholine, endothelin, and opioids, which bind to their G protein-coupled receptors; the coupling of several species of receptor to G proteins is responsible for the activation of signal transduction pathways that favor downstream amplification. G proteins activate in fact a group of hydrolyzing phospholipids enzymes, such as phospholipase C and D (PLC and PLD) that derive from PIP_2 messengers of glyco-phospholipidic origin, the IP_3 and DAG.

The IP_3 promotes the release of Ca^{++} from the sarcoplasmic reticulum, and DAG activates protein kinase C (PKC). PKC is a serine kinase that exists in different isoforms in the heart: the typical are α, β, and γ, employees from the DAG and calcium; δ, η, and ε employees only from DAG and the atypical isoform ζ that is independent from calcium and DAG.

PKC is activated by other numerous stimuli, including the production of ROS and NO and the increase in intracellular Ca^{++}.

On the contrary, the NO plays a central role in the late phase of preconditioning [15]; several studies have demonstrated that the increase in endogenous and exogenous drug-induced inducible nitric oxide synthase (iNOS) exerts its cardioprotective role through:

- Input inhibition of intracellular Ca^{++}
- β-adrenergic receptor antagonism
- Decreased contractility and myocardial oxygen consumption
- Opening of K_{ATP} channels
- Antioxidant action
- Activation of COX_2 with production of prostanoids

K_{ATP} channels are important mediators of cardioprotection and were described for the first time by Noma and colleagues in ventricular myocytes [16].

These ion channels are ATP sensitive since they can be inhibited by physiological levels of ATP, as well as modulated by pH, fatty acids, protein G, acetylcholine, and adenosine.

Subsequent studies showed that these agents can open K_{ATP} channels mimicking ischemic preconditioning and that their block instead abolishes this protection; that preconditioning role was given to the sarcolemmal K_{ATP} channel. Later, after the discovery of the existence of two types of K_{ATP} channels, those of the sarcolemma already known and those of the mitochondrial membrane, Garlid [17] showed that the mitochondrial K_{ATP} channel was the effector of the protective mechanism of the preconditioning.

The mitochondrial K_{ATP} channel consists of a potassium channel rectifying internal current (K_{ir}) associated with protein binding sulfonylureas (Sur). The glibenclamide and 5-hydroxydecanoate (5-HD) block the K_{ATP} channels, respectively, in a nonspecific and selective way, inhibiting mitochondrial channels in the micromolar range but not those of the surface.

11.5 Cardioprotective Role of Inhaled Anesthetics

The mechanism of drug-induced cardioprotection is a complex process, and just as ischemic preconditioning, it uses a series of reactions involving intracellular protein-coupled receptors, protein kinases, potassium ion of the mitochondrial and sarcolemmal channels (K_{ATP}), and reactive oxygen species (ROS).

In a study published in 1988, Warltier and colleagues [18] described a better recovery of myocardial function, after 15 min of occlusion of a coronary artery, when an inhalation anesthetic was administered before the occlusion.

The intracellular pathways of the anesthetic preconditioning, as that of the ischemic mechanism, remain, even after many years, in part unclear; one of the possible scenarios of the anesthetic preconditioning is that this starts with the increase of intracellular ROS [19]; this phenomenon has been suggested by the observation that the introduction of a scavenger of ROS during exposure to isoflurane or sevoflurane is able to block the anesthetic preconditioning response and that small increases in free radical production occur during the administration of sevoflurane in healthy hearts.

The sequence of reactions that occurs after the production of ROS is still not very clear, but there is certainly evidence of activation of PKC [20] and other kinases such as tyrosine kinases and the MAPK [21] that have as final effect the opening of mitochondrial K_{ATP} channels.

The opening of potassium channels generates a cytosolic and mitochondrial reduction of the calcium entry and improves the myocardial oxygen consumption during ischemia.

Moreover, the preconditioning effect of volatile anesthetics shows a cardioprotective role even when administered during reperfusion [22], an effect probably due to the anti-inflammatory properties of these drugs.

Several studies have shown the cardioprotective effects also of the xenon [23].

The calphostin C, a PKC inhibitor, and SB203580, an inhibitor of p38 MAPK, abolish the effects of xenon and isoflurane preconditioning. These data indicate that the PKC and p38 MAPK are key mediators in the preconditioning mechanism offered by xenon. By the use of a specific antibody against PKC-ε, it was shown that the xenon leads to a marked phosphorylation of the PKC-ε compared to controls [24] and that the calphostin C abolishes the effect of xenon on the phosphorylation of the PKC-ε. The xenon induces a significant increase in phosphorylation of p38 MAPK, and the calphostin C cancels this effect, demonstrating that p38 MAPK is located downstream of PKC in the preconditioning signal cascade induced by xenon [25]. The xenon increases the translocation of HSP27 in the particulate fraction and increases the polymerization of F-actin [25]. Other data indicate that, in addition to the p38 MAPK, also the kinase ERK is involved in the xenon preconditioning.

11.6 Opioid Analgesics

Experimental studies in animals have shown protection against ischemia-reperfusion mediated by opioid receptors.

In 1996 Schultz et al. show that 300 $\mu g.kg^{-1}$ of morphine administered 30 min before the occlusion of the anterior interventricular coronary artery decreases the infarcted area from 54 to 12 % in rats [26]. This infarct size reduction induced by morphine was also observed in models of isolated heart, the heart in situ, and in cardiomyocytes [27–29]. Both morphine and fentanyl showed ability to induce improvement in ventricular contractility after ischemia [30].

The involvement of opioid receptors in ischemic preconditioning, especially sigma receptors, has been observed in several animal species and in humans [27–29]. In 1995 Schultz et al. have shown that naloxone would block the cardiac protective effects induced by opioids in rats subjected to ischemic preconditioning, but there would be no effect in animals not subjected to preconditioning [31].

The cardiac protection induced by opioids seems to be modulated by the activation of cardiac receptors, independently from the action of these drugs on the central nervous system. It was proposed that the cardiac protection by opioids results from activation of ATP-dependent potassium channels, probably in the mitochondrial membrane [29, 30, 32].

11.7 Other Drugs

Some studies have suggested that propofol might attenuate mechanical myocardial dysfunction after ischemia, infarct size, and myocardial histological changes [33–36]. Due to its chemical structure similar to the chelating free radicals phenol derivative (vitamin E), propofol reduces the concentration of free radicals and their harmful effects [37]. Other authors have described that propofol reduces the calcium influx into the cells and reduces the activity of neutrophils, operating during critical phases of myocardial reperfusion [38, 39].

The administration of the intracellular transduction pathway blockers related to ischemic preconditioning, such as glibenclamide, does not inhibit the momentary protective effects of propofol [40].

Despite the established role of ketamine as an anesthetic agent for congenital heart surgery in patients with the development of cardiovascular shock, this drug appears to block the ways of ischemic preconditioning [41, 42] and to increase myocardial injury. Ketamine decreases the production of inositol-1,4,5-trisphosphate [43] and inhibits the ATP-dependent potassium channels in the sarcoplasmic membrane [44].

Levosimendan, a calcium sensitizer, has preconditioning properties due to its action on the K_{ATP} channels and for that is used in the high-risk patients, especially in the preoperative period [45, 46].

11.7.1 Thoracic Epidural Anesthesia

Thoracic epidural anesthesia was used to promote perioperative analgesia and decrease the oxygen consumption of the myocardium, by blocking the sympathetic fibers of the T1 to T5 nerve roots which provide sympathetic innervation to the heart.

Studies have shown that thoracic epidural anesthesia may attenuate endocrine-metabolic response secondary to surgery, with decreasing serum levels of catecholamines, resulting in lower oxygen consumption [47]. Thanks to the effectiveness of thoracic epidural analgesia, it is possible to decrease the doses of systemic opioids, thus decreasing the time of tracheal intubation and lung disease in the postoperative period of cardiac surgery [48–50].

However, despite the beneficial effects of thoracic epidural anesthesia on myocardial oxygen balance, no direct myocardial mechanism of increased tolerance to the phenomenon of ischemia and reperfusion has been described. In a recent meta-analysis of 28 studies and 2,731 patients [51], the thoracic epidural anesthesia in CABG surgery was not effective in reducing mortality (0.7 % versus 0.3 % general anesthesia) or the incidence of myocardial infarction (2.3 % versus 3.4 % general anesthesia). On the other hand, there has been a significant decrease of arrhythmias (OR 0.52), pulmonary complications (OR 0.41), and the time of tracheal intubation (4.5 h).

11.7.2 Noncardiac Surgery

The problem of perioperative cardiac protection is most important in noncardiac surgery, where the patient with ischemic heart disease does not get correction of his coronary disease, but increases the risk of intra- and postoperative acute myocardial infarction resulting in perioperative stress also in patient with no apparent injuries who may develop coronary myocardial damage until death.

The noncardiac surgery, globally, has a complication rate of 7 %, 42 % of which are cardiac complications. Considering the single European population, it means 167,000 cardiac complications per year, of which 19,000 at risk of life [52]. The need of clear guidelines is evident.

The patient at risk, studied with ischemia stress test and measuring the increase of the markers of myocardial damage (troponin and NT-proBNP), must be contextualized in his surgical risk that the recent guidelines has described as mild, moderate, and severe (risk of AMI <1 %, <5 %, or >5 %) depending on the invasiveness and duration of the surgical trauma itself. When the characteristics of the patient and the surgery carry a high risk of perioperative AMI, some strategies of myocardial protection through the use of cardioprotective drugs (beta-blockers), anti-inflammatory agents (statins), antiplatelet agents, preoperative revascularization, and perioperative hemodynamic optimization (GDT, goal-directed therapy) should be put in place. The systematic perioperative use of these strategies does not produce clear benefits, but rather an increase in morbidity, when implemented in low-risk patients undergone to mild- to moderate-risk surgeries [52].

In case of high risk patients (e.g., preoperative AMI associated with NYHA class >2, elevated creatinine level, COPD, METs ≤4, etc.) undergone to a high-risk surgery, it is suggested to programm a postoperative period of 12–24 h in intensive care unit.

As regards the technique of anesthesia or the choice of protective anesthetic drugs, it reached no consensus from clinical trials, differing from results obtained in cardiac surgery.

The protective role of halogenated anesthetics has not been shown [53], as well as uncertain appears the advantage of the techniques of regional anesthesia (as the neuraxial anesthesia) which, in literature, confirm some efficacy in reducing pulmonary complications, but inability to determine any advantage in terms of troponin release and reduction of perioperative AMI rate [54, 55].

11.7.3 Beta-Blockers

The effectiveness of these drugs, clearly $beta_1$-selective blockers, formed the cornerstone of perioperative cardiac protection especially in patients undergoing vascular surgery, described as high-risk surgery [56].

The efficacy of perioperative beta-blockade was especially confirmed by the work of the group of Poldermans [57] that summarized their use in various key points: obtain a therapeutic target such as the reduction in heart rate (<70 bpm), implement the dose within 4 weeks (to avoid deleterious effects on blood pressure), and always avoid the acute withdrawal in patients treated with such drugs. This therapeutical recipe resulted in drastic reduction in perioperative AMI, as showed by the clinical trials of this research group. But since the number of patients enrolled was inadequate to clearly demonstrate its effectiveness, a huge clinical trial, the POISE trial, has been recently prepared [58], which, in spite of

expectations, showed a reduction of perioperative AMI in the beta-blocked patients, but an increase in mortality due to hemodynamic events such as bradycardia, hypotension, and stroke.

These results have created a rising criticism related to previous guidance on perioperative beta-block, so to require a revision of the guidelines. In reality, the POISE trial [58], which provided for the immediate preoperative use of beta-blockers (2–4 h before surgery, with high and fixed dose of metoprolol), has bypassed the indication of tailored therapy, as indicated by Poldermans [57].

Clearly, if you give a high dose of beta-blocker acutely, the risk of hypotension, bradycardia, and subsequent stroke is expected. However the history of beta-blockers in the pre- and post-POISE periods has changed irreversibly, so that a recent meta-analysis showed that the beta-blockers were protective drugs only for the studies of Poldermans, but excluding these it is evident an increase in mortality from their use [59].

Finally, the guidelines show clearly the A class of evidence for the administration of beta-blockers: all patients with heart disease in the active phase and those already medicated with beta-blockers and undergoing high-risk surgery [52].

Agreeing with the indications of London [60], I summarize about the use of beta-blockers for the high-risk patients: who has to go to high-risk surgery, reaching the target (<70 bpm FC) in 2–3 weeks, avoiding, always, to suspend them acutely.

Moreover, the type of beta-blocker may be decisive on the results, avoiding to administer metoprolol (suspected of being responsible for stroke) in favor of bisoprolol or atenolol [61].

The ability to modulate the heart rate with the i.v. use of esmolol, a short-acting drug with an extremely favorable metabolism (rapid onset and offset), increases the potential of use of beta-blockers in the perioperative period [62], especially when the bowel, blocked by the surgical procedure, prevents the absorption of oral therapy.

According to the ESC/ESA 2014 guidelines, the use of beta-blockers is no longer recommended in patients scheduled for low- or intermediate-risk surgery [52]. The beginning of treatment with these drugs should not be considered routine in patients undergoing noncardiac surgery. The preoperative intake may be considered in patients scheduled for high-risk surgery or who have two or more risk factors or ASA status greater than or equal to 3 and who have a heart disease or ischemic myocardial ischemia. However a treatment with beta-blockers in high doses without titration is not recommended. For an oral beta-blocking treatment, atenolol or bisoprolol as a first choice can be considered [52].

11.7.4 Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are widely prescribed in patients with or at risk of ischemic heart disease (IHD) because of their lipid-lowering effect. Statins also contribute to plaque stabilization because they determine a decrease of lipid oxidation, inflammation, matrix metalloproteinases, and apoptosis and increase the production of tissue inhibitor of

metalloproteinases and collagen. These so-called non-lipid or pleiotropic effects may prevent plaque rupture leading to AMI in the perioperative period [63].

Some beneficial effects mediated by these processes are able to improve endothelial function. Just to the endothelium, the greater pleiotropic effect of statins is expressed through the upregulation of nitric oxide synthase (eNOS), reduction of the proliferation of vascular smooth muscle cells, platelet activity, oxidative stress, inflammation, and stabilization of atherosclerotic plaque. Furthermore, through cholesterol-dependent mechanisms, statins improve endothelial function due to the removal of LDL particles, thereby changing the plaque and reducing vascular inflammation and leukocyte activation.

Several studies report the reduction of cardiac complications in the postoperative period with the use of statins. Two trials, for a total of 600 patients, including the DECREASE III, showed a reduction of mortality and perioperative myocardial infarction in over 50 % of cases [64, 65]. ESC 2009 guidelines recommend (IB) starting statin therapy 30 days before surgery in patients at high risk [66].

The ESC/ESA 2014 guidelines recommend that the beginning of preoperative statin therapy should be considered in patients scheduled for vascular surgery, optimally at least 2 weeks before the operation. For patients undergoing noncardiac surgery who are already taking statins, the 2014 guidelines recommend to continue treatment over the period of postoperative hospitalization [52].

11.7.5 Antiplatelet

Patients undergoing coronary stent implantation and treated with antiplatelet therapy, candidates for cardiac and noncardiac surgery, represent a considerable and growing proportion of patients (4.8 % of patients need an unexpected noncardiac surgery within the first year of the implantation procedure of coronary stenting). The perioperative management of antiplatelet therapy in these patients has not been clearly and systematically defined. In fact, the current guidelines do not provide precise information and decision algorithms, but rather suggest you to make a multidisciplinary assessment case by case, in relation to the individualized ischemic and hemorrhagic risk that is not, then, well defined and stratified. This approach, not codified by clear and standardized protocols for the different types of surgical procedures, has led to considerable variability in perioperative management of antiplatelet therapy. Normally it is possible to suspend the double antiplatelet therapy (i.e., thienopyridines) and continue only the acetylsalicylic acid (ASA) after an appropriate period by the stent implantation (4 weeks from a bar metal stent and 6 months for drug-eluting stents) [67], except in cases of emergency surgery in which you can suspend the thienopyridine 5 days before surgery switching to an intravenous inhibitor of glycoprotein IIb/IIIa receptors and suspending it 2 h before the operation and then resume the thienopyridine postoperatively [68].

The routine ASA use in patients at risk of perioperative ischemic events is no longer supported [69]. It is determined that the use of low-dose ASA should be based on individual decisions that depend on the perioperative risk of bleeding balanced against the risk of thrombotic complications [52].

11.8 Preoperative Revascularization

Only a single randomized study examined the role of prophylactic revascularization before noncardiac surgery in stable patients undergoing vascular surgery. The CARP (Coronary Artery Revascularization Prophylaxis) trial was the first study comparing optimal medical therapy and revascularization (by CABG or PCI) in patients with stable IHD scheduled for a major vascular surgery [70].

Out of 5859 patients evaluated in 18 Veterans Affairs hospitals, 510 were randomized to one of the two treatments according to an inclusion criterion as the presence of cardiovascular risk factors in combination with the response to the noninvasive tests for ischemia, based on the assessment of a consultant cardiologist. A follow-up of 2.7 years showed no significant differences in the primary endpoint of long-term mortality (22 % in the revascularization group vs. 23 % in the group not submitted to revascularization, $p = 0.92$) nor in the incidence of perioperative AMI (12 vs. 14 %, $p = 0{:}37$) [70].

Various physicians, however, have scheduled coronary angiography and possible preoperative coronary angioplasty in patients undergoing high-risk surgery, even when patients suffered from stable coronary artery disease.

A study of 426 patients undergoing carotid surgery [71], divided into two groups A and B (A = preoperative coronary angiography and possible PTCA, B = no coronary angiography), analyzed intra- and postoperative events related to dual antiplatelet therapy.

The postoperative mortality was 0 % in group A and 0.9 % in group B ($p = 0.24$). Only one postoperative stroke (0.5 %) occurred in group A against two (0.9 %) in group B ($p = 0.62$). No postoperative infarction was observed in group A, while nine ischemic events were observed in group B, including a fatal myocardial infarction ($p = 0.01$). Binary logistic regression analysis showed that preoperative coronary angiography has been the only independent variable that can predict the presence of postoperative coronary ischemia after carotid endarterectomy. The odds ratio for coronary angiography (group A) showed that when all other variables are taken into account, a patient with preoperative coronary angiography before the carotid endarterectomy has four times less probability to have an ischemic cardiac event after carotid surgery. In this study, complications of coronary angiography or cervical hematoma were not observed in patients undergoing surgery under clopidogrel and ASA. In group A, coronary angiography revealed significant coronary stenosis in 68 patients (31.5 %). Among these, 66 patients were undergoing coronary artery stenting (PCI) and 2 undergoing coronary artery bypass grafting (CABG) before the carotid endarterectomy. The follow-up to 30 days showed three heart attacks in the group A (1.4 %) and 33 in group B (15.7 %) including 6 fatal. At 5 years, the rate of freedom from AMI was 97.5 ± 2.0 % in group A compared with 79.0 ± 3.8 % in group B (log rank, 28.0; $p = .001$) [72].

Conclusions

Nowadays, the most widely used method of myocardial protection during heart surgery with CPB is the infusion of cardioplegic solutions in their different ways, the regional and systemic hypothermia, that effectively reduce myocardial oxygen

consumption and preserve myocardial contractility. In patients undergoing CABG without CPB, the ischemic preconditioning has a well-established role, being also used in patients undergoing cardiac surgery with CPB. Some drugs, such as systemic or regional beta-adrenergic antagonists, have been shown to protect myocardial function in a similar manner to the protection given by cardioplegic solutions. Regional anesthesia techniques, considered protective, play no role, confirmed by clinical trials, in the protection of the heart. On the other hand, the inhaled anesthetics and opioids play an important role in protecting the heart.

In cardiac patients undergoing noncardiac surgery, a key role is assigned to the correct preoperative risk stratification and the planning of a multimodal strategy of myocardial protection involving the use of perioperative drugs, anesthetic techniques, and intra- and postoperative hemodynamic proper management (GDT, goal-directed therapy), designed to maintain the supply/demand ratio of oxygen balance.

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Regional Anesthesia in Ambulatory Surgery

12

Edoardo De Robertis and Gian Marco Romano

12.1 Introduction

Ambulatory surgery or day surgery (DS) refers to the clinical, organizational, and administrative possibility to perform diagnostic and/or therapeutic procedures, invasive or semi-invasive, in patients whose hospitalization is limited to 1 day [1].

The definition adopted in 2003 by the International Association for Ambulatory Surgery says, "*A surgical day case is a patient who is admitted for an operation on a planned non-resident basis and who nonetheless requires facilities for recovery. The whole procedure should not require an overnight stay in a hospital bed*" [2].

DS, representing a model of care that can improve and rationalize health services, is increasingly gaining attention in health systems.

The development of ambulatory anesthesia has seen a gradual improvement since 1984, when the "Society for Ambulatory Anesthesia" (SAMBA) was founded. The execution of diagnostic and therapeutic procedures in outpatients is strictly associated with the need of reducing costs of hospitalization, maximize resources, and at the same time, deliver health services with high-quality standards without sacrificing safety and efficacy.

The continuous evolution of surgical techniques toward a minimally invasive approach and the possibility of using ultrashort-acting anesthetic drugs and fast-track anesthesia protocols are key concepts of DS.

Today, many health services do not contest if a patient may be a good candidate for DS, but rather, whether there is justification to admit that patient to hospital. DS offers high quality, safety, and cost containment, and it is widely adopted for most of elective surgeries in many countries.

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In the United States and Canada, about 90 % of elective procedures are performed in DS, while in the Scandinavian countries about 75 % [3, 4].

Not only routine procedures, such as those for cataracts, hernias, and varicose veins, but also more and more complex interventions, such as those for shoulder, thyroid, gallbladder disorders, gastroesophageal reflux, and obesity, are now carried out in some countries in DS.

However, there are significant variations in DS practice, especially in Eastern and Southern Europe. Peduto et al. [5] in 2004 reported that only 14 % of all surgical procedures performed in Italy were in outpatients, while 31 % of patients were discharged within 48 h from admission. Although the long-term outcomes do not appear to be different for procedures performed in outpatients compared to inpatients, postoperative cognitive dysfunction seems to be less frequent in elderly outpatients [6].

Mortality related to ambulatory surgery is extremely low (1: 11.273), while the morbidity varies between 4–5 % intraoperatively and 6–7 % in the immediate postoperative period [7–9].

As more and more procedures are performed in DS with the possibility to include ASA physical status III patients, the anesthesia approach needs to be safe, with a rapid postoperative recovery and an optimal pain control.

Consequently, the choice of anesthetic technique has a significant influence on the recovery time and patient discharge in DS. Therefore, three are the key points for a safe extension of surgical practices in DS: patient eligibility, the anesthetic technique, and the organization of the clinical care path.

12.2 Which Patients May Be Good Candidates for Day Surgery?

Nowadays, DS should be regarded as a first choice over hospital admission. In order to reduce adverse events and intra- and postoperative complications, as well as delays and cancelations of surgery, it is essential to identify early in a patient all medical, surgical, psychological, and environmental factors, which may exclude him from DS.

Preoperative evaluation should be based on the following three points:

1. *Clinical and surgical criteria*:
   (a) Elective surgeries with short to medium duration (up to 2 h) and a low incidence of complications (particularly respiratory complications and bleeding) which are not extremely painful in the postoperative period and without important sequelae.
   (b) The extreme of ages do not constitute an absolute contraindication to the DS. However, children at risk for sleep apnea and infants (less than 5–6 months of age) should be excluded. ASA III patients may be candidates for DS only if the underlying disease is stable and the surgery does not interfere with it or with its treatment. Exclusion criteria are represented by sleep

apnea, obesity, severe cardiac or respiratory compromise, and medication or drugs that could favor complications.
2. *Psychological criteria*: ability to understand the indications of surgery and to follow the postoperative instructions/prescriptions.
3. *Environmental criteria*: necessity of having an adult supervisor who can drive the patient at home and attend him; social conditions that guarantee adequate domiciliary hygienic conditions compatible with the postoperative instructions/prescriptions; overnight accommodation near the hospital (not far more than 1 h from the hospital); possibility to easily communicate with the hospital or reference structure.

It is recommendable that the preoperative assessment of a patient should be done well in advance of the day of surgery, so that the anesthesiologist is able to have a specific evaluation of that patient and, in case, can require additional investigations. All exams and other investigations should be requested based on the type of surgery and the clinical condition of the patient. It is necessary to identify all possible postoperative complications.

The patient must be informed of his medical condition, the anesthetic technique chosen with its risks and complications, and the possibility that the anesthesiologist may change the anesthetic plan if required. The patient should also be made aware of the possibility of being subjected to transfusion and the risks related to them, although, as mentioned before, it is recommended to not perform surgical interventions in DS that may expose the patient to the risk of transfusions.

Before any procedures, anesthesiologist should provide to the patient all information related to the preparation for surgery (preoperative fasting, drug to be suspended/started, removal of implants, etc.) and the postoperative instructions/prescriptions to be observed (availability of a supervisor for 24 h after surgery, the complete rest, the prohibition of driving vehicles, signing documents and performing hazardous work, etc.).

In DS, the duration of the procedure and postoperative monitoring and the time needed to get an early recovery from the alterations induced from both surgery and the anesthesia should be taken into account.

Pain is often the most feared complication and represents a significant risk factor for hospital admissions or delayed recovery [10].

The anesthetic plan is of particular importance. In general, all types of anesthesia could be used. However, it is essential to prefer not only agents with short half-life and lower side effects, but also techniques that enable a fast recovery and avoid exposing the patient to postoperative complications.

The philosophy of the day surgery, in fact, is totally based on the possibility to obtain a quick return for the patient to a state of normality and independence, with a full recovery of all the physical, psychological, and social functions, which, in turn, make the hospital admission not helpful.

Consequently, regional anesthesia is highly effective in DS, because it offers the opportunity to keep the patient awake during the procedure with a better postoperative pain control and a less patient exposure to systemic effects of anesthetic drugs.

It is not a coincidence that in recent decades a better understanding of the neurophysiology and the technological development has gone hand in hand with the great interest in regional anesthesia.

12.3 Regional Anesthesia

Many are the advantages of regional anesthesia, such as reduced drugs consumption, better pain control, anti-inflammatory effect, attenuation of the catabolism, improved tissue perfusion, maintenance of bowel function, and less inhibition of the diaphragm [11].

It is true that the majority of the interventions in the DS are today performed under general anesthesia [12]. In a recent meta-analysis [13], neuraxial blocks were associated with prolonged recovery times compared to general anesthesia, while there was no difference between general anesthesia and peripheral nerve blocks. Of particular interest, the incidence of nausea and vomiting was lower only in patients with peripheral nerve blocks and not for patients undergoing neuraxial blocks compared with those who received general anesthesia. Pain control was superior for regional techniques (neuraxial blocks and peripheral nerve blocks) compared with general anesthesia, without significant differences in long-term outcomes.

Although the results of this study can be criticized both for the variety of surgical procedures included, both for the dosages and types of local anesthetics used for neuraxial blocks, it should be emphasized that regional anesthesia may require longer execution times and may be affected by the possibility of failure compared to general anesthesia.

Anyway, since DS has developed in the wake of a policy aimed to reduce health expenditure, the observation that regional techniques have a lower cost compared to general anesthesia plays a significant role. In addition, regional anesthesia eliminates the discomfort associated with the airway trauma induced by intubation or by the use of a laryngeal mask and reduces the consumption of opioids with possible improvement in nausea and vomiting. These positive effects of regional anesthesia techniques have a clear effect and impact on early postoperative recovery. The advantages of regional techniques, however, do not expose the patient to a zero risk. Although rare, there are, in fact, complications, even series, which can complicate the postoperative course. A recent French study shows 56 major complications after regional anesthesia in 158,000 interventions in inpatients and outpatients, including 9 cardiac arrests and 12 cases of permanent peripheral nerve damage [14].

In recent years, the interest has focused on the promotion of a better postoperative management with the application of concepts such as the enhanced recovery after surgery (ERAS) [15].

Today, we are starting to consider the techniques of regional anesthesia as complementary to strategies to improve the postoperative recovery and no more as therapeutic modalities designed to inhibit the nociceptive stimulus and limit organ dysfunction and metabolic stress induced by surgery.

Regional techniques allow a fast recovery (fast-track) with a direct transfer of patients from the operating room to environments destined for patient discharge, bypassing the postanesthesia care unit (PACU). In a study conducted in five US centers, 90 % of patients undergoing local anesthesia with sedation followed a path of fast recovery compared to only 32 % of patients undergoing general anesthesia [16].

However, in DS, three aspects should be carefully considered, especially for subarachnoid and epidural anesthesia: the time required to perform the block, the slow recovery of the mobility of the legs, and the time to void.

Spinal anesthesia and epidural techniques are useful for surgery of the lower abdomen, perineum, and lower limbs. The advantages of subarachnoid anesthesia compared to general anesthesia include the rapid onset, the good acceptance of the procedure by the patient, and prolonged postoperative analgesia. The epidural anesthesia has similar advantages, although with a slower onset, with the additional benefit of the presence of the catheter that allows to modify the duration and level of anesthesia, as well as to provide a better postoperative analgesia. However, epidural anesthesia is technically more difficult, requires longer execution times, and is associated with risk of intravascular/intrathecal injection or incomplete block. There are, to date, little evidences on the use of epidural techniques in outpatients.

To pursue a fast-track protocol, the choice of the local anesthetic for neuraxial block is crucial. The use of local anesthetics of a short duration of action (lidocaine, prilocaine, 2-chloroprocaine) is preferable to bupivacaine and ropivacaine when the duration of surgery is expected to be less than 60–90 min. Lidocaine injected into the intrathecal space is not recommended because of the potential risk of developing transient neuropathic symptoms (TNS), which is greater for lidocaine than other local anesthetics (prilocaine, bupivacaine, or procaine) [17, 18]. In addition, it is preferable to use hyperbaric solutions of local anesthetic than the plain ones, because hyperbaric solutions have a greater reliability and increased speed of recovery of the block [19].

The use of spinal anesthesia with low doses of local anesthetic such as lidocaine 10–30 mg, bupivacaine 4–7 mg, or ropivacaine 5–10 mg, in combination with a lipophilic opioid (fentanyl 10–25 μg, or sufentanil 5–10 μg), produces an effective block, with fast recovery of motility and sensitivity (Table 12.1) [25–27, 29–31]. It is also true that lowering the anesthetic dose may increment the risk of a failure block [32].

Spinal 2-chloroprocaine preservative-free solution (i.e., not containing sodium bisulfite, which proved to be neurotoxic), recently reintroduced, at a low dose (40 mg), resulted in a block of about 40 min in duration with a more rapid recovery of motility (about 30 min) compared to a low dose of lidocaine (40 mg) [20].

Compared to 7.5 mg of bupivacaine, 40 mg of 2-chloroprocaine produced a similar sensory block but with a shortening of discharge times of about 80 min [22].

The addition to spinal 2-chloroprocaine of fentanyl 20 mcg or clonidine 15 mcg allows an elongation of about 15 min of the anesthesia time but prolongs the recovery of motor function [33, 34].

Table 12.1 Pharmacological characteristics of some local anesthetics used in spinal anesthesia

Local anesthetic[a]	Onset (min)	Peak block (dermatome)	Average duration of the motor block (min)	Average duration of the sensory block (min)	Mean time to voiding (min)
Plain/hyperbaric lidocaine 2 % 40–60 mg [20, 21]	5–10	T8–T6	134–155	116–127	134–238
Plain 2-clorprocaine 2 % 40 mg [20, 22]	5–10	T8–T7	104–113	104–113	104–113
Hyperbaric prilocaine 2 % 40–60 mg [23, 24]	5–10	T10	92–140	30–130	195–227
Plain bupivacaine 7.5–10 mg [22, 25]	10–15	T10–T9	190–210	140–190	190–224
Hyperbaric bupivacaine 3.75–15 mg [21, 26–28]	10–15	T9–T4	23–395	20–343	163–428
Plain ropivacaine 7.5–14 mg [26, 29]	10–15	T9–T3	135–189	130–192	189–233

[a]As the dose of local anesthetic is reduced, the risk of a failure block increases

Anyway, the use of low doses of 2-chloroprocaine (30–40 mg) with or without adjuvants allows a recovery time and fast discharge (100–130 min) compatible with DS.

Prilocaine, an amino amide local anesthetic with a short duration of action, seems to be equipotent to lidocaine in a dose range of 50–80 mg, with a lower risk of TNS [21]. Prilocaine (plain solution) 20 mg + fentanyl 20 mcg injected into the subarachnoid space has shown to have a faster onset, an early recovery of the motor block, and a lower incidence of hypotension than bupivacaine 7.5 mg + fentanyl 20 mcg patients undergoing arthroscopy [35]. The prilocaine hyperbaric solution presents a more rapid onset of sensory and motor block and a reduction of recovery times compared to the plain solution, and it is therefore to be preferred for outpatients [23].

However, the use of hyperbaric prilocaine 60 mg resulted in urinary retention in 25 % of patients (out of a total of 86 patients analyzed) in an observational study [36], while with a dose of 50 mg of plain solution, the reported rate was of 8.3 % (out of a total of 36 patients) [24]. Urinary retention appears to be more common when using spinal levobupivacaine (10 mg plain) or ropivacaine (15 mg plain) compared to lidocaine (60 mg plain) [37].

Among the side effects of prilocaine, it is worth noting the development of methemoglobinemia. Hepatic metabolism of prilocaine forms some compounds (o-toluidine) which can oxidize hemoglobin to methemoglobin. This reaction appears to be dose dependent and be linked to genetic variants of microsomal enzymes CYP-450 [38].

The addition of lipophilic opioids or low doses of intrathecal clonidine as adjuvants should be considered carefully in DS, while other agents (adrenaline,

morphine, neostigmine) should be avoided for the known side effects and/or the increase of the time required for discharge.

Spinal fentanyl (10–25 mcg) and sufentanil (5–10 mcg) have been used in association with different local anesthetics with improvement of quality of analgesia, without prolongation of discharge time, but with a greater incidence of pruritus, nausea, and vomiting [39, 40].

Spinal clonidine (15 mcg) in combination with ropivacaine or 2-chloroprocaine improves the quality of anesthesia without altering the recovery time. In addition, with a low dosage like 15 mcg, the known side effects of clonidine such as hypotension, bradycardia, and sedation are infrequent [32, 41, 42].

It is worth mentioning the selective subarachnoid anesthesia technique. Advantages of this block is the lesser dose of anesthetic, the speed of the offset, and the lower incidence of side effects (nausea, vomiting, and hypotension); among the disadvantages are the possibility of failure, incomplete block, or not appropriate to the duration of surgery [42].

With adequate doses of local anesthetic using selective subarachnoid anesthesia, the duration of recovery times are comparable to procedures performed under general anesthesia [43]. It seems clear that the choice and the proper dosage of local anesthetics in neuraxial blocks are critical, considering that 1 mg of bupivacaine can prolong the recovery time of about 21 min [28].

Despite the advantages, neuraxial anesthesia has some limitations in DS. One is the incidence of TNS after spinal anesthesia performed with local anesthetics with short duration of action. The second is the urinary retention and the need to wait until voiding before discharge [44]. However, the need to wait until spontaneous micturition after spinal anesthesia at low dosages of local anesthetics may be a criteria for discharge only in high-risk cases (hernia, anorectal surgery, history of urinary retention) [45].

In case where it is necessary, a prolonged anesthesia at the level of lower or upper limbs, a block of the brachial plexus (axillary, infraclavicular, or interscalene), or sciatic-femoral-popliteal nerve can be extremely useful in DS. Compared to general and neuraxial techniques, peripheral nerve blocks reduce side effects, lead to a more stable hemodynamics, improve postoperative analgesia, and facilitate the recovery process [46]. In a study of 1,200 patients undergoing knee surgery in DS, the use of femoral-sciatic block was associated with better pain control and a lower risk of hospitalization than general anesthesia [47].

Furthermore, the possibility to extend the block by continuous perineural infusion of local anesthetics is another advantage; the use of a perineural catheter improves the degree of satisfaction of the patient and reduces opioid consumption [48, 49]. In selected patients and for procedures that are particularly painful in the postoperative period, a continuous peripheral nerve block may be adopted also at home [50]. With a single-shot technique, the benefits of peripheral nerve block may last from 8 to 12 h, depending on the type of local anesthetic used. The use of peripheral nerve blocks is associated with reduced costs, a rapid recovery time, and a prolonged analgesia in hand surgery [46], shoulder surgery [51], knee surgery

[52], and for inguinal hernia repair [53]. The peripheral nerve blocks more frequently used in DS are the axillary, the interscalene, and ankle blocks. Moreover, it seems that anesthesiologists are less willing to early discharge (before full recovery of sensory and motor functions) a patient with a long-lasting blockade of the lower limb compared to one of the upper limb [54].

The use of the interscalene brachial plexus block, especially when not performed under ultrasound guidance, is associated with high incidence of phrenic nerve palsy and should be used with caution in patients with chronic lung disease, as well as when adopting a continuous perineural infusion [55].

Disadvantages of the peripheral blocks are represented by the time required to perform them, the onset of the block that can be prolonged when long-acting local anesthetics are used (bupivacaine, levobupivacaine, ropivacaine), inadequate or failed block, and complications of intraneural or intravascular injection, which can be reduced by using ultrasound-guided techniques [56]. In a prospective study [57] which included more than 2000 patients who received peripheral nerve blocks of the upper and lower limbs with ropivacaine 0.5 %, the need for conversion to general anesthesia was 1–6 % (higher in the blocks of the lower limbs), the incidence of complications was very low (1.6 %), and the majority of patients (98 %) was highly satisfied with the choice of anesthesia.

The postoperative pain control can accelerate the process of functional recovery and return to daily activities [58]. A multimodal approach that exploits the opioid-sparing effect (which reduces opioid requirements) promotes a rapid recovery after discharge. Postoperative pain is one of the most frequent causes of unexpected admissions after surgery in DS. The type of surgery heavily influences the incidence of postoperative pain, with orthopedics, urology, general, plastic, and ENT surgery associated with the highest incidence [59]. In addition, the duration of the intervention appears to be a predictor of postoperative pain, with an increase in pain intensity for prolonged surgical times [60]. In this context, the locoregional techniques have the advantage of a better control of postoperative pain than general anesthesia [61].

12.4 Recovery and Discharge

The recovery process begins with the end of surgery and continues until the patient returns to its preoperative physiological state. This process is divided into three phases:

1. Early recovery, which encompasses the period after the interruption of the administration of anesthetic agents until the recovery of the protective reflexes and sensorimotor function
2. Intermediate recovery, when the patient reaches the discharge criteria
3. Late recovery, when the patient returns to his preoperative physiological state [61]

The numerical score of Aldrete and Kroulik [62] assigns a score from 0 to 2 to the motor, respiratory, and cardiocirculatory functions, to consciousness and to the color of the skin, with a total maximum score of 10.

The modified Aldrete score [63] uses the arterial saturation of oxygen evaluated with pulse oximeter in place of the clinical parameter of the evaluation of the skin color. Based on these scoring systems, when the patient reaches a score ≥9, it is considered eligible for discharge from the PACU to the ambulatory surgery unit where it begins the phase two of recovery. White and Song [64] added to the modified Aldrete score the evaluation of postoperative pain and the presence of postoperative nausea and vomiting (PONV), with a maximum score of 14 (when the score is ≥12 the patient is considered eligible for discharge from PACU). The more recently introduced WAKE score [65] seems to be more suitable for the evaluation and fast-tracking of outpatients undergoing regional, general, or monitored anesthesia [44]. This score not only incorporates the modified Aldrete score (maximum score = 10), but introduces the "Zero Tolerance Criteria," which assess postoperative pain, PONV, shiver, itching, and orthostatic symptoms (dizziness, hypotension).

Locoregional anesthesia can potentially accelerate the discharge from PACU and promote the process of fast-track anesthesia, as it is associated with a better control of postoperative pain and a lower incidence of PONV, and it does not necessitate to wait for the recovery of the protective reflexes of the airway and for an oriented and cooperative level of consciousness [61].

In deciding whether a patient has completed the second phase of recovery and could be discharged from the hospital, the Postanesthesia Discharge Scoring System (PADS) [66] may be adopted. This score is based on five criteria: vital signs, ambulation, PONV, pain, and surgical bleeding. To each of these criteria is assigned a score from 0 to 2, with a maximum of 10. A patient with a PADS ≥9 is considered eligible for discharge. The majority of patients can be discharged 1–2 h after surgery [67].

The patient's discharge from the facility should be carried out under the following conditions:

- Full recovery of temporal-spatial orientation (or conditions comparable to those before surgery)
- Hemodynamic stability (or conditions comparable to those before surgery)
- Recovery of the airway protective reflexes
- Absence of respiratory compromise (or conditions comparable to those before surgery)
- Spontaneous micturition
- No bleeding
- Minimal pain and nausea (compatible with a home management)
- Ability to take fluids
- Recovery of the sensorimotor function and proprioception
- Ability to ambulate (or to perform movements similar to those made preoperatively and permitted by the type of intervention)

Before discharge, the patient and the accompanying person must be informed, in writing if possible, of the possible complications that may occur in the days following the operation. It should be clearly differentiated all the discomforts, predictable and considered inevitable for that particular operation, from unforeseen complications that may pose a danger to the patient.

It should be also given to the patient clear rules of conduct in case of disturbances, abnormal symptoms, and complications. The structure that provides the service of Day Hospital must ensure telephone availability for a surgical or anesthesia consultation 24 h on 24 and, when necessary, a supply emergency, directly or via other structure reference.

The incidence of unexpected hospital admissions varies between 0.5 and 9.5 % [68–70].

The causes of unexpected admissions after surgery in DS can be divided into surgical, anesthetic, medical, and social causes. Most of the hospitalizations occur for surgical complications, such as bleeding. Among the anesthesia causes, the most significant ones are the postoperative pain, PONV, and dizziness.

Regional anesthesia leads to a better control of postoperative pain and is associated with a lower incidence of PONV [71]. The consensus guidelines [72] for the management of PONV in DS of the SAMBA report some strategies to reduce the risk of PONV:

1. To avoid general anesthesia and prefer the regional techniques
2. Preferential use of propofol
3. To avoid nitrous oxide
4. To avoid volatile anesthetics
5. To minimize the use of opioids
6. Adequate hydration

The worsening of preexisting pathological conditions such as diabetes, asthma, sleep apnea or the presence of new complications including bronchospasm, arrhythmias, and hypotension represents the medical causes of unexpected hospitalization, while the absence of adequate support at home is an important social cause.

Conclusions

Locoregional techniques provide an effective, efficient, and at low-cost plane of anesthesia in ambulatory surgery. These techniques have advantages (Fig. 12.1) compared to general anesthesia, but there are medical conditions that do not allow their execution. The presence of allergy to local anesthetics, patients who refuse the procedure, infection at the injection site or coagulopathy represents absolute contraindication to regional anesthesia.

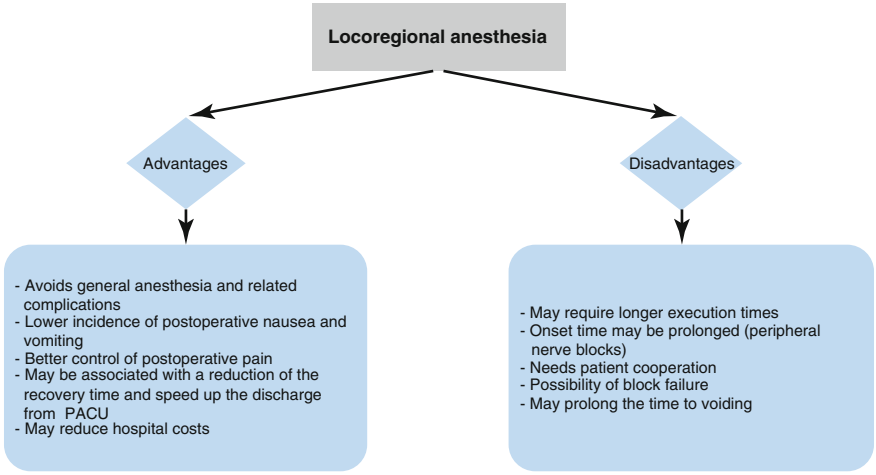

Fig. 12.1 Advantages and disadvantages of regional techniques in ambulatory surgery

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One-Lung Ventilation in Anesthesia

13

Giorgio Della Rocca and Luigi Vetrugno

13.1 Introduction

The purpose of one-lung ventilation (OLV) is to provide a good surgical exposure of a collapsed lung while ensuring adequate gas exchange with the other. Currently, double-lumen tubes (DLTs) or bronchial blockers (BBs) are used to obtain it. *The separation of the lungs today means a completed "anatomical" sealing with DLTs, and the isolation of the lung means a "functional" sealing with BBs* [1–3]. In the first case, there are some *absolute indications in which a* protective strategy for the contralateral lung *is needed*, including life-threatening conditions such as massive bleeding, pneumonia with pus, and bronchopleural and bronchocutaneous fistulae, since they offer a low-resistance pathway during positive pressure ventilation, as well as giant unilateral bullae that may blow. Some surgical interventions as sleeve pneumonectomy or bronchopulmonary lavage for alveolar proteinosis or cystic fibrosis still require lung separation. In all the other situations, in which lung *separation* is a relative indication, lung *isolation* could be used [4, 5].

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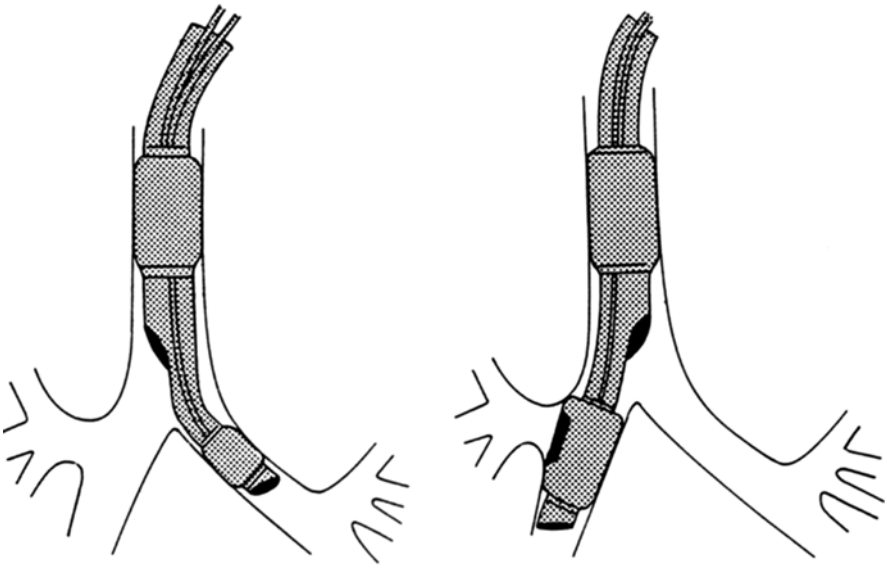

Fig. 13.1 Left and right double-lumen tubes (DLT)

13.2 Methods for One-Lung Separation (OLV)

At first, decades ago, a single-lumen endobronchial tube with a Fogarty catheter used as a bronchial blocker was utilized to achieve OLV. However, it was a difficult technique, as the shape of the balloon is round and not designed for airway blockade and the advancing of the catheter is unguided.

In modern practice, endobronchial double-lumen tubes (DLTs) are most widely employed (Fig. 13.1). These tubes have a fixed curvature and do not have a carinal hook to avoid tracheal laceration and reduce the likelihood of kinking. Numerous manufacturers produce clear disposable Robertshaw design DLTs, which are available in French sizes from 35 to 41 [6]. Essentially, they all have similar features but modify cuff shape and location. A colored bronchial cuff, commonly blue, permits its easy identification by fiber-optic bronchoscopy. The right endobronchial cuff is donut shaped and allows the right upper lobe ventilation slot to ride over the right upper lobe orifice. Most authors refrain from using right-sided DLT simply to avoid potential obstacles. Instead of its extensive use, one of the major challenges for a DLT is the lack of an objective method and guideline for selecting the proper size and its optimal depth. The most accurate method to select a left-sided DLT size is to measure the left bronchus width and the outer diameter of the endobronchial lumen of the DLT, then the largest tube that safely fits that bronchus can be selected [7]. For a right-sided DLT, there is no study available that addresses the issue of optimal size for a determined

patient. *In general, a 37 French DLT can be used in most of the adult females, while 39 French can be used in the average adult male.* Keeping in mind that undersized or oversized DLTs could lead to serious airway complications, including tracheobronchial rupture. The optimal depth of insertion for a left-sided DLT is strongly correlated to the patient's height. In general, the depth of insertion for a DLT should be between 27 and 29 cm at the marking of the incisors [8, 9]. An inadvertent deep insertion of a DLT could lead to rupture of the left main stem bronchus. Three other sizes (26 and 28 French for pediatrics and 32 French for small adults) have recently been introduced in the market. When a conventional laryngoscopy reveals a grade III view (only the epiglottis) or a grade IV view (only the soft palate) in the Cormack-Lehane scale, an airway may be termed difficult [10]. When the separation of the lung is strictly indicated, the use of tubes such as DLT or Univent, which are inherently difficult to insert, cannot be recommended [11–14]. If the patient has a recognized difficult airway, awake intubation with fiber-optic bronchoscopy (FOB) can be attempted using a single-lumen tube (SLT) (Table 13.1). The same approach may be used for the patient with an unrecognized difficult airway. However, thoracic anesthesiologist expertise and propensity with a DLT rather than BB and vice versa, and their knowledge in fiber-optic tracheobronchial anatomy, plays an important role in that choice. On the other hand, for the non-thoracic anesthesiologist, DLTs and bronchial blockers are difficult to use, and none of these devices provide any advantage one over the other [15].

In modern clinical practice, this instrument has been replaced by three different types of 9 French BBs with a steering mechanism and a patent 1.6 mm lumen to facilitate the collapse of the lung and/or oxygen insufflations through continuous positive airway pressure (CPAP) to the nondependent lung [16]. Of these three devices, the Arndt blocker is available in 7 and 5 French for small adults and pediatrics; it uses a wire-guided mechanism [17]. The Cohen blocker possesses a rotating wheel that allows it to flex the tip of the blocker [5]. Both blockers use a multiport adapter. The Uniblocker, which has a fixed curve similar to a hockey stick, has been recently introduced in clinical practice. It is essentially the same blocker as the Univent tube which is somewhat bulky, but now available as an independent blocker [18].

Table 13.1 Indication for the use of endobronchial blockers

The upper and lower difficult airway
Patients with a predicted or unpredicted difficult airway
Patients post-laryngeal/pharyngeal surgery
Patients with tracheotomy
Patients with distorted bronchial anatomy from aneurysm compression or intraluminal tumor
Patients who require nasotracheal intubation
Patients with an immobility or kyphoscoliosis

13.3 Double-Lumen Tubes: First Step – The Positioning

Following intubation, the tracheal cuff should be inflated first, and then the tube's correct position should be confirmed. To avoid mucosal damage from excessive pressure applied by the bronchial cuff, the cuff is inflated with incremental volumes until air leaks disappear. Inflation of the bronchial cuff seldom requires more than 2 mL of air. Bilateral breath sounds should be rechecked to confirm that the bronchial cuff is not herniating over the carina and impede the ipsilateral lung ventilation. An important step is to verify that the tip of the bronchial lumen is located in the designated bronchus. One simple way to check this is to first clamp the tracheal lumen, then observe and auscultate. Usually, inspection will reveal unilateral ascent of the ventilated hemithorax. Following proper auscultation, the bronchial lumen is cross-clamped to ventilate the tracheal lumen. Each time a right-sided DLT is used, appropriate ventilation of the right upper lobe should be ensured. This can be accomplished by a careful auscultation over the right upper lung field or more accurately by fiber-optic bronchoscope [19, 20]. When a left-sided DLT is used, the risk of occluding the left upper lobe bronchus by the bronchial tip advanced too far into the left main bronchus should be always kept in mind. If the peak airway pressure is 20 cm H_2O during two-lung ventilation, for the same tidal volume, that pressure should not exceed 40 cm H_2O on OLV.

It has been recently shown that fiber-optic bronchoscopy revealed a malposition in 20–48 % of the DLTs thought to be correctly positioned by inspection and auscultation only [21]. The simplest method to evaluate proper positioning of a left-sided DLT is bronchoscopy via the tracheal lumen. The carina is then visualized, while only the proximal edge of the endobronchial cuff should be identified just below the tracheal carina. Herniation of the bronchial cuff over the carina to occlude partially the ipsilateral main bronchus should be excluded. Bronchoscopy should then be performed via the bronchial lumen to identify the patent left upper lobe orifice [22]. When using a right-sided DLT, the carina is visualized through the tracheal lumen. More importantly, the right upper lobe bronchial orifice must be identified while the bronchoscope is passed through the right upper lobe ventilating slot. This is somewhat complex to accomplish and requires a relatively skilled endoscopist.

Several sizes of bronchoscope are available for clinical use: 5.6, 4.9, and 3.9 mm of external diameter. *The 3.9 mm-diameter bronchoscope can easily pass through a 37 French or larger tube, while it is a tight fit through a 35 French tube* (Fig. 13.2) [19–22].

13.4 Tube Exchanger

The airway guide may be used for inserting an SLT over a DLT and vice versa or simply inserting a difficult tube. Several tube exchangers are available. All of these airway guides are commercially made (depth is marked in cm), are available in a wide range of ODs, and are easily adapted for either oxygen insufflation or jet ventilation. Critical details to keep in mind to maximize benefit and minimize risk of airway injuries are as follows: first, the size of the airway guide and the size of the

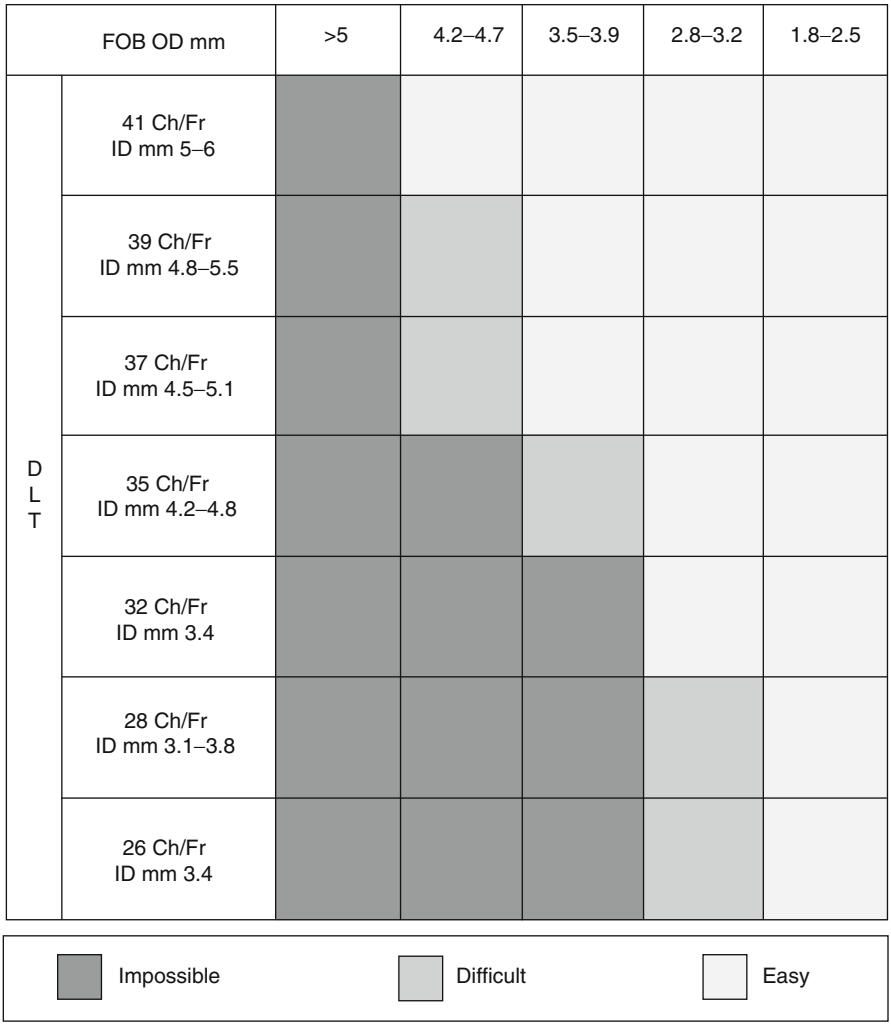

Fig. 13.2 Sizes of bronchoscope reported in mm of external diameter (*OD*) fit differently from 26 to 41 Fr double-lumen tubes (*DLT*) with different internal diameters (*ID*)

difficult tube must be determined and should be tested in vitro before the use of the airway guide. Second, the airway guide should never be inserted against a resistance; the clinician must always be aware of the depth of insertion. Two reported perforations of the tracheobronchial tree have occurred [23, 24]. Third, a jet ventilator should be immediately available in case the new tube does not follow the airway guide into the trachea, and the jet ventilator should be preset at 25 psi by the use of an additional in-line regulator [25]. Finally, when passing any tube over an airway guide, a laryngoscope should be used to facilitate the passage of the tube over the airway guide past the supraglottic tissues. Because of the potential injury to the

bronchial tree from the stiff tip of the tube exchanger, a new catheter has been designed with a soft tip to reduce the risk of trauma.

13.5 Mechanical Ventilation

Traditionally, ventilation during OLV has been performed with tidal volumes equal to those used in two-lung ventilation (TLV), high FiO_2, and zero end-expiratory pressure (ZEEP). This practice was recommended to control hypoxemia, because large tidal volumes (10–12 mL/kg) were shown to improve oxygenation and decrease shunt fraction [26–28]. Recently, however, retrospective case series have shown that high ventilating pressures and high tidal volume are significantly associated with lung injury [29, 30]. Studies using both animal models and humans have evaluated the impact of protective lung strategies versus conventional ones during OLV. They report an increase in inflammatory proteins when high volume is used [31, 32]. Patients undergoing esophagectomy and receiving low tidal volumes have been found to present an attenuated systemic proinflammatory response and a lower extravascular lung water index compared with those receiving high tidal volume [31]. Only one prospective study has been performed that analyzes the postoperative period in 100 patients undergoing lung resection. In this case series, patients in the lower tidal volume (6 mL/kg) group were associated with better postoperative gas exchange and lower postoperative complications, with reduced atelectasis and ALI episodes than that in the high tidal volume group (10 mL/kg) [33]. No differences between groups were found for hypoxemia events, whereas in the high tidal volume group, more patients recorded a peak inspiratory pressure exceeding 30 cmH_2O. *These studies provide strong support for the use of a protective lung ventilation strategy in patients undergoing OLV.* Although the causes of perioperative ALI are clearly multifactorial, hyperinflation and repetitive inflation/deflation cycles of lung functional units are now thought to contribute to injury, and excessive tidal volume is associated with insults in susceptible patients. This leads to the primary recommendation for PLV during OLV: the tidal volume should be reduced to a maximum of 6 mL/kg of IBW. *It is interesting to note that the normal mammalian tidal volume is 6.3 mL/kg* [34]; it may thus be that PLV represents physiologic lung ventilation. However, it must be kept in mind that PLV exposes the lung to atelectasis and lung recruiting maneuvers (LRM) are necessary and mandatory to reduce its formation. *LRM consists of an increase of airway pressure up to 40 cm H_2O with a PEEP up to 20 cm H_2O for a short time to recruit the most of the atelectatic alveoli* [35]. Furthermore, low Vt with PEEP may cause dynamic hyperinflation secondary to the increase in respiratory rate to maintain $PaCO_2$. OLV itself may be injurious to both the ventilated and non-ventilated lung, and this injury depends on the duration of OLV. It may be best to avoid OLV whenever possible by applying continuous positive airway pressure to the non-ventilated lung. This is a particularly attractive option in minimally invasive intrathoracic surgery which does not involve the lungs (i.e., cardiac, vascular, or esophageal surgery). Selective lung re-expansion with the use of either a second circuit or

transient isolation of the nonoperative lung allows application of targeted pressure to the atelectatic operative lung while avoiding pulmonary tamponade and hypotension. After recruitment of the operative lung, TLV needs to be established with a protective ventilation strategy. The ventilation setting during OLV is also land of debate. Pressure-control ventilation (PCV) versus volume-control ventilation (VCV) during OLV has been studied by Tuğrul et al. in favor of PCV, particularly in patients with poor preoperative lung function [36]. However, other groups have failed to reproduce the oxygenation benefit of PCV during OLV [37, 38]. A recent study by Pardos et al. comparing PCV and VCV with a tidal volume of 8 mL/kg during OLV failed to demonstrate a significant difference in arterial oxygenation between the two ventilatory modes [39]. This study confirms previous work on the comparison of volume-control versus pressure-control ventilation for OLV. No benefit in oxygenation was associated with either ventilatory mode. *The risk of ALI and fluid overload increases proportionally to the extension of the lung parenchyma resection, and historically, thoracic surgery has been the first type of surgery in which anesthesiologists adopted the restricted fluid approach, but recently the emergence of new data shows that the risk of renal insufficiency after lung resection surgery is about 6–24 %* [40]. So it is necessary to specify two major branches: in patients undergoing pneumonectomy, the restrictive fluid approach seems to be up-to-date, but for lesser resection, a goal-direct-therapy approach should be considered. It is still debated whether total intravenous anesthesia could inhibit the protective effect of hypoxic pulmonary vasoconstriction less. Compared with controls under propofol anesthesia, inhaled anesthetics result in attenuation of cytokine elevations in both the ventilated and the operative lung [41]. This approach appears to translate into better outcomes, as patients in the sevoflurane arm experienced less composite adverse events [42]. Pressure-supported ventilation with PEEP is more likely to maintain optimal lung volumes during emergence. Postextubation oxygenation in high-risk patients can be improved with CPAP or noninvasive ventilation.

13.6 Techniques to Improve Oxygenation

Switching from two-lung to OLV, the non-ventilated lung leads inevitably to transpulmonary shunting and, occasionally, to hypoxemia. Rates as low as 1 % have been reported, but more recent data indicate an incidence around 8 % in patients undergoing minimal invasive mediastinal surgery [43]. In a recent study, hypoxemia during OLV, defined by a decrease in arterial hemoglobin oxygen saturation to less than 90 %, occurred in 4 % of patients whose lungs were ventilated with a fraction of inspired oxygen greater than 0.5. Hypoxemia during OLV may be treated causally. First the position of the double-lumen tube should be checked, then clear the main bronchi of the ventilated lung from any secretions, and finally improve/change the ventilation strategy. A DLT allows easy fiber-optic access to both lungs, which may be crucial if bleeding or secretions are a problem. Both left- and right-sided DLTs are frequently misplaced or dislodged (surgical manipulation) which may lead to

impaired oxygenation and inadequate lung separation [19, 20]. If all these efforts are ineffective, several other techniques can be employed to improve oxygenation. In PLV, the lung is exposed to atelectasis and LRM are needed to restore lung aeration.

OLV ventilation has been associated with significant changes in RV dimensions, suggestive of both pressure and volume overload [44–46]. Intraoperative TEE is frequently used during lung transplantation in order to detect and manage acute RV dilation and dysfunction, as may occur after induction of anesthesia, institution of one-lung ventilation, and clamping of the pulmonary artery. In non-transplant thoracic surgery, there is little evidence to support routine use of TEE [47]. *The most effective maneuver for improving PaO_2 is the application of the two-lung ventilation, if the surgical phase is stable.* You could also apply 5 cmH_2O of CPAP to the nondependent lung. It consists of insufflation of oxygen under positive pressure to keep a "quiet" lung, while preventing it from collapsing completely. The beneficial effect of CPAP is not due to the positive pressure effect, potentially causing blood flow diversion to the dependent perfused lung, but from distending the alveoli with oxygen to allow gas exchange. Using an FiO_2 of 1.0 during OLV may increase the risk of atelectasis and would preclude the use of nitrous oxide. Other additional techniques to improve oxygenation are the use of nitric oxide (NO). NO have selective dilating effects on the pulmonary circulation without effect on the systemic circulation. NO 1 to 20 ppm decreased pulmonary vascular resistance [48, 49]. Large clinical trials are required to establish the safety and efficacy profile of inhaled epoprostenol to improve oxygenation during OLV [50].

Conclusion

Thoracic anesthesia includes the world of one-lung ventilation during anesthesia. The indications classified as absolute or relative are more representative of the new concepts in OLV: it includes either the separation or the isolation of the lungs. DLTs are most widely employed to perform OLV including the concept of one-lung separation. Endobronchial blockers are a valid alternative to DLTs, and they are mandatory in the education of lung separation and in case of predicted difficult airways as they are the safest approach (with an awake intubation with an SLT through a FOB). Protective lung ventilation with a TV less than that used for two-lung ventilation (i.e., 4 to 6 mL/kg) and with the lowest feasible peak airway pressure, I:E ratio of 1:2, with a rapid respiratory rate is considered the standard of care for the ventilation strategy. Recruiting maneuvers should be used to reduce the amount of atelectasis in the dependent lung. They should be applied with sustained peak pressure of 40 cmH_2O to be effective. Also CPAP and iNO or inhaled epoprostenol could improve oxygenation in selected cases. Fluid administration should be limited during thoracic surgery procedures to avoid fluid overload. Finally, a balanced anesthetic technique with inhalational agents and opioids to reduce the required concentration of potent inhaled agent appears the best choice during OLV.

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