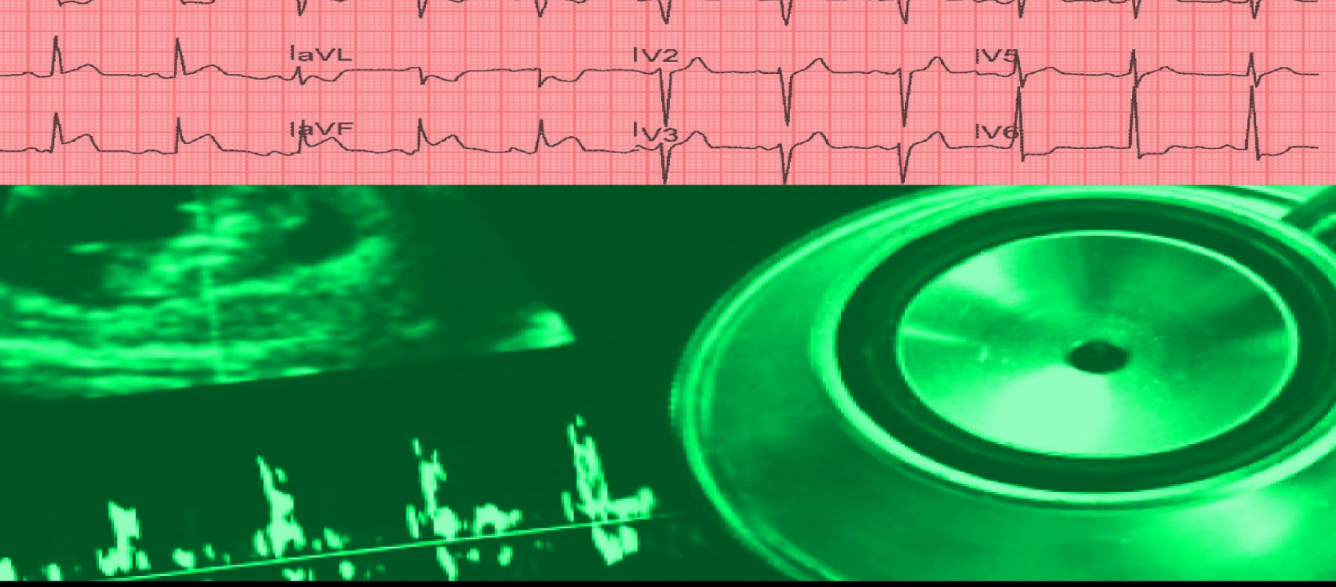

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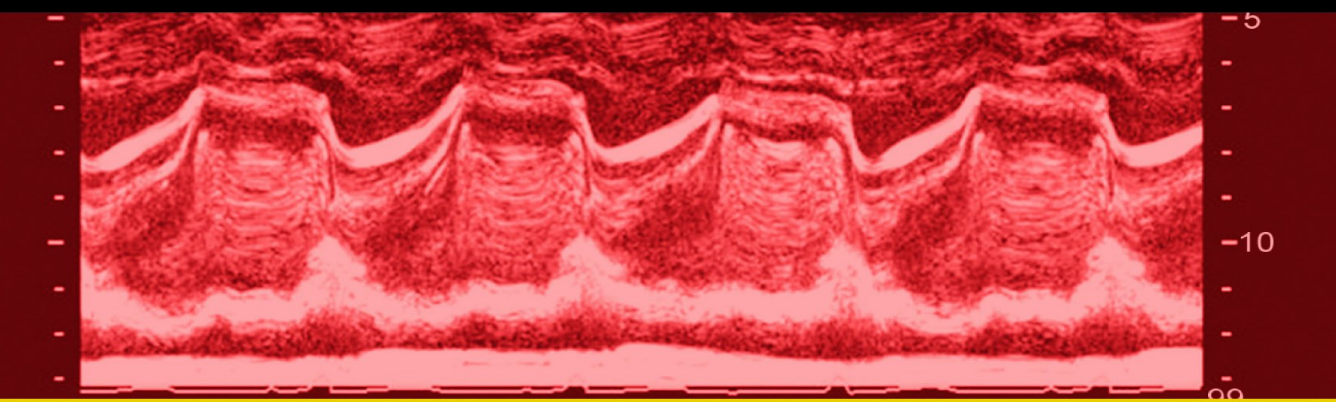

Jayant C Bhalerao

Foreword
George J Taylor

JAYPEE

Essentials of
CLINICAL CARDIOLOGY

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CLINICAL CARDIOLOGY

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Dedication

This book is affectionately dedicated to my beloved late father

DADA SAHEB

(Dr CK Bhalerao, MBBS)

Who had been, and will always remain, a constant guiding light and an eternal source of inspiration.

"No greater opportunity, responsibility, or obligation can fall the lot of human being than to become a physician. In the care of suffering he needs technical skill, scientific knowledge, and human understanding. He who uses these with courage, humility and wisdom will provide a unique service for his fellow man, and will build an enduring edifice of character within himself. The physician should ask of his destiny no more than this; he should be content with no less."

Dr Tinsley R Harrison
(Birmingham, Alabama, USA 1950)

Foreword

All our fourth year medical students do specialty rotations, and a month on the cardiology service is a popular one. The students usually ask for recommendations for reading, and they are typically looking for books that offer them the big picture from a text that can be digested within a month. Dr Jayant Bhalerao's collection of lectures aptly satisfies that need.

Dr Bhalerao is reputed for his clinical skills, particularly his organized way of approaching a patient's problems. These facets are ably documented in this well-organized and eminently well-written book.

The conversational tone used in the book will be well appreciated by students. Reading about the right ventricular infarction syndrome, for example, is like stopping a seasoned attending cardiologist in the hallway, having him tell you, "RV infarct? Great case! Here's what you need to know about that..." Jay's enthusiasm for teaching comes across just like that. There is a tendency for young clinicians' reviews to be surveys of clinical trial. That has its place, but you will find that cutting to the chase with " what you really have to know" is more efficient when you need to survey a big area of medicine in a relatively short time. This is not a reference manual to keep on the shelf, but rather it is designed to be read through, and in less than a fortnight.

The author of a brief but general text needs to make a judicious choice of what to include and what to leave out. Who better to make such decisions about relevance than a master clinician? Dr Bhalerao has provided an excellent answer to "what you should know" after a month in the cardiology service. A student who imbibes the material in this book will be well prepared to work as a resident on the cardiology service.

This book will be also a worthy read for residents and general physicians who are preparing for board or recertification exams. More than half of the ABIM board exam covers cardiac and vascular diseases. With this concise yet thorough review, medical resident will find themselves well prepared indeed!

George J Taylor MD FACP FACC
Professor of Medicine (Cardiology)
The Medical University of South Carolina, USA

Preface

This book is written for medical students, interns and residents. It is not a textbook. I have purposely written it in an informal, conversational language avoiding the staid, starch-like formality and dry monotone of standard professional journals and books. I have avoided the epidemiology, population studies and complex jargon. Details of electrophysiology and interventional cardiology are beyond the scope of this book. Readers can easily retrieve this information elsewhere. Attempt has been made to keep the language simple and easy to understand. Emphasis is placed where I feel necessary so that a student realizes the gravity of a given statement. It encapsulates my clinical experience and is written with a clinician's vantage point.

Discipline of cardiovascular medicine is difficult and demanding. Understanding of basic principles is very essential because so much depend on this. Some old therapies and concepts are excluded so as not to dilute the message.

It is my sincere wish that reader would find this endeavor helpful.

Jayant C Bhalerao

Acknowledgments

Dr Sharad Mehta, MD, Chicago, USA, for writing the chapter on Nuclear Imaging.

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Everyone at Jaypee Brothers Medical Publishers for tolerating last minute additions to the manuscript.

My wife, Shailaja, for giving me the space I needed during the completion of this book.

Contents

CHAPTER 1

Coronary Artery Disease

Jayant C Bhalerao

ATHEROSCLEROSIS

Atherosclerosis is a chronic, progressive disease of aging in which low-density lipoprotein (LDL) "bad" cholesterol migrates from blood circulation to the subintimal layer of an artery where it accumulates slowly over the years to occlude its lumen. Atherosclerosis is for all practical purpose is the sole cause of coronary artery disease. Coronary artery spasm is a rare cause as in Prinzmetal's angina or cocaine abuse, while coronary arteritis is even rarer cause like in giant cell arteritis or Takayasu's disease.

Atherosclerosis begins by oxidation of LDL cholesterol by oxygen-free radicals which is taken up by foam cells and gets embedded in intimal wall of the artery. Inflammatory process ensues and soon the lipid core is surrounded by monocytes, lymphocytes and fibroblasts. Fibrous tissue is eventually laid down to stabilize the plaque. As the plaque assumes larger size, it impedes the blood flow in coronary artery. It creates ischemia in distal myocardium which results in a peculiar chest pain called angina pectoris or just angina. As long as the plaque remains stable, the angina also remains stable. When the plaque ruptures and becomes unstable (Fig. 1), the angina becomes unstable until the artery occludes completely to produce acute myocardial infarction (Figs 2A and B).

ANGINA PECTORIS

Symptoms

Most patients with coronary artery disease are asymptomatic, and sudden death or acute myocardial infarction may be the first symptom. Presence of multiple risk factors should prompt physicians to suspect underlying coronary artery disease and initiate investigations rather than wait for any symptoms. This is particularly true in patients with diabetes, strong family history of premature coronary artery disease, heavy smoking and those with familial hyperlipidemia. Some of the symptoms are:

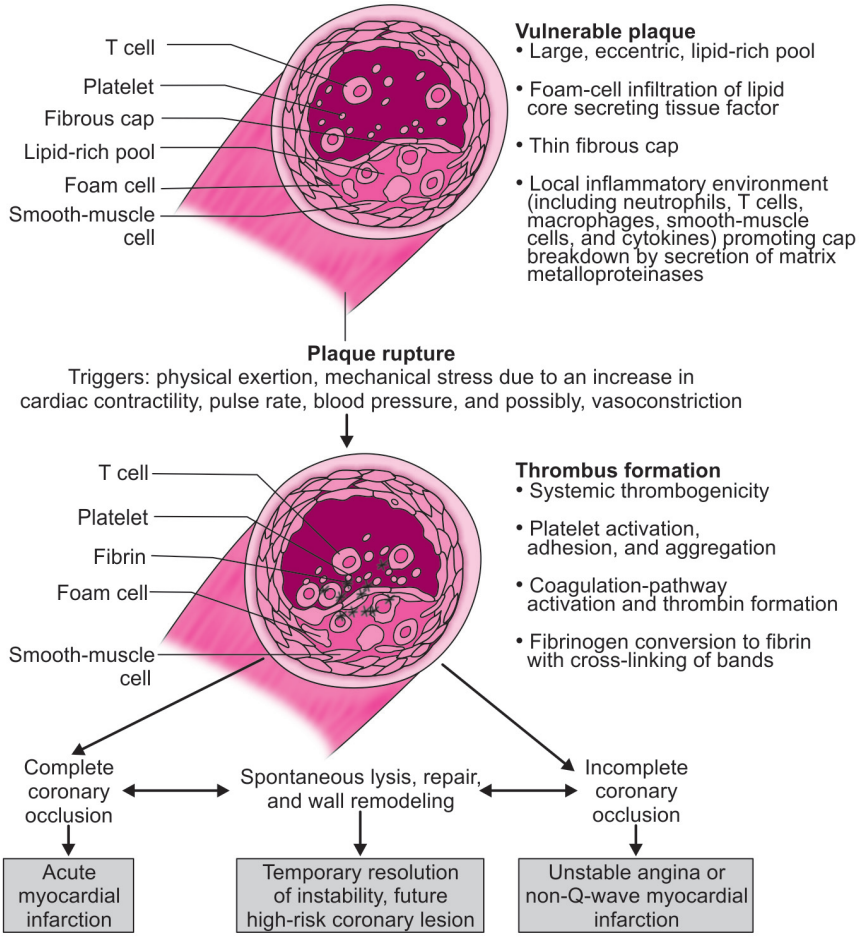
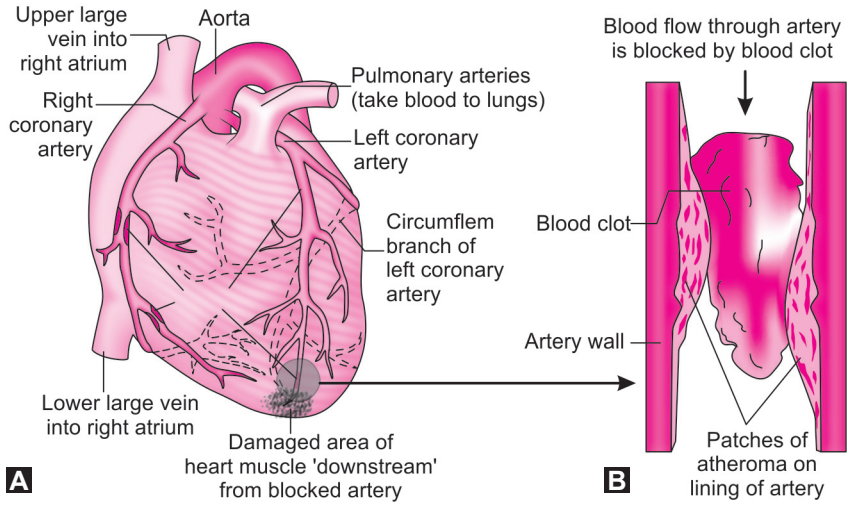


Fig. 1: Pathophysiologic events culminating in the clinical syndrome of unstable angina

- Typical chest pain (discussed below)
- Unusual fatigue
- Unexplained dyspnea
- Frequent premature ventricular contractions (PVCs) or other arrhythmias

Chest pain or discomfort caused by inadequate oxygen supply to myocardium is referred to as angina or angina pectoris. Virtually always this is due to coronary atherosclerosis but can also occur in perfectly normal coronary arteries in some instances like severe anemia, cocaine abuse, coronary spasm (Prinzmetal's angina). This chest discomfort has classical features, and careful attention to history can easily help in making the diagnosis. Chest discomfort is described as heaviness, tightness or dull ache in the retrosternal area, which is brought on by exertion, and relieved in few minutes by resting. It is not sharp, stinging or fleeting and does not change by breathing, position or pressing on the chest wall. Chest discomfort may occur after heavy meal but is never relieved by food like in duodenal ulcer. Sublingual nitroglycerin usually



Figs 2A and B: Myocardial infarction. (A) Heart, front view, showing patches of atheroma, (B) Cross section of coronary artery showing patches of atheroma

relieves the discomfort within a minute. Pain may not be in the chest, may be only in epigastrium and may be confused with indigestion, but nitroglycerin will help in diagnosis. Sometimes the pain is only in shoulder, interscapular region, arms or jaws, but as opposed to musculoskeletal pain, it never changes with position or pressure. Prompt relief of this pain or discomfort by sublingual nitroglycerin is suggestive of angina. Angina is often associated with cold perspiration, at times profuse and disproportionate. This is highly suggestive of angina and no matter how severe the musculoskeletal pain; it will never have such diaphoresis. Other classical feature associated with angina is profound and inordinate fatigue following the chest pain. No other condition other than angina will have this feature. Other associated features may include dyspnea, dizziness, nausea, palpitations and lethargy.

As the coronary stenosis becomes more severe, it takes less physical effort to bring on the angina. The frequency and duration of pain increases (crescendo angina) until patients start getting angina at rest or at night (nocturnal angina). One must understand, however that the frequency of angina is a poor indicator of severity of coronary artery disease because most patients with coronary artery disease have no symptoms. If physicians want to be extraordinary, he/she should learn to diagnose coronary artery disease in patients who have no symptom of it! Patients with severe coronary artery disease may have little angina and patients with little coronary disease may have frequent angina. Angina indicates coronary artery disease. Frequency of angina has nothing to do with the prognosis. It is the severity and location of coronary artery disease that determines prognosis. Therefore, the fundamental responsibility of a physician is to determine the extent of coronary disease and not befooled by infrequent angina. Just like in the real estate, the fundamental principle in cardiology is location, location and location (read as coronary anatomy, anatomy and anatomy). Any coronary artery disease is bad, but certain anatomical locations are particularly worse. Coronary artery diseases in order of risk are:

1. Left main coronary artery: Simply because it supplies so much of the myocardium in prime location. That is why lesion in this area is called "widow maker".
2. Dominant left anterior descending artery in its proximal distribution.
3. Dominant right coronary artery in its proximal distribution.
4. Multivessel disease which is also called "left main equivalent".
5. Distal lesions supply smaller area of myocardium than proximal ones thus less risky.
6. Nondominant right coronary lesion.

Since frequency of angina has little prognostic significance (in general), how do we "quantify" risk? There are following ways:

- Exercise Treadmill test combined with either nuclear studies or echocardiography (Figs 3 and 4)
- Coronary computed tomography (CT) scan for calcium score
- Cine magnetic resonance imaging (MRI) of coronary arteries
- Coronary angiography, which is the gold standard
- Unstable angina or preinfarction state, which signifies that the atheromatous plaque has ruptured, and the clot is forming or formed at the site of rupture. Common sense should dictate that if immediate intervention is delayed, acute heart attack is imminent.

Stress test is performed in several ways, but the basic idea is to increase the oxygen demand of the heart and see if the coronary circulation is competent enough to come up with the increased demand. Abnormal test would show typical ischemic changes in cardiogram or nuclear study or wall motion defects caused by ischemia by echocardiography. Usual accuracy of this test is about 80% if predicted maximum heart rate is achieved. False positive tests are common in women therefore if in doubt, get additional studies.

Physical Findings in Angina

Ischemia makes the ventricles stiff and noncompliant therefore atria have to pump harder. The fourth heart sound (S4) therefore becomes loud. Ischemia of papillary muscle may lead to mitral regurgitation. These physical signs are not dependable and one should not depend on them. Absence of any abnormal clinical finding is not uncommon. Symptoms described by the patient is the guide for diagnosis.

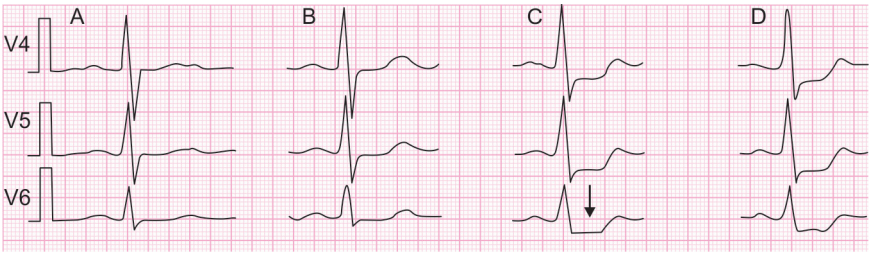


Fig. 3: Fifty-year-old female. Panel A: at rest, Panel B: 75% predicted heart rate, Panel C: Typical ishemic ST-T depression and Panel D: peak exercise

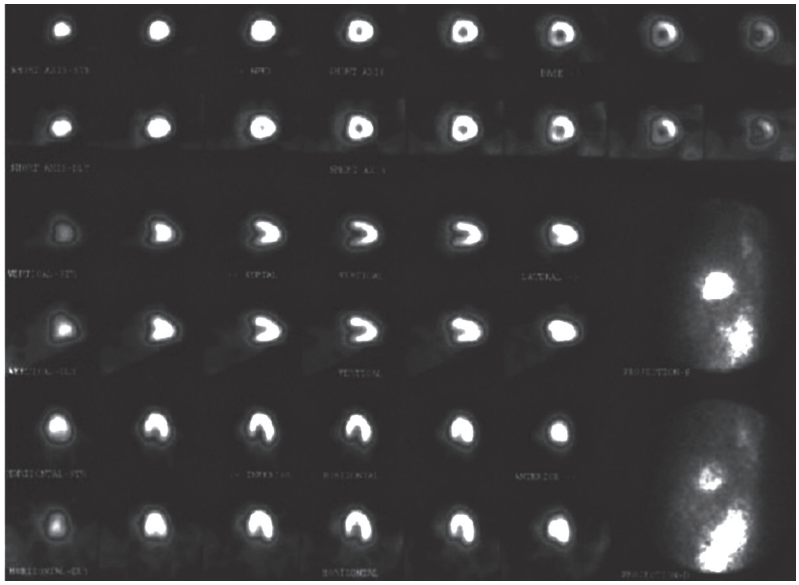


Fig. 4: Fifty-year-old female (same patient as in Figure 3). Normal thallium scans. False-positive Treadmill stress test. If the patient is male with diabetes, strong family history of premature coronary artery disease and smoker, do more tests and even coronary angiogram

Laboratory Studies

- Start with routine complete blood workup: blood counts and hemoglobin, thyroid functions, lipid profile, including LDL, especially dense LDL and high-density lipoprotein (HDL), and urine analysis
- Electrocardiography (ECG)
- Chest X-ray posteroanterior (PA) and lateral views: look for aortic dilatation, cardiomegaly and pulmonary pathology
- Echocardiogram to detect wall motion abnormalities and valvular heart disease (like severe aortic stenosis or regurgitation). Hypertrophic cardiomyopathy and pericardial disease (like effusion)
- Treadmill stress test
- Coronary angiography based on cumulative information and judgment.

Predisposing Factors (Risk Factors) for Coronary Artery Disease

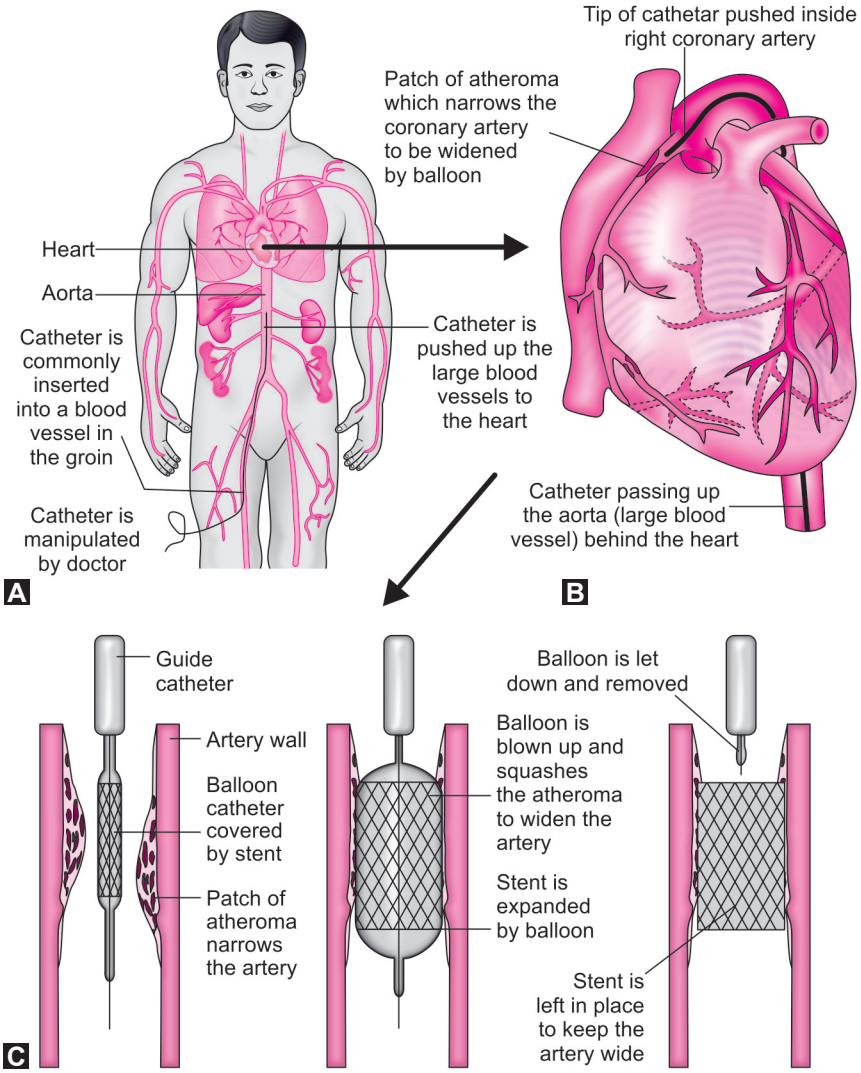
In descending order of gravity, these are the factors which predispose one to develop coronary artery disease:

- Strong family history of premature coronary disease (multiple members have had heart attacks or sudden death, or developed angina below age of 50 years). Never take a patient lightly if there is such a family history. Never stop at just the stress test. Investigate these patients to the fullest even if the stress test is normal. These are the type of patients who for some reason tend to have more unstable plaques. It is always better to do more than less in such cases

- Diabetes: Patients with diabetes are prone to developing coronary artery disease even if diabetes is well controlled. Reasons are complex and not fully understood
- Smoking: This is by far the worst acquired risk factor for development of coronary artery disease. Author studied around 500 patients with documented coronary artery disease under the age of 45 years and never found one who was a nonsmoker unless he had one of the above two factors. Smoking increases free radicals, which are damaging to the intimal integrity, besides other detrimental effects
- Elevated dense LDL, elevated lipoprotein (a) [Lp(a)] and low HDL
- Hypertension
- Stress
- Inactivity and obesity.

Treatment of Angina

- Medical treatment
- Percutaneous interventional (PCI) treatment like angioplasty and stent (PCI): Dr Andreas Gruentzig, a young cardiologist from Switzerland, developed it in mid-1970s. Basically, a balloon tipped catheter was introduced in femoral artery and advanced under fluoroscopic guidance in the affected coronary artery over a guide wire. The balloon is inflated to squeeze out the soft plaque material clearing a passage for the blood to flow through (Figs 5A to C). In later years, a metallic spring (stent) was developed which was deployed in this area to prevent restenosis. Nowadays, most of the stents are drug-eluting type, most common being sirolimus-eluting stent. They slow down the smooth muscle hyperplasia, a common cause of restenosis. Use of newer drugs like glycoprotein (GP) IIb/IIIa receptor inhibitors like abciximab prior to the angioplasty has improved prognosis. Newer methods like intravascular ultrasound (IVUS) and Doppler study for fractional flow reserve (FFR) measurements have improved understanding of plaque behavior. Angioplasty is ideal for up to 1- or 2-vessel disease (less the better) with concentric lesion. It cannot be done if the vessel lumen is very small or in left main lesions or if the lesion is eccentric or adjacent to a bifurcation, or if the lesion is diffuse. Bypass surgery offers better results in such complex cases.
- Surgical treatment: Aortocoronary bypass surgery came in to vogue in the late-1960s. (In this procedure a piece of a vein harvested from leg veins is attached to the ascending aorta on one end and the diseased coronary artery beyond the blockage on the other, creating a "bypass"). Coronary angiography developed by Dr Mason Sones at Cleveland Clinic, opened the floodgates of possibilities in treating coronary artery disease. Coronary artery bypass graft (CABG) soon became very popular and changed this disease forever. There is no dispute anymore that bypass surgery, although not curative, can certainly improve morbidity and mortality. It gives patients a second chance at life. Surgical skills have improved greatly, reducing the mortality rate to around 1%. It soon became the most commonly performed surgery around the world. Methods of vein harvesting, cardioplegia, heart-lung machines, all improved. Now it is being



Figs 5A to C: Coronary angioplasty. Figure shows the heart, main artery (blood vessels) and catheterization

done on beating heart to avoid microembolic complications of heart-lung machine (Prime Minister of India, Dr Manmohan Singh, had this type of CABG). Use of internal mammary arteries, when possible, instead of veins, prolonged the patency of grafts.

- Exercise rehabilitation
- Emotional support
- Dietitian support

Medical Treatment of Angina

- Nitrates and beta-blockers are the mainstay of medical treatment
- Calcium channel blockers

- Aspirin prophylaxis
- Lipid lowering drugs have significantly improved prognosis
- Adequate control of hypertension, diabetes and weight
- Smoking cessation is an absolute must. Physicians can never succeed as long as patient continues to smoke
- Anticoagulants have no role in managing chronic angina. It only helps in preinfarction state

Never forget that the basic idea in managing coronary artery disease is to determine the extent and location of the coronary artery disease and not be hung up with the frequency of angina. More than half the patients with coronary artery disease die suddenly without ever having any chest pain. That simply proves the point that physicians' job is to keep looking out for high-risk patients and screen them for coronary disease whether they have chest pain or not. Physicians are managing coronary artery disease, which kills people, not angina. This is without a doubt the single most difficult principle that non-cardiologists fail to understand. In my opinion, anyone who fails to understand this simple logic should not take care of cardiac patients.

Things to Remember

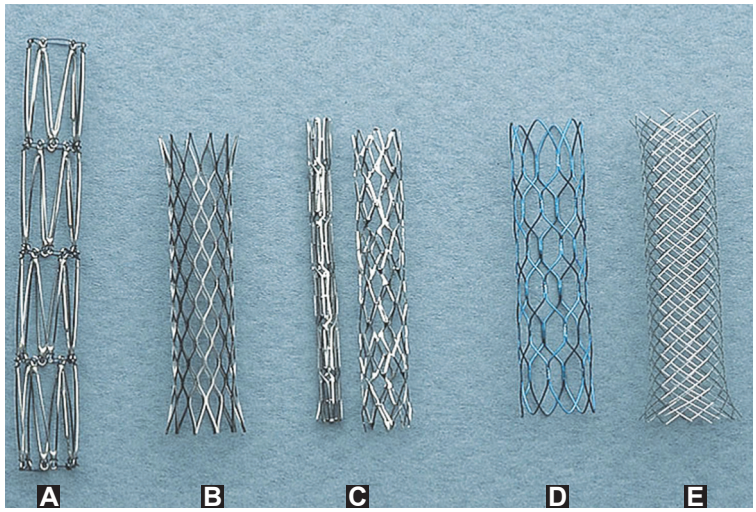
- Make sure to rule out coronary artery disease in adults with unexplained chronic fatigue and/or shortness of breath
- Never discard chronic PVCs as stress induced until underlying coronary artery disease is ruled out
- Never discard a case of recurrent gastrointestinal distress such as hiatus hernia, gastroesophageal reflux disease (GERD) or chronic cholecystitis, until underlying coronary artery disease is screened out by stress test
- Remember, no one dies of GERD but millions die of coronary artery disease. Besides, both conditions can coexist.

Interventional Management of Angina

Angioplasty and stent placement has radically changed the prognosis of coronary artery disease. It basically squeezes out the atheroma plaque, which is occluding the passage and then kept open with a metal spring (stent), which is left in place permanently. Stents used these days are drug-eluting variety, which reduces the smooth muscle hyperplasia a common problem with these stents (Figs 6A to E). It has not only improved morbidity but has no doubt improved mortality. Many interventions, like rotational atherectomy and laser atherectomy have also been in use. There are certain anatomical lesions, which make angioplasty more risky like left main lesion, eccentric lesion or bifurcation disease and diffuse multivessel disease. Bypass is a better choice for patients who are not suitable candidates for angioplasty/stent.

Surgical Management of Angina: Coronary Artery Bypass

Coronary angioplasty is ideal for 1- or 2-vessel disease; but in patients with multivessel disease, one has to weigh the risk/benefit ratio of such



Figs 6A to E: Various stents

interventions. It is better to consider coronary artery bypass surgery in more complex cases. Surgical results are outstanding with mortality rates around 1–2%.

In author's opinion, coronary artery disease is a mechanical problem and requires a mechanical solution (such as angioplasty or bypass). Nothing works like free flow of oxygenated blood to a starving myocardium. No medicine can ever match that result. Only precaution is proper case selection and existing surgical results.

Acute Myocardial Infarction and Preinfarction State

Logical consequence of worsening atherosclerosis is plaque rupture. It is this event, which separates stable angina to an unstable and preinfarction stage and then acute myocardial infarction (coronary thrombosis). These are three different stages of the same disease process and names signify what is happening inside the coronary artery. (As a clinician, you have no way to know what stage of this process a patient is in when he presents with chest pain to your clinic or hospital. It is, therefore, prudent to hospitalize every case of chest pain for observation unless you are quite sure of a noncardiac etiology. It is better to be safe than sorry).

The characteristics of chest pain in acute myocardial infarction are no different than angina, except that they are more prolonged and not completely resolved by nitroglycerin. There is more panic and prostration.

Physicians facing such patient must know that the plaque has become unstable (ruptured) and thrombus is rapidly closing the coronary artery lumen. Their immediate goal of treatment is to try and reopen the artery. The extent of myocardial injury is directly dependent on the time factor. The sooner they succeed more heart muscle they save. This is race against time. Muscle means life, scar means death. More muscle they save, longer the patient lives. All

hospitals and clinics must have a set protocol to deal with this life-threatening emergency. All outcomes must be analyzed and reviewed for improvement. Egos have no place here. Doctors, nurses, pharmacists, respiratory technicians and all support staff must know their role by periodic rehearsal.

Diagnosis of Acute Myocardial Infarction

- Electrocardiography
- Biochemical markers: Serial blood tests for 24 hr—Creatine phosphokinase (CPK), low-density lipoprotein (LDL), troponin T and troponin I
- Imaging studies: (a) Echocardiography showing wall motion defect and (b) Nuclear imaging.

Differential Diagnosis

- Aortic dissection
- Acute pericarditis
- Acute pulmonary embolism
- Spontaneous pneumothorax

HOW TO REOPEN A THROMBOSED CORONARY ARTERY?

There are two ways:

1. Thrombolytic Therapy Using IV Streptokinase, or Recombinant Tissue Plasminogen Activator: Physicians should decide well in advance what agent they will use. Streptokinase costs $100.00 while recombinant tissue plasminogen (r-tPA) costs $1,500.00 per dose. Both work great. Regular anticoagulants such as heparin and warfarin only prevent thrombosis but have no effect on an already formed thrombus. Therefore, thrombolytic agents are needed which activate the plasminogen and break up the already formed clot.

Protocols for using these agents are easily available and should be part of standard orders. If used within 1 hour of onset of pain, success rate is over 80–90%. As this time gets longer, the success rate trails off and after 4 hours it is practically worthless. Thrombus formation is never a one shot deal. It is more like ocean waves. It is sometimes difficult to gauge the exact time of onset. If physicians are not sure, and patient is in severe pain, definitely give it a try.

Thrombolysis is noticeable within 1–2 hours of therapy. Physician can tell this by abrupt improvement of chest pain, rapid improvement in ECG findings, onset of "reperfusion" ventricular arrhythmia (primary ventricular tachycardia or fibrillation) and marked rise in CPK as the accumulated kinins are flushed out. It is an impressive site. Author still remember his first case in 1982.

After successful thrombolysis, the goal is to prevent re-thrombosis. Heparin therapy is initiated for this purpose. Protocols for this should be standard.

Once patient is electrically and hemodynamically stable over the next day or two, author prefers to do coronary angiogram, because the goal now is to correct the residual stenosis. Seven out of ten patients will need some sort of intervention to correct underlying coronary disease. Bypass surgery even 1–2 days after successful thrombolysis is quite routine.

2. Primary Angioplasty: If a hospital is equipped to perform coronary interventional procedure with lightening speed, such option is acceptable. In my estimate, reality is never that perfect. There are many centers around the world where this is the preferred choice with excellent result. I feel every institution must make this choice based on ground realities and not to satisfy any ones ego.

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

- Classical clinical presentation
- Electrocardiography changes: Marked rise in ST segment with upward coving (STEMI or transmural myocardial infarction) is the hallmark of an electrically inactive zone. It represents complete obliteration of lumen
  In non-STEMI, there is only partial obliteration of lumen. It is also referred to as non-transmural myocardial infarction. ECG shows ST depression
- Cardiac enzyme elevation: Creatine phosphokinase-MB is released from the damaged myocardium within hours. Its rise correlates to the extent of myocardial injury. It returns to normal in 3–4 days. However, after successful thrombolysis, this can go 100-fold higher than baseline. That is a good sign. It means thrombolytic therapy was successful
- Cardiac troponin: Same as CPK but can be detected in blood much earlier
- Echocardiogram: Shows wall-motion defect in affected area
- Chest X-ray: It may show pulmonary vascular congestion

Make sure physicians understand that no time should be wasted in performing these tests or waiting for the blood test results before the thrombolytic agents are used.

DISCHARGE PLANNING

When the patient is ready for discharge, make sure the social-worker, dietitian and exercise therapist has a chance to visit the patient. Most patients will remember very little as to what transpired mainly due to fear or denial. Be compassionate. Author had one woman patient who went through a heart attack, thrombolytic therapy, cardiac resuscitation, coronary angiography, bypass surgery and cardiac rehabilitation had asked the author 4 months later that she never knew that she had anything wrong with her heart. Shocking as it may be, it happens. Patients are not tuned in when they are going through this horrifying experience and what physicians tell them may not register. So, be patient with them.

LONG-TERM MANAGEMENT

Now that the crisis has been averted, goal has to shift toward controlling risk factors. This is called secondary prevention. It needs a multidisciplinary approach. Support staff can do most of the teaching and answer the questions.

Usual discharge prescription would look like this:

- Low-cholesterol diet
- Beta-blockers, e.g. metoprolol or atenolol 25–50 mg daily. It is the most important part of therapy because every study around the world has

consistently shown its benefits in improving survival and preventing sudden cardiac death
- Low-dose aspirin—81 mg daily
- Lipid lowering agent, e.g. simvastatin 20–40 mg daily
- Angiotensin-converting-enzyme (ACE) inhibitor, e.g. lisinopril 10 mg daily. ACE inhibitors prevent progressive left ventricular dilatation after acute myocardial infarction and must be used unless contraindicated
- Recheck electrocardiogram, echocardiogram and stress test in 6 months

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CHAPTER 2

Thrombolytic Therapy in Acute Myocardial Infarction

Jayant C Bhalerao

INTRODUCTION

Thrombolytic therapy in acute myocardial infarction is one of the most important discoveries of our time. It all started in 1981, while doing a coronary angiogram, patient developed acute myocardial infarction due to a clot at the catheter tip. As a measure of desperation, large dose of streptokinase was given as intracoronary artery bolus. It resulted in prompt improvement. Clot disintegration was documented on angiogram. This led to one of the biggest scientific expedition in cardiology.

Before this, treatment of acute myocardial infarction was just passive. Physician watched the onslaught of complications and treated them as they arose. Now, with the advent of thrombolytic therapy, physician could participate actively in the disease process.

Intravenous (IV) streptokinase (streptase) protocol was established. Thousands of patients were enrolled in double blind trials around the globe. Notable among them were GISSI trial from Italy and ISIS trial, both published in Lancet in the 1987-1988.

All trials uniformly showed 60% reduction in mortality when used within 4 hours of onset of myocardial infarction and also showed significant preservation of LV function. Relationship of LV function (as measured by ejection fraction) to the prognosis was another major development of that era. The better the left ventricular (LV) function, better is the prognosis. Patients with LV ejection fraction over 40% did better than those with lower ejection fractions.

Soon, a fibrin-specific, tissue plasminogen activator (tPA) was developed by using recombinant technology, termed recombinant tissue plasminogen activator (r-tPA). Many other thrombolytic agents such as urokinase and anisoylated plasminogen activator complex (APSAC) were developed. They all shared the same beneficial effect in dissolving freshly formed clot.

By virtue of producing early thrombolysis, all these agents showed the following:

- Limiting the infarct size
- Preserve LV function, thus improving long-term prognosis

PROTOCOL FOR THERAPY

- As soon the patient with suggestive symptoms arrives in emergency room, within 4 hours, electrocardiography (ECG) must be done and read by an attending physician. If it confirms ST-elevated myocardial infarction (STEMI), start infusion of thrombolytic of choice for your hospital, as soon as possible if contraindications are excluded (they include recent major surgery in 3 months, recent stroke or head injury, or any condition where large bleeding will pose grave risk) (Figs 1 and 2)
- Give four chewable tablets of sublingual aspirin
- Don't do arterial sticks for blood gases or subclavian sticks for central line
- Intravenous streptokinase (streptase) is given as follows:
  - 1.5 million units dissolved in 500 cc diluents given over 1 hour

  or
  - Recombinant tissue plasminogen activator (Activase) is given as follows:
    - 10 mg bolus IV followed by 50 mg in next hour followed by 40 mg in next 2 hours, for a total of 100 mg. Do not exceed 140 mg total dose

  or
  - APSAC 30 mg in 5 minutes bolus

COMPLICATIONS

Reperfusion Tachycardia

Usually indicates successful re-perfusion and occurs around 1–2 hours after the infusion is started. IV lidocaine was used prophylactically but its use is superfluous, because these arrhythmias are self-limiting. It is no longer recommended (Fig. 3).

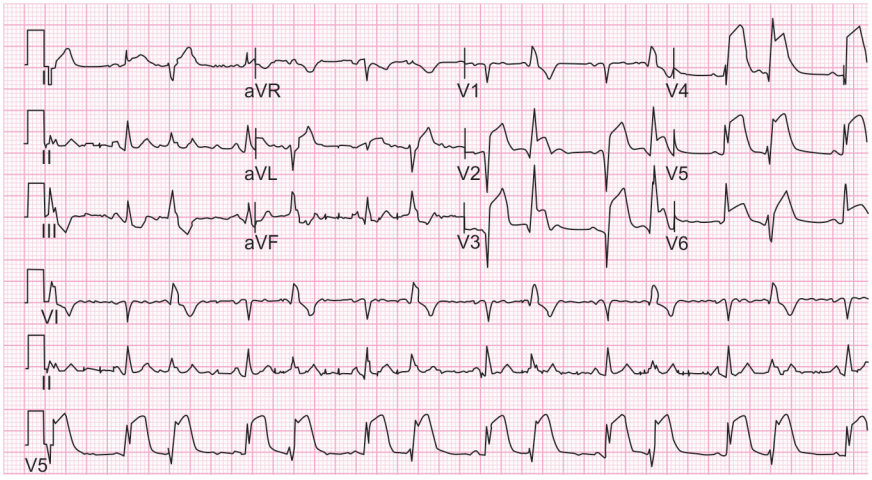

Fig. 1: Anterior wall ST-elevated myocardial infarction (STEMI)

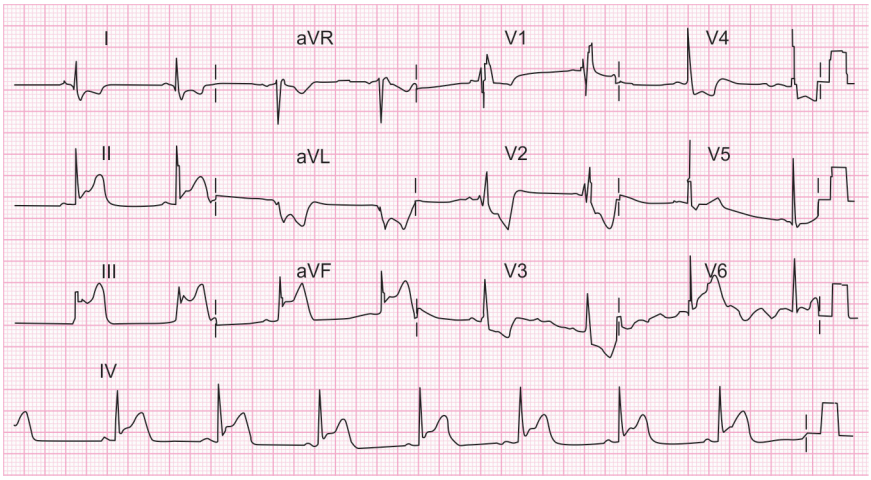

Fig. 2: Acute inferior wall ST-elevated myocardial infarction (STEMI) with right bundle branch block (RBBB)

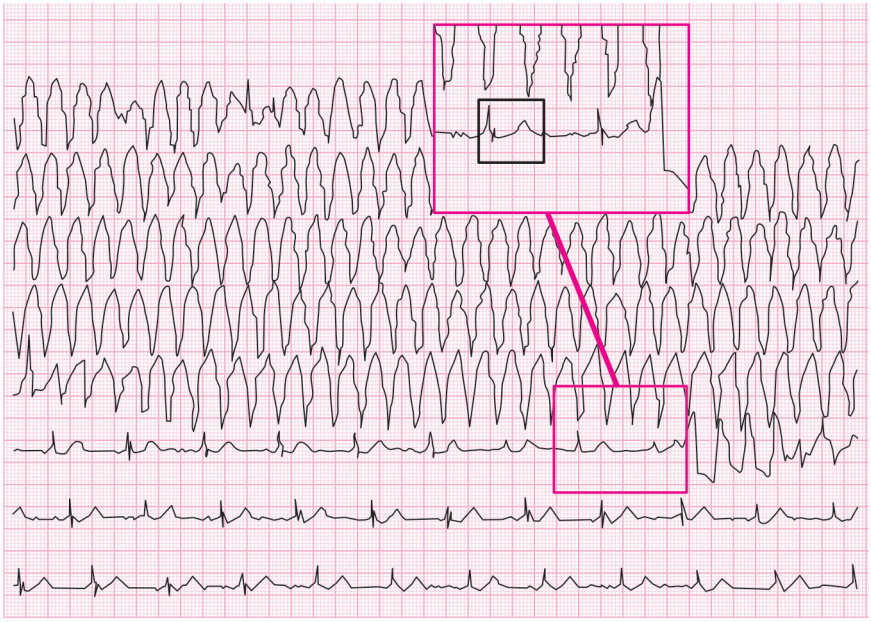

Fig. 3: Reperfusion arrhythmia (ventricular tachycardia)

Hypotension

It is common in IV streptokinase. Just slow down the IV infusion rate, and push fluids if it persists.

Bleeding

Major bleeding, especially intracranial bleeding occurs in less than 1% cases. There is no difference in incidence between different drugs.

Allergic Reaction

Streptokinase is derived from group C *Streptococcus*. There is 1% chance of allergic reaction, which can be treated with IV corticosteroids.

WHAT HAPPENS AFTER SUCCESSFUL THROMBOLYSIS?

- Simple logic should dictate that if an artery can occlude once, it could do so again for the same reasons. To prevent re-occlusion (which occurs in 15–20% cases), cautious IV heparin therapy is recommended. In r-tPA treated cases IV heparin therapy is started immediately after conclusion of the therapy, but in IV streptokinase patients, it should be delayed for 8 hours. There is no need to wait for PTT results prior to starting heparin therapy
- Aspirin should be continued indefinitely
- ACE Inhibitors are helpful in preventing progressive LV dysfunction due to remodeling
- Beta-blockers should be started after patient is hemodynamically stable
- Calcium channel blockers have no place in treatment.

RESIDUAL LESION

Thrombolysis only dissolves the clot but does nothing to the plaque, which had ruptured and left a crater and residual stenosis. It is generally accepted practice to subject patients for diagnostic coronary angiography when they are stable in 2–3 days. Residual lesions are then corrected by either PTCA/stent or bypass surgery then corrects residual lesions. Bypass surgery is safe even 1–2 days after successful thrombolysis in acute myocardial infarction.

REVERSAL OF ATHEROSCLEROSIS

Logical question amongst everyone is, can physicians reverse atherosclerosis and/or prevent plaque rupture?

Reversal is definitely possible by aggressive management of risk factors. Earlier the physicians start, the better are the results. Uses of three-dimensional positron emission tomography (3D PET) scan and intravascular ultrasound (IVUS) technique have helped in early diagnosis. Smarter and easier policy is to popularize risk modification practices to general public.

IMPORTANCE OF COLLATERAL CIRCULATION IN CORONARY ARTERY DISEASE

Since the advent of coronary angiography, it has become abundantly clear that patients who sprout copious collaterals in response to coronary occlusion do better than those who don't. This possibly has a genetic basis. Intense therapeutic efforts are under way to modulate growth of collaterals in order to improve prognosis.

Myocardial blood flow is the product of epicardial coronary and collateral arterial flow. Coronary collaterals are either spontaneously visible or

recruitable (dormant). Myocardial ischemia is the strongest stimulus to activate collaterals.

Rentrop Classification of Collaterals

Class 0: No visible collaterals

Class 1: Faintly visible filling the distal branches

Class 2: Clearly visible distal branches but not the distal artery

Class 3: Complete collateral filling of branches and distal artery

Collateral flow can be measured by special electrode during angiography or by intravascular ultrasound techniques.

Therapeutic Measures to Improve Collaterals

- Regular exercise is the best-known method to promote growth of collaterals
- Drug therapy: No drugs have shown any benefit even though statins and angiotensin-converting enzyme (ACE) inhibitors have shown to promote vessel growth in animal studies
- Biological therapy: Use of stem cell therapy to promote neo-angiogenesis has shown promise and many trials are underway. The big question is would this cause unintended neo-angiogenesis in other organs such as brain or eyes. Success of these trials will spell the relief for everyone because once physicians learn to regulate collateral circulation, they can blunt the damaging effects of arterial occlusion

REMODELING OF HEART

One should understand some basic facts about the healing process following acute myocardial infarction. Necrotic myocardium undergoes "remodeling" over the next few weeks by proliferation of fibroblasts, which is "good" remodeling (also known as "adaptive remodeling"). However, at times, more so in large anterior wall myocardial infarction, progressive fibroblast proliferation leads to weak and scarred myocardium, which is unable to cope with the intraventricular pressure and begins to dilate. It is called "progressive LV dilatation" or "progressive LV dysfunction". This part of remodeling is "bad" remodeling or "maladaptive" remodeling. Similarly, LV hypertrophy in response to hypertension is an example of "adaptive" or "good" remodeling. It is due to an appropriate proliferation of active myosites, whereas in hypertrophic cardiomyopathy, this hypertrophy is an example of "bad" or "maladaptive" remodeling.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

Electrical Complications

Various dysrhythmias and atrioventricular (AV) conduction defects are commonly seen during acute myocardial infarction. AV conduction defects are

very common in large inferior wall myocardial infarction because the dominant right coronary artery also gives off a branch to AV node just proximal to the posterior descending branch. Large inferior wall myocardial infarction is one where the "dominant" right coronary artery (i.e. the one which gives off the posterior descending artery) is occluded. It causes significant reciprocal ST segment depression in opposing anterior wall on ECG. When the left circumflex coronary artery gives off the posterior descending artery, it is called the "dominant" artery).

Atrioventricular conduction abnormalities are mostly transient and self-limited. Sometimes patient may need IV atropine or a temporary pacemaker. It does not affect the prognosis.

Development of a new complete left bundle branch block (LBBB) in acute anterior wall myocardial infarction indicates a very proximal occlusion of a dominant LAD resulting in massive, widespread injury to the left ventricle. It carries a poor prognosis.

Cardiac arrhythmias are the commonest cause of mortality in acute myocardial infarction.

Mechanical Complications

Mechanical problem is the leading cause of morbidity after acute myocardial infarction. There are three different ways mechanical problems arise:

- Loss of contractile element as a result of myocardial necrosis
- "Maladaptive" remodeling of LV causing progressive LV dysfunction and dilatation
- Rupture of free wall, inter-ventricular septum or papillary muscle: Typically occurs around 5th day when the necrosis at its peak. More common in large anterior wall myocardial infarction. Rapid and persistent tachycardia on admission is anonymous sign. Be prepared for something bad to happen in such cases.

Embolic Complications

Mural thrombus from infarct site can dislodge.

Autoimmune Complications

Dressler's syndrome and "Shoulder-hand" syndrome, typically occurring few weeks after acute myocardial infarction.

Psychological Complications

(Discussed in chapter 31)

KILLIP CLASSIFICATION

In 1960s, prior to the availability of echocardiogram, a clinical classification was developed to predict prognosis in acute myocardial infarction based on their hemodynamic profile:

Class 1: No clinical evidence of congestive heart failure (CHF)

Class 2: Clinical evidence of CHF, S3, pulmonary congestion, etc.

Class 3: Presence of frank pulmonary edema

Class 4: Cardiogenic shock

Predictably, the prognosis had a linear correlation to the Killip class on admission. Others have used pulmonary capillary wedge pressure by using Swan-Ganz catheter showing poor prognosis in those with pulmonary capillary wedge pressure was over 18 mm Hg. Echocardiography has changed all that. Calculation of LV function by echocardiogram is the gold standard. Patient with ejection fraction over 40% do better than those below.

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CHAPTER 3

Right Ventricular Infarction

Jayant C Bhalerao

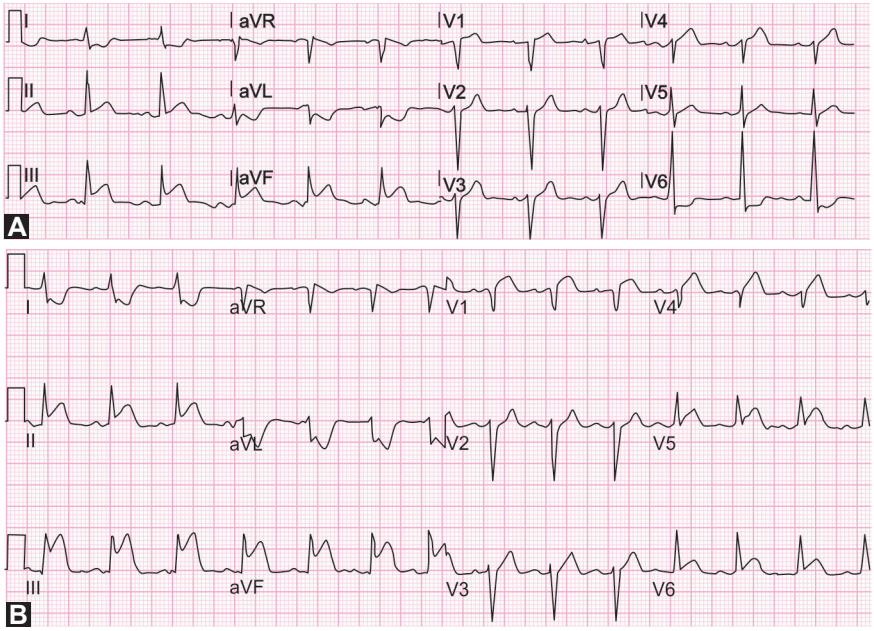
INTRODUCTION

Whenever physicians talk of myocardial infarction, they always are talking about left ventricle. Isolated right ventricular infarction is very rare. Right ventricular infarction is almost always associated with inferior wall myocardial infarction. It commonly causes severe hypotension. Hypotension is typically made worse by reducing the preload by either by nitroglycerin or dehydration or loss of atrioventricular (AV) sequence as in AV dissociation or atrial fibrillation (all commonly associated factors). By loosing RV contractility, these patients are very sensitive to preload. This is treated by pushing intravenous (IV) fluids and avoiding the nitrates.

- It is caused by proximal occlusion of dominant right coronary artery. The occlusion has to be proximal to the origin of marginal branch, which supplies blood to right ventricle (RV)
- Distal right coronary artery supplies blood to the AV node and inferior wall of the left ventricle. That is why large inferior wall infarction is often associated with advanced AV block (usually transient and resolves in 4–5 days)
- The first branch of right coronary artery supplies blood to sinoatrial node (SA) node and right atrium. If the occlusion is proximal to these branches, it will result in SA block or atrial fibrillation

DIAGNOSIS

- Physicians must suspect RV infarction in every case of inferior wall ST-segment elevation myocardial infarction (STEMI)
- Diagnosis becomes even more suspicious if a patient of inferior STEMI also has hypotension
- Once physicians suspect RV infarction, the electrocardiography (ECG) changes are absolutely classical! They cannot possibly miss the diagnosis
- Electrocardiography changes of RV infarction in presence of inferior STEMI are:
  - ST elevation is higher in lead III compared to lead II (Figs 1A and B)



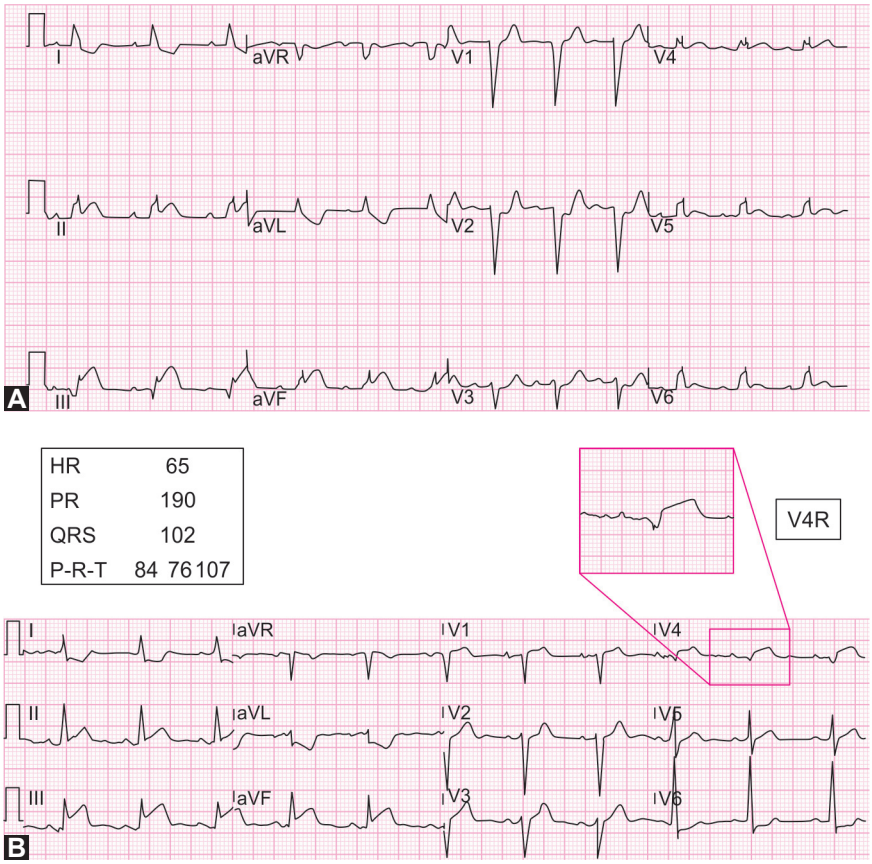
Figs 1A and B: Typical electrocardiography in right ventricle infarct. Note ST elevation in lead III is higher than lead II

- ST elevation in V1 is greater than V2
- If the ST segment is isoelectric in V1, it is invariably markedly depressed in V2 (Figs 2A and B)
- If ST is elevated in V1 and depressed in V2, it is highly specific of RV infarct
- Record chest leads on right chest in mirror image of usual left chest leads. ST is always elevated in V4 (usually V3–V6)

- Markedly distended internal jugular veins but the lungs are clear
- Swan-Ganz catheter will show high right atrium (RA) and RV pressures, but normal pulmonary artery (PA) and pulmonary artery wedge (PCW) pressures
- Usually, loud systolic murmur of tricuspid regurgitation is heard
- Watch for interventricular septal perforation causing severe ventricular septal defect (VSD)
- Echocardiogram to exclude cardiac tamponade.

TREATMENT

- Early diagnosis is important
- Rapid IV fluid infusion
- Watch for advanced heart block and treat early with temporary biventricular pacing. Atrioventricular sequence is very necessary
- Swan-Ganz catheterization to guide hemodynamic balance and exclude pulmonary embolism.



Figs 2A and B: Typical right ventricle infarct. Note if the ST segment is not elevated in V1, there is always ST depression in V2

PROGNOSIS

Once they overcome the hemodynamic instability, the prognosis is fair. The Swan-Ganz catheter showing O_2 step-up at RV level can easily diagnose septal-perforation causing severe VSD. This has dire consequences. Emergency surgery is needed.

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CHAPTER 4

Coronary Artery Disease in Women: A Special Consideration

Jayant C Bhalerao

Coronary artery disease (CAD) is leading cause of death in women in America. Until recently, all the inference about CAD was drawn from studies on middle aged men. It is quite clear now that women present differently with CAD. Their nontraditional risk factors, description of chest pain, results of stress test, surgical mortality rates and risk-modification techniques are different. Physicians have to take into account their unique biologic, physiologic and epidemiologic characteristics, and new approaches to management have to be considered.

- Age of onset: Cardiovascular disease generally starts about 10 years later in women compared to men. Their myocardial infarction (MI) usually appears 20 years later than men
- Mortality rate: Women have higher mortality rate than men. The rates are even worse in African-American women (67% higher)
- Risk factors: Effect of various risk factors and result of intervention is quite different than men
- Hormone therapy: Once thought beneficial in postmenopausal women, is now considered to increase their risk for fatal heart attacks
- Smoking: Incidence of smoking has steadily increased in American women compared to men
- Clinical presentation: Description of chest pain is often atypical. Mortality rates and congestive heart failure (CHF) rates are higher in women
- Myocardial infarction is ominous in women. Those who survive, recurrence rates are higher. Their Killip classification on presentation is higher; arrhythmias and conduction defects are higher. They have higher incidence of shock, CHF, recurrent angina, and myocardial and aortic rupture are all quite higher than men
- Women are treated less aggressively than men. They have much lower (50%) chance of getting coronary angiography, stent, thrombolytic therapy and bypass surgery
- Women have much higher incidence of major bleeding after thrombolytic therapy

- Treadmill test: Women are notorious to have false-positive treadmill stress tests. False-positive thallium scans are also quite common in women
- Size of coronary arteries is smaller in women than men. There is higher incidence of spasm
- Hyperlipidemia: High-density lipoprotein cholesterol (HDL-C) levels are much lower in women than men. Postmenopausal women have higher total cholesterol and low-density lipoprotein (LDL) levels
  When cholesterol levels are below 200 mg/dL, the incidence of CAD is very low in women, but if the cholesterol level rises even slightly (level above 220 mg/dL), the risk almost doubles!!
- Age: Incidence of CAD is approximately 10/1,000 women below age 55 years, but it increases steadily to 30/1,000 after age 65 years
- Triglycerides: Their role in CAD is debatable, but in women, the triglyceride level is a strong independent risk factor of CAD
- Diabetes: Diabetes is the single most powerful risk factor in women—five-fold higher prevalence than nondiabetics. Even slight hyperglycemia (sugar over 130 mg/dL) sharply raises the incidence of CAD in women
- Hypertension: African-American women die of strokes at a much higher rate than white women (80% higher)
- Obesity: Incidence of obesity in postmenopausal women is quite high. Forty percent of the coronary events were attributed to obesity
- Psychological problems: Women tend to have a higher incidence of emotional instability after a coronary event or bypass surgery
- Inactivity: Postmenopausal women tend to be less active than men. This is an independent risk factor for women
- Aspirin: Aspirin is not as beneficial in women compared to men in preventing heart attacks or stroke

Aggressive management of risk factors like diabetes and hyperlipidemia is very necessary in women. The benefits are much more impressive in women than men. That should be the moral of the story.

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CHAPTER 5

Epidemic of Coronary Artery Disease in Indians: A Special Consideration

Jayant C Bhalerao

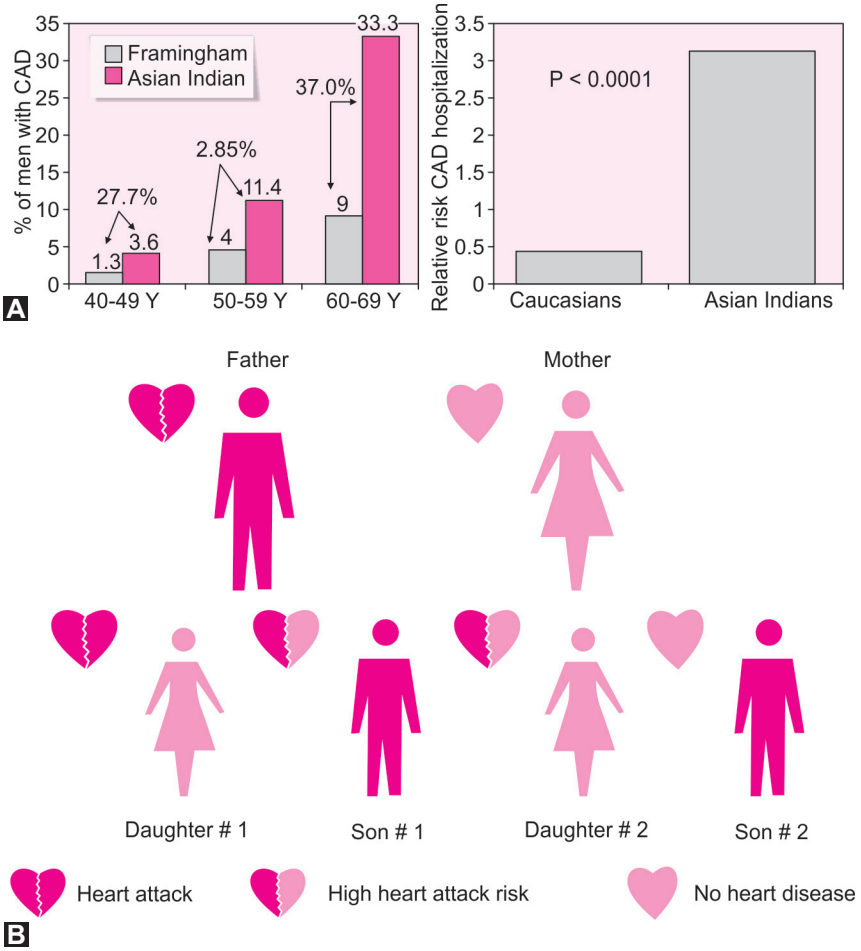
In 1967–1968 author's thesis subject for Doctor of Medicine was "Study of serum enzymes in acute M.I.". In 2 years of this project, he had great difficulty in finding even 25 patients with acute myocardial infarction (MI) in a large University hospital in Indore. Today, when he visits India, almost half of his friends have had either coronary artery bypass graft (CABG) or angioplasty! Quite a few of them have died of coronary artery disease (CAD). Diabetes has become so rampant! How could such transformation take place within few decades? In 1960s, smoking in India was extremely common. Today, almost all the Bidi factories have gone out of business and closed. Statins were not invented and there was virtually no national campaign against risk factors. There were no blood pressure medicines like what we have today. Indians were more inactive then than now. Despite all these risk factors and lack of good medicines, the incidence of CAD was most definitely very low.

Well, whatever has transpired in these few decades, we certainly have a major problem facing us. If this trend continues unchecked, we have a huge disaster ahead! These fears are borne out in various worldwide studies (Figs 1A and B).

It is not only true for Indians living in India but also true for Indians all over the world (United States, United Kingdom, Australia and Singapore to name a few). What seems to be our problem? Have we suddenly mutated our genes? Obviously no. While doing cardiology fellowship in Chicago, author heard of one or other Indian having heart attack every few weeks. Several doctors doing residency with him, many from South India were the common targets. Our eating and culinary habits have remained same for centuries. Was that because these Indians had more trouble adjusting to the western culture? I don't have the answer to any of these questions; just have a lot of questions.

At the same time, Dr Enas, a doctor originally from Kerala, started in Chicago a well-planned study to find the answers. It was called "CADI" study (Coronary Artery Disease in Indians). He made it his life's work.

The National Institutes of Health (NIH) program "Healthy People 2010" designated Asian Indian immigrant Population in the United States as a "high risk group for heart disease".



Figs 1A and B: (A) Data suggests that people of Asian Indian origin have more heart disease than other ethnic groups. (B) This knowledge may help prevent your children and their progeny from suffering the ravages of heart disease

World Health Organization (WHO) estimated that about 60% of world's heart disease patients will be Indians by year 2010, and that seems to be true.

World Health Report of 2002 projects cardiovascular disease and stroke to be the largest cause of death and disability in India by 2020.

Even though the conventional risk factors like hypertension, obesity, smoking and consumption of red meat, are lower than rest of the population; the incidence of premature and accelerated atherosclerosis, severe three-vessel CAD, diffuse CAD, higher relative rate of MI, severe LV dysfunction all seem to be higher in Indians.

Hospitalization rates for CAD among Asian Indians in United States are four times higher than Whites, Japanese, Chinese and Filipinos. Indian women are at a much higher risk of CAD and its complications even though most of them are vegetarians and nonsmoker.

Risk factors for CAD have been discussed earlier. What risk factors are more common to Asian Indians?

- High lipoprotein(a): Strongly implicated, however, even though the Africans have the highest levels, their incidence of CAD is much lower than Indians. Also, if lipoprotein(a) [Lp(a)] is the culprit, it had to be there 50 years ago too. It fails to explain the recent surge of CAD
- High low-density lipoprotein (especially small remnant particles)
- High very-low-density lipoprotein
- Metabolic syndrome of insulin resistance and obesity
- Diabetes and prediabetes
- Low high-density lipoprotein
- High serum ferritin levels in South Indians
- High comprehensive lipid tetrad index: total cholesterol X triglyceride X Lp(a)/high-density lipoprotein
- Impaired "reverse cholesterol transport in Asian Indians": Dr Robert Superko, Berkeley HeartLab
- Role of infectious agents such as *Helicobacter pylori*, Cytomegalovirus, Herpes virus, Chronic gingivitis, *Chlamydia pneumonia*

None of these factors have come about suddenly. They have to be in existence forever. Then why is the epidemic now? Obviously, we don't know the precise reason. Instead of pushing a square peg in a round hole, it is better to admit our limitation. But until we get better answers, early and more aggressive management of even minor elevation of risk factors is warranted in Asian Indians. Author think we should at least do what we know how to do.

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CHAPTER 6

The Paradox of Coronary Artery Disease: Some Answers/Questions

Jayant C Bhalerao

Over the last 40 years, while the death rate from heart disease is dropping, the incidence of heart disease is increasing. The American Heart Association's (AHA) data show that between 1979 and 1996, medical procedures for heart disease increased from 1.2 million to 5.4 million a year! Better screening techniques, easy availability, patient expectations and defensive medicine may all have contributed to uncovering more cases but it still cannot explain such massive increase especially when, during this same time, we have excellent drugs and education program to, low cholesterol diet, control of risk factors. Reduced mortality simply means we have gotten better at correcting the problem, but not decreasing its incidence has come in to play.

It has raised questions:
Has the low-fat diet adopted by Americans actually contributed to this rise? Quite a radical stance!

The Lyon Diet Heart Study (Michel de Lorgeril, 1994) had to be stopped prematurely because people eating the low-fat AHA diet were dying young, while those eating the healthy higher-fat Mediterranean diet, including olive oil, olives, nuts, avocados and fish were doing fine.

Another study, the Healthy Ageing: a Longitudinal study in Europe (HALE) Project, found that over 10 years healthful lifestyle practices in an older population (70–90 years old), including higher-fat, Mediterranean diet, moderate physical activity, non-smoking status and moderate alcohol consumption, were associated with nearly 70% reduction in death from any cause (Kim TB Knoops et al., 2004).

The Harvard Nurses' Health Study, which involved 300,000 women, studied over a 10-year-period to find out if there were any correlation between dietary fat and heart disease. The study found no connection between the two. Dr Willett, the lead researcher for the project tried unsuccessfully to change the government public policy.

Is it due to consumption of "bad" carbohydrates that is the worse than fat consumption? (Ronald P Mensink et al., 2003)

In response to the government policy on low-fat products, the food industry started adding sugars to their products to enhance taste. Many believe that is probably where the problem lies.

Are there external factors like pesticides or fertilizers or hormones that are being used in agriculture and food industry that deserve the blame?

The message is: we have to think outside the box. Liberate your thinking. Think differently if we want to crack this code.

WHAT ARE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS?

There are "good" fats (monounsaturated fats such as Extra Virgin olive oil and nuts), "bad" fats (refined polyunsaturated fats, vegetable oils) and "ugly" fats (hydrogenated oils or trans fats).

Whether or not a particular fat is healthy or unhealthy depends largely on the kind of information the fat communicates to the genes. To communicate these various messages, molecules from fat cells bind to special receptors on the nucleus called peroxisome proliferator-activated receptors (PPARs) (Ronald M Evans et al., 2004).

Different types of fats interact with PPARs in different ways. "Bad" fats turn these receptors "off" while "good" fats bind the same receptors but turn them "on" and help to burn fat and make more insulin-sensitive (George A Bray et al., 2002 and Chambrier C et al., 2002).

Thus, PPARs activated by good fats lead to lower insulin resistance, a major cause of "Metabolic syndrome" and "prediabetes"—both common denominators to atherogenesis.

The take home message is that it is the "type" of fat you eat that is more important than the "amount" of fat you eat.

WHAT IS THE ROLE OF CARBOHYDRATES?

Carbohydrates, just like fats, have "good" and "bad" varieties. Good carbohydrates are vegetables, fruits and whole grains. Bad carbohydrates are processed food such as white sugar, white flour and junk foods.

Carbohydrates in vegetables contain phytonutrients, which are powerful antioxidants, and thus reduce oxidative stress (responsible for atherogenesis). Food processing depletes these phytonutrients. Plant derived carbohydrates high in fiber content which is the critical factor to abbreviate the insulin surge.

Pima Indians (American Indians) are the best example of what "bad" carbohydrates can do to a society (Figs 1A and B). Just 50 years ago, they were the healthy, thin and fit. They were free of diabetes, heart disease and obesity. Their diet was rich in good carbohydrates. Just one generation later, they have become one of the most obese in the world, 80% are diabetic before the age of 30 and their life expectancy dropped to 46 years! What caused this catastrophe? They changed to eating refined carbohydrates!

In just one generation, our obesity rate has tripled since 1960! Diabetes and heart disease has rapidly followed suit. This humongous damage to a generation of entire human population has been caused by two dietary shifts in our culture: (1) concept of a low-fat diet and (2) high-glycemic load by refined carbohydrates.

Figs 1A and B: Photographs of Pima Indians from (A) previous generation and (B) present generation

The take home message is simple and straightforward. The two worst man-made foods, unknown to human biology are: (1) high-fructose corn syrup (HFCS) and (2) hydrogenated oil. Neither of the two has any nutritional value and must be abolished.

WHAT IS HIGH-FRUCTOSE CORN SYRUP?

Introduced in the 1970s as "super sugar", its consumption increase 1,000% in 20 years from 1970–1990. It now represents 40% of caloric sweeteners added to food and beverages. Normal sugar is a combination of glucose and fructose and commonly known as sucrose.

Fructose is found in fruits. It does not stimulate insulin production and does not need insulin to enter a cell. It does not stimulate production of "leptin", a satiety hormone, which tells the brain that you are full and thus stop eating. Fructose, the way nature intended it to be eaten, in a fruit limits the amount of fructose you consume. Besides, you get fiber, and other polynutrients and vitamins.

When the fructose is processed to HFCS, it is absorbed more quickly. Once inside a cell, it becomes an uncontrolled source of carbon (acetyl CoA) and is converted in to triglyceride and cholesterol. HFCS is the most common cause of fatty liver and abnormal lever function tests. Try cutting out HFCS from the diet and see how fast the triglyceride and cholesterol drops. Since HFCS does not stimulate leptin, you cannot control your appetite, and thus gain weight. That is why physician recommend stopping all soft drinks.

Artificial sweeteners are substituted in diet drinks. It contains aspartame. It is equally harmful (Russell Blalock, 1996).

COMMON-SENSE SOLUTIONS

- Return to basics. Eat fresh. Avoid bad fats and bad carbohydrates. Avoid HFCS and refined sugar
- Increase public awareness
- Lean on the government agencies making public policies and the food industry
- Follow the recommendations from HALE Project (discussed in this chapter)
- Moderate exercise and absolute abstinence from smoking

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CHAPTER 7

Pulmonary Embolism

Jayant C Bhalerao

INTRODUCTION

Pulmonary embolism is an acute event, at times a catastrophic, caused by a dislodged piece of blood clot, air or amniotic fluid traveling from pelvis, legs or fractured large bone obstructing the pulmonary artery or its branches. Symptoms depend on the size of the clot and the extent of hemodynamic disturbance. Sudden death from a massive clot is not uncommon.

PREDISPOSING FACTORS

- Age more than 50 years
- Estrogen use
- Immobilization: either postsurgery or travel
- Underlying cancer of any organ
- Prior deep vein thrombosis (DVT)
- Obesity
- Dehydration
- Rarely, thrombophilia disorders like protein C and S, antiphospholipid antibodies, factor V Leiden mutation.

SYMPTOMS

They depend on the size of the thrombus.

- Sudden onset of pleuritic pain
- Sudden dyspnea
- Cough, hemoptysis
- Palpitation
- Syncope
- Acute shock-like state.

SIGNS

- Tachycardia is present in more than 70% patients with significant pulmonary embolism
- Cyanosis
- Loud P2
- Sudden atrial fibrillation
- Distended jugular veins.

DIAGNOSIS

High index of suspicion is most important in making early diagnosis and always rule out of any underlying malignancy in patients with recurrent DVT.

- Electrocardiography: Shows sinus tachycardia. Twenty percent patients show acute right ventricular (RV) strain like S1, Q3, T3 pattern, right axis deviation and complete right bundle branch block (Fig. 1)
- Chest X-ray: Maybe completely normal or may show pleural effusion. It basically helps in ruling out other causes of chest pain and dyspnea like pneumonia, etc.
- Arterial blood gases: Low pO_2 and respiratory alkalosis
- Computed tomography (CT) chest with contrast (CT pulmonary angiogram) is the most widely used test and has replaced ventilation/perfusion (VQ) scan for diagnosis (Fig. 2)
- D-dimer blood test: Helps only if it is normal, which can exclude pulmonary embolism.
- Pulmonary angiogram: If none of the above tests fails to give the diagnosis
- Venous Doppler lower extremities: To confirm DVT in proximal veins of the thigh. DVT in distal veins in legs are much less likely to cause pulmonary embolism
- Echocardiogram: Rarely helps. McConnell's sign showing akinesis in free wall but normal apical movement is of little help in most cases.

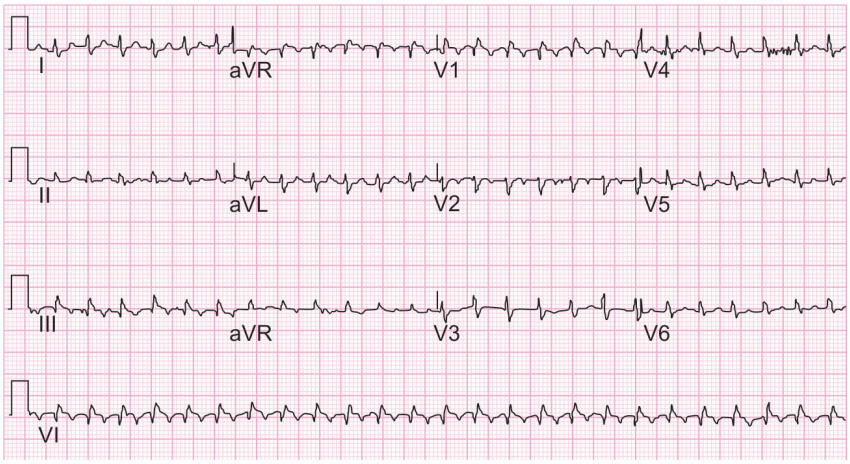

Fig. 1: Typical electrocardiography in large pulmonary embolism showing atrial flutter, S1, T3, Q3 pattern and right ventricular strain

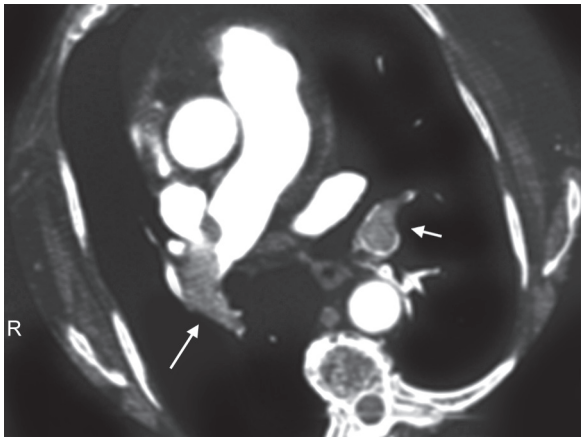

Fig. 2: Computed tomography with intravenous contrast showing filling defects (emboli)

There are confusing scoring systems like Wells' scoring system, Geneva rule, pulmonary embolism rule-out criteria (PERC) rule. Author has not found them of much help.

TREATMENT

- Oxygen 4 L/min
- Intravenous heparin for 6–8 days followed by oral warfarin therapy for 4 months
- Lifelong warfarin is needed in patients with recurrent pulmonary embolism
- Thrombolytic therapy is only used for massive pulmonary embolism with shock
- Pulmonary endarterectomy or suction procedure has been tried
- Inferior vena cava filter (Greenfield filter) can be introduced via femoral vein. It prevents large emboli from traveling past it while allowing blood to flow normally
- Avoid estrogen
- Hydration
- Practice prevention of DVT

PROGNOSIS

Largely depends on the size of the emboli. However, patients treated with heparin early on, do well even despite fairly large emboli.

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CHAPTER 8

Lipid Metabolism

Jayant C Bhalerao

INTRODUCTION

Liver plays a pivotal role in the lipid metabolism, just like the thyroid in iodine metabolism. Liver needs to absorb almost all of the circulating lipids in order to manufacture bile. Minor amount of remaining lipids are used to form cell membranes and hormones. Excess is stored in adipose tissue. Since steady supply of lipid is vital, nature has also provided an alternate system in the liver to produce lipids even if the intake is zero such as in newborn, during famines or during prolonged illness, etc.

Circulating lipids are basically two types: (1) cholesterol and (2) triglyceride. Lipids can't just float in the bloodstream. They have to bind with a protein, which escorts it to target organ. This union is called "Lipoprotein". Lipoproteins are either type A or non-A (i.e. type B, C and E).

ENDOGENOUS SOURCE OF CHOLESTEROL

In basal state (i.e. fasting state) cholesterol is circulating as low-density lipoprotein (LDL) attached to an apolipoprotein (Apo) B100. As it passes through liver by hepatic arterioles, liver tries to absorb as much LDL as it can. It depends on the number of Apo B100 receptors it has. Unabsorbed LDL goes back in recirculation via hepatic vein and tries its luck over and over again. The longer is the LDL in its circulation, the greater are its chances of being oxidized by free radicals, taken up by foam cells and attaching to the arterial intima to produce atherosclerosis. Genetics determines the number of Apo B100 receptors on hepatic cell surface, because higher the number, lesser is the circulating LDL and lesser the chance of atherosclerosis.

To this basal cycle, when a person ingests fat, it starts another cycle—the exogenous cycle. The LDL from exogenous cycle differs in the fact that it has Apo B48 lipoprotein instead of Apo B100. It therefore enters the liver cell through different receptor (gate), i.e. Apo B48 receptors.

EXOGENOUS SOURCE

- Ingested lipids are absorbed from ileum to the thoracic duct in the form of chylomicron. These are fluffy, large particles. It is very lightweight and therefore also called very low-density lipoprotein (VLDL). This is unloaded in the venous blood. It carries mostly (95%) triglyceride and less than 5% cholesterol
- Once in the bloodstream, its remodeling starts. Since its molecule is so large, it takes three different non-A lipoproteins to escort it. They are Apo B48, Apo C and Apo E. Apo CII activates an enzyme lipoprotein lipase, which breaks down this big fluffy molecule. As the remodeling progresses, it sheds more, and cells for energy production and storage take up more triglyceride, which breaks down free fatty acid
- As its size gets smaller, it does not need the extra lipoproteins to carry it, and it sheds Apo CII and Apo E lipoproteins
- This smaller and denser version is called LDL. LDL has only one lipoprotein escorting it—Apo B48. Most of its triglyceride load has been shed and what remains in the core is 50% cholesterol
- This LDL enters the liver cell via Apo B48 receptors, but once inside the liver cell, it takes up Apo B100. This is akin to the ink mark at election time which shows you have voted. Here Apo B100 inclusion identifies that this LDL has gone through the liver. This is how the liver differentiates LDL from exogenous source and the LDL of endogenous source. Most of this LDL is used upto make bile. Excess is released in the circulation. It re-enters the liver cell over and over again. If the liver cell is genetically blessed with lots of Apo B100 receptors, more of this LDL is consumed (to make harmless bile)
- Chromosome 17 regulates the number of Apo B100 receptors in liver cell.

REVERSE CHOLESTEROL PATHWAY OR HIGH-DENSITY LIPOPROTEIN PATHWAY

Nature provides us with a scavenging system (clearing system) to pick up remnants and LDL attached to foam cells. This is done by HDL, which is attached to an Apo A-lipoprotein(a) [Lp(a)]. LDL picked up by this HDL is brought back to the liver. This LDL enters the liver via alpha-receptors in the liver cell and used up.

FAMILIAL HYPERCHOLESTEROLEMIA

Autosomal dominant forms have absolute lack of Apo B100 receptors on liver cell, thus leading to extreme hypercholesterolemia. It is incompatible with life. Lesser degrees of genetic penetration are often seen in clinical practice. It is often associated with subcutaneous nodular xanthoma, arcus senilis, and premature atherosclerosis. The defect is in chromosome 17. Genetic engineering might have a solution for such defect in future.

FAMILIAL HYPERTRIGLYCERIDEMIA

The defect in breakdown of chylomicron by lipoprotein lipase leads to very high levels of triglycerides. Cholesterol levels are normal. Despite massive increase in triglycerides (usually over 1,000 and even up to 10,000), it does not increase risk for atherosclerosis. There is high risk of developing pancreatitis in these cases. Fredrickson classification of lipid disorders is given in Table 1.

Table 1: Fredrickson Classification of Lipid Disorders

Type	*Lipoprotein elevated*	*Lipid elevated*	*Incidence*
1	Chylomicron	TRG (major) and C+ (minor)	Very rare
2a	LDL	C	Familial hypercholesterolemia
2b	LDL+VLDL	C (major) and TRG (minor)	Combined familial hyperlipidemia
3	IDL	C/TRG	Rare
4	VLDL	TRG	Familial hypertriglyceridemia
5	VLDL	TRG/C	Very rare

Note: Only 2a, 2b and 4 are common.

Abbreviations: C: Cholesterol, IDL: Intermediate-density lipoproteins, LDL: Low-density lipoprotein, TRG: Triglycerides, VLDL: Very low-density lipoprotein

MIXED HYPERLIPIDEMIA OR FAMILIAL COMBINED HYPERLIPIDEMIA

This is the most commonly seen hyperlipidemia in clinical practice. Both the serum cholesterol and triglyceride levels are elevated. Virtually, always triglyceride/cholesterol ratio is less than 5:1. When triglyceride/cholesterol ratio reaches over 5:1 or usually 10:1, the defect is familial hypertriglyceridemia (type 5 if cholesterol level is also high and type 1 if cholesterol is normal).

Diabetes, hypothyroidism, obesity, nephrotic syndrome and lupus are often associated factors. Diet will increase the VLDL levels for up to 9 hours, and thus, predominantly, affect triglyceride levels. Total serum cholesterol levels are not affected by meals.

LOW HIGH-DENSITY LIPOPROTEIN OR HYPOALPHALIPOPROTEINEMIA

Just as elevated LDL is detrimental, low HDL level is equally bad. Most Indians have low HDL levels. Very high HDL levels are seen in octogenarians. HDL levels are genetically determined and are difficult to elevate. There are wonderful drugs, such as statins, to lower LDL but none such effective drugs are available to raise HDL level. Nicotinic acid, clofibrate, regular exercise, moderate consumption of red wine and smoking cessation is of some benefit. ("Impaired reverse cholesterol transport" as a result of low HDL causes increased oxidation of LDL and thus the endothelial injury).

METABOLIC SYNDROME

Hyperlipidemia associated with high glucose level, high blood pressure and increased abdominal girth is referred to as metabolic syndrome. It is a common denominator in most cases of atherosclerosis.

TREATMENT OF HYPERLIPIDEMIA

- Statin drugs lower LDL
- Niacin mildly raises HDL
- Clofibrate lower triglyceride

GOALS

- Keep LDL below 80 mg/L
- Keep HDL above 50 mg/L
- Role of triglyceride is not as important in my opinion, although literature states to keep it below 200 mg/L

ROLE OF LIPOPROTEIN(A) IN ATHEROSCLEROSIS

Apolipoprotein(a) also known as Lp(a) is a subclass of lipids. Genetic and numerous epidemiological studies have identified it as an independent risk factor for atherosclerosis and coronary artery disease (CAD).

African-Americans and African tribes in Tanzania have the highest levels of Lp(a).

Lp(a) very much resembles plasminogen and tissue plasminogen activator (tPA). It therefore competes with its binding site, leading to reduced fibrinolysis. Since it carries cholesterol, it contributes to atherosclerosis.

Diet, exercise, statins and environmental factors have no effect on the Lp(a) levels. Only Niacin and Aspirin can significantly lower the Lp(a) levels.

Vegetarians have higher levels of Lp(a) than fish-eaters, therefore fish oil supplements have been tried with some benefit.

Lp(a) should be checked in patients with strong family history of premature CAD or if there is recurrent CAD despite statin therapy.

Ideally, Lp(a) levels should be kept below 15 mg/dL. Borderline levels are between 15 mg/dL and 30 mg/dL. Highest risk is at levels over 50 mg/dL.

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CHAPTER 9

Hypertension

Jayant C Bhalerao

DEFINITION

Hypertension is a term used to describe persistent elevation of blood pressure above 140/90 mm Hg. It is a measurement of the force exerted by a column of blood on the vessel wall as the heart pumps. It has a systolic and a diastolic component. Systolic component reflects stroke volume and diastolic component reflects peripheral resistance. Normal blood pressure is 120/80 mm Hg. Usually both the readings are elevated but at times there is isolated systolic hypertension which can't be explained by physiological states such as stress, exercise, etc. Isolated systolic hypertension is equally harmful and requires treatment. Since systolic hypertension is volume dependent, diuretics should be the first choice of treatment. Persistent diastolic hypertension reflects increased vascular resistance generally from aging, responds best to vasodilator drugs such as calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) blockers, alpha blockers and hydralazine. Any blood pressure over 180/100 mm Hg, if taken correctly, must be treated without delay.

ETIOLOGY

In 9 out of 10 cases, no etiology is found. There is no point in detailed investigation to find underlying etiology in every case of hypertension, unless under following conditions:

- Refractory, severe hypertension
- Very labile hypertension
- Very early age of onset
- Very late age of onset
- Very susceptible to hypokalemia
- Presence of epigastric bruit and/or extensive atherosclerosis
- Presence of unusual endocrine or electrolyte disorder.

In 9 out of 10 cases, hypertension is caused by (a) genetic inefficiency of kidney to handle sodium load and/or (b) up-regulated sympathetic nervous

system and/or (c) overactive renin-angiotensin system. Other environmental factors also contribute. This is referred as "essential hypertension" because a person cannot demonstrate or correct underlying pathology. Onset of hypertension in most cases is around 40 years.

MANAGEMENT

Unless the presenting blood pressure is over 180/100 mm Hg, there is no hurry to start lifelong antihypertensive therapy. Nine out of ten patients with hypertension have no symptoms. It is therefore difficult to convince a patient that lifelong treatment is needed which has cost factor, inconvenience factor, side effect factor and a daily reminder that they have some "illness". It is physician's fundamental duty to make sure the patient and family are thoroughly educated about the consequences of untreated hypertension namely stroke, heart failure, kidney failure and heart attack. One of the biggest problems in clinical practice is that the definition of "disease" is screwed up. Patients have grown up thinking that pain and fever are the only criterion of disease. And if they don't have pain or fever, they are okay. Unfortunately, just about every serious disease, which afflicts older patients, has neither pains nor fever. Hypertension, diabetes, emphysema, atherosclerosis, cancer, stroke, kidney failure, heart failure and dementia—none have pain or fever, these two yardsticks used by patients to measure illness. Such explicit explanation will make them more compliant to treatment. If a patient fails to understand this basic fact, no treatment will ever succeed. All the brilliance and hard work is worthless if patient does not take medications as prescribed. In this disease, just like in diabetes, patients hold the trump card. It is author's routine to take as much time as it takes to make sure he has made his case and that the patient confirms his understanding of the situation. Explain that once the serious complication such as kidney failure or stroke, etc. has occurred, life will be very hard and then there is no going back. Author also explains that the treatment is relatively easy and just about every case can be controlled. There are so many effective drugs available that physician can always find—a drug that works and is well tolerated. Sometimes it may take some trial of different drugs, but almost always suitable combination is possible. Eight out of ten patients usually will need just one pill a day.

Patient cooperation will spell the difference between success and failure. No drug is more effective than this.

PRELIMINARY INVESTIGATIONS

Only basic investigations are needed in 9 out of 10 cases. Start with:

- Urinalysis
- Complete blood count, blood glucose, urea, creatinine, thyroid functions, sedimentation rate
- Electrolytes, anti-nuclear antibody
- Electrocardiography (Fig. 1)
- Chest X-ray
- Dietetic history

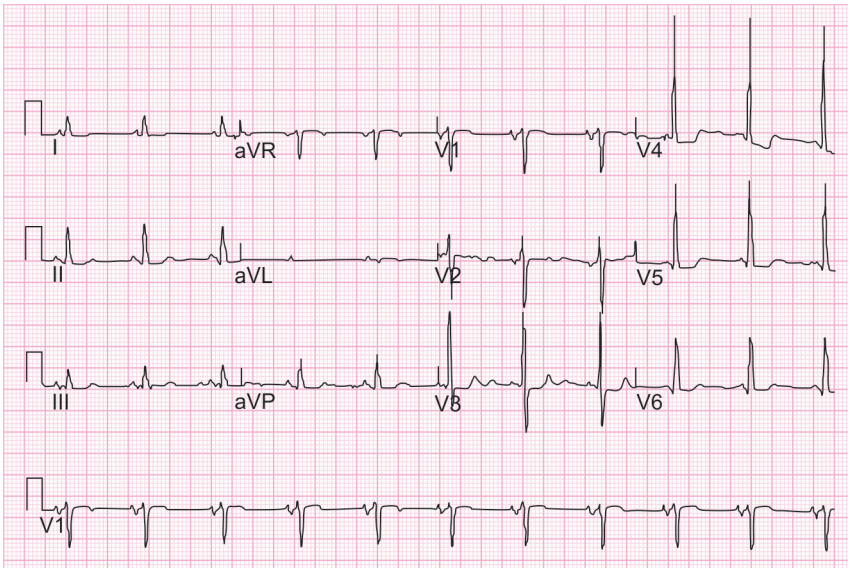

Fig. 1: Electrocardiography of left ventricular hypertrophy (pressure overload)

PHYSICAL EXAMINATION

- Fundus examination
- Neck examination for thyromegaly and carotid or thyroid bruit
- Blood pressure and status of arterial wall
- Pedal and femoral pulse, femoral bruit
- Routine cardiac and respiratory examination
- Epigastric bruit, look for renal enlargement
- Signs of overt endocrine abnormalities such as Cushing's syndrome and thyrotoxicosis
- Make sure there is no sign of any kidney disease.

MANAGEMENT OF SEVERE REFRACTORY HYPERTENSION

Refractory or intractable hypertension is considered when three or more drugs have failed to control blood pressure below 140/90 mm Hg. Before subjecting any woman to these investigations, make sure they stop birth control pills or any estrogen preparation for 2 months. Estrogen therapy is a common cause of severe refractory hypertension in women.

Nine out of ten such cases will have pathology in or around the kidney. Here how author starts:

- Stop estrogen therapy
- Rule out renal artery stenosis by either renal artery ultrasound or Cine magnetic resonance imaging (MRI) or angiography. This is the most common cause of refractory, severe, labile hypertension. In a busy cardiology practice, physician should be able to diagnosed at least one case every other month. Author routinely started doing renal angiogram in patients who are going for coronary angiography and had severe hypertension.

Physicians will be surprised how many cases of renal artery stenosis they will find
- Twenty-four hour urine sodium, potassium and catecholamines
- Plasma catecholamine level
- Look for coarctation of aorta by echocardiogram
- Nephrology consultation for possible kidney biopsy
- Plasma cortisol level at 8 am and 4 pm

TREATMENT CONSIDERATION OF REFRACTORY SEVERE HYPERTENSION

Author's choice is:
- Nifedipine ER 90 mg daily
- Metoprolol succinate (long acting) 100 mg daily
- Spironolactone 50 mg daily
- Furosemide 40–80 mg once or twice a day

If this is ineffective, author switches nifedipine with minoxidil 10 mg once a day. Minoxidil is a potent vasodilator and is godsend for such patients. It has three side effects that physicians must know before starting it: (1) fluid retention, (2) hair growth and (3) tachycardia.

Women may not like facial hair growth but given the extreme situation, might accept it. Significant fluid retention makes it essential that furosemide must be used along with it. Daily weight record will help to make sure patient is not getting fluid overload. It should not be used in patients with renal insufficiency. Patients can gain 40–50 lb weight within days due to fluid retention. Patients with renal insufficiency in such cases should be considered for dialysis much earlier.

RENAL ARTERY STENOSIS

- Fibromuscular hyperplasia is the usual cause in younger patients. More common in women under 40 years of age (Fig. 2)
- Atherosclerosis is the usual cause in elderly patients, usually males
- Epigastric bruit especially the diastolic component along with systolic, is highly suggestive, but absence of the bruit does not rule out renal artery stenosis (Figs 3 to 5).
- One kidney smaller than the other is suggestive
- Renal artery ultrasound is quite good in diagnosis
- Cine MRI helps
- Renal angiogram is the gold standard
- Renin level is high. Aldosterone level is also high

Treatment of Renal Artery Stenosis

- Angioplasty/stent
- Surgical revascularization

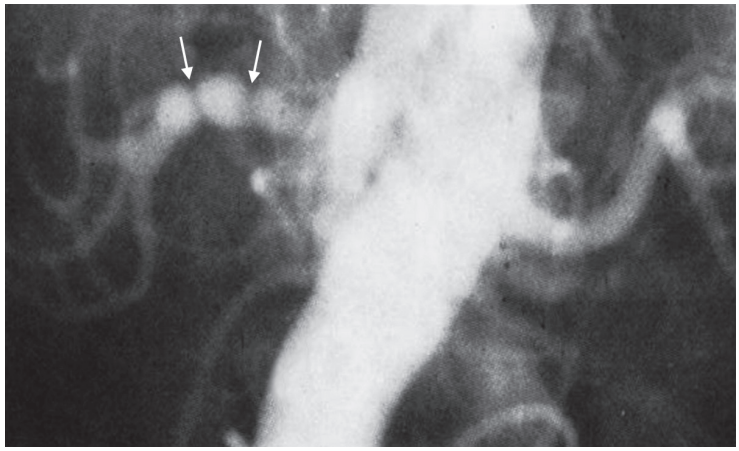

Fig. 2: Renal arteriogram showing bead-like stenosis in fibromuscular hyperplasia

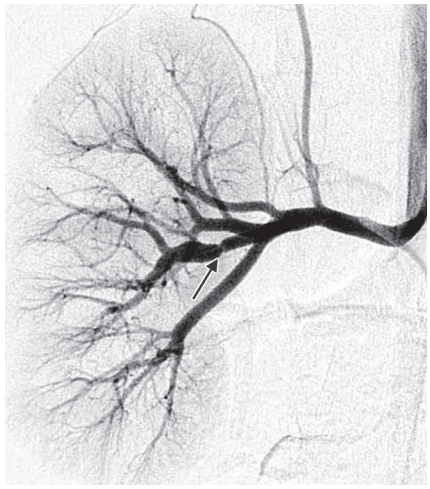

Fig. 3: Renal artery stenosis (arrow) right in a 20-year-old male

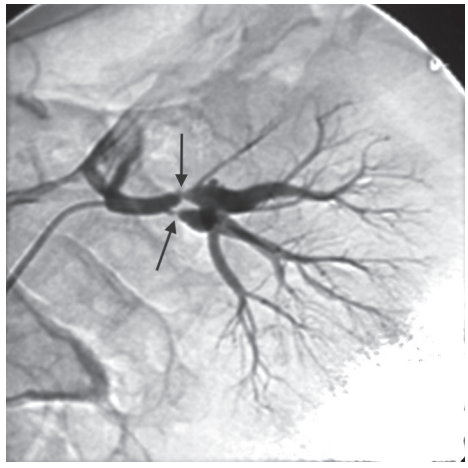

Fig. 4: Left renal artery branches showing stenosis (arrows)

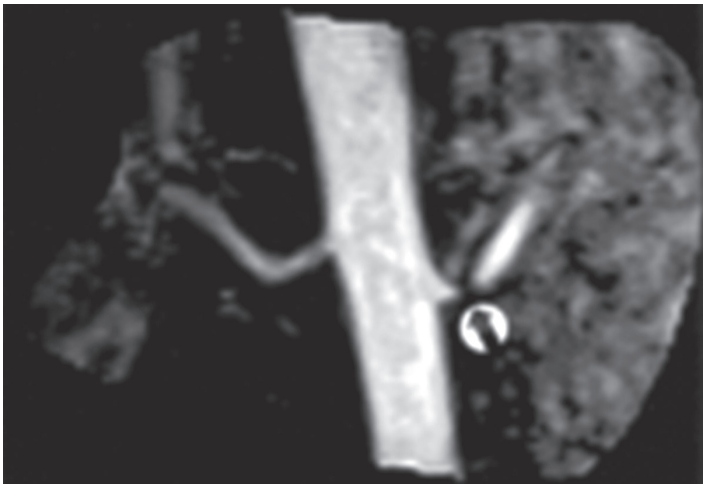

Fig. 5: Severe left renal artery stenosis (arrow)

If the hypertension is just not responsive, removing the "bad" contracted kidney is quite effective.

PHEOCHROMOCYTOMA

This is benign tumor of the adrenal gland which secrets copious amount of catecholamine.

Signs and symptoms of pheochromocytoma:

- Severe labile hypertension often associated with headache and sweating
- Severe constipation
- Palpitations, flushing

Diagnosis of pheochromocytoma:

- Plasma catecholamine level
- Twenty-four hour urine metanephrine level
- Computed tomography (CT) scan of adrenal glands (Fig. 6).

Treatment of Pheochromocytoma is surgical:

- Preoperative preparation with alpha-blockers (oral dibenzyline 10–40 mg three times a day), or doxazosin 2–8 mg daily for 2 weeks. Once alpha-receptors are blocked adequately, and then start beta-blockers—not sooner!
- Forced hydration to expand blood volume to maximum
- Arterial line, right heart catheterization in preoperative holding room
- Keep few units of fresh frozen plasma on hand and also keep intravenous (IV) nitroprusside on hand
- Surgery
- Watch for severe ischemic changes in extremities even gangrene due to massive catecholamine exposure
- Be prepared for severe hypotension as soon the tumor is excised
- Massive shifts in blood pressure such as which have never seen or heard during surgery while the tumor is being handled. Use IV nitroprusside to maintain blood pressure as best as possible
- Pray a lot until the patient is out of surgery.

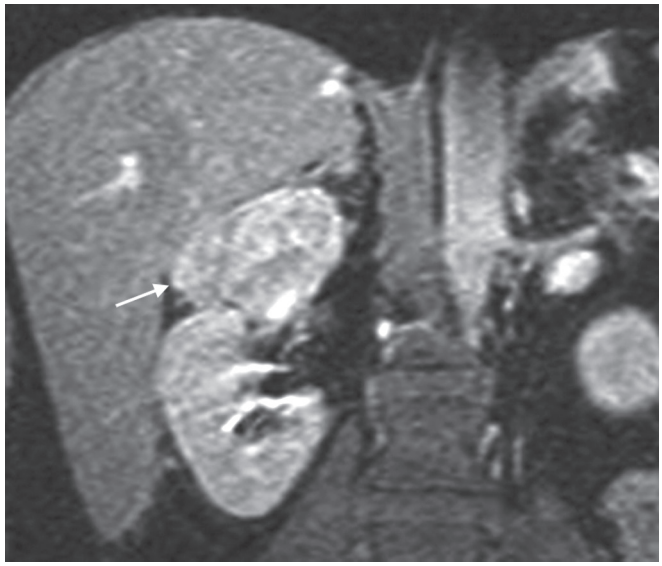

Fig. 6: Computed tomography scan of abdomen with intravenous contrast showing large adrenal medullary tumor (pheochromocytoma)

PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)

- Seventy percent of the time it is due to bilateral idiopathic hyperplasia
- Thirty percent of the time it is due to benign adenoma, which is usually small and may not be seen in CT scan.

Clinical Feature

- Labile hypertension
- Marked hypokalemia
- Alkalosis.

Diagnosis

- High serum aldosterone level
- Low serum renin level
- Abdominal CT scan.

Treatment

- Adrenal cortical hyperplasia is treated medically with oral spironolactone
- Adenoma is treated surgically.

CUSHING'S SYNDROME

- Seventy percent are caused by pituitary tumor (chromophil tumor)
- Twenty-five percent caused by adrenal cortical hyperplasia
- Five percent caused by iatrogenic factors.

Signs and Symptoms

Truncal obesity, telangiectasia, moon face, buffalo hump on neck, excessive sweating, hirsutism, purple-red stria, baldness, diabetes, osteoporosis and muscle weakness.

Diagnosis

- Dexamethasone suppression test (adrenocorticotropic hormone level before and after 2 mg oral decadron)
- Twenty-four hour urine cortisol
- Plasma cortisol level at 8 am and 4 pm (showing elevation and loss of diurnal variation)
- Computed tomography scan of abdomen
- Magnetic image resonance scan of pituitary fossa.

Some of the conditions of which physician must be aware of:

- Chronic and severe cardiac or cerebral ischemia can often be the underlying cause of refractory and labile hypertension just as renal ischemia
- Acute intracerebral bleeding is often associated with severe accelerated hypertension. It is the effect of the acute cerebral injury. It is due to massive outpouring of catecholamine. Moderation is needed in lowering such hypertension. Don't be too aggressive
- Acute intermittent porphyria causes severe hypertension during porphyric crisis. Author had one such case. Tachycardia and accelerated hypertension was a good way to diagnose impending crisis.

Never forget the role of estrogen in severe hypertension. For 9 out of 10 patients start with:

- Low salt (4 g) diet
- Hydrochlorothiazide 25 mg once a day
- Angiotensin-converting enzyme inhibitor or angiotensin receptor blockers such as enalapril 10–20 mg once a day
- Add metoprolol succinate 50–100 mg once a day if needed
- If beta-blockers are contraindicated, use calcium channel blockers such as amlodipine 10 mg once a day.

Combination of amlodipine and ACE inhibitors are excellent choice if patient does not like diuretics. One of the best methods to see compliance is to encourage patients to use digital blood pressure instrument at home and keep a record. Author uses a software program called "my-blood-pressure.com" to keep my blood pressure record on computer. Author will highly recommend it to everyone.

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CHAPTER 10

Primary Pulmonary Hypertension

Jayant C Bhalerao

DEFINITION

Permanently elevated pulmonary artery pressure above 30 mm Hg without any usual known cause is termed primary pulmonary hypertension. The usual causes of pulmonary hypertension are: left heart failure, mitral stenosis, chronic obstructive lung disease (COPD), interstitial pulmonary fibrosis and pulmonary embolism. This may be familial and uniformly progressive with average survival less than 5 years. No effective treatment is available. Most cases, by the time they are diagnosed, are far gone. Its etiology remains unclear.

SYMPTOMS

- Progressive dyspnea, chest pain
- Dizziness and fainting usually with exercise
- Marked fatigue.

SIGNS

- Clubbing, cyanosis due to Eisenmenger's physiology
- Symptoms of right heart failure
- Severe right ventricular hypertrophy (RVH) evident on clinical examination and electrocardiogram
- High B-type natriuretic peptide (BNP) level.

DIAGNOSIS

- First exclude all the usual causes of secondary pulmonary hypertension
- Swan-Ganz catheterization showing pulmonary artery (PA) pressure more than 30 mm Hg; Normal pulmonary capillary wedge pressure and pulmonary vascular resistance greater than 3 Wood unit (or 240 dynes/sec)

- Echocardiogram showing evidence of RVH and right ventricular (RV) enlargement and signs of pulmonary hypertension
- "Six-minute walk" is a good way to follow up clinical status.

CAUSES

- Idiopathic in majority of cases
- Familial
- Drug induced: Fen-Phen (weight loss drug now banned), cocaine, methamphetamine (street drugs).

TREATMENT

- Nothing seems to work. Digoxin, diuretics, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers all have been tried with minimal to no success
- Anticoagulation is recommended because clots may form on damaged intima causing microemboli to distant circulation
- Newer drugs:
  - Prostaglandins, such as prostacyclin, given as intravenous (IV) infusion via Hickman catheter
  - Endothelin receptors antagonist, e.g. Tracleer (Bosentan)
  - Sildenafil (Revatio)

  None have sustained effectiveness.
- Surgery: It is a desperate attempt in a dying patient. Atrial septostomy to divert the right atrial blood to the left side
- Lung transplant.

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11 CHAPTER

Congestive Heart Failure

Jayant C Bhalerao

DEFINITION

Failure of the heart to perform its assigned task of supplying oxygenated blood for tissue perfusion, leads to a clinical syndrome, which is referred to as congestive heart failure. Dyspnea, although not unique to this syndrome, is the hallmark of this syndrome. Heart has two basic functions:

1. Systolic function, i.e. pumping blood and
2. Diastolic function, i.e. reservoir of blood

Dysfunction in either or both of these functions leads to proportionate hemodynamic deterioration and decreased cardiac output. With advancing defect, the symptoms of dyspnea also deteriorate proportionately, leading to orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema and lastly cardiogenic shock.

CAUSES

Common causes of heart failure are:

- Valvular heart defects
- Coronary artery disease
- Hypertension is the most common denominator in congestive heart failure (CHF)
- Primary heart muscle diseases (cardiomyopathy)
- Congenital heart defects
- Chronic alcohol abuse
- Viral myocarditis
- Autoimmune disorder
- Tachycardia associated cardiomyopathy: chronic tachycardia may lead to CHF
- Doxorubicin (Adriamycin) induced cardiomyopathy
- Diabetic cardiomyopathy
- Familial cardiomyopathy: an autosomal dominant disease.

SYMPTOMS AND SIGNS

- Decline in cardiac output: It leads to poor tissue perfusion. Muscle fatigue, malaise, decreased urine output, lack of mental alertness
- Venous stasis: Since the left ventricle is unable to deal with the continuous venous return, it creates a bottleneck. Venous blood backlogs, first affecting the lungs, flooding them with transudate, causing dyspnea, cough and poor oxygenation which cause central cyanosis and hemoptysis. Venous blood backlogs further in the pulmonary veins and right ventricle and then vena cava, jugular veins, liver and portal veins and systemic veins leading to distended jugular veins and facial puffiness, liver enlargement and tenderness, ascites and leg edema
- Cardiac enlargement generally results as compensatory efforts failure.

COMPENSATORY CHANGES

- Heart tries to compensate the failing cardiac output by stimulating the (1) sympathetic nervous system (2) bradykinin system via cardiac reflexes (3) renin-angiotensin-aldosterone axis and (4) humoral activation
- Atrial distension as a result of venous stasis releases atrial natriuretic polypeptide (ANP). It dilates afferent glomerular arterioles and promotes sodium and water excretion thereby relieving the vascular congestion. ANP can be measured in blood and are used in diagnosis of heart failure.

PHYSICAL FINDINGS

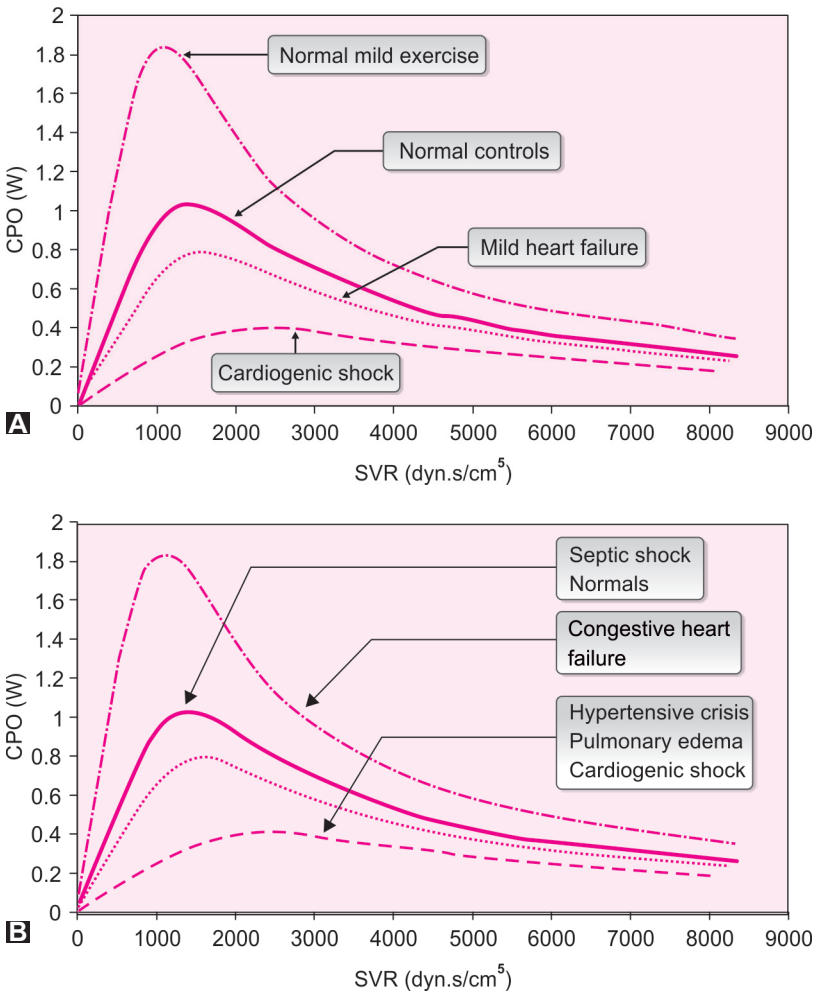
- On general examination the patient shows chronic debility, general weakness, labored breathing, puffy and cyanotic face, frequent dry cough, decreased alertness and lethargy
- Jugular venous distension. Make sure that physicians are talking about internal jugular venous distension and not external jugular venous distension. Internal jugular veins truly reflect the right atrial pressure. External jugular veins penetrate the platysma and can be distended due to anatomical factor and may not be a true reflection of right intracardiac pressure
- Persistent tachycardia, low pulse pressure and pulsus alternans
- Pitting edema on dependent portion of body such as ankle and legs
- Cardiomegaly is often present. S3 gallop is a good sign of a failing left ventricle (LV) which is not able to deal effectively with the venous return. Cardiac murmurs must be carefully sought for especially mitral stenosis
- Lungs show signs of venous congestion, i.e. crepitations, signs of pleural effusion, and X-ray signs
- Liver is often enlarged and tender. Ascites and scrotal edema generally occurs in more severe cases
- Blood pressure: Majority of elderly patients with heart failure will have either history of or evidence of poorly controlled high blood pressure.

DETERMINANTS OF CARDIAC OUTPUT

Since decline in cardiac output is the basic defect in heart failure, it is worthwhile to understand what factors regulate it. There are three determinants of cardiac output:

- Myocardial contractility
- Preload
- Afterload

Myocardial contractility is governed by Starling's law which states that within a certain clinical limit, the more we stretch the myocardium the stronger it contracts, and thus higher is the cardiac output. However, beyond certain limit the myocardium is unable to keep up and the cardiac output begins to decline. This is referred to as the stage 4 of Starlings curve. Patients who present with heart failure are in this stage (Figs 1A and B).



Figs 1A and B: Schematic presentation of Starling curve

Preload refers to the filling pressure of the ventricle. End-diastolic pressure is the measure of preload. It can be measured directly by cardiac catheterization of the LV cavity. In clinical practice, easier way to measure preload (filling pressure) is by Swan-Ganz catheterization and measuring the pulmonary capillary wedge pressure, as long as there is no mitral stenosis or severe regurgitation (which can also increase the sedge pressure). Pulmonary capillary wedge (PCW) pressure closely correlates to the LV end-diastolic pressure. It can differentiate a low cardiac output state due to dehydration in which case the preload is quite low whereas in heart failure it is quite high. For optimum cardiac output, the preload should be around 10–15 mm Hg. Nitroglycerin lowers the preload and helps a improve LV function. One shortcoming of this treatment is that patients develop resistance to it.

Afterload refers to peripheral resistance. Arterial blood pressure is the biggest determinant of afterload. It offers impedance to the cardiac output. Optimum cardiac output is when the afterload (i.e. the blood pressure) is around 90–100 mm Hg. Lowering the afterload is by far the most effective long-term solution in managing heart failure. It does not have the drawback of resistance development like nitrates.

INVESTIGATIONS AND MANAGEMENT

- Immediate objective of management is to optimize the hemodynamic abnormality by improving the preload, contractility and afterload
- Next, the medium-range aim is to exclude coronary artery disease and primary valvular heart disease, because these two are the easiest to correct
- Lastly, the long-range aim is to decide if the patient would be a candidate for cardiac transplant.

Acute Management

- Depending on the functional class, decide if hospitalization is required. Class 3 and 4 represent great urgency and must be managed in a hospital setting. Routine blood work up (including renal functions, thyroid functions, electrolytes and complete blood count), chest X-ray, electrocardiography, arterial blood gases and echocardiogram should be ordered
- Start with oxygen 3–4 L/min by cannula. Intubation will be needed in class 4 patients if they fail to respond to treatment rapidly. Intravenous (IV) sedation with morphine may be necessary in class 3 and 4 patients
- Start an IV Line and give furosemide 40 mg IV and repeat in 2–4 hr if needed
- Insert a Foley catheter
- More severe cases may benefit from Swan-Ganz catheterization for hemodynamic monitoring, although this is not essential in every case
- Start afterload reducing agents [such as angiotensin-converting enzyme (ACE) inhibitors] and titrate till the blood pressure has been brought down to around 100 mm Hg if tolerated
- Start preload reduction with nitrates oral, transdermal patch or IV
- Increase myocardial contractility by digoxin, and if needed, IV dobutamine. Digoxin is especially helpful if patient has cardiomegaly or has

atrial fibrillation (Fig. 2). It rarely helps if thyrotoxicosis is responsible for tachycardia or if patient has hypertrophic cardiomyopathy where it is contraindicated

- Use of spironolactone is beneficial in natriuresis. It also accentuates the effect of furosemide. Watch for hyperkalemia. Do not combine it with oral potassium supplement
- Use of beta-blocker in CHF has major beneficial effects both in improving the cardiac output, as well as improving long-term survival, by making the heart electrically more stable. Start it only after the acute heart failure is controlled and stable
- Hemodynamic adjustment in severe cases is a complex undertaking and requires considerable expertise and should be left to a cardiovascular specialist. Careful monitoring of metabolic status is mandatory.
- As patient makes clinical recovery, IV medications can be tapered off and patient is switched to oral or transdermal agents. Salt restriction is a long-term requirement. Long-term fluid restriction is only necessary in more severe cases. Daily or weekly weight record is very effective means of gauging progress and clinical status. Patients can thus participate in their own clinical care.

Usual discharge prescription of a patient would look like as follows:

- Low salt (2–4 g/day) diet, daily weight and blood pressure record
- Lanoxin 0.125 mg or 0.25 mg daily
- Furosemide 40–80 mg once or twice a day
- Spironolactone 25–50 mg daily
- Lisinopril 10–40 mg daily to maintain blood pressure around 100 mm Hg or as low as tolerated
- Isosorbide mononitrate 30–60 mg daily
- Carvedilol 3.25–25 mg twice a day (or metoprolol 25–50 mg once a day)
- Check electrolytes and creatinine in 2 weeks then every 2–3 months along with digitalis level

  CoQ10 is an alternative treatment quite popular in California.

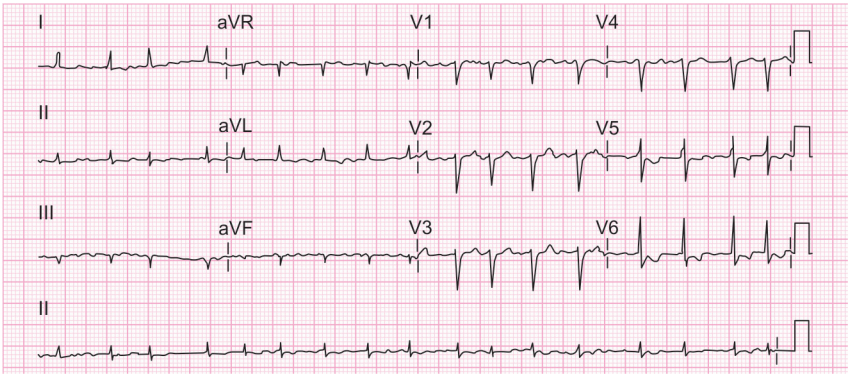


Fig. 2: Typical electrocardiography change is digitalis effect. Note down-sloping ST segment with "reverse check" sign in ST segment in V5 and V6. Underlying rhythm is atrial fibrillation

Cardiac Remodeling

Following myocardial infarction and even in primary dilated cardiomyopathy, there is a process called "remodeling" which leads to progressive LV dysfunction. ACE inhibitors and beta-blockers have shown to reverse this process.

Mid-Range Management

- Begin to rule out underlying coronary artery disease. Echocardiogram done on initial visit can easily rule out valvular or congenital heart defects. Always schedule a cardiac catheterization and coronary angiography. Majority of these patients have significant underlying coronary artery disease even if they have no history of angina. Following this, protocol can significantly reduce mortality
- Biventricular pacing with implantable cardioverter-defibrillator (resynchronization therapy): Major improvement can be shown in properly selected cases. Sudden cardiac death due to ventricular arrhythmia is common; therefore early use of implantable cardioverter-defibrillator is prudent.

Long-Term Management

- Heart transplant is no longer an experimental treatment. It must be decide early on because 5-year success rate is over 75%. It is a viable option if the patient is under the age of 55 years. Overwhelming infections due to immunosuppression in older patients makes it impractical
- Ventricular assist devises (LVAD) can serve as a bridge to transplant to buy time until a donor is available
- Volume reduction surgery (Batista procedure) and aneurysmectomy help in improving LV function by decreasing O_2 consumption (Laplace's law = O_2 consumption directly proportional to wall tension).

PROGNOSIS

Long-term prognosis has substantially improved with modern management and patients may survive several years of productive life. Sudden electrical death is common therefore, implantable cardioverter-defibrillator, which now is part of all biventricular pacemakers, is well justified. Progressive LV mechanical dysfunction is the other common issue, and in younger patients below the cut-off age of 55 years, cardiac transplant should be considered early on.

CARDIOMYOPATHIES

Some of the commonly seen cardiomyopathies are:

- Familial dilated cardiomyopathy
- Diabetic cardiomyopathy

- Alcoholic cardiomyopathy
- Postpartum cardiomyopathy
- Viral myocarditis
- Ischemic cardiomyopathy
- Idiopathic cardiomyopathy
- Hypertrophic cardiomyopathy
- Hemochromatosis and Wilson's disease
- Chagas disease.

DIFFERENTIAL DIAGNOSIS

The commonest difficulty is posed by pericardial disease such as effusion or constrictive pericarditis. Echocardiography has made it much easier to differentiate with other causes, which clinically pose difficulty in diagnosis.

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12 CHAPTER

Hypertrophic Obstructive Cardiomyopathy

Jayant C Bhalerao

Hypertrophic cardiomyopathy (also known as idiopathic hypertrophic subaortic stenosis and asymmetric septal hypertrophy) is a primary heart muscle disorder. It is an autosomal dominant genetic disorder, which causes massive hypertrophy of interventricular septum without any secondary etiology such as hypertension or fixed valvular heart disease. It leads to marked diastolic dysfunction and diastolic left ventricular (LV) failure. There is a high incidence of sudden cardiac death.

It is caused by a genetic mutation of sarcomeric genes affecting myosin heavy chains. Sarcomere is the contractile element in heart. This sarcomere replicates uncontrollably causing severe hypertrophy. Normal alignment of heart muscle cells is disrupted (myocardial disarray). There is disruption of electrical function of heart leading to cardiac arrhythmia.

CLINICAL FEATURES

- Patients are generally in their teens or midlife when they present with dyspnea on exertion
- Post-exersional syncope or lightheadedness
- Chest pain
- Loud systolic murmur in left parasternal area which increases in intensity in upright position and diminishes in squatting position
- Murmur becomes louder after nitroglycerin and diuretics and post-Valsalva maneuver
- Murmur accentuates after a premature ventricular contraction (PVC) (Brockenbrough phenomenon)
- Bisferiens arterial pulse (spike and plateau pulse)
- Electrocardiography showing features of large anterior infarction and severe left ventricular hypertrophy (LVH)
- Family history of sudden cardiac death
- Echocardiogram shows massive hypertrophy of interventricular septum and systolic anterior motion of the anterior mitral leaflet—a diagnostic hallmark. As opposed to valvular aortic stenosis, which is far more

common in older population over 60 years and often associated with aortic regurgitation, valvular calcification and dilatation of ascending aorta (poststenotic dilatation), none of these features are seen with hypertrophic cardiomyopathy.

DIAGNOSIS

- Electrocardiogram shows severe LVH and features of large anterior myocardial infarction without any such clinical history (Fig. 1)
- Chest X-ray shows normal cardiac size, LVH, absence of aortic calcification, absence of aortic root dilatation
- Echocardiogram with amyl nitrate inhalation (also sublingual nitroglycerin) accentuates the echocardiographic features of hypertrophic cardiomyopathy (Fig. 2)
- Cardiac catheterization showing subvalvular pressure gradient in left ventricle, post-PVC decrease in aortic systolic pressure (Brockenbrough phenomenon)
- Cardiac magnetic resonance imaging.

TREATMENT

Medical

- Reduce heart rate (negative chronotropic) by beta-blockers or verapamil; this prolongs the diastole allowing increased LV filling
- Reduce the force of contraction of left ventricle (negative inotropic) by same agents
- Avoid hypovolemia—must avoid diuretics as much possible
- Avoid increased inotrope—avoid exercise, avoid straining, avoid digitalis and avoid nitrates
- Pacemaker: It stimulates the right ventricle (RV) first thus it gives a little extra time for left ventricle to fill

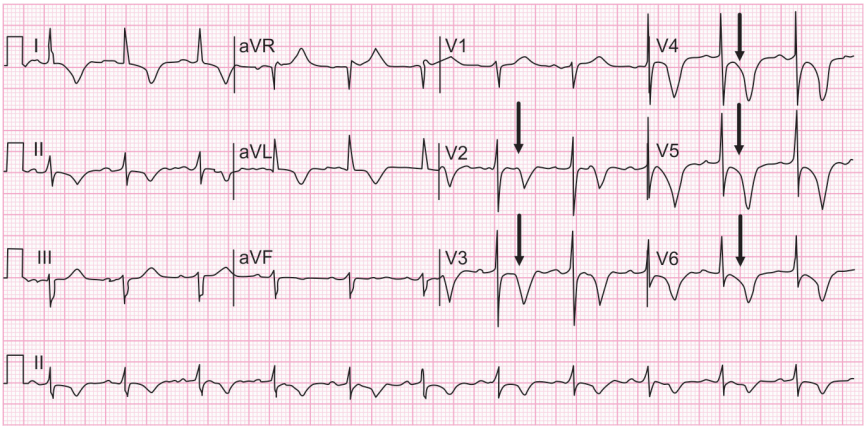


Fig. 1: Electrocardiogram shows left ventricular hypertrophy and myocardial infarction

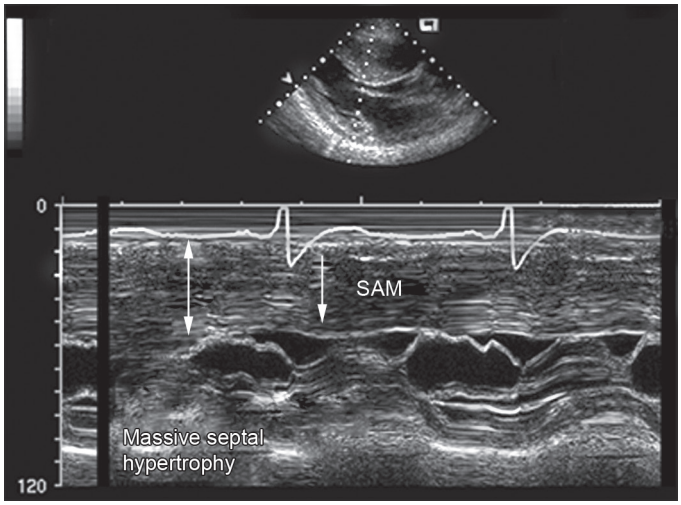


Fig. 2: Echocardiogram in hypertrophic cardiomyopathy showing typical "systolic anterior motion of anterior mitral leaflet, severe left ventricular hypertrophy and narrow left ventricular outflow tract

- Implantable cardioverter-defibrillator with pacemaker to protect from sudden cardiac death
- Sotalol therapy to control ventricular arrhythmia and atrial fibrillation (which is very poorly tolerated by these patients).

Surgical

- Septal myectomy to relieve the outflow obstruction
- Alcohol ablation of septum—inject alcohol in the septal perforator branch of left anterior descending
- Cardiac transplant—in survivors of sudden cardiac death or with advanced symptoms

Alcoholic cardiomyopathy is quite common. Beer drinkers' cardiomyopathy is due to cobalt toxicity (cobalt was used to give beer a good "head"). It improves remarkably with strict abstinence.

Dr William Meadows, a professor in author's university in Chicago, described postpartum cardiomyopathy. It is also quite common and may occur up to few months after childbirth.

Author had only one case of Chagas disease, who was the father-in-law of one of my colleague. He was from South America. His serum titers were diagnosed. It produced severe diastolic dysfunction (diastolic heart failure).

Diabetic cardiomyopathy and viral myocarditis is very commonly seen in clinical practice.

Author has only seen few cases of familial cardiomyopathy. He had only one case of confirmed hemochromatosis causing congestive heart failure (It is so rare!).

Ischemic cardiomyopathy is extremely common and physicians will see a lot of them.

Doxorubicin (Adriamycin) is used in many cancers. The cardiac toxicity is dose related and irreversible. When the total cumulative dose exceeds 500 mg/m^2, cardiotoxicity is highly eminent.

13

CHAPTER

Acute Circulatory Collapse (Shock)

Jayant C Bhalerao

DEFINITION

This is a catastrophic condition where the cardiac index drops acutely below 1.5 L/min/m^2 leading to extreme hypoperfusion. Hallmark is severe hypotension (40% below basal level), oliguria (less than 0.5 cc/kg/hr), mental confusion and restlessness.

HINSHAW AND COX CLASSIFICATION

Cardiogenic Shock (Vasoconstricted Shock)

It results from massive acute myocardial injury and/or acute electrical failure, e.g. cardiac arrest. It has the worst prognosis of any known medical condition with mortality rate over 80% in the best of hands. Hypotension is caused by loss of contractile force in the heart. Peripheral vascular resistance is markedly increased due to compensating sympathetic activation. This is how it is differentiated from septic shock where the peripheral resistance is low due to vasodilatation caused by endotoxemia. It is also referred as "vasoconstricted shock".

Septic Shock (Endotoxic Shock, Vasodilated Shock or Distributive Shock)

Both gram-positive and gram-negative endotoxemia can cause septic shock. Endotoxins dilate the peripheral vessel, which is the cause of hypotension; that is why it is also called vasodilated shock.

Hypovolemic Shock

Many disease states may culminate in causing hypovolemic shock. Loss of volume by gastrointestinal loss, burns, crush injury, etc. may deplete blood

volume and cause hypotension. It is easy to diagnose and treat. It carries by far the best prognosis.

Obstructive Shock

Conditions that restrict left ventricular filling like massive pulmonary embolism, cardiac tamponade and tension pneumothorax cause shock.

PATHOPHYSIOLOGY OF SHOCK

There are four phases of shock. They are not sequential by any means:

1. Initial phase: Severe hypotension causes tissue hypoxemia leading to cell membrane damage. It increases its permeability and thus lactic acidosis ensues.
2. Compensatory phase: Body triggers neural, hormonal and biochemical mechanisms to restore homeostasis.
   - Lactic acidosis leads to hyperventilation in an effort to eliminate CO_2
   - Sympathetic system stimulation causes tachycardia and vasoconstriction in order to increase the blood pressure (Cushing reflex)
   - Renin-angiotensin system activation leads to aldosterone production. This helps kidneys to conserve water and sodium to increase the blood volume.
3. Progressive phase: Compensatory mechanisms begin to exhaust and fail. Tissue permeability increases and fluid begins to migrate in to the extracellular space (the so-called "third space").
4. Refractory phase: Organs begin to fail in a domino-like fashion and death ensues.

GOALS OF MANAGEMENT

- Immediate fluid replacement: 1–2 L in 10 minutes while Swan-Ganz catheter is being placed in
- Packed red cell transfusion to maintain hemoglobin over 10 g
- Keep mean blood pressure over 60 mm Hg
- Maintain urine output over 0.5 cc/kg/hr
- Keep central venous pressure between 8–10 mm H_2O
- Maintain oxygenation

Unfortunately, it is easier said than done. With the exception of hypovolemic shock, all other causes of shock are not easily amenable to any of these measures, cardiogenic shock being the worst.

DRUG THERAPY

- Intravenous dobutamine 5–20 mg/kg/min drip
- Broad-spectrum antibiotic therapy without waiting for blood culture results

- Intravenous levophed (norepinephrine) drip: 8–12 mcg/min till blood pressure over 60 mm Hg then maintenance dose of 2–4 mcg/min
- Left ventricular assist device (LVAD): In cardiogenic shock, virtually all other measures are an exercise in futility. They rarely work long enough for the damaged heart muscle to heal. With the advent of LVAD, author thinks efforts should be directed towards these modern devises, which can take over the mechanical function long enough to let the heart heal, just like a mechanical ventilator does in respiratory failure.

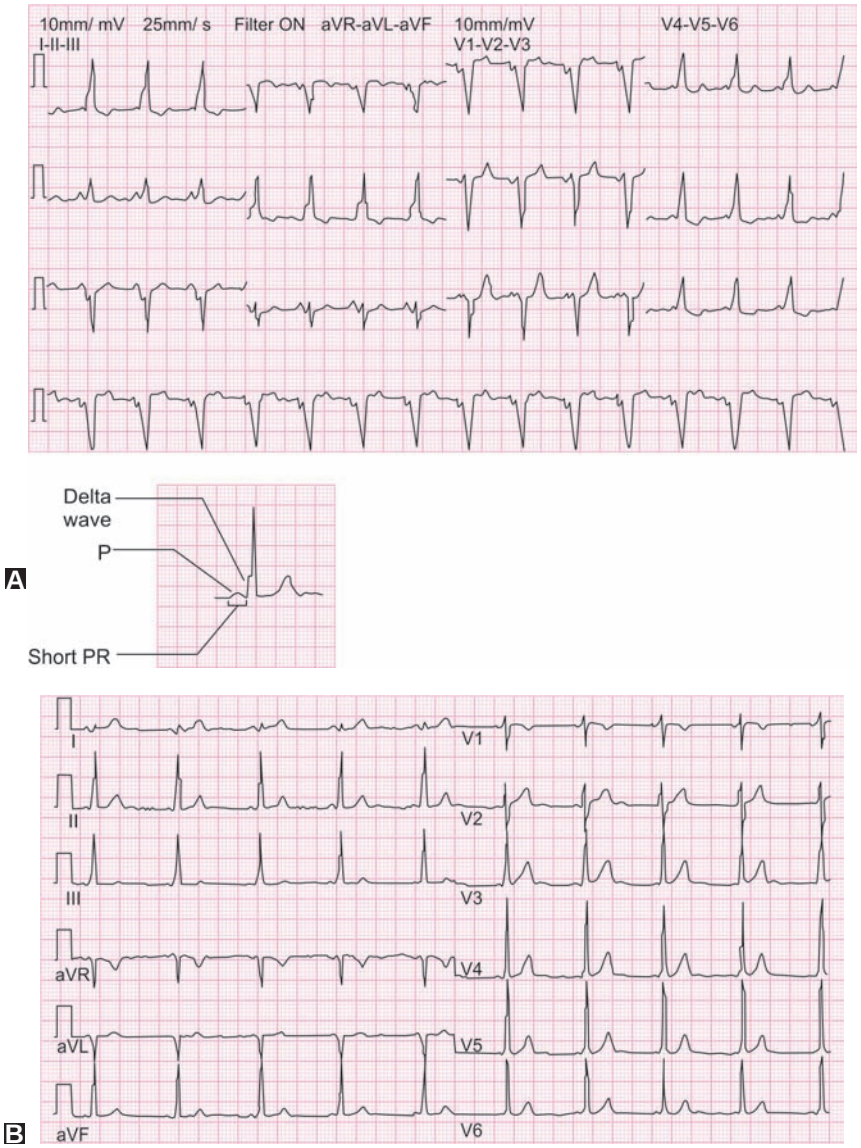
14 CHAPTER

Atrial Arrhythmia

Jayant C Bhalerao

Atrial fibrillation is the most common arrhythmia in clinical practice. Although atrial fibrillation, atrial flutter and paroxysmal atrial tachycardia (PAT) all originate from atria, atrial fibrillation is a completely different breed of animal than atrial flutter and PAT. Everything about it is different. Its etiology, pathology, physiology, clinical course, prognosis and management are different.

- All atrial arrhythmias except atrial fibrillation need atrioventricular (AV) node for its genesis and sustenance. Atrial fibrillation does not need AV node for its existence
- Atrial fibrillation is caused by increased automaticity where as PAT and atrial flutter is caused by reentry mechanism
- Thromboembolic complications are part of atrial fibrillation, whereas never in PAT and only very rarely in atrial flutter
- Atrial fibrillation is almost always associated with underlying structural problem with atria or heart whereas it is not so with others except Wolff-Parkinson-White (WPW) syndrome (Figs 1A and B)
- Treatment options, need for anticoagulation, urgency in obtaining resolution is different in atrial fibrillation. Before a patient with atrial fibrillation is discharged from physician's care, there must be a long-range plan of action properly thought out
- It takes a very larger voltage (e.g. 200 W/sec) to convert atrial fibrillation compared to just 25 W/sec or 50 W/sec for PAT or atrial flutter
- Maintenance drug therapy is always needed in atrial fibrillation but not always in PAT or atrial flutter
- Underlying, long-standing hypertension is a common denominator in atrial fibrillation but not so in others
- Atrial fibrillation is not easily amenable to ablation therapy whereas, PAT and atrial flutter can be cured rather easily by catheter AV node ablation
- Nine out of ten atrial fibrillation starts in left atria, whereas nine out of ten of the PAT and Atrial flutter starts in right atria, making it easily amenable to ablation without needing to invade the arterial (left) side of the heart for prolonged period



Figs 1A and B: Electrocardiograms of Wolf-Parkinson-White syndrome (often associated with paroxysmal atrial tachycardia)

- Magnesium therapy is hugely beneficial in atrial fibrillation but not so in other atrial arrhythmias.

In my opinion, the difference between atrial fibrillation and other atrial arrhythmias is same as the difference between a tiger and a cat.

Physicians have to learn to treat atrial fibrillation with a lot of respect. It has major consequences if handled haphazardly. Every department must have a published standard protocol for treating atrial fibrillation.

Having said that, let us discuss atrial fibrillation.

ATRIAL FIBRILLATION

Atrial fibrillation is a disease of "aging and stretching". Its incidence rises rapidly beyond age of 50 years.

- Aging makes the left ventricle noncompliant (stiff) even without associated hypertension. This dilates the left atria creating stretch marks in atrial wall just like pregnancy does to abdominal wall
- Other causes, such as long-standing hypertension, mitral or aortic valve disorders and pulmonary hypertension, from any cause, such as chronic obstructive pulmonary disease (COPD), pulmonary embolism, pneumonia, congenital heart defects, coronary artery disease, and post-coronary artery bypass graft (CABG), create the same situation
- Cardiac stimulants such as thyroid hormone excess, alcohol and drug abuse, nicotine and diet pills all increase atrial automaticity thus predisposing to atrial fibrillation
- Pericardial disease cause direct irritation to atrial wall thus increases autonomy.

Origin of Atrial Fibrillation

Atrial fibrillation typically originates from around the openings of the pulmonary veins in the posterior wall of left atria. Enhanced automaticity is the usual cause. When this ectopic atrial rhythm crisscrosses through a stretched and scarred atrial wall, hundreds of circular movements take place each giving rise to an electrical activity. Hundreds of mature and immature P waves are formed; some manage to reach the AV node and go through to elicit a ventricular response (QRS). Since there is no regular pattern to this, ventricular activity (i.e. pulse or heart rate) is "irregularly irregular" (Fig. 2). If all the atrial activity were to reach the AV node and thus the ventricle, patient could not survive such rapid heart rate. Nature has provided AV node as a filter. By virtue of its refractory period, it is responsive only during certain part of the electrical cycle.

Classification of Atrial Fibrillation

For clinical descriptive ease, atrial fibrillation is classified as follows:

- First detected atrial fibrillation
- Paroxysmal atrial fibrillation—usually self terminates within 7 days
- Persistent atrial fibrillation—lasts longer than 7 days (up to 3 months)

Permanent or chronic atrial fibrillation—duration over 1 year

Chronic atrial fibrillation rarely converts to and stays in sinus rhythm, and therefore not worth rhythm control. Only rate control is needed in such cases.

First detected atrial fibrillation and paroxysmal atrial fibrillation require oral antiarrhythmic agents. In such cases rhythm control is justified even though studies have failed to show improvement in ultimate prognosis over just rate control.

To summarize, acute cases of less than 1-year duration (preferably less than 3 month) deserve attempts to rhythm control along with rate control, whereas chronic cases (over 1 year duration) should be selected for rate control only.

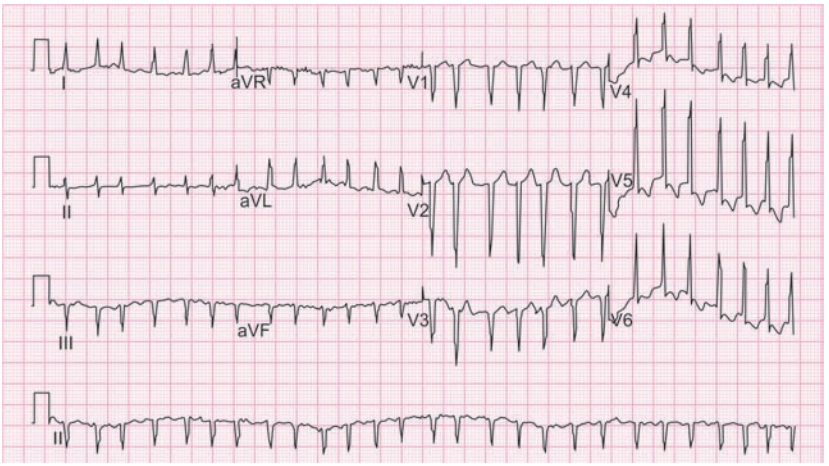


Fig. 2: Electrocardiogram showing rapid atrial fibrillation, left ventricular hypertrophy with strain

Rate Control

- Beta-blockers
- Digoxin
- Magnesium 400 mg by mouth daily
- Calcium channel blockers—verapamil and cardizem.

Rhythm Control

Chemical Cardioversion (*i.e. Medicines*)

- Intravenous (IV) ibutilide (Corvert) 1 mg dissolved in 50 cc saline given over 10 minutes is ideal for acute onset atrial fibrillation like post-CABG.
- Sotalol 80 mg (twice a day by mouth) is a class III agent like amiodarone along with a beta-blocker property
- Amiodarone either IV or oral 200–400 mg once a day
- Magnesium either oral or IV can significantly improve success rate
- Watch for QT prolongation when using these drugs
- Always make sure the potassium level is above 4.0 mEq/L.

Long-Term Amiodarone Therapy

There are six major things to remember when amiodarone is used on a chronic basis:

1. It prolongs prothrombin time (PT/INR) so the dose of warfarin has to be decreased
2. It causes pulmonary fibrosis therefore get pulmonary function tests (PFT) and diffusion study and chest X-ray every 6 months
3. It causes decline in cognitive (intellectual) function
4. It affects thyroid functions therefore check thyroid-stimulating hormone (TSH) and free thyroxine (T4) every 6 months
5. It prolongs QTc interval, so check electrocardiogram every 6 months. Watch for torsade de pointes
6. It colors the nails and skin blue, and increases photosensitivity.

Electrical Cardioversion

Give IV magnesium sulfate 1 gm dissolved in 50 cc saline given over 30 minutes before elective cardioversion. It greatly improves success rate.

Compared to PAT and atrial flutter, which need hardly 25–50 W/sec, atrial fibrillation generally requires much bigger energy to convert. Always start with 200 W/sec and, if needed, go to 400 W/sec. If it fails, success is less likely.

All cardioversions especially elective electrical cardioversion must be done either in intensive critical care unit (ICCU) or preoperative holding area where all equipment of monitoring and resuscitation is readily available with adequate support staff and a nurse anesthetist to administer IV Brevital (methohexital sodium).

There is a small risk of dislodging a thrombus during cardioversion; therefore all elective cases should be adequately anticoagulated for 3 months prior to the procedure. Patient must be properly informed of this consequence. As stated earlier, even rate control is enough to treat such patients with same or better prognosis. The only advantage of rhythm control is in cases of CHF and hypertrophic cardiomyopathy where atrial kick is of significant value to improve the cardiac output.

Ablation Therapy for Atrial Fibrillation

Using three-dimensional mapping procedures, areas of electrical anomaly are isolated. In 9/10 times, it is located around the opening of four pulmonary veins in posterior wall of left atria. Using a catheter guided in to the left atrium via transseptal approach, radiofrequency waves are delivered to cauterize (ablate) the tissue around all four pulmonary vein openings. This disrupts the offending electrical activity in 8/10 cases. The procedure is lot more difficult and prolonged (compared to the ablation for flutter or PAT which is usually around the opening of inferior vena cava which is very easy to access and ablate). Since it is in the arterial side of the heart for 5–6 hours, chances of thromboembolism are high. Furthermore, the procedure is only helpful for patients with paroxysmal atrial fibrillation who have no valvular or other structural heart problems. It does not help in chronic atrial fibrillation where atrial fibrillation has been there for over a year. All in all, much needs to be accomplished in this area.

Surgical Correction (Maze Procedure)

In patients where atrial contribution to cardiac output is of overbearing importance, maze procedure can be considered. It is an open heart surgery and rather time consuming. Success rate are 50-50. In this procedure atria are opened and with the surgical blade intima is cut in a maze-like fashion hoping to interrupt the atrial electrical activity (Fig. 3). It is best suited for patient undergoing other surgical procedure such as CABG or heart valve surgery.

Thromboembolism in Atrial Fibrillation

Since the atria are not contracting but just quivering, blood tends to stagnate. This leads to thrombus formation, which generally forms in the crevasses like the atrial appendage. Often they dislodge and create systemic embolism

leading to strokes, blindness and gangrene depending on where it migrates. Celiac artery embolism causes sudden extreme abdominal pain and rapidly leads to bowel gangrene. Any patient with atrial fibrillation with acute abdominal pain must be considered for urgent abdominal exploration unless other etiology is proven quickly.

Lifelong anticoagulation is therefore essential. In very old and frail elderly patients, the risk of complications from anticoagulation like retroperitoneal hemorrhage may outweigh the risk.

Risk of embolism is less in patients with "lone atrial fibrillation" who are typically less than 60 years of age and have no underlying disease even hypertension. Embolic risk is highest in patients with valvular defects like mitral stenosis and they always need anticoagulation. Nonvalvular atrial fibrillation may be treated with newer agents such as Pradaxa (dabigatran) 150 mg once a day. It is a direct thrombin inhibitor. There is no need for monthly prothrombin time, which is a drawback with warfarin therapy.

Special Consideration

Some patients are extremely symptomatic with atrial fibrillation. Ventricular irregularity is overwhelmingly intolerable to such patients. In such cases, if the attempts to cardioversion or ablation have failed, one may consider to completely destroy the AV node with catheter ablation and implant a permanent pacemaker. Author recall just one patient who fell in this category.

Symptoms

- Palpitation, dizziness, chest pain, dyspnea usually accompany atrial fibrillation. However, many times it is an accidental diagnosis in asymptomatic patient

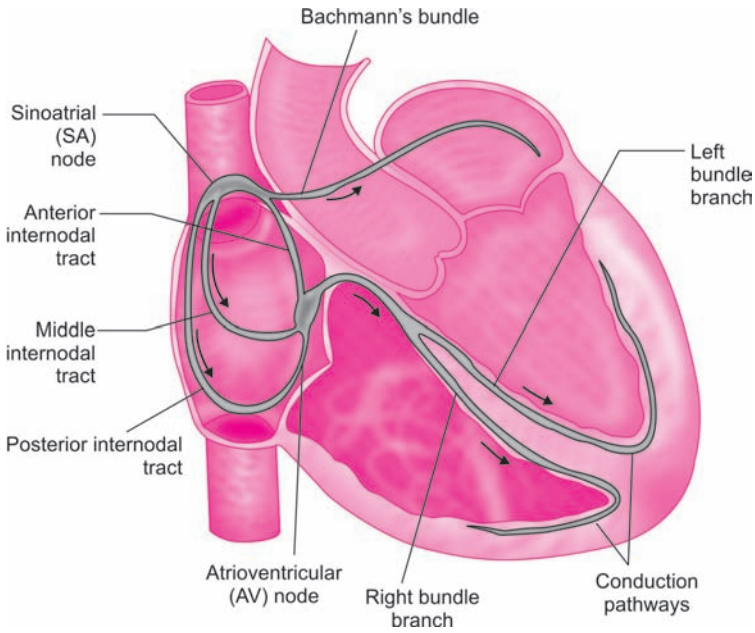


Fig. 3: Electrical conduction system of the heart

- Embolic event may be the first event before the atrial fibrillation is diagnosed.

Diagnosis

- Clinical exam in most cases is enough to diagnose an irregularly irregular pulse
- Electrocardiography is confirmatory.

Investigations

- Blood work up to include CBC, thyroid functions, electrolytes, kidney functions and metabolic profile, prothrombin time (and partial thromboplastin time)
- Electrocardiography, chest X-ray
- Echocardiogram to look for valvular heart disease, LV function
- Transesophageal echocardiogram to look for thrombus in atrial appendages.

Standard Protocol for Managing Atrial Fibrillation

- If the duration is less than 3 months, try to cardiovert either chemically or electrically
- Rate control is needed regardless of the duration by beta-blockers such as atenolol or metoprolol 50–100 mg daily. Add digoxin 0.125 mg daily if needed
- Add sotalol 80 mg twice a day preferably in hospital under telemetry monitoring. It is also available in long-acting form, which can be used once a day (amiodarone alternatively 200–400 mg once a day)
- Warfarin 5 mg daily at night, adjust dose depending on PT/INR
- Secondary causes to be treated accordingly
- Aspirin and antiplatelet therapy is clearly ineffective
- Chronic atrial fibrillation needs rate control and lifelong warfarin therapy.

PAROXYSMAL ATRIAL TACHYCARDIA: ATRIOVENTRICULAR NODE REENTRANT TACHYCARDIA

Paroxysmal atrial tachycardia is usually seen in patients without any underlying heart disease. It is a rather benign tachycardia caused by reentry in AV node initiated by a premature atrial contraction (PAC). It is easy to diagnose and easy to treat (Fig. 4). Sometimes, the reentry occurs at the accessory electrical pathway as in WPW syndrome. Antegrade conduction usually goes down the slow pathway and the retrograde conduction via the fast pathway. Typically, a PAC goes down the slow pathway and returns back via the fast pathway. This creates a circus movement (Fig. 5). The tachycardia terminates when the conduction block occurs in slow pathway either spontaneously or due to vagal activation or drug intervention. Usually the heart rates are around 150–220 beats per minutes. In younger patients and in those with WPW syndrome, the heart rates may be even higher.

Symptoms

Patient presents with sudden rapid palpitations with spells of cough, dizziness and anxiety.

Use of cardiac stimulants, such as caffeine, alcohol, street drugs, etc. may precipitate the tachycardia but no stimulus is needed. It usually lasts for few minutes to few hours and eventually terminates even if no treatment is given.

Treatment

- Atrioventricular node ablation is the mainstay of treatment. It "cures" the condition in over 99% cases
- Medications: Beta-blockers are the safest. Other drugs line, such as calcium channel blockers, digoxin that prolong AV delay, may be dangerous, if patient has WPW syndrome, as these drugs increase the conduction velocity in accessory pathway (Fig. 5)
- Avoidance of cardiac stimulant is needed.

ATRIAL FLUTTER

This is also a reentry tachycardia, but the site of reentry is right atrial wall instead of AV node. It is common after CABG and may persist for weeks. In "typical" atrial flutter, the reentry is counter-clockwise going down the right atrial free wall and coming up the atrial septum. The P waves are typical sawtooth appearance (negative) in leads II and III (Fig. 6).

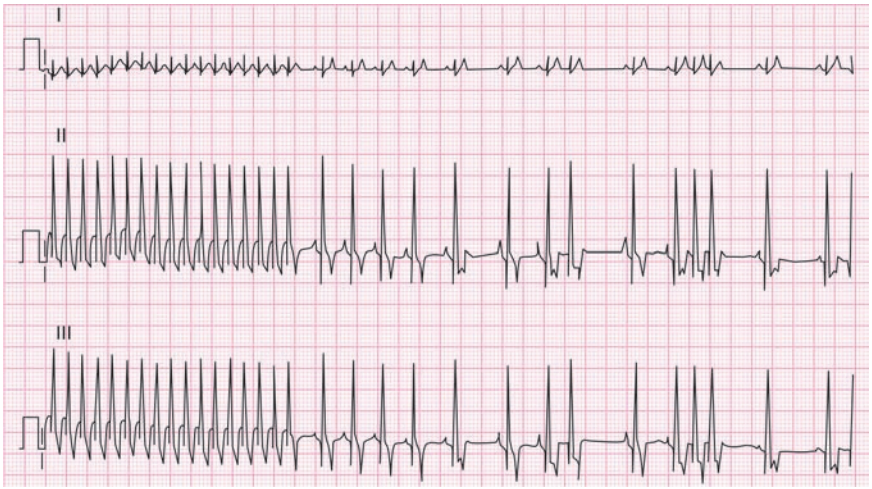


Fig. 4: Electrocardiogram showing paroxysmal atrial tachycardia. Note, the P waves are not seen; they are hidden within the QRS. A premature atrial contraction starts this narrow QRS tachycardia

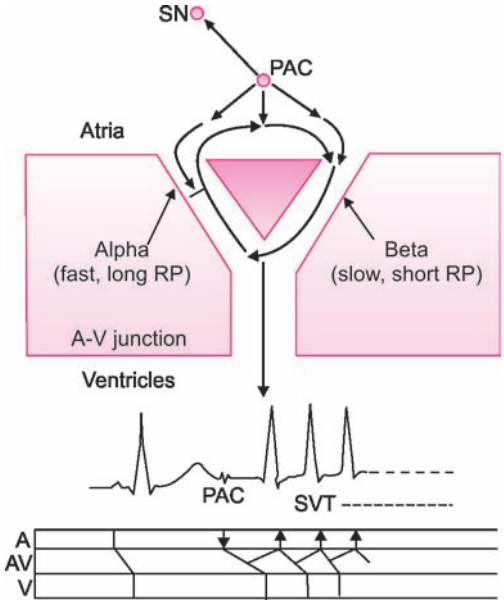


Fig. 5: Diagrammatic representation of underlying defect in re-entry tachycardia

In "atypical" atrial flutter, the exact opposite happens. The P waves are positive in lead II and III.

"Typical" atrial flutter is the most common variety.

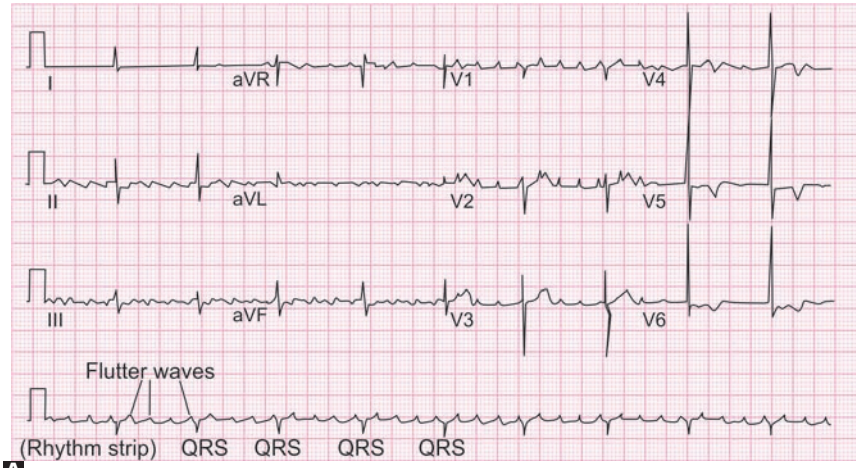
Diagnosis

Electrocardiography

Electrocardiogram shows saw-tooth P waves in lead II and III. Atrial rate is 240–300 beats per minutes and ventricular rate is around 150 beats per minutes (2:1 block). If the ventricular rate is exactly 150 beats per minutes and stays so for a long time, it is atrial flutter unless proven otherwise. Use vagal stimulation by carotid massage to slow the ventricular rate and physician will be able to see the typical flutter waves.

Treatment

- Medications: Digoxin, beta-blockers or calcium channel blockers, or Beta-pace (sotalol) or amiodarone
- Elective cardioversion: Use 25–50 joule energy for cardioversion
- Percutaneous radiofrequency ablation: Ninety-five percent success rate and it should be first-or secondline of treatment
- Need for long-term anticoagulation is debatable



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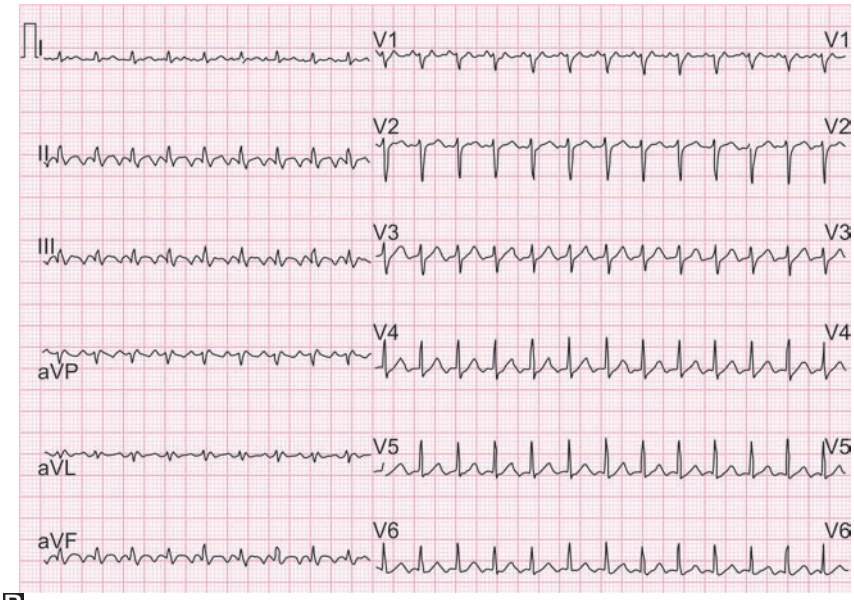

B

Figs 6A and B: Electrocardiogram in "typical" atrial flutter. Note: negative, saw-tooth P waves in leads II and III and positive P waves in lead V1. This ECG also represents the principle that if the ventricular heart rate is perfect 150/min, suspect atrial flutter with 2:1 block. Carotid massage will slow the ventricular rate and uncover the hidden P waves

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15 CHAPTER

Ventricular Arrhythmia

Jayant C Bhalerao

PREMATURE VENTRICULAR CONTRACTIONS

Causes

- Isolated premature ventricular contractions (PVCs) are usually due to cardiac stimulants such as caffeine, nicotine, stress, alcohol, diet pills, etc.
- Sometimes they are harbingers of underlying coronary artery disease
- Mitral valve prolapse syndrome
- Electrolyte disturbance such as hypokalemia and hypomagnesemia

When PVC alternates with a normal QRS, it is called bigeminal PVC and if it occurs after every two normal QRS, it is called trigeminal PVC and so on. They may be in pairs or triplets. Three PVCs in a row in called a "run".

Symptoms

Most patients are unaware of their presence but some are very symptomatic. Fear of the unknown makes it worse; therefore in highly sensitive patients, it is always better to investigate fully. It serves as a remedy for them.

Investigations

- Electrocardiography (ECG) and 24 hour Holter recording: to determine frequency, rule out prolonged QTc (Fig. 1)
- Electrolytes to rule out hypokalemia, hypomagnesemia
- Stress test to rule out underlying myocardial ischemia
- Echocardiogram to rule out mitral valve prolapse.

Treatment

- Avoid stimulants
- Reassurance
- Beta-blockers
- Do not use antiarrhythmic drugs [cardiac arrhythmia suppression trial (CAST) study]

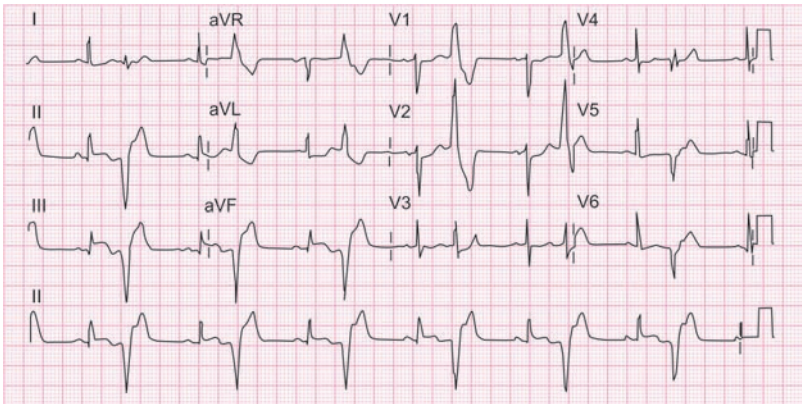


Fig. 1: Electrocardiography showing acute inferior wall myocardial infarction with prolonged QT and frequent PVCs (R-on-T phenomenon)

VENTRICULAR TACHYCARDIA

Based on morphology, ventricular tachycardia (VT) can be classified as: (1) accelerated idioventricular rhythm, (2) monomorphic VT, (3) polymorphic VT and (4) ventricular fibrillation

Accelerated Idioventricular Rhythm

It is usually caused by previous scar from infarction. It is monomorphic but the rate is usually below 100 beats per minute. It is caused enhanced automaticity. It is benign and does not require treatment.

Monomorphic Ventricular Tachycardia

It is caused by reentry phenomenon therefore all the complexes are alike and the rhythm is regular. It is benign. It is often seen in young adults, sometime idiopathic or genetic but at times due to stimulants. No treatment is generally needed but in cases where it is sustained and symptomatic, ablation therapy especially with the new "remote magnetic ablation". Success rate is almost 85%.

There is one variety of monomorphic VT, which deserves special mention. It is called right ventricular (RV) outflow tachycardia. It is caused by stimulation in the RV outflow tract as author often see during right heart catheterization or pacemaker insertion. This VT has a characteristic ECG pattern: upright wide R waves in V1–V6, but the R waves gradually decrease in amplitude after V3–V6 and the QRS is negative in lead I and aVL. It is benign; although it happens when physicians are first doing right heart catheterization; it is scary as well. It goes away as soon physician pull out the catheter or the pacemaker electrode. No treatment is needed.

Polymorphic Ventricular Tachycardia

This is a dangerous type of ventricular tachycardia and is often seen in patients with previous myocardial infarction or ischemia.

Causes

- Myocardial infarction old or new with ongoing ischemia. Polymorphic VT or ventricular fibrillation in the early course of acute myocardial infarction or angioplasty has little prognostic significance. Many of these are due to reperfusion. It is the late onset arrhythmias that affect prognosis (Figs 2 and 3)
- Drug toxicity
- Prolonged QT states, congenital or drug induced or electrolyte disturbance

One of the examples of polymorphic VT is called torsades de pointes.

Torsades De Pointes

This dangerous polymorphic VT is relatively common and every doctor should be very familiar with what causes it and how it is treated, because there are some common elements in it. When class I antiarrhythmic drugs, such as quinidine and procainamide, were in common use in the 1970s and 1980s, author saw a lot of them. Thank goodness! They are no longer in use. Quinidine was by far the worst.

Prerequisite Factors Associated with Torsades De Pointes

- Prolonged QTc more than 600 ms (Fig. 4)
- Bradycardia
- Drugs (commonest cause of prolongation of QT interval)
- Hypomagnesemia
- Hypokalemia

Prolonged QT Interval

Acquired causes:

This is by far the commonest cause of prolongation of QT interval and thus of torsades de pointes. Common offenders are as follows:

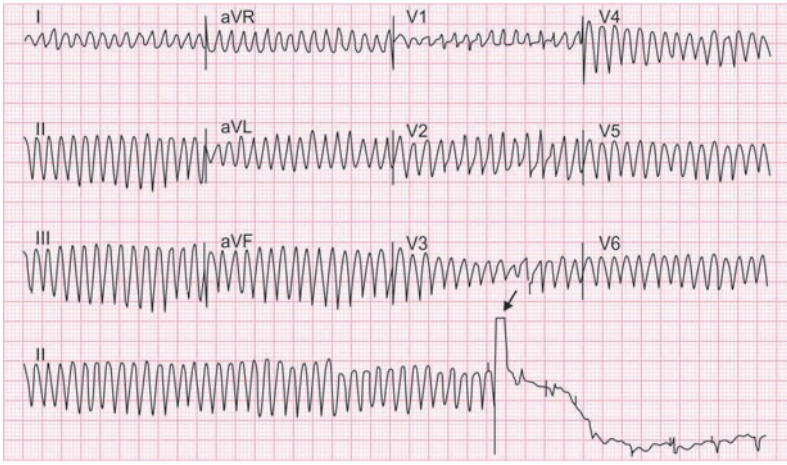


Fig. 2: Polymorphic ventricular tachycardia

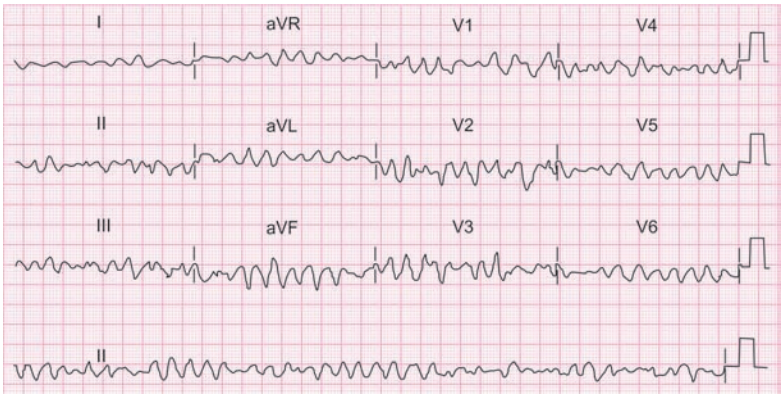


Fig. 3: Electrocardiography showing ventricular fibrillation

- Class I antiarrhythmic drugs such as quinidine and procainamide and flecainide (no longer in use)
- Class III antiarrhythmic drugs such as Sotalol, amiodarone and ibutilide
- Antibiotics such as erythromycin and antifungal drugs
- Antipsychotic drugs such as haloperidol
  Some antihistaminic (no longer in use)

Even though amiodarone constantly causes prolongation of QT interval, for some reason, torsades de pointes is not as prevalent as was with quinidine.

Congenital causes:
Familial "long QT syndrome" an autosomal dominant disorder, very common and must be carefully investigated in patients with family history of sudden death (Figs 5A to C).

Brugada syndrome:
Described in 1992 by two Spanish cardiologist brothers; this is a genetic disorder associated with demonstrable pathology in the right ventricle. It is the leading cause of sudden death due to ventricular fibrillation in Thailand and Laos.

Genetic defect: there is a genetic mutation that regulates sodium channel in myocytes. The gene, SCN5A is located on the short arm of the third chromosome (3p21). Over 160 mutations have been reported so far.

Electrocardiography shows persistent ST elevation in V1–V3 leads with right bundle branch block (RBBB) appearance, but in contrast to the conventional RBBB, it does not have the terminal S wave in lateral leads V5–V6.

- Brugada syndrome is common cause of sudden death in athletes and common in Southeast Asians (Figs 5A to C). Also note the absence of terminal S wave in V5–V6. It is treated by implantable cardiac defibrillator.
- Takotsubo cardiomyopathy: stress-induced cardiomyopathy

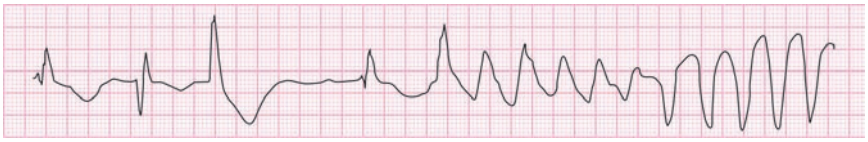
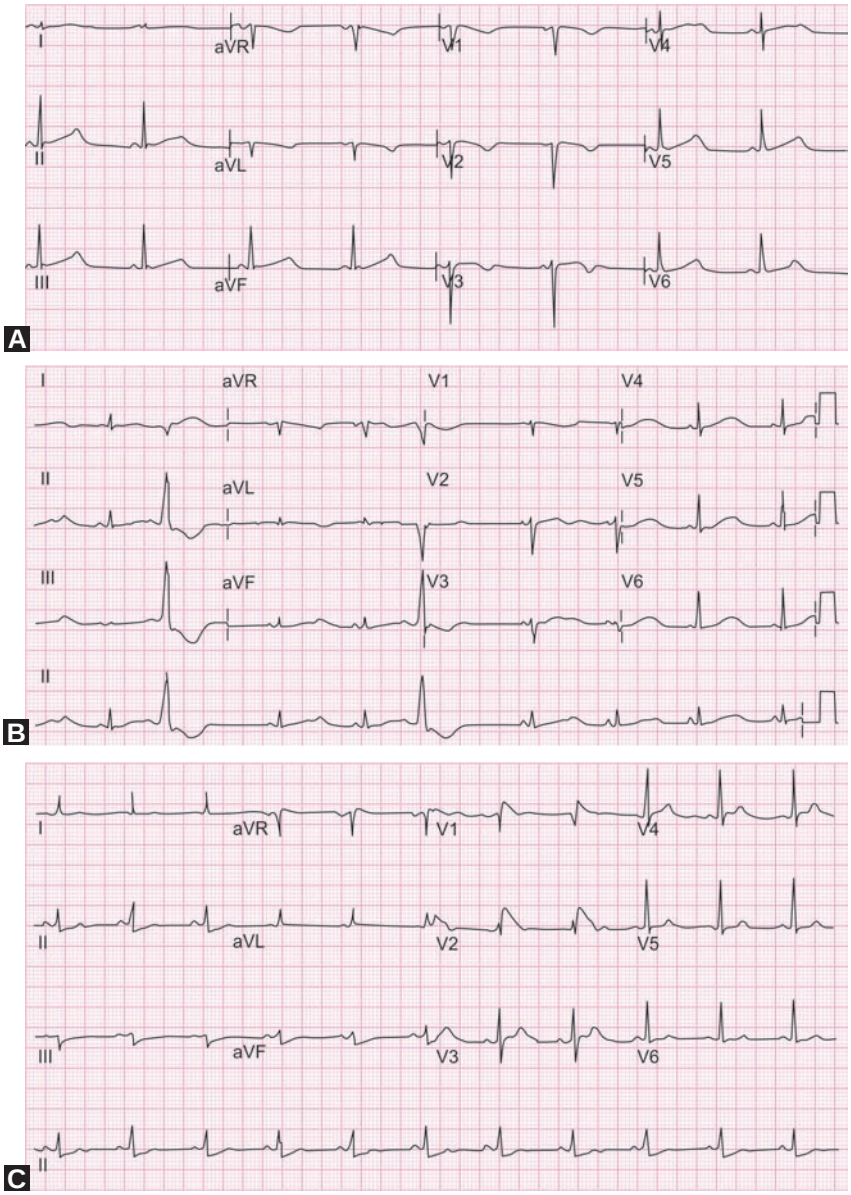


Fig. 4: Prolonged QT interval



Figs 5A to C: Congenital prolongation of QTc

All acquired conditions that prolong QT interval either decrease the outward flow of potassium current or interfere with the inward current of sodium and calcium currents.

Bradycardia

Bradycardia is virtually always present. Slower rate makes it easier for the depolarization current to wander off and create reentry.

Hypokalemia, Hypomagnesemia and Hypocalcemia

Role of magnesium in the genesis of torsades de pointes is very important. Hypokalemia is well understood by most but magnesium deficiency is often overlooked. Unless intravenous (IV) magnesium is infused, it will be very difficult to control torsades de pointes. Torsades de pointes is three times more common in women and white people.

Treatment of Torsades De Pointes

- Start cardiopulmonary resuscitation (CPR). Send blood for electrolytes and magnesium, but don't wait for the results
- Infuse IV magnesium stat; 1 gm magnesium sulfate dissolved in 50 cc normal saline give over 10 minutes and repeat in 10 minutes
- Add 80 mEq KCl to 1 liter normal saline and infuse 100 cc/hr
- Stop all offending drugs, if not sure, stop all existing drugs
- Ventilate
- Swan-Ganz pacing catheter can be quickly inserted via subclavian vein for overdrive pacing which is quite effective.

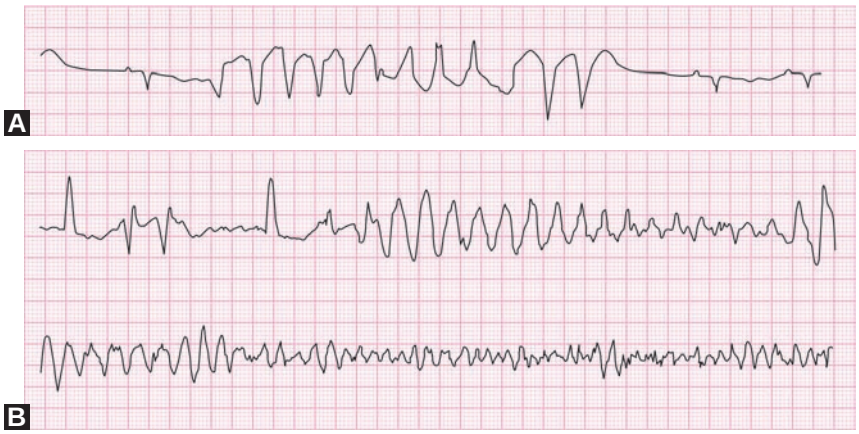
Usually most patients will survive even though things look very dire while physicians are treating them. Author remembers shocking a patient over 50 times over 2 hours before things settled down.

Educate patient about the offending drug. Obtain genetic counseling for familial long QT syndrome cases. Screen all family members.

Implantable cardioverter-defibrillator is a true lifesaver in congenital long QT syndrome patients.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA/ CARDIOMYOPATHY

It is a cardiomyopathy (primary heart muscle disease) caused by a genetic disorder characterized by diffuse fatty and fibrous tissue infiltration in the right



Figs 6A and B: Electrocardiogram in torsades de pointes

ventricular inflow track, apex and the infundibulum and is associated with peculiar ventricular tachycardia which looks like complete left bundle branch block (LBBB) with marked left axis deviation. The infiltrative defect leads to delayed activation, which is pivotal for re-entry and thereby ventricular tachycardia (Figs. 7 and 8). It is a common cause of sudden death in young athletes. The ECG criteria (Fig. 9A and B):

- Prolonged terminal activation duration in V1–V3, an indicator of activation delay.
- Ventricular tachycardia with complete LBBB morphology with superior axis.
- Multiple ventricular tachycardia morphology.

Seventy percent of the cases have mutations in genes encoding desmosomal proteins (PKP2 mutation) in chromosome 14. Myocardial biopsy is diagnostic.

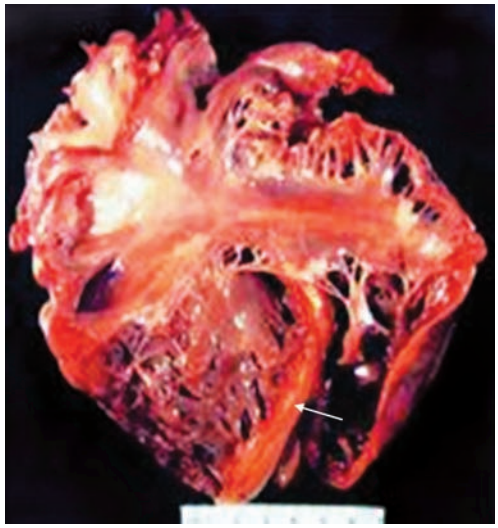


Fig. 7: Autopsy specimen of right ventricle showing diffuse fatty infiltrates in inflow track, apex and infundibulum

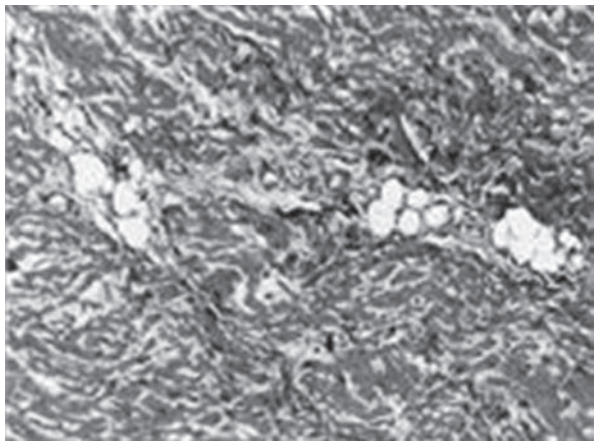
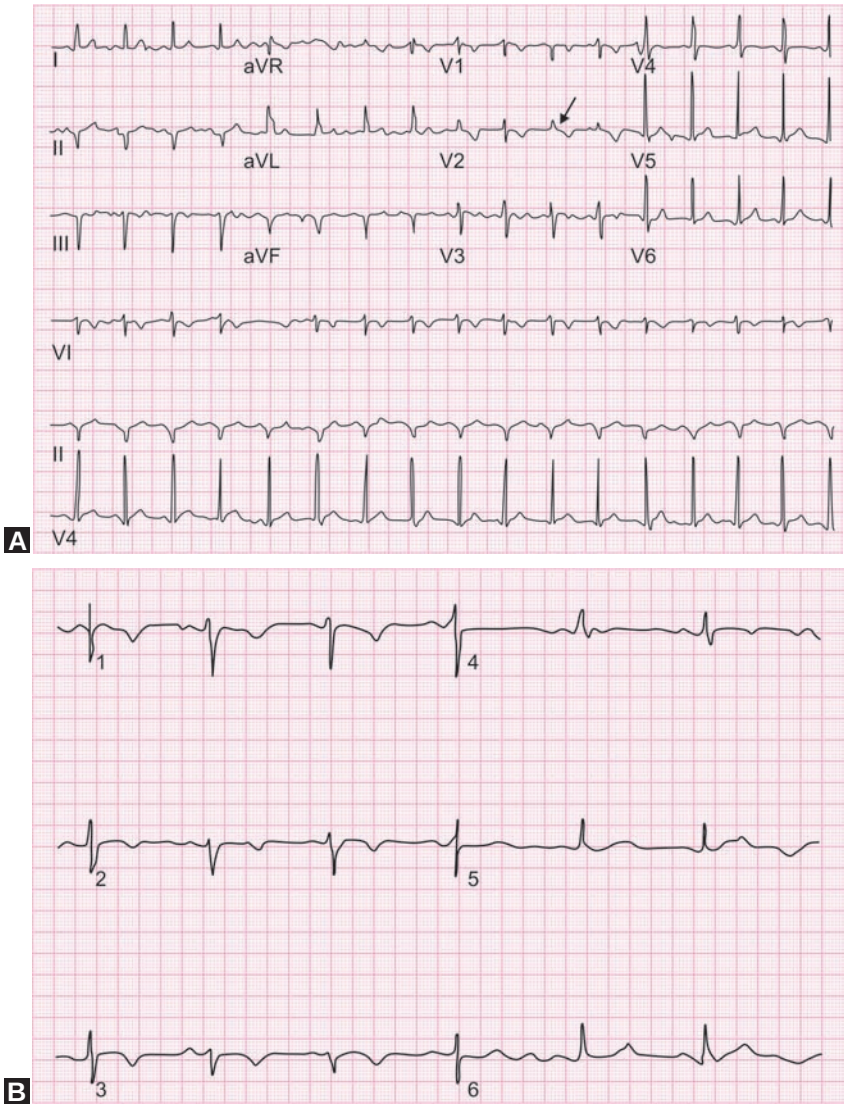


Fig. 8: Microscopic evidence of diffuse fatty and fibrous infiltrate in right ventricle



Figs 9: Electrocardiography in arrhythmogenic right ventricular dysplasia/cardiomyopathy

Exercise induced ventricular tachycardia is due to high catecholamine release during exercise.

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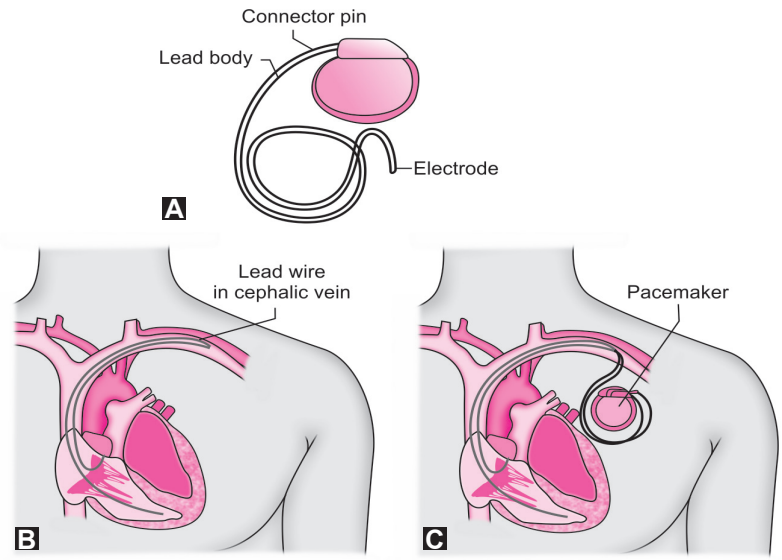
16 CHAPTER

Artificial Pacemakers

Jayant C Bhalerao

Artificial pacemakers are devices used to maintain adequate heart rate. They have two components: an electrode which delivers electricity to heart muscle and a battery (pulse generator) made of inert titanium (to prevent rejection) and a lithium battery good to last for 6–8 years or more (Figs 1A to C). Nowadays many of these pacemakers also have a defibrillator in the same unit (antitachycardia device). There are still other units, which are being used in treatment of advanced heart failure to improve synchronization of both ventricles.

With aging, the electrical system of the heart begins to degenerate. If only the sinoatrial (SA) node is degenerated, it leads to a chaotic tachy-brady arrhythmia (Sick sinus syndrome) (Fig. 2). When atrioventricular (AV) node is affected, various degrees of heart block develop restricting smooth 1:1



Figs 1A to C: (A) Artificial pacemaker, (B and C) implantation of artificial pacemaker

conduction of depolarization wave from atria to ventricles (Figs 3 and 4). Ventricular rates drop proportional to the AV block, which compromises the cardiac output. This may lead to pre-syncope or syncopal attacks known as Stokes-Adams attacks. Drugs such as digoxin, verapamil, amiodarone and beta-blockers can aggravate or create heart blocks but they are reversible. Only way to treat advanced heart block is permanent implantable pacemaker.

All permanent pacemakers are "demand pacemaker" meaning they only activate when the native heart rate falls below a preset limit. They "shut off" when the native heart rate is satisfactory. In fact, the native heart rate could go as fast it wants, but the only thing the pacemaker insures is that it will not go below a certain preset limit at which the pacemaker is adjusted like say 60 beats/minute. In acute inferior wall infarction, AV node is often affected because it shares the same blood supply (right coronary artery) frequently

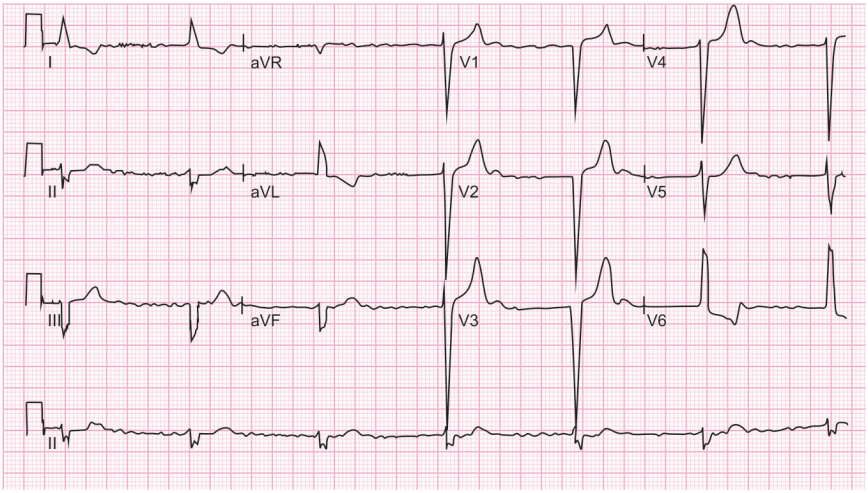


Fig. 2: Electrocardiogram showing atrial fibrillation with complete atrioventricular dissociation and idioventricular rhythm

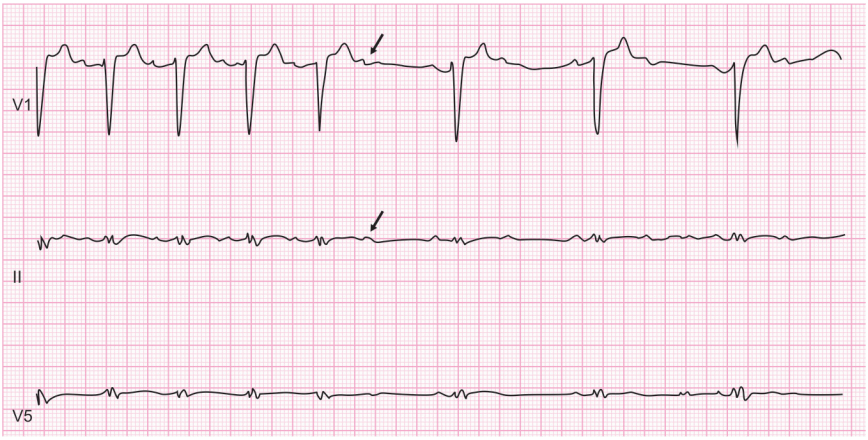


Fig. 3: Second degree heart block

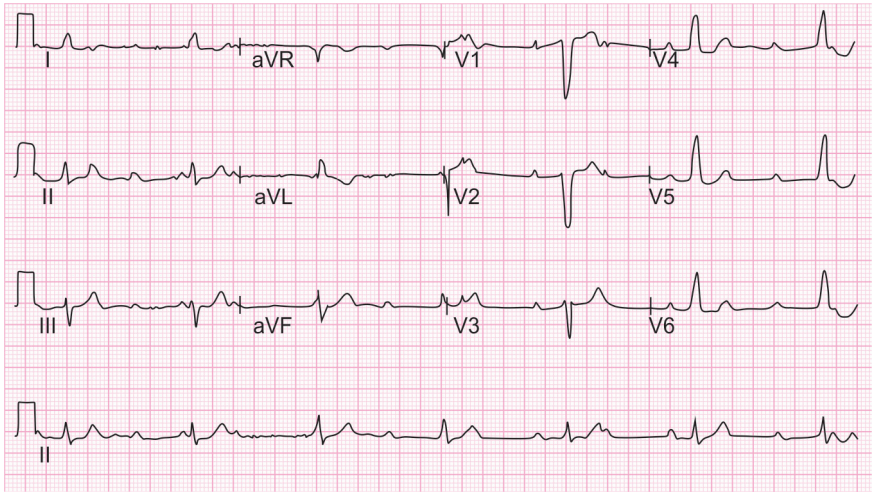


Fig. 4: Complete atrioventricular block (3rd degree heart block), P and QRS are no longer associated

causing transient heart block, which usually improves as the edema from acute myocardial injury recedes. Temporary pacemaker is generally used in such cases. The only difference from the implantable permanent pacemaker is that the pulse generator is outside the body and is attached to the electrode, which is threaded through the subclavian or femoral vein and positioned in the apex of the right ventricle. In permanent pacemaker, this generator is small and implanted under the skin in subclavian region.

All the pacemakers in adults are generally dual chamber and rate responsive (DDDR) unless if patient is in atrial fibrillation where atrial electrode is unnecessary and physicians use a single-chamber (VVIR) pacemaker. VVIR pacemaker has only one electrode, which senses and paces the right ventricle near interventricular septum. "R" stands for "rate responsive mode" whereby the electrode has an ability to sense that the patient is exercising and it automatically raises the pacing rate just like it happens in natural state (Fig. 5).

When patient is in sinus rhythm with advanced heart block, dual-chamber pacemaker (DDDR pacemaker) is the uniform choice. It requires two electrodes, one for the ventricle and the other for the right atrium. Both electrodes are passed through a venous sheath in subclavian vein under strict aseptic condition in operation room. First, the right ventricular (RV) lead is advanced under fluoroscopy in the RV apex. Trabeculations in this area prevent the lead from displacement. Right atrial lead is threaded through the same sheath and advanced, and lodged in the right atrial appendage. Over time, fibrous tissue forms around the tips and secures the leads in place.

Usually a trained technician from the pacemaker company is available for assistance. He/she will perform the diagnostic testing which basically include three things:

1. Threshold: This determines the lowest amount of electrical energy is being used to "capture" the ventricle, i.e. stimulate the ventricle. Ohms law is basically used. Both the volts and pulse width are checked.

2. Sensing: It makes sure that the lead is sensing the underlying native rhythm properly, because the "demand mode" can only work efficiently by this.
3. Impedance: This is to test the electrode integrity, meaning that the wire is not broken or the protective insulation has not worn off. If the wire is broken or fractured, impedance is very high. If the insulation material around the electrode is worn out, the impedance is very low.
   A hand held gadget in future follow-ups can check all these parameters. It can even be checked over the phone.

RESTRICTIONS

- Physical Activity: Dislodgement of the electrode can be a frustrating problem. It is most likely to happen in the first 6 weeks. The longer the electrode stays in place, the less is the likelihood of displacement because the fibrin material at the site will eventually hold the lead in place. Some cardiologists and surgeons use a screw-in lead. It is sown in the myocardium and less likely to dislodge. Author started using this type of lead after few embarrassing misses. He is very particular about advising patients not to use overhead activities or use upper arms vigorously for about 4–6 weeks. They have to be careful of the potholes on roads too!
- Intense magnetic fields, such as magnetic resonance imaging, and arc welding must be avoided. Usual home appliance including microwave oven do not interfere pacemaker function. Use of electric cautery in patients with pacemakers going for surgery is okay.

Usually the pulse generator will last 6–8 years or longer depending on how often it is in use. If patient's intrinsic heart rate is faster than the pacemaker for periods of time (as it happens in sick sinus syndrome), it may last many more years.

After a while, the lithium battery in the pulse generator will exhaust. Replacing the battery is easy outpatient procedure. Under local anesthesia in

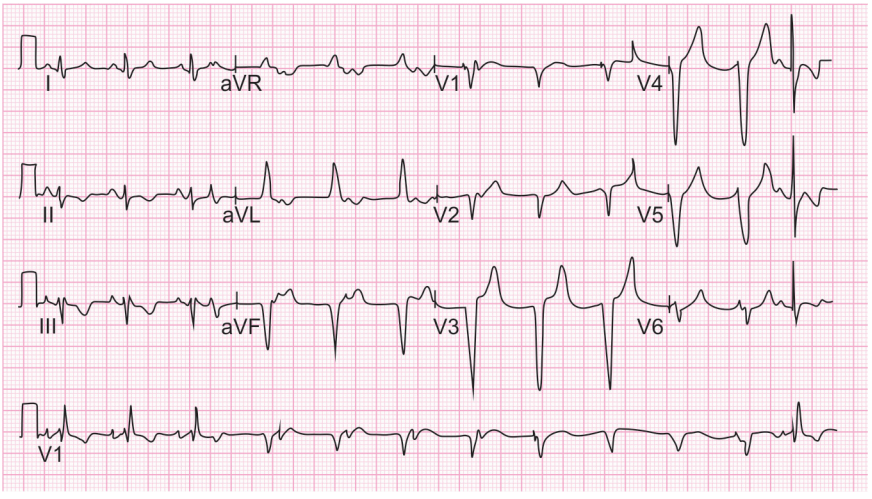


Fig. 5: Electrocardiogram showing paced beats. Pacing spikes are best seen in V4, V5 and V6

the operating room, pulse generator is exposed. Electrodes are disengaged and the old pulse generator is replaced with a new one. It takes about 15–20 minutes and the patient can go home. If the electrodes are damaged or fractured, then the whole new system has to be put in.

PACEMAKER MEDIATED TACHYCARDIA

If a patient with DDDR pacemaker develops refractory tachycardia, it is usually due to the pacemaker. Simply convert the DDDR mode to VVIR mode using the hand held programmer.

BIVENTRICULAR PACING (CARDIAC RESYNCHRONIZATION THERAPY)

This is a good advancement in the management of advanced heart failure where the ventricles are dilated and scarred (ejection fraction < 35%). The opposing walls of both ventricles do not contract in synchronous way because it takes too long for the depolarization wave to reach everywhere in time (QRS duration > 120 ms).

To correct this, biventricular pacemaker is used. In 50% of the cases, measurable clinical progress can be demonstrated.

In this procedure, one electrode (lead) is placed in the RV to stimulate the interventricular septum just as done in permanent pacing. Second electrode is passed via right atrium in to coronary sinus and advanced to the lateral wall of left ventricular as far down as possible, and if the patient is in sinus rhythm, a third electrode is passed through the same venous sheath in subclavian vein in the right atrium just as physicians do in dual-chamber (DDD) pacing. These three electrodes are connected to a special pulse generator. Since the incidence of sudden cardiac death is high in patients with advanced CHF, these days the pulse generator also has a built in defibrillator. The 46th Vice President of the United States, Dick Cheney had this implanted and is doing well.

With time, the pulse generator will sag down on the chest wall due to gravity and its weight. Newer pacemakers are smaller and weigh less than the old ones. Reassurance is all that is needed.

Sometimes the ventricular lead may stimulate the diaphragm. Lead adjustment is needed in such cases. RV wall is rather thin. Caution is needed not to perforate it while placing the RV lead.

Infection in the pocket will generally damage the pulse generator even though it is hermetically sealed. Sometimes, terminally ill patients may ask to have the pacemaker and other life support measures turned off. It is a legal issue, and proper consultations should be made before obliging patient's wishes.

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CHAPTER 17

Rheumatic Fever

Jayant C Bhalerao

Rheumatic fever is a systemic inflammatory disease caused by the antibody to Group A beta-hemolytic *Streptococcus*. It affects mainly heart, joints and collagen tissue, nervous system, kidney and skin. It generally follows a throat infection from above strain of *Streptococcus* by about 2–3 weeks, and starts with fever 38–39°C and severe arthralgia which is typically migratory and has no joint swelling. Rising titer of streptolysin O is highly suggestive of the disease. Sometimes the disease and inflammation may percolate along for several years causing extensive scarring in left sided cardiac valves especially mitral valve.

DIAGNOSIS

Since many other diseases may have few of the features described above, Jones classification was developed to help in making a confident diagnosis of rheumatic fever:

Major Criteria

- Migratory polyarthralgia without swelling
- Pancarditis with pericardial, myocardial and endocardial involvement
- Rheumatic nodules: It is painless nodules on bones or tendons
- Erythema marginatum on trunk and extremities but never on face (Fig. 1)
- Sydenham's chorea.

Minor Criteria

- Fever 38–39°C
- Streptolysin O titer
- History of recent throat infection
- High sedimentation rate and C-reactive protein (CRP)
- Leukocytosis
- Electrocardiography changes such as AV block, nonspecific STT changes and signs of acute pericarditis.

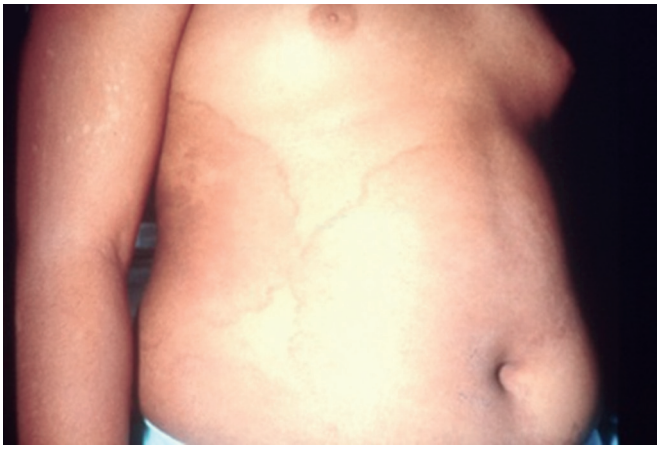

Fig. 1: Erythema marginatum

Physicians need two major or one major and two minor criteria to diagnose rheumatic fever.

Acute rheumatic fever is a pediatric disease. It is quite rare in adults. Symptoms are usually self-limited but in some, the inflammation smolders along causing extensive scarring in cardiac valves, generally left side ones, especially mitral valve. There is no other cause of mitral stenosis except rheumatic fever.

TREATMENT

- Antibiotics: Penicillin orally for 10 days. (Penicillin VK 500 mg, three times a day for 10 days). Erythromycin may be substituted in case of penicillin allergy
- Anti-inflammatory agents: Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) or prednisone depending on severity of inflammation. Cortisone really works wonders in resolving excruciating joint pains and acute pericardial pain. It also decreases the valvular fibrosis
- Bed rest for as long the signs of inflammation are not abated. Use sedimentation rate and heart rate for follow-up
- Relapses are not uncommon. Long-acting penicillin myocardial infarction may be used once a month for 4 years. Alternatively, low dose oral penicillin has been used for up to age 40 years.

Indiscriminate use of antibiotics in developing countries including India has inadvertently decreased the incidence of rheumatic fever!

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CHAPTER 18

Valvular Heart Disease

Jayant C Bhalerao

MITRAL STENOSIS

Mitral stenosis meaning narrowing of the mitral valve occurs exclusively due to rheumatic fever, which causes inflammation and then scarring of the valve. It impedes the flow of blood from left atrium to left ventricle. Blood backs up in left atrium and then pulmonary veins, pulmonary artery, right ventricle and systemic veins. All the symptoms and signs in mitral stenosis can be attributed to these pathophysiological changes.

Symptoms

- Dyspnea due to decreased cardiac output and pulmonary congestion
- Palpitation due to atrial dilatation causing atrial fibrillation
- Hemoptysis and cough due to pulmonary venous congestion and pulmonary congestion
- Systemic venous congestion causing edema, ascites and dyspepsia
- Hoarseness as markedly enlarged left atrium compresses recurrent laryngeal nerve.

Signs

- Diastolic murmur at apex which accentuates in end-diastole due to atrial contraction
- Opening snap as leaflet open with increased pressure gradient
- Pulmonary crepitations due to increased pulmonary venous pressure
- Enlarged left atrium causes percussion dullness in left 2nd intercostal space
- Right ventricular (RV) enlargement causing left parasternal lift
- Jugular venous distension
- Tender hepatomegaly
- Ascites
- Peripheral edema
- Central cyanosis due to pulmonary congestion.

Diagnosis

- Electrocardiography: P "mitrale"+ RV hypertrophy is the diagnostic hallmark of mitral stenosis unless patient is in atrial fibrillation (Fig. 1)
- Chest X-ray: Enlarged left atrium causes "mitralization" of left cardiac border, pulmonary congestion of varying degree (Fig. 2)
- Echocardiogram: This has made the diagnosis very easy and instantaneous. There is no need to feel inadequate if physicians are unable to hear the opening snap! (Fig. 3)

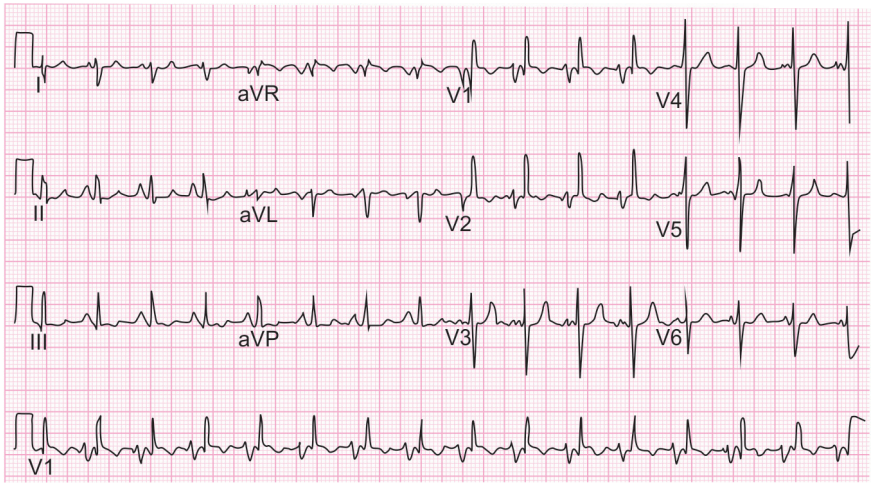

Fig. 1: Classical electrocardiogram in mitral stenosis. Look for prominent left atrial P wave in V1 and right ventricular hypertrophy

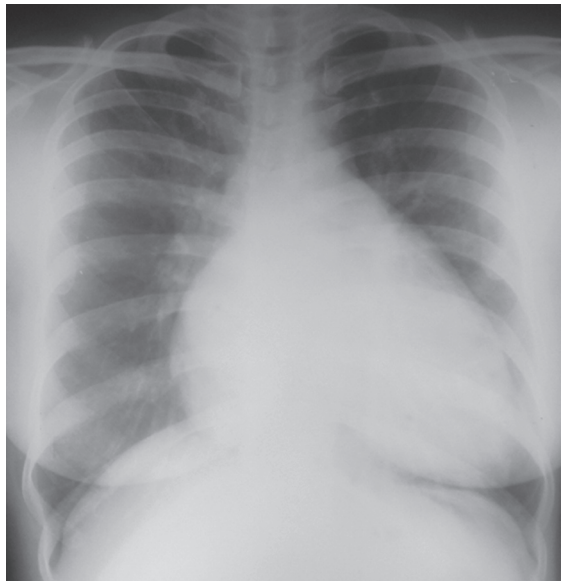

Fig. 2: Chest X-ray shows enlarged left atrium

- Cardiac catheterization: It is the gold standard. No cardiac surgeon is going to replace the mitral valve just on the basis of echocardiography finding (Figs 4 and 5).

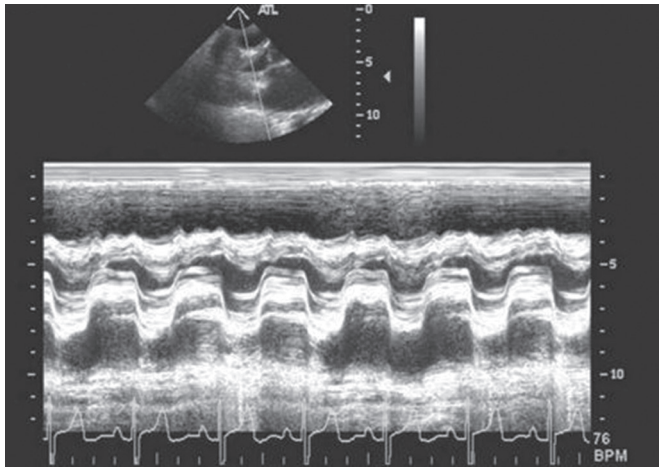

Fig. 3: Echocardiogram showing thickened leaflets and anterior motion of posterior mitral leaflet in diastole, which is the diagnostic hallmark. EF slope (which directly correlates to the rate of transvalvular blood flow) is flat indicating severe stenosis

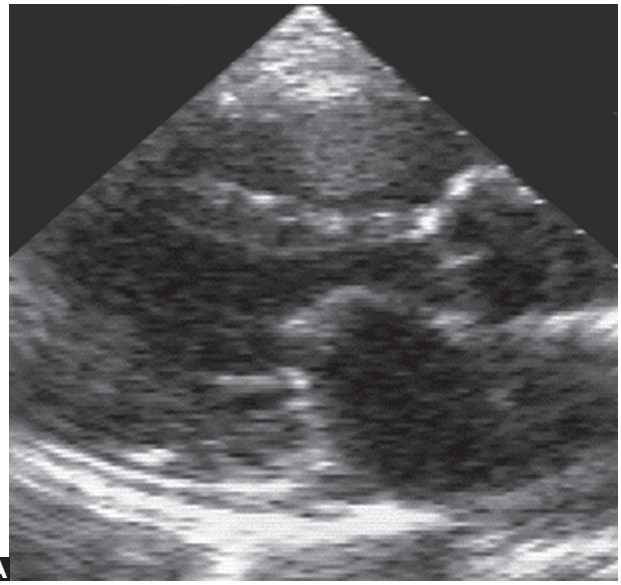

Fig. 4A

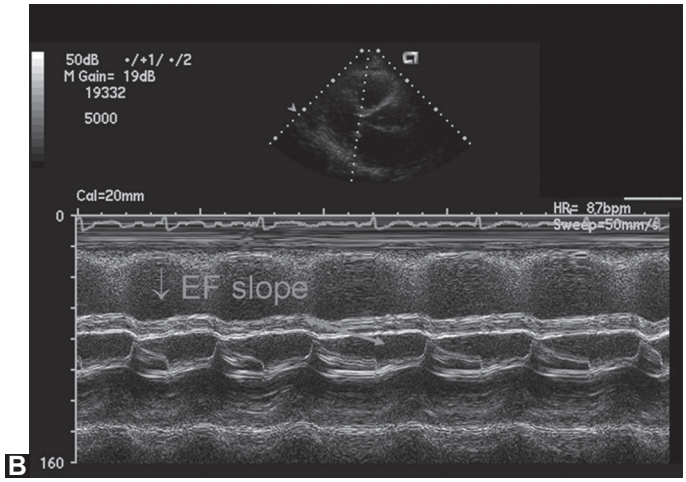

Fig. 4B

Figs 4A and B: Two-dimensional echocardiogram showing typical findings of mitral stenosis. Note hood-like opening of anterior mitral leaflet

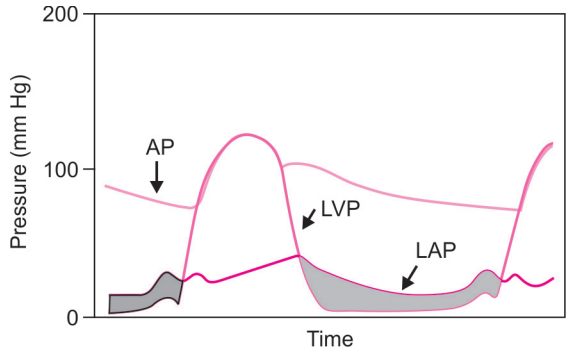

Fig. 5: Cardiac catheterization data in mitral stenosis. Abbreviations: AP, Aortic pressure; LAP, Left atrial pressure; LVP, Left ventricular pressure

Treatment

- Treatment is surgical in New York Heart Association (NYHA) class III and IV. Surgery is recommended if mitral valve area is less than 1.00 cm^2. Porcine (bioprosthetic) valve is ideal for elderly patients because it may not last as long as mechanical valves and tends to degenerate over 15 years. It has the advantage that it obviates the need for anticoagulation. In younger patients, metallic valves, such as St. Jude's, Björk-Shiley, or medtronic valves are popular because they last longer
- Percutaneous balloon valvuloplasty: India has the largest experience in the world. Restenosis rates are high. It is ideal for emaciated and malnourished, high-risk patients who may not tolerate an open heart surgery and valve replacement

- Commissurotomy (valvulotomy) either open or closed: Usually in noncalcified valve when valve replacement is not suitable. Usually, open commissurotomy is preferred
- Bacterial endocarditis prophylaxis is mandatory prior to any surgical procedure
- Anticoagulation will be necessary if patient develops atrial fibrillation
- NYHA class I and II patients are treated by conventional management of heart failure.

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19 CHAPTER

Mitral Regurgitation

Jayant C Bhalerao

Normal mitral valve has four components:

1. Two leaflets
2. Fibrous annulus ring to which these leaflets are attached
3. Papillary muscles (anterior and posterior) and
4. Chordae tendineae, the fibrous cords that are attached to the papillary muscles on one end and the mitral leaflets on the other. Their job is to hold the leaflets closed securely during ventricular systole

Dysfunction in any one of these components can result in leakage of blood through the mitral valve—a condition called mitral regurgitation.

CAUSES

- Defect of mitral leaflets: Damaged by either rheumatic fever or bacterial endocarditis
- Defect in the annulus: Usually caused by dilated left ventricle
- Defect in papillary muscles: Usually damaged by acute myocardial infarction. Rupture of any papillary muscle leads to loss of support to chordae tendineae and a flail mitral valve. This leads to acute, severe mitral regurgitation requiring urgent valve repair or replacement
  Chronic ischemia of the papillary muscles due to coronary artery disease can lead to suboptimal function causing milder forms of regurgitation
- Defect in chordae tendineae: This is the most common cause of mitral regurgitation in clinical practice. Longer than needed chordae tendineae as seen in mitral valve prolapsed syndrome and Marfan's syndrome lead to prolapse of the leaflets in to left atrial cavity. This generally leads to milder form of mitral regurgitation unless the chordae tendineae rupture.

SYMPTOMS

They largely depend on the severity and duration of regurgitation.

- Acute regurgitation is generally severe and needs urgent surgery

- Chronic regurgitation produces left ventricular (LV) strain leading to hypertrophy and then dilatation. Congestive heart failure (CHF) ensues as the left ventricle begins to exhaust.

SIGNS

- Pansystolic murmur at apex
- Signs of LV hypertrophy and dilatation with a heaving apex beat
- Increased pulse pressure
- S3 gallop over the apex
- Pulmonary congestion
- Signs of CHF.

DIAGNOSIS

- Electrocardiography: Left ventricular hypertrophy with strain pattern
- Chest X-ray: Cardiomegaly and left atrial dilatation
- Echocardiogram: It is not only diagnostic; it also helps determine the severity of the regurgitation (Fig. 1)
- Cardiac catheterization: It is the gold standard. Regurgitant fraction is calculated as follows:

  Regurgitant fraction (RF) = V mitral – V aorta/V mitral X 100

  (Where, V stands for velocity)
  - RF over 50 indicates severe mitral regurgitation and surgery is indicated
  - Never depend on ejection fraction to decide valve replacement in any regurgitant valve defect be it mitral or aortic. It may remain normal until very late
  - End-systolic diameter and volume is a much better measure. If the end-systolic volume is twice the normal range, surgery should be considered.

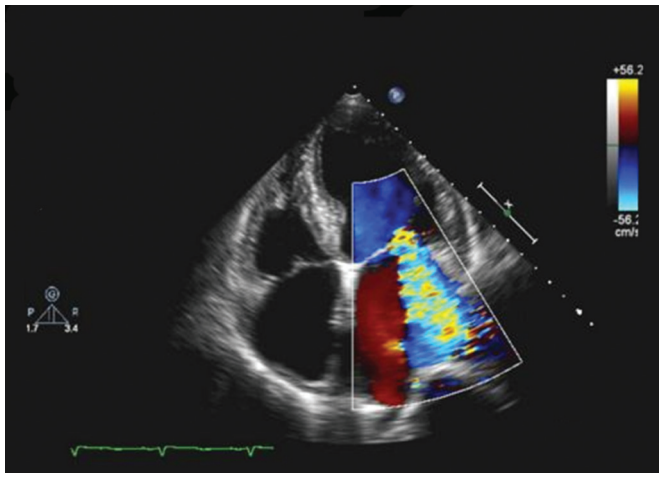


Fig. 1: Echocardiogram showing mitral regurgitation

INDICATIONS FOR VALVE REPLACEMENT

- High regurgitant fraction over 50
- End-systolic volume greater than twice the normal level
- Pulmonary artery pressure over 50 mm Hg.

TREATMENT OF NONSURGICAL MITRAL REGURGITATION

- Nitrates in any form are extremely effective in reducing the regurgitation flow and should be the cornerstone of any medical management of acute or chronic mitral regurgitation
- Usual treatment of CHF
- Endocarditis prophylaxis is necessary.

20

CHAPTER

Mitral Valve Prolapse Syndrome (Barlow's Syndrome)

Jayant C Bhalerao

INTRODUCTION

This is a minor anatomical defect of the mitral valve associated with disproportionate somatic complaints. It has strong familial association, most common in females with certain body habitus and psychological makeup indicating a possible genetic defect of autosomal dominant type. It is not caused by rheumatic fever. Patient is born this way.

ANATOMICAL DEFECT IN MITRAL VALVE PROLAPSE

There are two basic defects:

1. Disproportionately long chordae tendineae which leads to the bulging of mitral leaflet more than 2 mm in to the left atrial cavity during ventricular systole, and
2. Myxomatous degeneration of mitral valve making it thicker than 5 mm.

Every mitral leaflet has to bulge in the left atria during systole because of the great hydrostatic pressure generated, but this bulging is less than 2 mm. This does not constitute mitral valve prolapse syndrome, which is a pathological condition.

AUTONOMIC INSTABILITY IN MITRAL VALVE PROLAPSE

Most patients with typical mitral valve prolapse will have plethora of symptoms due to autonomic instability such as palpitations, nervousness, skip beats, vasovagal syncope, cold extremities, etc. Rare incidence of sudden cardiac death due to ventricular arrhythmia is noted.

PSYCHOSOMATIC COMPONENT OF MITRAL VALVE PROLAPSE

Most patients will exhibit anxiety, depression, bipolar disorder, obsession with somatic function, tension, headaches, inability to deal with daily stress, sharp stabbing left pectoral pains, etc.

TYPICAL BODY HABITUS

Most of these patients have similar body habitus. They are usually tall, slender, flat chested, chest deformities such as pectus or scoliosis, etc. Females outnumber males by 10:1.

SIGNS

- Cardiac exam shows loud mid-systolic click and late systolic murmur, which corresponds the prolapse. It accentuates by maneuvers that decrease left ventricular (LV) volume like standing, Valsalva maneuver or nitroglycerin. Sometimes the click and murmur may not be audible, or its intensity may vary
- Marfan's syndrome is almost always associated with mitral valve prolapse syndrome.

DIAGNOSIS

- Echocardiogram is diagnostic. Amyl nitrate inhalation exaggerates the findings and may uncover them (Fig. 1)
- Electrocardiography shows nonspecific ST-T changes
- Stress test is often false positive
- Overdiagnosis of this condition is common and must be watched.

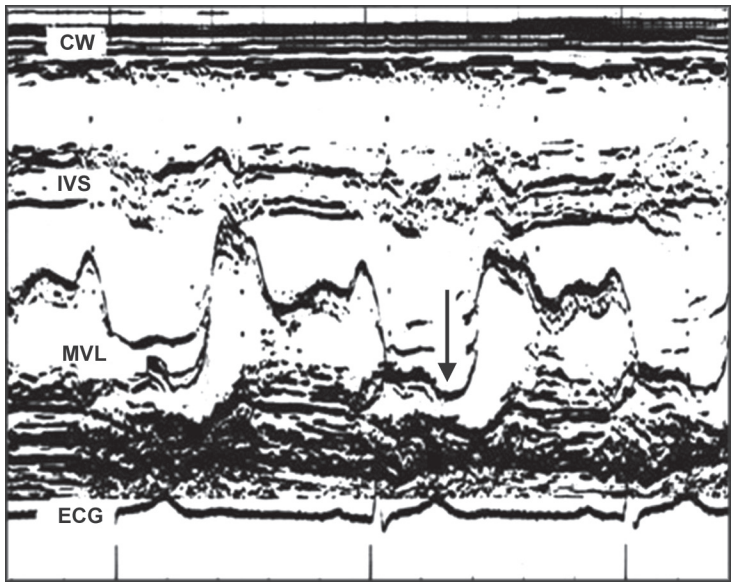


Fig. 1: Echocardiographic scan of the heart. Abbreviations: CW, Chest wall; ECG, Electrocardiogram; IVS, Interventricular septum; MVL, Mitral valve leaflet

TREATMENT

- Beta-blockers are effective in controlling many of the symptoms associated with autonomic instability and premature ventricular contractions
- Bacterial endocarditis in needed only if there is myxomatous degeneration
- Sometimes the chordae tendineae rupture causing flail mitral valve and severe acute mitral regurgitation. This requires mitral valve repair or replacement
- Psychological counseling is helpful
- Thorough explanation of the relatively benign nature of the condition is very essential.

21 CHAPTER

Valvular Aortic Stenosis

Jayant C Bhalerao

Narrowing of the aortic valve is referred to as aortic stenosis. In 90% of the times it is caused by calcific degeneration of aortic leaflets and 10% of the times it is due to rheumatic fever.

Normal aortic valve has three leaflets (tricuspid). In 30% of the times it has only two cusps (bicuspid). Bicuspid aortic valve degenerates due to wear and tear much earlier. Calcific aortic stenosis in bicuspid aortic valve typically starts before 50 years of age whereas in tricuspid valve, it typically starts after 65 years.

Normal aortic valve is about 1.6–2 cm^2 in size. It is considered critically narrow when it narrows down to half the size, i.e. 0.8 cm^2. Normally, the systolic pressure across the aortic valve is equal. In severe aortic stenosis, it increases above 70 mm Hg in left ventricle compared to ascending aorta (pressure gradient) (Fig. 1).

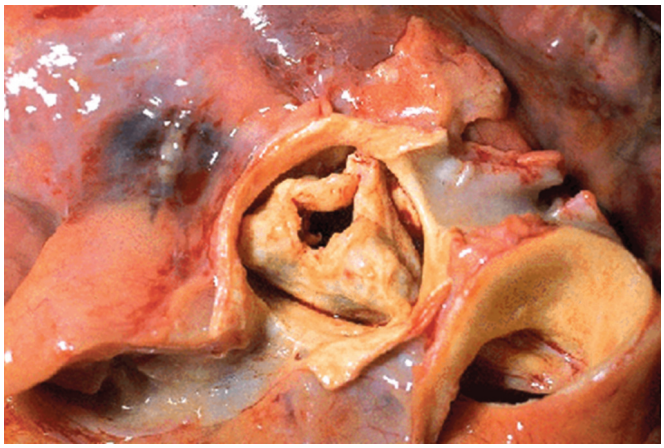


Fig. 1: Note the thick and stenosed aortic valve. Normal aortic valve is about the size of a US silver dollar

SYMPTOMS

- Dyspnea
- Angina
- Syncope
- Conduction defects due to encroachment of calcium from aortic valve to the nearby atrioventricular node
- Congestive heart failure.

SIGNS

- Ejection systolic murmur best heard in right 2nd intercostal space
- Delayed carotid artery upstroke "pulsus parvus et tardus"
- Left ventricular hypertrophy.

DIAGNOSIS

- Electrocardiography: Left ventricular hypertrophy and conduction defects (Fig. 2)
- Chest X-ray: Calcification of aortic valve, post-stenotic dilatation of ascending aorta
- Echocardiogram (Figs 3A and B)
- Cardiac catheterization is gold standard.

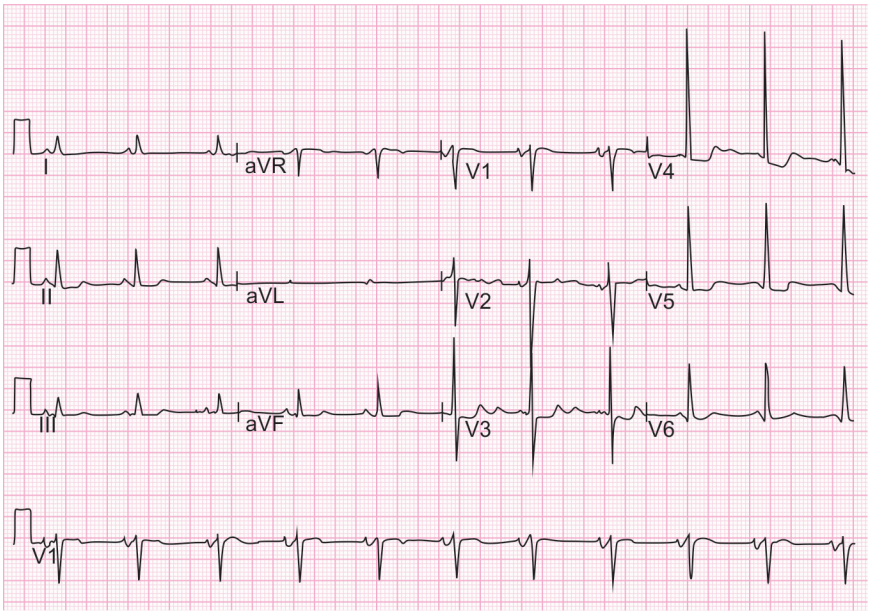
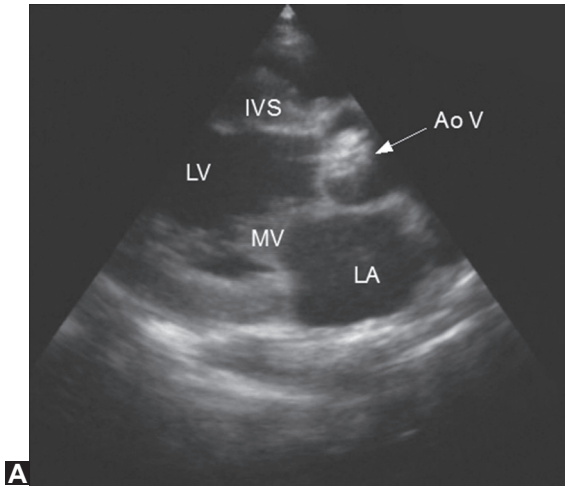
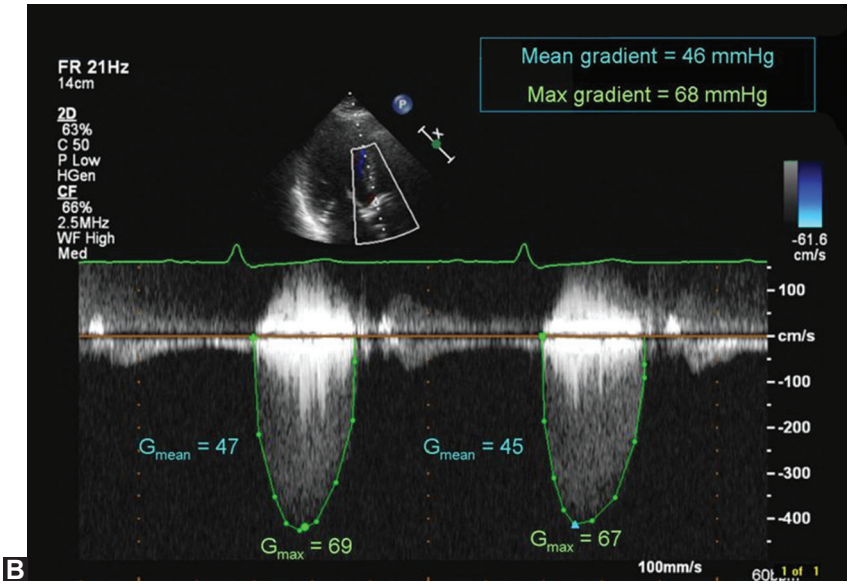


Fig. 2: Electrocardiogram showing severe left ventricular hypertrophy with left atrial enlargement in aortic stenosis





Figs 3A and B: (A) Echocardiogram showing aortic stenosis. (B) Evaluation of aortic stenosis by continuous wave Doppler echocardiography. Abbreviations: AoV, Aortic valve; IVS, Interventricular septum; LA, Left atrium; LV, Left ventricle; MV, Mitral valve

TREATMENT

- Surgery: Bioprosthetic (porcine) valve for elderly patients, metallic valves for younger patients. Life-long warfarin treatment is mandatory for metallic valves
- Percutaneous balloon valvuloplasty not possible in heavily calcified valve
- Percutaneous aortic valve replacement
- Bacterial endocarditis prophylaxis is mandatory.

22

CHAPTER

Aortic Regurgitation

Jayant C Bhalerao

Aortic valve generally has three cusps. These leaflets close at the end of left ventricular systole thereby preventing leakage of blood back in to the left ventricle. Failure of this basic function leads to aortic regurgitation.

ETIOLOGY

- Idiopathic in most cases
- Hypertension is the most common underlying cause in clinical practice
- Bicuspid aortic valve (congenital)
- Rheumatic heart disease
- Aortic root dilatation: Marfan's syndrome, aortic dissection, syphilis and aging
- Collagen diseases and ankylosing spondylitis
- Bacterial endocarditis
- Trauma: Surgical (during other cardiac procedures) or blunt chest trauma.

SYMPTOMS

Progressive and chronic increase in the workload of left ventricle leads to dilatation, hypertrophy and ultimate exhaustion and failure.

SIGNS

High pulse pressure so common to this condition has been used to concoct numerous "signs" with fancy names for posterity. They are good to impress fellow students but are of zero value if there is no diastolic murmur. The moral of the story is that the diastolic murmur is the king. Learn to diagnose the faint almost a whisper-like murmur along the left sterna border. With some practice, it will become easy. Physicians have to train their ears to listen to it.

Let us recite those countless signs for the last time and eulogize them and let them rest in peace from now on:

- Watson's water hammer pulse
- Corrigan's pulse
- De Musset's sign (head nodding with systole)
- Quincke's sign: pulsations of capillary bed in nails
- Traube's sign: pistol shot sound heard over femoral artery in systole
- Duroziez's sign: systolic and diastolic murmur over femoral artery when compressed with stethoscope
- Lighthouse sign: alternate blanching and flushing of forehead
- Landolfi's sign: alternate constriction and dilatation of pupil
- Baker's sign: pulsatile retinal vessels
- Müller's sign: pulsatile uvula
- Mayen's sign: diastolic of 15 mm Hg with arms raised
- Rosenbach's sign: pulsatile liver
- Gerhardt's sign: enlarged spleen
- Hill's sign: more than 20 mm Hg difference in popliteal and brachial systolic pressure
- Ashrafian sign: pulsatile pseudo-proptosis.

Author strongly feels this is an overkill. Time must not be wasted any more in teaching these worthless signs. The diagnosis has already been made by a simple diastolic murmur!

DIAGNOSIS

- Electrocardiography: Left ventricular hypertrophy with strain pattern
- Chest X-ray: Dilated aortic root, cardiomegaly and aortic valve calcification
- Echocardiogram makes instant diagnosis and accesses severity
- Blood test for syphilis and collagen disease
- Computed tomography of the chest
- Cardiac catheterization is the gold standard
- Never depend on ejection fraction to decide surgery in regurgitant valve disease! Best guide is either regurgitant fraction or end-diastolic volume (greater than twice the normal is a good indication for surgery).

TREATMENT

- Medical for mild to moderate cases: Afterload is very important factor in aortic insufficiency. Angiotensin-converting enzyme inhibitors and calcium channel blockers are helpful in decreasing the regurgitant volume
- Surgical treatment: Severe regurgitation is treated by valve repair or replacement.

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23 CHAPTER

Tricuspid Valve Disorders

Jayant C Bhalerao

Tricuspid stenosis is extremely rare.

TRICUSPID REGURGITATION

Causes

- All conditions with pulmonary hypertension such as cor pulmonale due to chronic obstructive pulmonary disease, primary pulmonary hypertension and left ventricular (LV) failure, mitral stenosis
- Right ventricular infarction
- Bacterial endocarditis
- Ebstein's anomaly (named after Wilhelm Ebstein in 1866)
- Carcinoid syndrome (high 5-hydroxyindoleacetic acid level in urine).

It is rarely affected by rheumatic fever.

Diagnosis

- Pansystolic murmur along lower border of sternum, which increases with inspiration
- Large V wave in neck
- Signs of right ventricular hypertrophy
- Electrocardiography: Right ventricular hypertrophy and P-pulmonale
- Echocardiogram is gold standard.

Treatment

Surgical replacement may be needed in severe cases such as endocarditis.

EBSTEIN'S ANOMALY

This is congenital displacement of the tricuspid valve leaflets almost near the right ventricular apex. They are attached to the free wall and septal wall instead of

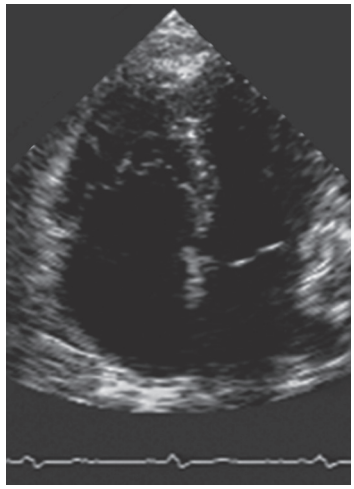

Fig. 1: This is a common question for cardiology boards and one must know this condition

the annulus, which remains in its normal position. It is very often associated with atrial septal defect and Wolff-Parkinson-White syndrome and severe tricuspid regurgitation. Right ventricular cavity is very small due to the "atrialization".

Children usually present with paroxysmal atrial tachycardia due to reentry tachycardia through accessory pathway.

Electrocardiography: Giant P waves, the so-called "Himalayan P waves", Wolff-Parkinson-White syndrome, first-degree atrioventricular block that encourages the conduction via accessory pathway to cause paroxysmal atrial tachycardia.

Echocardiogram: On 2D-echocardiogram, downward displacement of the tricuspid valve is easily seen (Fig. 1).

CARCINOID SYNDROME

It is caused by excessive vasoactive amines such as serotonin hormone in circulation. It is produced by carcinoid tumor commonly present in ilium after it metastasizes to liver. High levels of serotonins lead to fibrosis of right atrium and tricuspid, and pulmonary valves causing tricuspid regurgitation and pulmonary stenosis. Other presenting features are flushing in upper body, and head and abdominal pain with diarrhea. Elevagted 5-hydroxy-indole-acetic acid in 24-hour urine is diagnostic.

PULMONARY VALVE DISORDERS

They are relatively rare in adult cardiology. Usually same diseases that affect tricuspid valve, would affect pulmonary valve also causing regurgitation.

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24 CHAPTER

Congenital Heart Defects

Jayant C Bhalerao

INTRODUCTION

Incidence of congenital heart defects in adult cardiology in the USA is rare. Pediatric cardiologists are very efficient in diagnosing and correcting them long before these patients reach adulthood. Atrial septal defect (ASD) (secundum type) is the most commonly seen congenital heart defect and that also is very infrequent. Ventricular septal defects (VSD) and patent ductus arteriosus are even less common. They present with loud systolic murmurs, which are hard to miss and thus easily diagnosed in childhood physical examinations. ASD is a bit more difficult to diagnose because the murmur is often quite faint and may fall through the cracks and remain undiagnosed till adulthood.

The author has restricted this chapter mostly to the ASD since it requires some specific information to diagnose and treat.

ATRIAL SEPTAL DEFECT

In adult heart, the atrial septum generally separates the two atria completely, thus preventing admixture of oxygenated blood from left atrium to mix with the venous blood in the right. In fetal heart, the interatrial septum is only partially developed which leaves behind a large gap or hole (foramen ovale), which allows the blood to enter freely from right atria to the left. In fetus, the venous blood bypasses the nonfunctional pulmonary circulation and goes from right atria to the left and then to the aorta and placenta. After birth, pulmonary circulation is activated and interatrial septum slowly grows down and closes the foramen ovale. A dimple on the septum is the only reminder of its previous existence. It is called fossa ovalis. In about 20% patients, foramen ovale may remain partially open. It is called patent foramen ovale (PFO). Usually, there is no significant amount of blood crosses through it. More about the PFO is discussed later.

In approximately 1 out of 1,500 live births, this interatrial septum is underdeveloped leaving the foramen open even after birth. Since the pressure in left atria is greater than the right, oxygenated blood begins to shunt through this hole from left to right (L-R shunt). This is what we refer to as ASD.

TYPES OF ATRIAL SEPTAL DEFECTS

Over 95% of the ASDs are secundum type (For all practical purpose, this is what physician will see).

Other types are septum primum defects, sinus venosus defects and coronary sinus defect, which are rare (Fig. 1).

HEMODYNAMIC CONSEQUENCES OF ATRIAL SEPTAL DEFECTS

Depending on the size of the defect, large amount of blood is shunted from the left atria to the right. Over several years, it leads to significant volume overload in the right heart.

The first chamber to get affected is the right atria, which dilates to accommodate the extra blood. It leads to atrial fibrillation and other atrial arrhythmias. First degree atrioventricular (AV) block is not uncommon.

Incomplete right bundle branch block (RBBB) pattern (rsR' pattern in V1) is the diagnostic hallmark of ASD. Physicians have to rethink the diagnosis if this finding is not present on ECG (Fig. 2).

Enlargement of pulmonary artery on the chest X-ray is another diagnostic hallmark. Pulmonary hypertension usually is a late complication (usually beyond 40 years of age) (Fig. 3). It is a serious complication and the

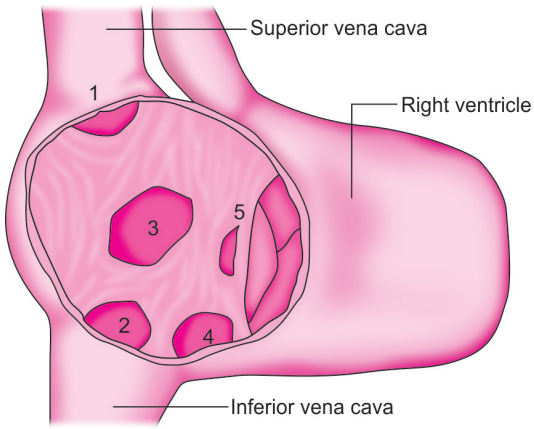

Fig. 1: Types of atrial septal defects. In this Figure "1" and "2" are sinus venosus defects, "3" is the commonest type (the secundum defect), "4" is coronary sinus defect and "5" is primum defect

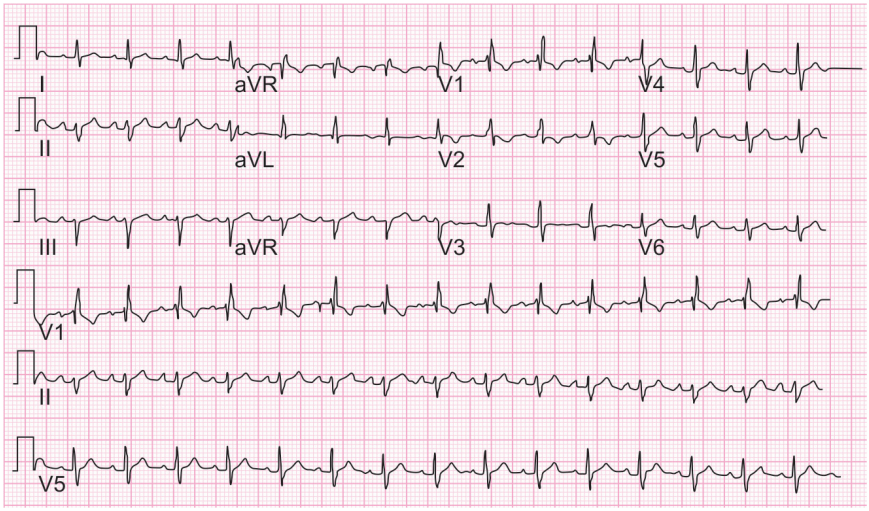

Fig. 2: Typical ECG in atrial septal defects secundum type. Note rsR' in V1

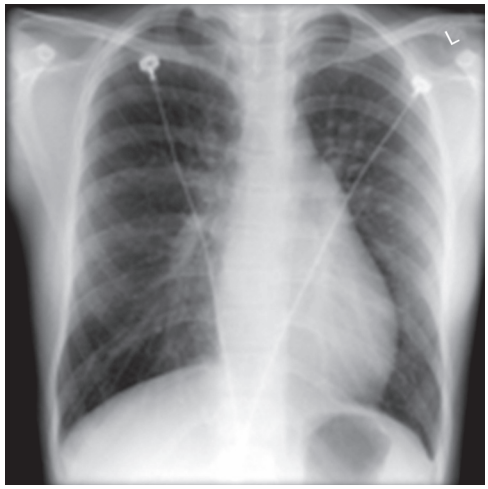

Fig. 3: Chest X-ray in atrial septal defects showing prominent pulmonary artery and pulmonary congestion in upper lobes

author's lead to reversal of shunt from right atria to the left (Eisenmenger syndrome).

Frank congestive heart failure is the ultimate consequence.

SYMPTOMS

Most patients are asymptomatic. Palpitation, dyspnea and hemoptysis are the some of the symptoms. Some may present as stroke.

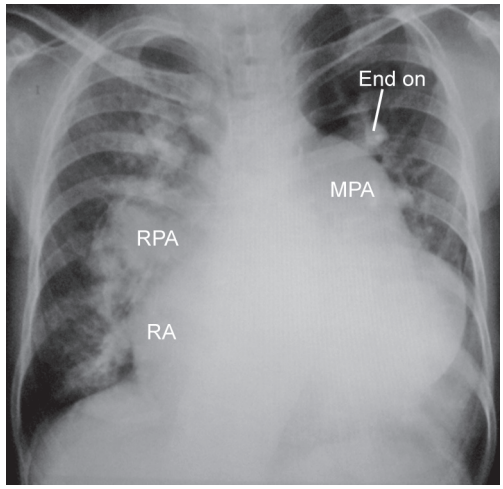

Fig. 4: Chest X-ray in atrial septal defects with severe pulmonary hypertension.
Abbreviations: MPA, Main pulmonary artey; RA, Right atrium; RPA, Right pilmonary artery

PHYSICAL FINDINGS

On auscultation, a faint systolic flow murmur is noted in pulmonic valve area (left second intercostal space). Large volume of blood passing through the normal pulmonic valve is the cause of this flow murmur.

Fixed Splitting of S2

This is the diagnostic hallmark of ASD. Normally, P2 moves farther from the A2 during inspiration because of the increased venous return. But in ASD, since the amount of blood in right heart is already to its maximum, the P2 can no longer shift any more, thus seemingly "fixed" during inspiration.

ECG and chest X-ray findings have been discussed already.

Echocardiography

Both transthoracic as well as transesophageal echocardiography have made the diagnosis rather easy. Paradoxical septal motion confirms right ventricular volume overload. Color Doppler can show the L-R shunt at atrial level. Agitated saline given as a rapid intravenous bolus can also help show the L-R shunt (Fig. 5).

Right Heart Catheterization

Oxygen step-up at the atrial level is confirmatory. Using the formula given in the chapter "Miscellaneous", L-R shunt can be estimated. Greater than 1.5:1 shunt is an indication of surgical closure.

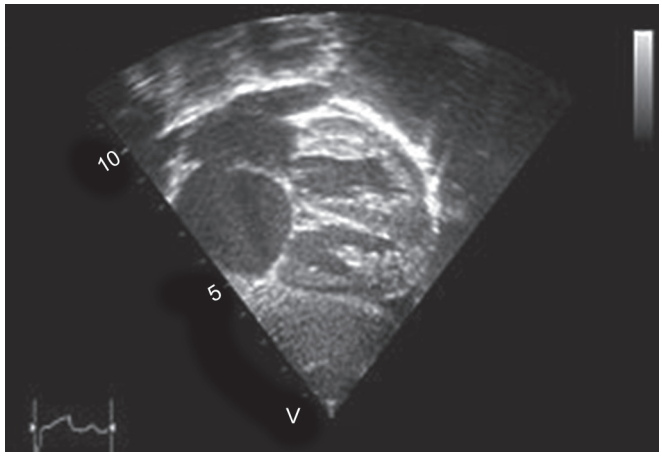

Fig. 5: Echocardiogram in atrial septal defects, secundum type. Atria are toward the left and the apex toward the right. Secundum defect is seen as a discontinuation of interatrial septum. Dilated right atrium is noted inferiorly. Enlarged pulmonary veins are seen entering left atrium above

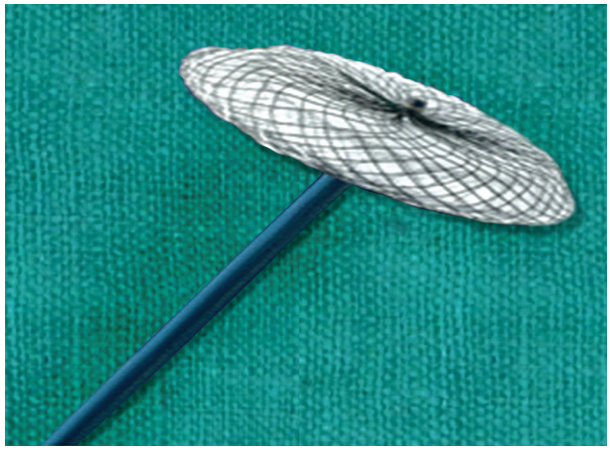

Fig. 6: Septal occluder

TREATMENT

Closure of ASD is one of the easiest things to accomplish either by open heart surgery if the defect is very large and close to the vena cava opening, or by percutaneous catheter intervention (Fig. 6).

Surgical results are excellent as long as the pulmonary artery pressure is normal. That is why, closure is recommended before patient reaches adulthood. Once the pulmonary artery pressure gets above 40 mm Hg, the risks/reward equation becomes less attractive. Once Eisenmenger physiology has set in, it is worthless to operate.

PATENT FORAMEN OVALE

Approximately 20–25% of adults have PFO. It is commonly associated in patients with migraine and mitral valve prolapse syndrome. One of the dangers is "paradoxical embolism". Venous thrombus can travel from right atrium to the left circulation via the PFO causing stroke or other manifestations of systemic embolism. This happened to Ariel Sharon, the Prime Minister of Israel, who ended up with a stroke due to PFO.

Any patient going for scuba diving, must be specifically checked for PFO by echocardiography. PFO allows the nitrogen during decompression to escape via PFO to the brain causing decompression sickness or the "Benz".

Patent foramen ovale must be checked in any young patient who suffers a stroke or has repeated migraines.

Septum primum defect is due to under development of the AV cushion which constitutes the inferior part of the atrial septum. It is always associated with severe mitral regurgitation and marked left axis deviation.

Patent ductus arteriosus caused shunting of blood from aorta to pulmonary artery. It is associated with unmistakable loud, continuous systolic and diastolic murmur in the left 2nd space.

VENTRICULAR SEPTAL DEFECT

Ventricular septum separated the two ventricles. It has two parts:

1. Membranous part, which makes up the superior portion and the most common cause of VSD seen in adults.
2. Muscular part, which makes up the mid and inferior portion of the septum. Up to 50% newborns have muscular VSD, which closes spontaneously within the 1st year (Figs 7 and 8).

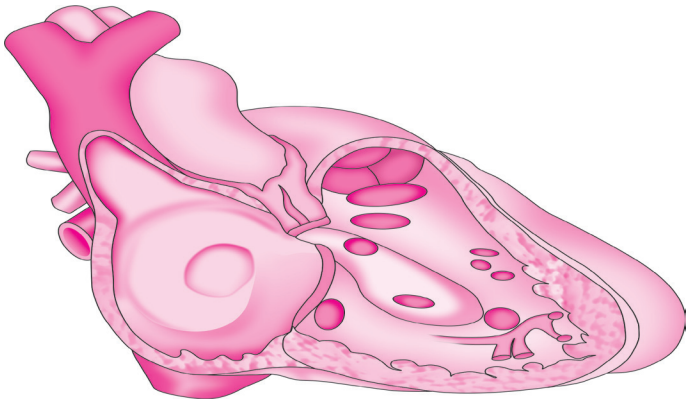

Fig. 7: View of the right atrium and ventricle showing example of ventricular septal defects

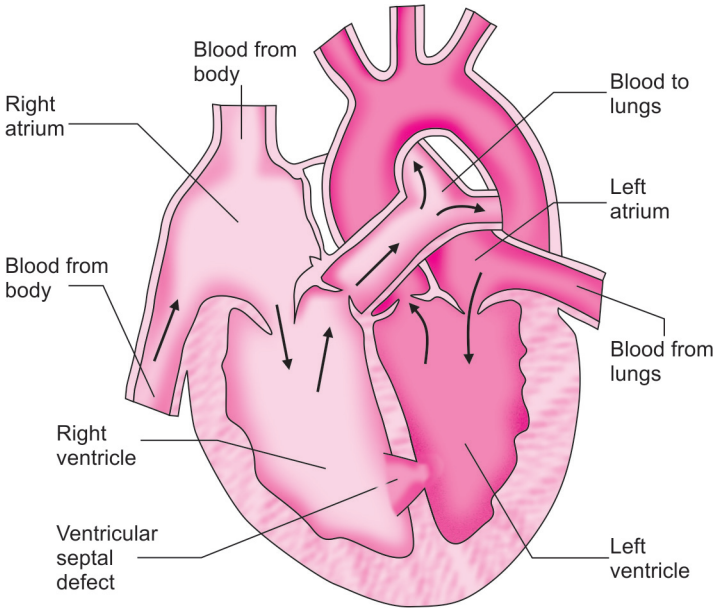

Fig. 8: Ventricular septal defect

Diagnosis (Figs 9 and 10)

- Loud pansystolic murmur at left sternal border is typical. It should be differentiated from murmurs of tricuspid and mitral regurgitation
- Echocardiography has made it easy to confirm the diagnosis of VSD (Fig. 10)
- Clinical features of right ventricular volume overload
- Clinical features of left ventricular strain

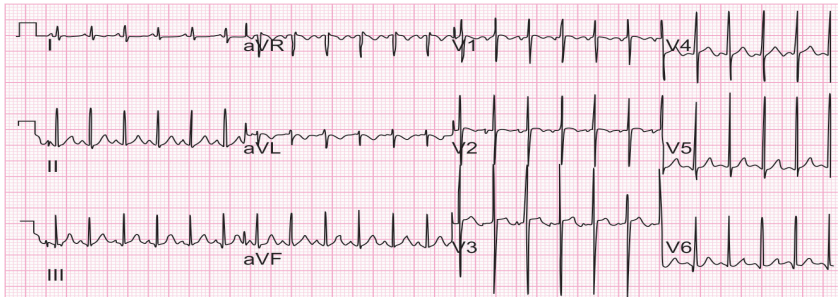

Fig. 9: ECG in a 6 months old child recorded at half voltage. Note biventricular hypertrophy

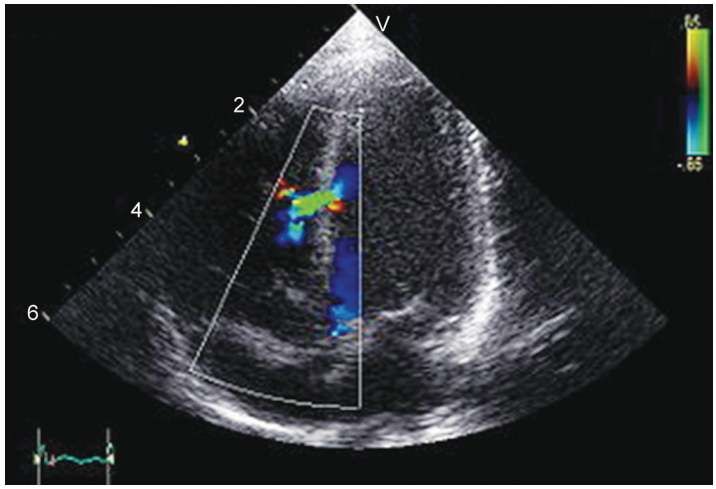

Fig. 10: Echocardiographic image of ventricular septal defect

- Cardiac catheterization shows oxygen step-up at ventricular level. L-R shunt can be calculated by various formulae given in the chapter "Miscellaneous". Shunts of 1.5:1 or greater require surgery
- Genetic defect with NKX2-5 gene

Congenital ventricular septal defect is often associated with other congenital defects like Down's syndrome.

Treatment

Although percutaneous intervention is possible, it is not popular in the USA. Because of high risk of AV conduction defect due to catheter-induced trauma to AV node, surgical closure is the most popular choice.

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25 CHAPTER

Bacterial Endocarditis

Jayant C Bhalerao

GENERAL CONSIDERATION

Infection of the heart valves is a serious condition requiring prolonged intravenous (IV) antibiotic therapy for several weeks and high probability of valve destruction leading to severe leakage and then congestive heart failure requiring valve replacement. Septic emboli may complicate clinical picture further.

Endocarditis can affect perfectly normal valves but the chances are much higher if the valve is previously damaged from prior rheumatic disease or myxomatous degeneration from mitral valve prolapsed.

- In general population, left sided (mitral or aortic) valves are most commonly affected. A low virulence bacterium, *Streptococcus viridans*, is the common offender. It leads to a subacute form of endocarditis and responds nicely to IV penicillin for 6 weeks without much local destruction. Oral cavity is the common source and history of dental extraction often precedes the valve infection
- In IV drug users, it is the right-sided valves that are the predominant target. *Staphylococcus aureus* is the most common bacteria, which cause acute form of endocarditis, capable of severe local destruction and abscess formation
- If the blood culture grows *Streptococcus bovis*, look for associated colorectal cancer
- If the blood culture grows Enterococci, the source is urinary tract infection
- If patient develops endocarditis within 60 days of prosthetic valve surgery, the cause is nosocomial (i.e. hospital acquired) and often from skin contaminant *Staphylococcus epidermidis*
- If the patient develops endocarditis after 60 days of prosthetic valve surgery, the cause is community-acquired infection
- If everything points to endocarditis but the blood cultures are negative, the commonest cause is prior antibiotic therapy
- Chronic low backache with low-grade fever is a common presenting sign to suggest endocarditis

- Blood culture growing fungus almost always is due to contamination during valve surgery or IV drug abuse
- Long standing indwelling IV catheters, Foley catheters are common sources of bacteremia and endocarditis. Care should be taken in long-term use of these catheters

SIGNS AND SYMPTOMS

- Low-grade fever, malaise, low backache and chills
- Recent history of dental extraction or dental work
- Janeway spots: Red, macular painless patches on palms and soles seen in *Staphylococcus aureus* endocarditis of drug addicts (Fig. 1)
- Osler's nodes: Painful, palpable small subcutaneous erythematous lesions on pads of fingers and toes. These are due to immune complexes and are also seen in immune vasculitis (Figs 2A to D)
- Roth's spots on retinal examination: It is bloody spots on retina
- Splinter hemorrhages on nail bed, along the nail growth line, are septic emboli
- Clubbing and hepatosplenomegaly
- Changing heart murmur

DIAGNOSIS

Endocarditis is not proven merely by three positive blood cultures [minimum inhibitory concentration (MIC) > 0.1 mg/L]. A more elaborate system has been developed in1994 by Duke Endocarditis Service and revised in 2000. There are two major and four minor diagnostic criteria:

Major criteria

1. Two positive blood cultures drawn 12 hours apart or three positive blood cultures drawn 1 hour apart
2. Positive echocardiogram (transesophageal echocardiogram is the gold standard) (Fig. 3).

Minor criteria

1. Presence of predisposing factors known as valve defect, IV drug use and recent dental extraction
2. Fever more than 38°C
3. Evidence of embolism: Arterial or pulmonary, Janeway spots and conjunctival hemorrhage
4. Immunological problems: Osler's nodes and glomerulonephritis.

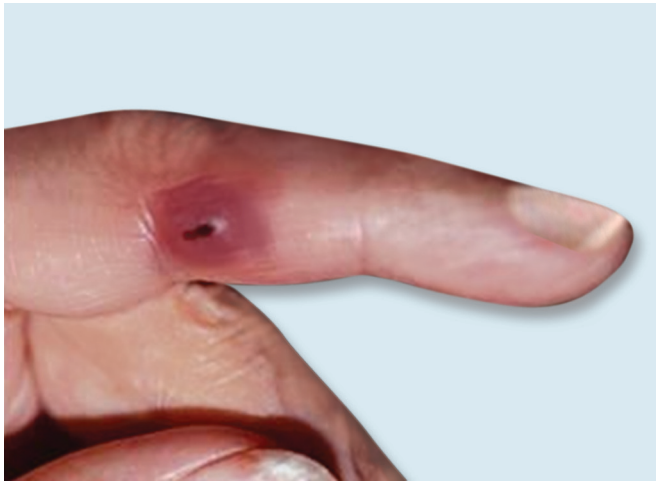
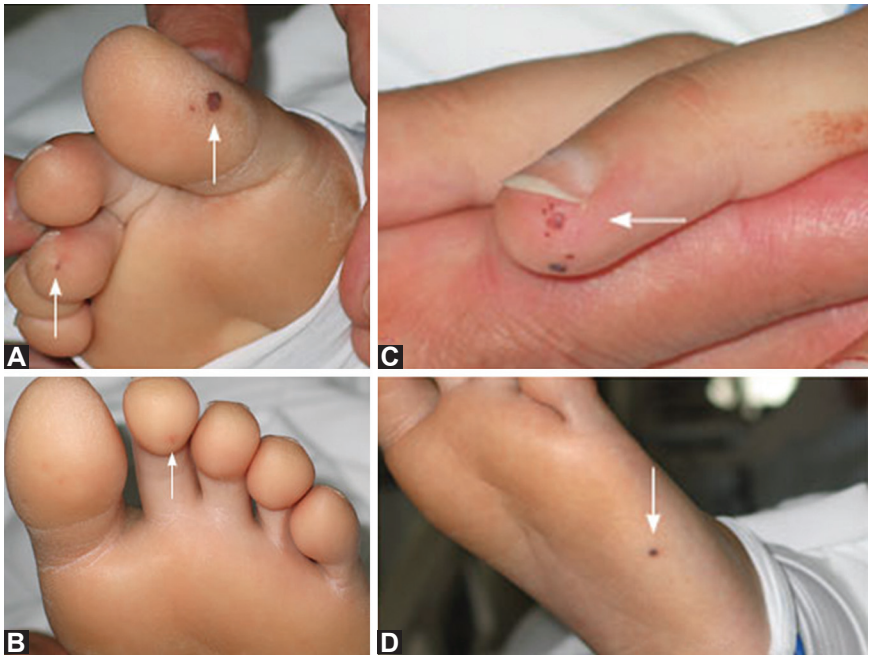


Fig. 1: Janeway spot (usually seen in staphylococcal endocarditis; it is painless, septic emboli)



Figs 2A to D: Osler's nodes (painful, immune complex microvasculitis)

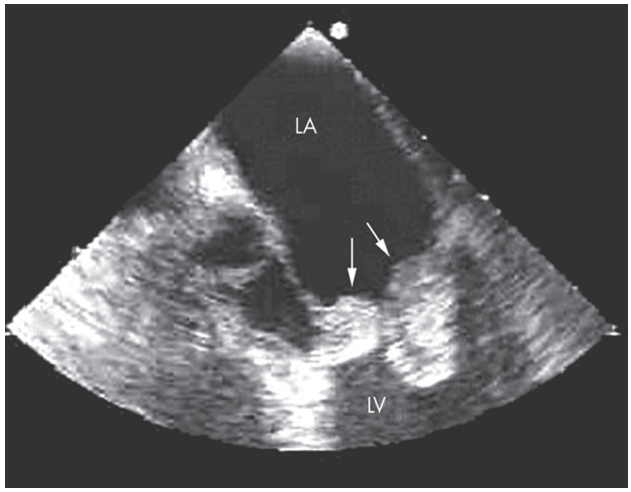


Fig. 3: Transesophageal echocardiogram of infected mitral bioprosthesis. Abbreviations: LA, Left atrium; LV, Left ventricle

To establish a diagnosis of infective endocarditis, physicians need the following:

- Two major criteria, or
- One major + three minor criteria, or
- Four minor criteria

TREATMENT

- *Streptococcus viridans* endocarditis—IV crystalline penicillin 2 mega units every 4 hr for 2–4 weeks
- *Staphylococcus aureus* endocarditis—IV oxacillin 2 g every 4 hr for 4–6 weeks + IV gentamicin 1 mg/kg every 8 hr for 5 days. For prosthetic valve infection, add rifampin 300 mg every 8 hr for 2 weeks

In general, prosthetic valve infection needs extra 2–4 weeks of antibiotic therapy.

Development of heart failure in presence of infective endocarditis indicates valve damage or local abscess formation. If possible, antibiotic course should be completed. If the heart failure worsens and further waiting is hazardous, immediate valve replacement is necessary.

PROGNOSIS

In *Streptococcus viridans* the prognosis is good. In more virulent endocarditis, it is guarded. In these cases chances of valve perforation, myocardial abscess formation and embolism is high. Comorbid conditions, such as immune disorders and diabetes, adversely affect the prognosis.

PROPHYLAXIS

Given the seriousness of the condition, it makes sense to use care when dealing with predisposing conditions. Routine dental work does not require prophylaxis unless echocardiogram shows deformed valve. All other surgical procedures, which involve bleeding, should be covered by preoperative antibiotic on the day of surgery.

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26 CHAPTER

Pericardial Diseases

Jayant C Bhalerao

Pericardial diseases are quite common and may present in one of the three forms:

1. Acute pericarditis
2. Pericardial effusion and tamponade
3. Constrictive pericarditis.

ACUTE PERICARDITIS

This is an acute onset of febrile illness with self-limiting course over 7–10 days.

Causes

- Most cases remain idiopathic. Sometimes recurrent viral: Coxsackie virus, or echovirus
- Bacterial: Tuberculosis or any other bacteria
- Reactive: Acute myocardial infarction (MI) (more common in anterior than inferior MI) or adjoining pneumonia, post-coronary artery bypass graft (CABG), Dressler's syndrome
- Metabolic: Uremia
- Trauma: Blunt chest injuries
- Radiation therapy
- Malignancy.

Symptoms

- Acute chest pain, which has "pleurisy-like" character, increases with respiration and cough, worsened in supine position and relieved in sitting position with forward stoop, and increases during swallowing
- Dyspnea
- Atrial arrhythmias
- Fever
- Other features of collagen disease, or renal failure may be present

Signs

- Typical, scratchy friction rub widely heard over the pericardium with systolic and diastolic components. It sounds superficial and may get more intense by pressing the stethoscope. As fluid accumulates between the visceral and parietal layers, the friction rub may get less intense.

Diagnosis

- Electrocardiogram is typical. It shows sinus tachycardia and widespread ST elevation with "upward coving" (Fig. 1)
- Chest X-ray may show cardiomegaly if significant effusion is present
- Echocardiogram may show pericardial effusion
- Computed tomography (CT) scan of chest gives better pericardial definitions than magnetic resonance imaging (MRI).

Treatment

- Anti-inflammatory agents, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Avoid corticosteroids in acute MI (increased risk of myocardial perforation)
- Colchicine is quite effective for idiopathic recurrent pericarditis.

PERICARIDIAL EFFUSION

This is often a consequence of acute pericarditis. It should always raise the possibility of myxedema. Sudden, large accumulation of pericardial fluid does not allow time for hemodynamic adjustment and may lead to cardiac tamponade, a serious medical emergency. Usually such cases are due to malignancy. Tamponade is a stage, when pericardial effusion causes sudden, significant hemodynamic change such as hypotension or shock.

Clinical Signs

- Beck's triad: Distended jugular veins, muffled heart sounds and hypotension
- Pulsus paradoxus is not specific
- Electrocardiogram: Electrical alternans is a very good diagnostic sign (Fig. 2)
- Right heart catheterization: Equalization of right atrium, right ventricle, pulmonary artery and pulmonary capillary wedge pressures. It happens in large effusions only
- Echocardiogram: It is very diagnostic. If it shows clear separation of visceral and parietal pericardium in systole as well as diastole, the effusion is greater than 250 cc and usually over 700 cc in tamponade. In tamponade, there is diastolic compression or "collapse" of atrial and right ventricular wall. There is also marked attenuation of venous inflow across mitral and tricuspid valve and inferior vena cava (Fig. 3)
- Computed tomography scan of chest is excellent tool to confirm the diagnosis

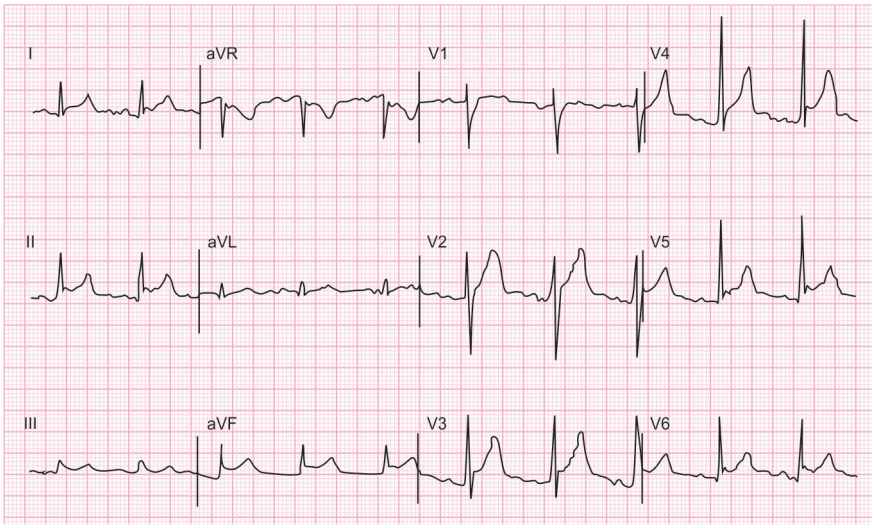

Fig. 1: Electrocardiogram in acute pericarditis showing diffuse upsloping ST segment elevations seen best in leads II, III, aVF, and V3 to V6. There is also subtle PR segment deviation (positive in aVR, negative in most other leads). ST segment elevation is due to a ventricular current of injury associated with epicardial inflammation; similarly, the PR segment changes are due to an atrial current of injury which, in pericarditis, typically displaces the PR segment upright in lead aVR and downward in most other leads. *Courtesy*: Ary Goldberger, MD

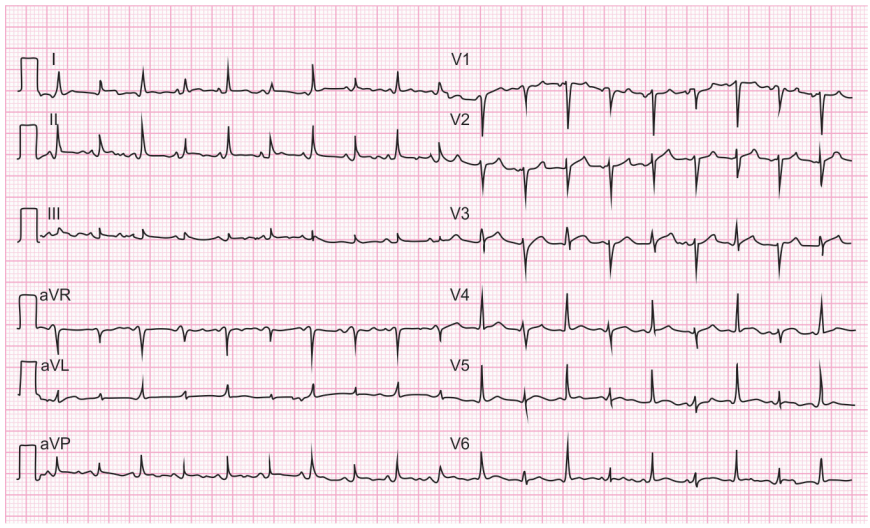

Fig. 2: Electrocardiogram showing electrical alternans. Changing R wave amplitude in alternate beats as the heart swings back and forth in the large pericardial effusion

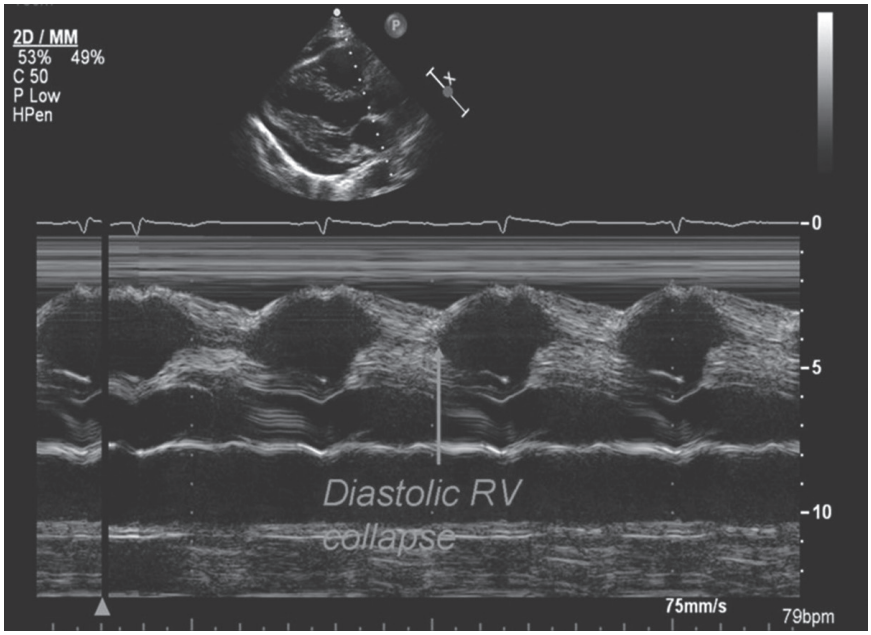

Fig. 3: Echocardiogram showing right ventricular diastolic collapse in cardiac tamponade

- Pericardiocentesis: Pericardial fluid must be sent for tuberculosis smear and culture, viral and bacterial cultures, cytology for malignant cells, antinuclear antibody serology (ANA), along with routine analysis for proteins, sugar and cell count

Treatment

- Pericardiocentesis is both diagnostic as well as therapeutic. In tamponade, it is urgently needed. When removing large quantities of pericardial effusion, make sure IV volume replacement is done simultaneously to avoid sudden hypotension. Indwelling catheter is usually left in pericardial space for 3–4 days. Author follows this with CT chest to make sure the catheter is placed properly
- Anti-inflammatory agents. Corticosteroids are very beneficial
- If myxedema is diagnosed, slow oral thyroid replacement therapy is initiated. Usually, pericardiocentesis is not necessary because pericardial fluid accumulates over a very long period, allowing hemodynamic adjustment. It recedes nicely over 2–3 months with thyroid replacement therapy
- Bloody pericardial fluid is usual indicative of malignancy invading the heart. Cytology should confirm this. Prognosis is uniformly bad
- Surgery: "Pericardial window" is quite effective in benign cases.

CONSTRICTIVE PERICARDITIS

This is a consequence of chronic pericarditis with effusion. Exudative pericardial effusion being so rich in protein, usually leads to extensive fibrosis. This leads to a condition of constrictive pericarditis. As a result of constriction, right cardiac chambers are unable to fill adequately. Its consequence is felt downstream in the left cardiac chambers also and stroke volume drops. Bacterial infections especially tuberculosis is a common cause.

Diagnosis

- Clinical signs are typical. Usually patient presents with markedly distended jugular veins, ascites and edema, but clear lungs
- Kussmaul's sign: Jugular veins instead of decreasing, increase during inspiration, as right heart is unable to accept larger blood volume
- Diastolic thud: Very typical and very easy to hear. It can be mistaken for S3 heart sound
- Dyspnea on exertion
- Atrial fibrillation is common
- Blood test for brain natriuretic peptides (BNP) is always normal as opposed to restrictive cardiomyopathy (often a differential diagnostic dilemma)
- Computed tomography scan of chest is much better than MRI
- Echocardiogram: (1) flat posterior wall during diastole (2) paradoxical septal motion ("septal bounce") (3) distended inferior vena cava with "absent inspiration collapse" and (4) decreased inflow pattern in tricuspid and mitral valves
- Right heart catheterization (Swan-Ganz catheterization): Very typical "square root sign" in right atrial wave, rapid C-D slope and A-C slope indicating a gasping right heart for blood.

Treatment

- Surgery: Decortication offers excellent result in 90% cases. Watch for damage to coronary arteries during the procedure.

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27 CHAPTER

Diseases of the Aorta

Jayant C Bhalerao

AORTIC DISSECTION

Tear in the intima of the aorta causes blood to enter the layers of aorta. As it flows through the layers, it peals the layers apart to various lengths. This is called aortic dissection or dissecting aneurysm of aorta. The initial tear is usually spontaneous. It may occur in the 3rd trimester of pregnancy or due to trauma. Most of the dissection starts about an inch of the aortic valve. It generally affects the structural support to the valve mechanism and leads to severe aortic regurgitation. Long standing hypertension is the most common denominator in the etiopathogenesis of aortic dissection. Ninety percent of these patients die within a day or two of the onset; therefore, immediate diagnosis and treatment provides the only slim chance. Dr Michael DeBakey, the famous heart surgeon from Houston, Texas, who first classified the aortic dissection, himself suffered from it at the age of 97 years and survived surgery and returned to full-time work for 2 years before dying of other causes.

Classification

Everyone now uses the Stanford classification. DeBakey classification is now obsolete.

Stanford Classification

- Group A: Involves the ascending aorta no matter where it originates
- Group B: Involves the descending aorta

Group A needs urgent surgery and Group B is treated medically. It is the Group A, which creates the greatest mortality and must be diagnosed as soon possible if there is any hope of saving these patients.

Signs and Symptoms

Patient generally presents with sudden boring pain in the chest with extreme restlessness. This pain is so intense that even after huge doses of narcotics it remains uncontrolled. The patient is writhing with pain even after intravenous

(IV) Brevital. Their eyes are saturated with fear. There is panic in patient's gaze as he tosses and turns in the bed. Physicians may see hundreds of patients with acute myocardial infarction (MI), but will never see a patient with this degree of pain and discomfort. Once physicians see a case or two, it will always stay with them. This realization is very important in suspecting the disease. Physicians cannot diagnose this condition antemortem if they do not think about it. Emergency room physician who usually sees them first have the awesome responsibility. If thrombolytic therapy is initiated (because acute MI is considered), certain doom is to be expected. This happened in case of John Ritter, a famous television star in America. He died and the doctors were sued for missing the diagnosis.

Dissection is often associated with severe aortic regurgitation. If the dissection involves the coronary artery opening, electrocardiogram (ECG) will look like acute MI. Dissection generally progresses antegrade, but at times goes retrograde tearing up the layers of pericardium causing tamponade. Usual antegrade progression will affect the arch and the arteries originating from it. This may lead to stroke, sudden obliteration of subclavian arteries, etc. If physicians miss the initial diagnosis, none of what happens in the aftermath is of value because the battle is already lost.

Diagnosis

Diagnosis is made by paying attention to the character of pain and the associated restlessness and intense panic in patient's eyes. If physicians suspect it, they will easily diagnose it. To quote the famous pathologist William Boyd, "Your eyes only see what your mind already knows".

- Chest X-ray in the emergency room will further arouse suspicion if the mediastinum is widened. Notify the surgical team of a possible case early rather than late. Arrange four units of packed red cells. Transesophageal echocardiogram is ideal if it can be done without causing more distress to an already panic-stricken patient
- Echocardiogram is done while patient is being wheeled in for magnetic resonance imaging (MRI) or computed tomography (CT) scan of chest. Patient's restlessness makes these procedures difficult
- Electrocardiogram may show wildly changing patterns of anterior or inferior MI
- Blood D-dimer level less than 500 ng/mL can rule out dissection:
  Magnetic resonance imaging is the gold standard
  Do not waste time in useless tests.

Treatment

- Surgery as soon as possible. Patient is generally sent to operating room straight from the emergency room
- Intravenous nitroprusside and labetalol to keep blood pressure as low as possible.

Causes

- Long-standing hypertension is a common denominator
- Marfan's syndrome causes medial necrosis, predisposing to dissection.

Group B Dissection

Dissection starts in descending aorta. It is a rare complication of pregnancy and seen in 3rd trimester or during labor. It is treated medically with management of hypertension and beta-blockers.

COARCTATION OF THE AORTA

This congenital disorder of aortic arch development is rare in adult cardiology. Most cases are diagnosed and taken care of by pediatric cardiologist. Still, it is good for adult cardiologists and internists to know a little bit about it especially in the context of hypertension. Commonest variety in adults is post-ductal variety. The aortic constriction is distal to the origin of left subclavian artery. It leads to ischemia distally and often presents with hypertension (renal ischemia), and intermittent claudication (leg ischemia).

Basic Embryology

Of the six pairs of aortic arches, only 3, 4 and 6 are important in the development of aortic arch. Other pairs degenerate and disappear. The third arch constitutes internal carotid artery, 4th arch constitutes aortic arch and right subclavian artery and the 6th aortic arch constitutes pulmonary arteries and ductus arteriosus.

Clinical Signs

- Post-stenotic dilatation of aorta gives “figure of 3” sign on chest X-ray
- “Notching of the ribs” due to collateral circulation on chest X-ray
- Hypertension
- Weak arterial pulses in lower extremities.

Diagnosis

- Magnetic resonance imaging of chest is the gold standard
- Echocardiogram
- Chest X-ray.

Treatment

- Surgical correction
- Angioplasty.

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28 CHAPTER

Pregnancy and Heart Disease

Jayant C Bhalerao

Pregnancy causes major hemodynamic changes which peak in second trimester. These physiological changes are:

- 50% rise in blood volume
- 10–15 beats/min rise in heart rate
- 10–20 mm Hg drop in blood pressure
- 50% increase in cardiac output
- Decrease in systemic resistance as placental vessels develop

These changes usually cause a systolic flow murmur and S3 gallop during pregnancy.

Predictors of maternal risk for cardiac complications—A rating system:

- Prior cardiac events such as congestive heart failure, transient ischemic attack and cerebrovascular accident 1 point
- Prior arrhythmias such as sustained paroxysmal atrial tachycardia or bradyarrhythmias 1 point
- New York Heart Association (NYHA) class III or IV 1 point
- Obstructive valvular heart defects 1 point
- Myocardial dysfunction such as ejection fraction less than 40, idiopathic hypertrophic subaortic stenosis, etc. 1 point

Percentage of maternal cardiac event goes from 5 to 75% when there are more than three points.

GESTATIONAL HYPERTENSION

Hypertension is the major cause of maternal morbidity and mortality. There are three types:

1. Chronic or preexistent
2. Gestational hypertension: New onset high blood pressure without proteinuria
3. Preeclampsia: New onset with proteinuria.

Gestational hypertension usually resolves with pregnancy but there is high incidence of developing chronic hypertension.

TREATMENT CONSIDERATIONS

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and Spironolactone are contraindicated in pregnancy
- Thiazide diuretics should be avoided during pregnancy.
- Best options are old time tested drugs such as alpha methyldopa, labetalol, hydralazine and nifedipine
- Magnesium sulfate is particularly helpful in preeclampsia.

POSTPARTUM CARDIOMYOPATHY

Congestive heart failure developing with 3 months of pregnancy is considered to be due to side effect of pregnancy either due to some toxins or unknown factors. It typically resolves in few months but may reappear during the next pregnancy.

ANTICOAGULATION THERAPY IN PREGNANCY

Managing proper anticoagulation therapy during pregnancy poses many challenges and anyone taking care of such patient, should familiarize himself or herself with it. Prosthetic valves especially metallic mitral valves are the greatest challenge.

Since warfarin crosses the placenta, it can harm the fetus. It affects cartilage formation especially in the first 4 months of pregnancy. It is called "warfarin embryopathy". Patients need anticoagulant therapy during pregnancy (such as in prosthetic heart valves and atrial fibrillation) must be immediately switched to low-molecular weight heparin (LMWH). Usual dose is 1 mg/kg twice a day. Trough and peak levels of factor 10 (anti-factor Xa) are done periodically to adjust the dose. Trough level is done 1 hour before and peak level is done 4 hours after the dose of Lovenox (LMWH). Trough level should be 0.7 and peak level 1.2–1.5. One problem is that the test results may take up to a week to get back, which basically defeats the purpose. Some like Dr Uri Elkayam, MD of UCLA Medical Center, Los Angeles, CA, believe Coumadin is safe after 16 weeks of pregnancy because by now most of the cartilage is formed.

Biggest problem is in prosthetic mitral valve. They are far more liable to develop thrombus because of low pressure gradients as compared to prosthetic aortic valve.

Long-term heparin use causes osteoporosis. Vitamin D and calcium supplement should be used. Thrombocytopenia is other problem with long-term use of heparin and should be watched carefully.

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29 CHAPTER

Heart Transplant

Jayant C Bhalerao

Since Dr Christiaan Barnard performed the world's first successful human-to-human heart transplant, the procedure has become an accepted medical procedure in treating end-stage cardiac conditions. Survival rates are 90% in 1st year and 70% in 5 years. Many are living 25 years after receiving a heart transplant.

All transplants are "allograft" meaning the donated heart comes from another human being who has been declared "clinically dead".

Almost all are "orthotopic" meaning the patient's heart is removed and replaced by the donor heart.

Over the years, three major developments have boosted the success rates:

1. New legal definition of "death": Instead of waiting for the electroencephalography (EEG) to become straight line, now the organ procurement for donation can start when two physicians declare a person "clinically dead" or "brain dead" or "beating heart cadaver", when brain injury is unlikely to reverse. In such cases, usually trauma cases, heart is still beating when it is procured for transplantation. Enormous efforts are needed to educate the society to consider this option for their loved ones.
2. National transplant registry: Utilization and prioritization has become more equitable since the establishment of National and International registry. Needy patients get the priority. Younger patients get preference over older ones. Biocompatibility information of all patients is stored on computer. Patients over the age of 55 years are not considered for transplant because of high mortality rates from sepsis.
3. New antirejection medicines: Combination of corticosteroids, cyclosporine and azathioprine has reduced the chances of rejection and thus improved survival.

COMPLICATIONS

- Sepsis
- Rejection of donor heart: highest risk is in first 3 months
- Side effects from antirejection medicines
- Posttransplant severe hypertension.

FOLLOW-UP

- Constant reconnaissance for rejection is mandatory. Periodic myocardial biopsy by a special catheter inserted via subclavian vein
- Periodic echocardiogram.

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30 CHAPTER

Cardiac Tumors

Jayant C Bhalerao

INTRODUCTION

Cardiac tumors may be either Primary (almost always benign) or, Secondary (usually metastatic and malignant). Almost all primary tumors of the heart are benign and almost all the secondary tumors are malignant metastatic (from breast or lung cancer).

PRIMARY TUMORS OF THE HEART: ATRIAL MYXOMA

Diagnosing atrial myxoma on echocardiogram is one of the most exhilarating experiences in medicine. These are benign tumors arising from the wall of the atria, usually from left, sometimes from the right. Usually these are elderly females. Sometimes, familial transmission is noted.

SYMPTOMS

- Features suggesting bacterial endocarditis, e.g. chronic fever and joint pains, which lead one to echocardiography and make the diagnosis of myxoma
- Dyspnea
- Syncope
- Chest pain
- Palpitations
- Sometimes the tumor fragments embolize and cause stroke, blindness, etc.

DIAGNOSIS

- Echocardiogram: The features of myxoma are unique. There is a large echo-dense image from atrium squeezing down to the ventricle back and

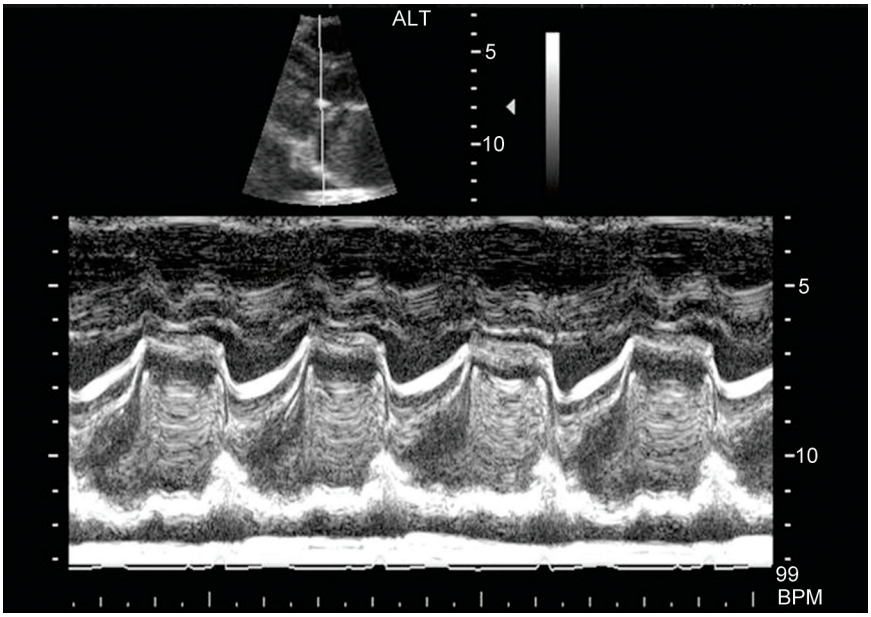

Fig. 1: Echocardiogram showing left atrial myxoma. Note the clear lag period after opening of mitral leaflet

forth through the mitral or tricuspid valve. It can be differentiated from large vegetation attached to the valve by a well-defined lag period after the valve opening (Fig. 1)

- Angiography.

TREATMENT

- Surgical excision is curative
- Watch for pulmonary embolism from the surgical site in right atrial myxoma.

SECONDARY TUMORS OF THE HEART

These are usually metastatic from breast or lung cancer. They present with massive pericardial effusion or advanced conduction defect. Prognosis is uniformly grave.

Sarcoidosis can involve myocardium frequently causing advanced heart block. It is a benign granuloma and resolves nicely with corticosteroid therapy.

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CHAPTER 31

Depression in Post-Myocardial Infarction and Post-Coronary Artery Bypass Graft Patients

Jayant C Bhalerao

Depression is very common in post-myocardial infarction (MI) and post-coronary artery bypass graft (CABG) patients. Both are soul-stirring experiences and must affect patients deeply. Jokingly physicians say that 70% admit being depressed and the other 30% are liars! No matter how much physicians explain that patients will be able to resume doing what they did before, it just does not sink in. It only improves after patients are able to return to work and their normal daily activities. Cardiac rehabilitation is extremely beneficial in restoring confidence in these patients.

Persistent depression beyond a year after MI or CABG is a serious problem. Mortality rates in such patients are three times higher. Psychological intervention and serotonin reuptake inhibitors (SSRIs) do help the symptoms but do not alter the prognosis. Although beta-blockers are routinely used in such cases, they are usually not a cause of major depression.

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32 CHAPTER

Miscellaneous Topics

Jayant C Bhalerao

OXYGEN DISSOCIATION CURVE

This is an important concept in medicine and it is worth discussing briefly. It is a favorite board question, so pay attention and understand the basic principle. Oxygen saturated hemoglobin also known as oxyhemoglobin (SO_2) in pulmonary capillaries, gives up this oxygen in peripheral tissues because the partial pressure of oxygen (PO_2) gradually decreases. In other words, there is an inverse relationship between O_2 affinity of oxyhemoglobin and PO_2. If we plot a graph with PO_2 on horizontal X-axis and SO_2 in vertical Y-axis, we can obtain a curve. This curve is called oxygen dissociation curve. This curve has a sigmoid shape (Fig. 1).

If physicians look at the top right of the curve, SO_2 is 100% at PO_2 of 100 mm Hg. This is in pulmonary capillaries. As the blood reaches peripheral tissues (left side of the curve), the PO_2 drops, making it difficult for the oxyhemoglobin to retain all its four molecule of O_2 and they are released in the surrounding fluid and the SO_2 level drops. (Remember: SO_2 level is inversely related to the O_2 affinity with the only exception of CO toxicity). A point where the SO_2 reaches 50%, it is referred to as P-50. In a normal person, it occurs when the PO_2 drops to about 26.5 mm Hg. This part of the curve is seen at the level of peripheral, systemic capillaries.

Let us presume, this person is exercising or has high fever. Both conditions increase O_2 demand. In such conditions, the P-50, or the dissociation curve shifts to the right, meaning that the O_2 will be released quickly at a higher PO_2. Acidosis does the same. Remember a mnemonic, "CADET, face right!"which stands for CO_2, Acid, 2-3 DGP, Exercise and Temperature. P-50 shifts to the left in opposing conditions such as hypothermia, alkalosis and carbon monoxide poisoning.

DOPPLER EQUATION

Echocardiography and cardiac Doppler has become a common diagnostic tool in medicine. It makes sense to know some fundamentals of Doppler equation.

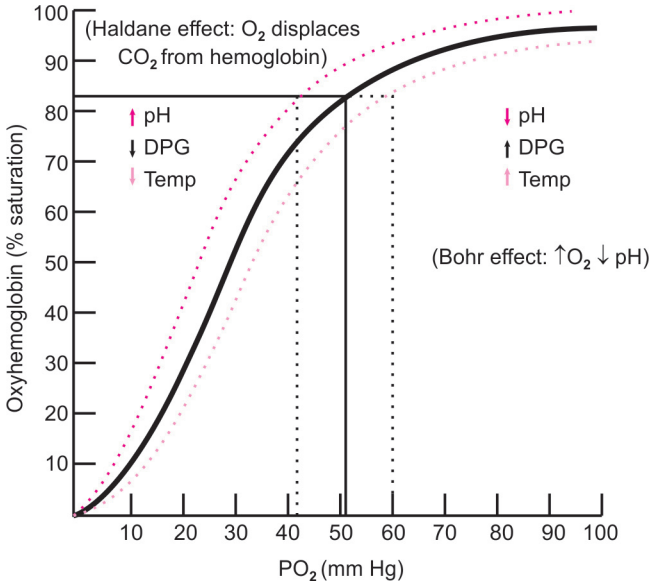


Fig. 1: Oxygen dissociation curve

Doppler principle states that sound waves coming towards you get louder and sound waves going away from you get fainter. Using the Doppler equation, physicians can calculate the velocities of these returning sound waves (Doppler shift).

Doppler equation:

$$Fd = 2Ft.V.\cos\theta/C$$

Fd = Doppler shift
Ft = transmitted beam
C = speed of sound in tissue
V = velocity of blood
cos θ = angle of incidence between ultrasound beam and the direction of blood flow

Thus, if the value of Ft, C and cos θ is constant:

$$Fd = V$$

Once we know the velocity of blood at any given location, various formulae can help calculate the Valvular stenosis or cardiac output.

Doppler devise is fancy speedometer designed to detect red cell motion (blood flow) and measure its speed (velocity).

Transducer acts both as transmitter and receiver of sound waves (velocities). These velocities are converted to audible sounds and pictures. Flow coming towards the transducer is red and the one going away is blue.

There are two forms of velocities (flow):

1. Laminar flow: smooth, uniform and pleasant sound
2. Turbulent flow: harsh, rough sound

Normal blood flow in blood vessels is laminar. When the vessel is stenosed, the flow changes to turbulent flow, which has higher velocity and the Doppler envelope becomes broad (spectral broadening).

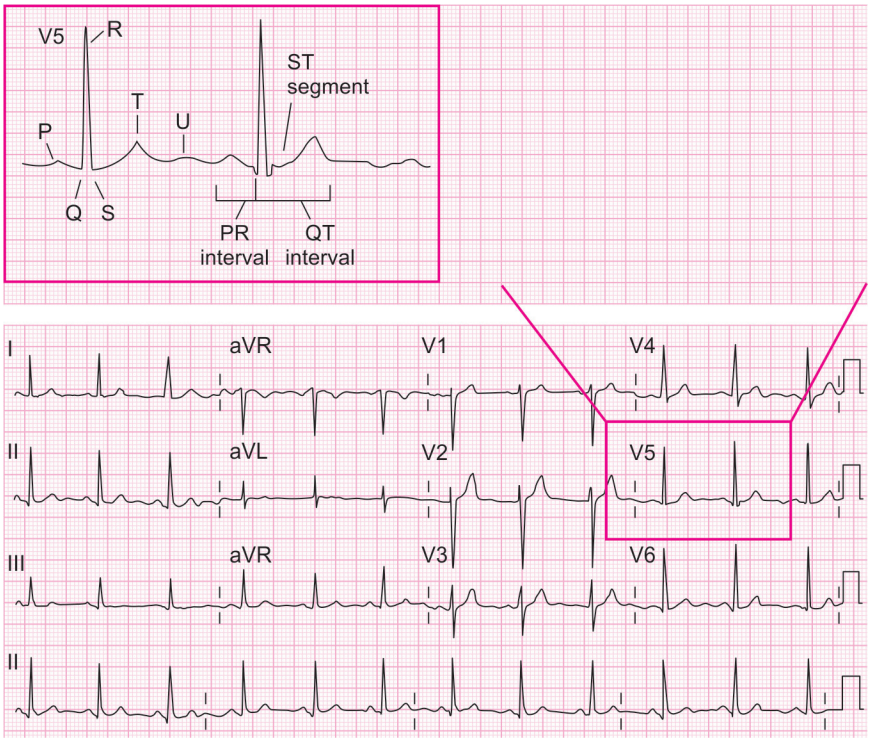
POTASSIUM AND THE ELECTROCARDIOGRAPHY

The most common electrolyte abnormality physicians come across in cardiology is serum potassium (normal level: 3.5–4.5 mEq/dL). It is important to know the electrocardiographic changes in various potassium levels. For this reason, author shows an electrocardiogram when the potassium level is 4, 8 and 2 mEq/dL (Figs 2A to C). Metabolic acidosis either due to renal failure or cardiogenic shock, are the common causes (Fig. 2B).

CARDIAC ELECTROPHYSIOLOGY: ACTION POTENTIAL

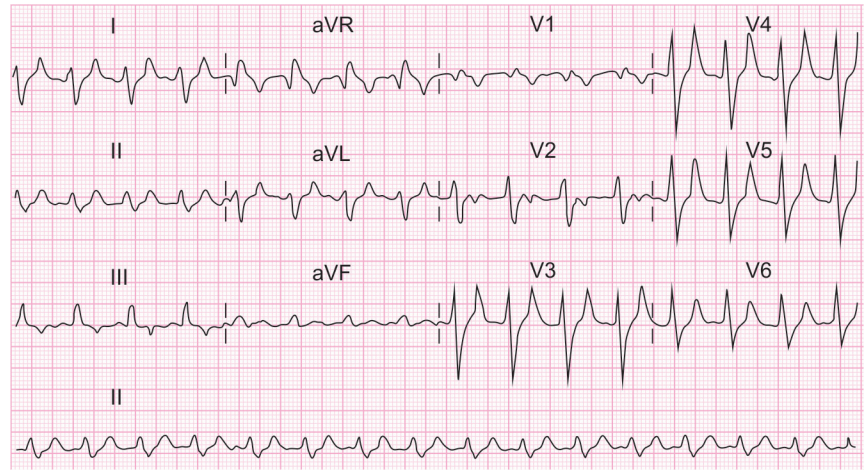
For a clinician, understanding the electrophysiology is difficult, but essential. Author gives a simple explanation of this complex subject.

In response to electrical stimulation, the cell is activated (depolarized). This process is regulated by influx of cations and anions into the cardiac myocyte. Sodium ions, potassium ions and calcium ions play the pivotal role. There are gates on the cell wall, which allow entry and exit for these ions. Normal myocyte (contractile element of the myocardium) is negatively charged at rest. When depolarized (stimulated), positively charged Na^+ and Ca^+ ions enter the cell making it "less negative". Once fully depolarized, these ions slowly leave the myocyte till it comes back to the resting phase. Calcium plays the role of



A

Fig. 2A



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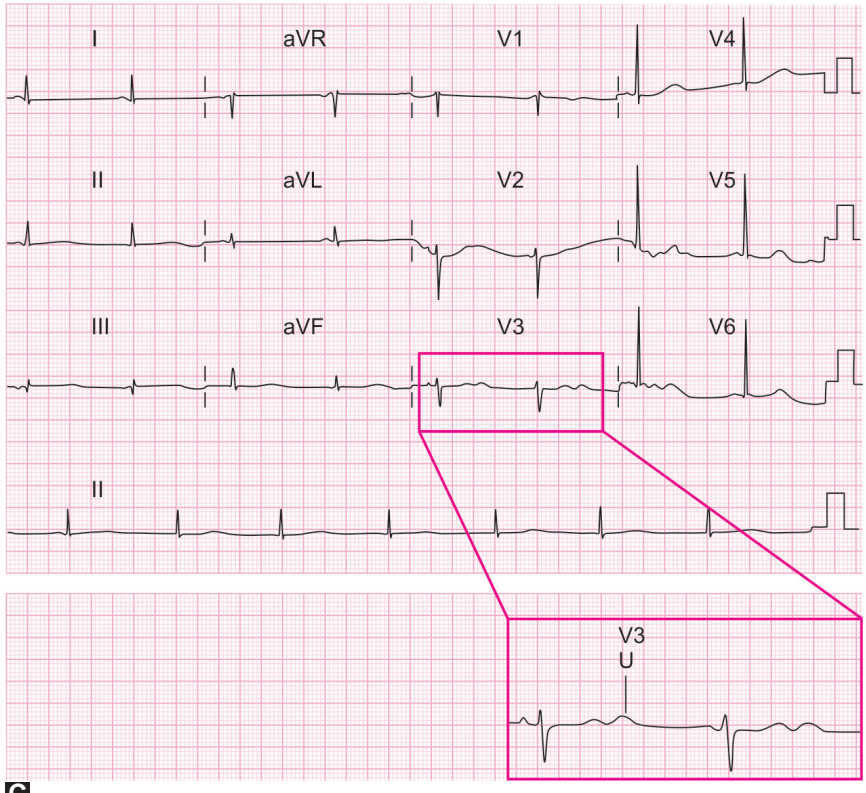

C

Figs 2B and C

Figs 2A to C: Just watch the T waves. Higher the potassium, taller is the T wave. (A) Potassium level 4 mEq/dL (normal). (B) Potassium level 8 mEq/dL. Watch the T waves in V4, V5 and V6. (C) Potassium level 2 mEq/dL. Keep an eye on the T waves in limb leads

keeping the K^+ ions inside the cell as long as possible and thus sustaining the contraction (depolarization).

Actual action potential curve in myocardium has five stages (stage 0 to stage 4).

Resting potential is stage 4, which is normally around -90 mV. When electrically stimulated, Na^+ ions start to enter the myocyte slowly (Fig. 3).

In phase 0, the Na^+ and K^+ ions very rapidly enter the cell. Since they are positively charged, the resting potential begins to get less negative and as it reaches around -45 mV, Ca^+ ions begin to enter the cell. They will sustain the depolarized state. Once reaching +50 mV, K^+ ions begin to leave the cell.

Stage 1: All the positively charged ions, Na^+, K^+ and Ca^+ are inside the myocyte at this stage. K^+ ions are the first to leave but Ca^+ ions try to blunt the effect in order to sustain the contraction phase.

Stage 2 (Plateau phase): Ca^+ ions are trying to hold back the K^+ ions inside the cell thus creating a plateau.

Stage 3 (Rapid depolarization phase): Ca^+ ions no longer can hold back the K^+ ions from leaving the cell, leading to rapid depolarization wave. As the positively charged ions leave the cell rapidly, the action potential begins to change to negative till it reaches the resting potential of -90 mV. Phase 4 starts with slow replenishment of Na^+ ions inside the cell.

In contrast to the action potential of the myocyte, AV node has a special property of being depolarized without any external stimulation. This is because the resting membrane potential is much less negative (-60 mV instead of 90 mV). Ca^+ and K^+ ions play a bigger role in this action potential (Fig. 4).

Stage 4 starts with slow Na^+ influx via I-f channel till the action potential reaches -45 mV when the Ca^+ channels open allowing Ca^+ influx making the

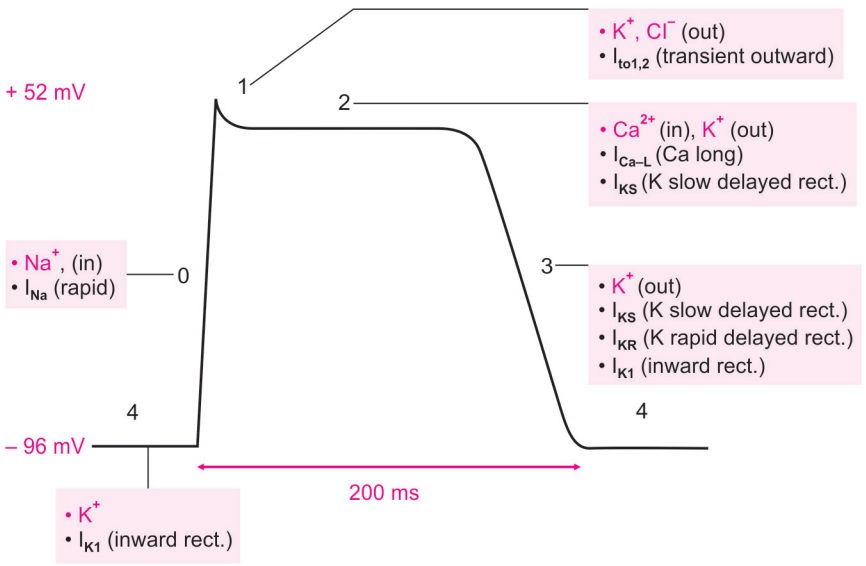

Fig. 3: Actual action potential curve in myocardium

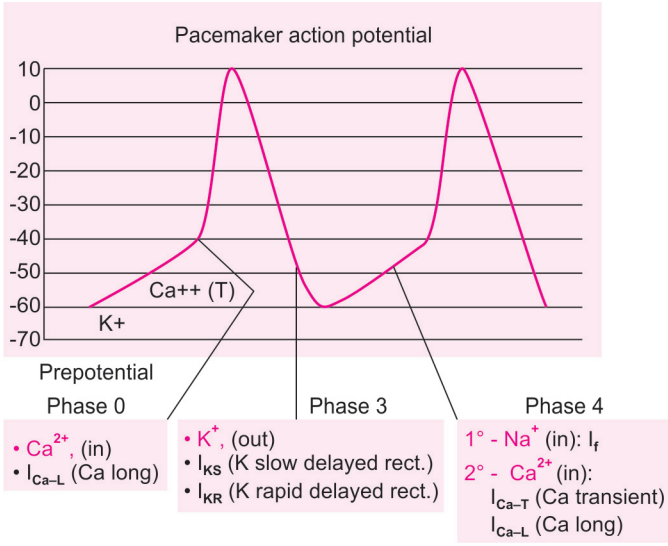

Fig. 4: Automaticity of the sinoatrial node

action potential more positive till it reaches 0–10 mV. K^+ start to leave the cell at this level till the resting membrane potential of -60 is reached and the cycle repeats.

This is just a simplistic version of this rather complex physiology.

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CHAPTER 33

Exercise Electrocardiographic Testing

Jayant C Bhalerao

BACKGROUND

It is a known fact that resting electrocardiogram (ECG) may remain normal even in severe coronary artery disease. Exercise increases O_2 demand of the myocardium and can uncover latent underlying coronary artery disease. Exercise induced ST-T changes became a better way to evaluate patients for coronary artery disease. It has one drawback. It has low sensitivity and specificity. ["Sensitivity" means how accurate it is in diagnosis of significant coronary artery disease (CAD) when the test is reported abnormal. "Specificity" means how accurate it is in excluding significant CAD when it is reported normal.]

To increase its sensitivity and specificity, other modalities, such as nuclear imaging or wall motion studies (echocardiogram), are being used routinely.

Exercise can be performed by treadmill or bicycle, treadmill being the most popular. Various protocols have been developed using different speeds and grades. Most popular are Bruce protocol, modified Bruce protocol and Naughton protocol. For the test to provide meaningful result, patient has to achieve certain heart rate based on age and weight (predicted maximum heart rate). Nomograms have been developed and most treadmill machines can automatically give this information.

INDICATIONS

- Diagnosis of CAD
- Diagnosis of arrhythmia and therapeutic efficacy of treatment
- Evaluation of functional capacity
- Exercise prescription evaluation.

CONTRAINDICATIONS

- Unstable angina
- Unstable hemodynamic state
- Unstable hypertension

- Complex cardiac arrhythmia
- Severe aortic stenosis.

PROCEDURE

- Patient preparation: Patient may have a light breakfast prior to test. Comfortable walking shoes and appropriate clothing is recommended. Patients must avoid using creams or lotions to chest wall as they can interfere in lead stability. Avoid smoking and caffeine prior to stress test. Hairy chest will require shaving. Skin over chest is scrubbed with alcohol before applying ECG electrodes. All stress test machines give diagrams for lead placement (Fig. 1)
- Record resting ECG and blood pressure, which should be recorded every three minutes
- Limiting symptoms: Test is terminated if patient expresses fatigue, dyspnea, chest pain, severe hypertension (over 240/120 mm Hg), and dizziness or if complex arrhythmia is noted. Drop in blood pressure during exercise may indicate high-grade coronary artery disease
- Recovery phase: Vital signs are monitored until they are back to resting levels.

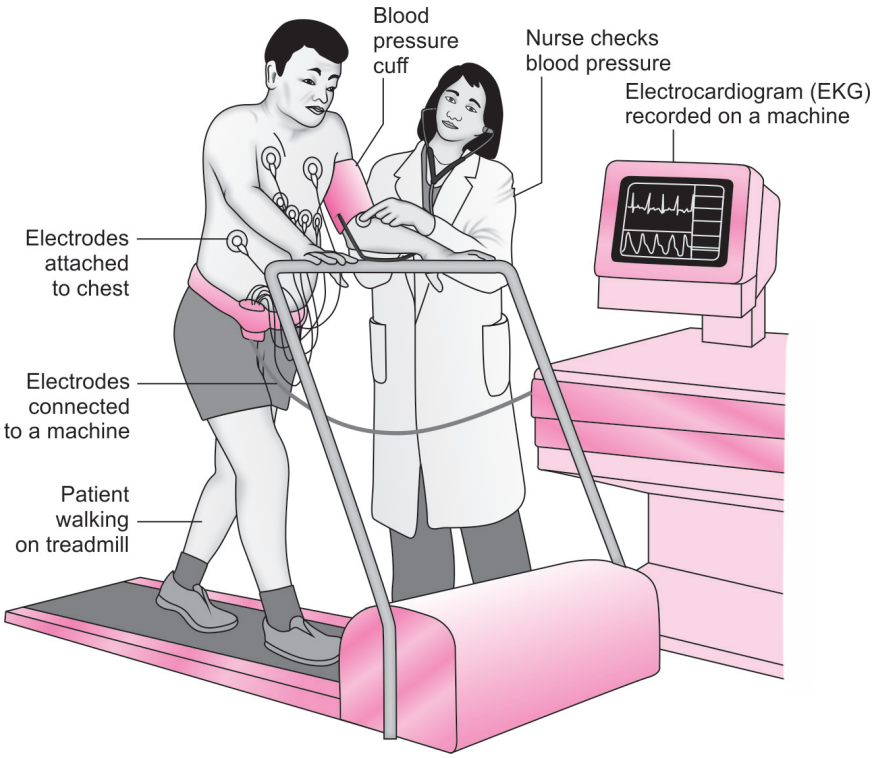

Fig. 1: An illustration of a patient having stress test. Electrodes are attached to the patient's chest and electrocardiogram is recorded on a machine. Blood pressure of patient is recorded while he walks on a treadmill

INTERPRETATION

- ST-T changes: Ischemia is indicated when ST segment is depressed by at least 1 mm (in women 2 mm), flat or down-sloping, lasting for at least 1 or more minutes in recovery phase. Most commercial systems use ST integral (ST depression lasting at least 80 mm from J point). Up sloping or rapidly normalizing ST segment in recovery phase is often due to "false-positive" response and quite common in women
- ST elevation: In absence of prior Q wave myocardial infarction (MI), indicates marked ischemia. ST elevation in presence of Q wave MI indicates dyskinesis
- ST segment "normalization": Baseline ST depression may "normalize" during exercise. It indicates ischemia
- ST-T changes late in recovery phase: Development of ST-T changes only in late recovery phase are of questionable significance
- R wave amplitude may change during exercise. It has little significance.
- T and U wave changes: T wave inversion without ST changes is not a diagnostic feature of ischemia during exercise. U wave inversion is common in electrolyte imbalance and left ventricular hypertrophy (LVH). It may also indicate ischemia if these other factors are excluded
- Symptoms, such as classical angina, with or without ST change are obviously abnormal

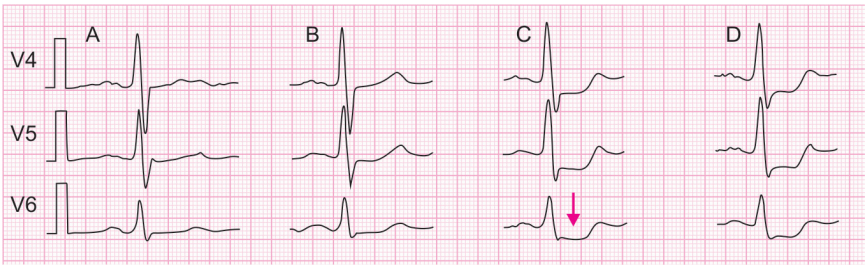

Fig. 2: Stress electrocardiogram of a patient

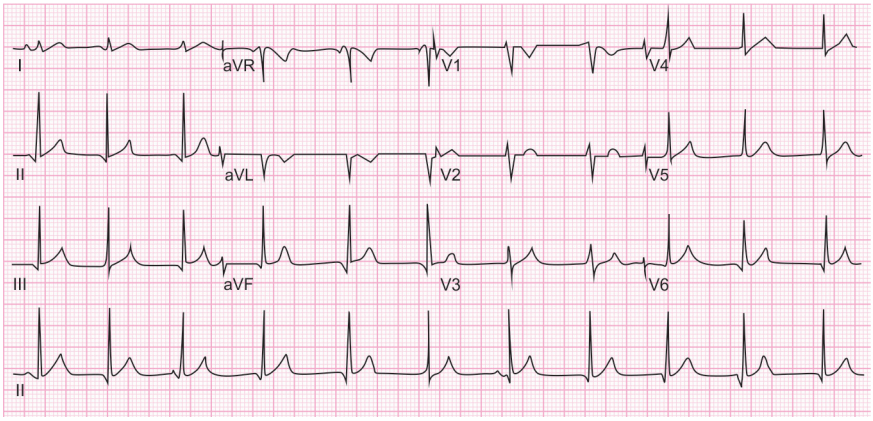

Fig. 3: Resting electrocardiogram of a patient

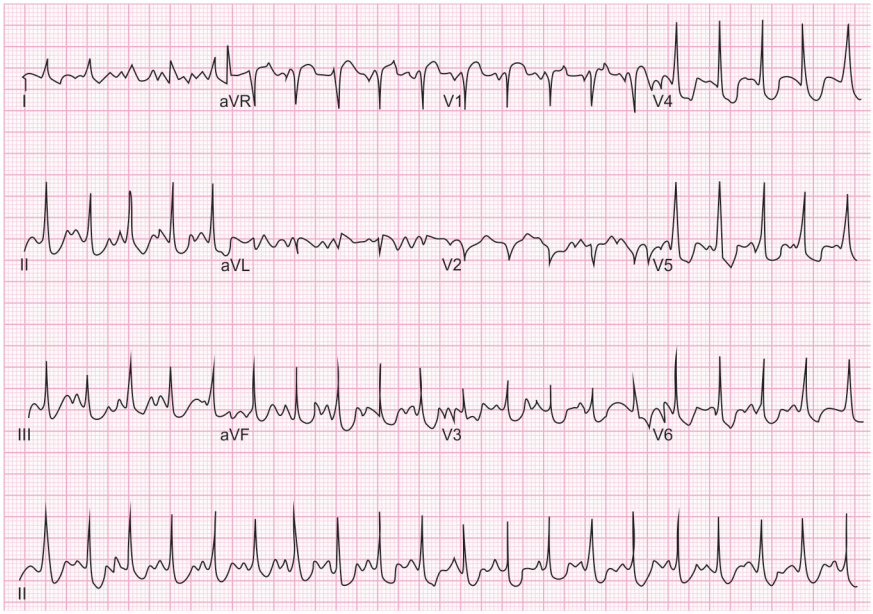

Fig. 4: Post-exercise electrocardiogram showing ischemic ST changes

- Complex arrhythmia may indicate underlying CAD or electrolyte imbalance
- Sudden drop in blood pressure during exercise often indicates high grade CAD
- Accelerated blood pressure response may uncover underlying hypertension
- Functional capacity correlates with prognosis in CAD.

FACTORS INFLUENCING INTERPRETATION

- Drugs: Digoxin is a common cause of false positive response. Beta-blockers can blunt the heart rate response and may give false negative response
- Electrolyte imbalance: Hypokalemia will lead to false positive response
- Baseline ECG abnormalities: Complete left bundle branch block, Wolff-Parkinson-White syndrome, LVH will obscure ischemic changes during exercise stress test
- Women and patients with mitral valve prolapse syndrome have high incidence of false positive response.

COMPLICATIONS

Serious complications during stress test are extremely rare (0.1%). Isolated premature ventricular contractions are common and do not represent ischemia. Onset of typical angina with ST changes should be a cause of

immediate termination of test regardless of whether adequate heart rate response is achieved or not. It is foolish to push harder in such instances.

As stated earlier, the sensitivity and specificity of the stress test is low, therefore physicians generally combine with either a nuclear imaging or echocardiography, which gives another dimension for evaluation of ischemia.

In stress echocardiography, echocardiogram is recorded in resting and post-exercise period along with the routine ECG recording. Wall motion is compared in post-exercise from resting echocardiogram. Ischemia leads to segmental wall motion defect. It is the preferred screening test for women.

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34

CHAPTER

Nuclear Imaging in Cardiology: An Overview

Sharad Mehta

INTRODUCTION

Nuclear imaging has helped improve sensitivity and specificity over standard exercise stress test. It not only gives physiologic information, it also helps in prognostic information. Single photon computed tomography (SPECT) with technetium-99m is the most commonly used procedure used along with treadmill stress test.

INDICATIONS

- Diagnosis of coronary artery disease (CAD)
- Assessment of physiologic importance of known CAD
- Assessment after therapeutic intervention used routinely after PTCA or coronary artery bypass graft (CABG)
- Risk stratification
- Diagnosis of myocardial infarction (MI) showing "fixed" perfusion defect (Figs 1 and 2)

EQUIPMENT

Gamma camera is used to detect gamma rays emitted by radioisotopes. There are three types of Gamma cameras (Figs 3A and B):

1. Single-crystal camera.
2. Multi-crystal camera, and
3. Positron camera.

TECHNIQUES

- Planar images: These are acquired in three views: anterior, left anterior oblique (LAO) and steep LAO or left lateral (LLAT)
- SPECT images: Series of planar images are reconstructed in a 3D and reported as short axis, vertical long axis and horizontal long axis. A computer quantifies the count density

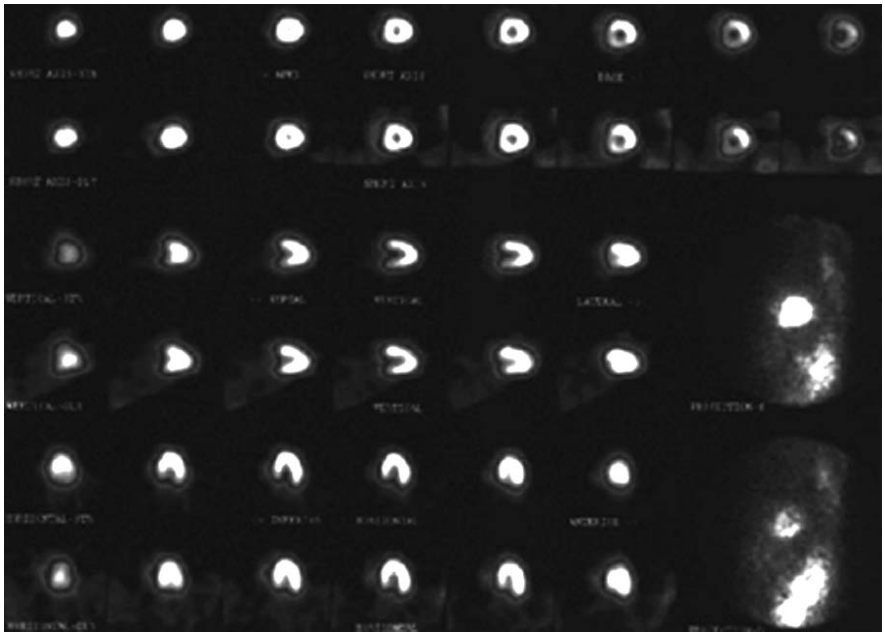


Fig. 1: Example of a normal perfusion scan

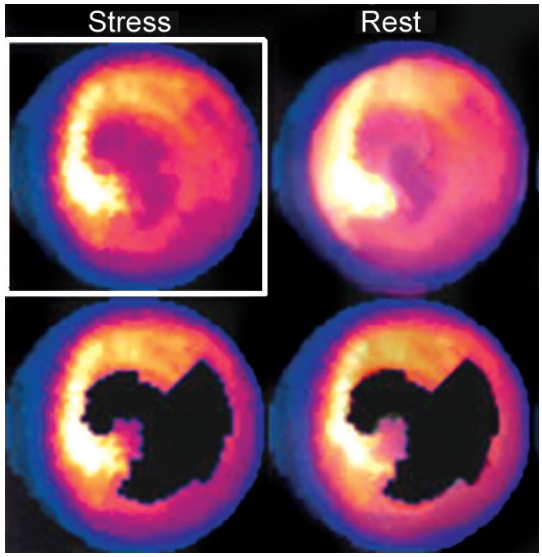
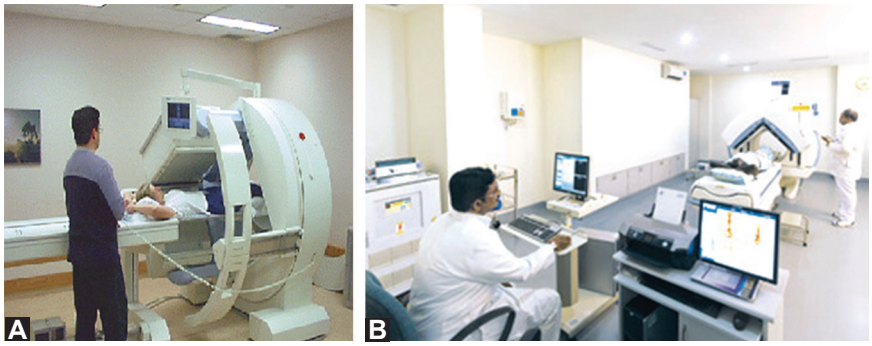


Fig. 2: Example of a "fixed" perfusion defect indicating old myocardial infarction in rest and post-exercise

RADIOISOTOPES (RADIOPHARMACEUTICALS)

- Thallium-201: Half-life 73 hours. Normal myocardium takes up thallium uniformly. Uptake is lower in ischemic segment. Over time the count becomes equal. It is injected at peak-exercise and immediate imaging is done and followed 2–4 hours later, by resting (redistribution) images



Figs 3A and B: Gamma cameras

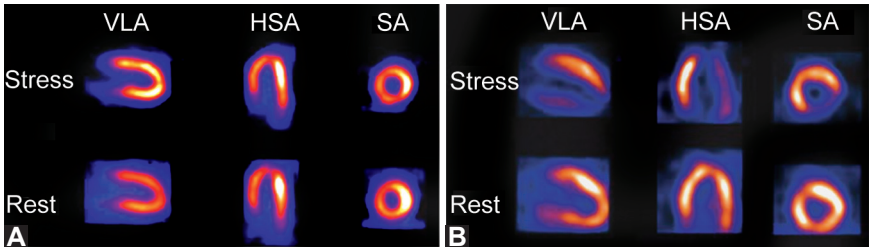
- Technetium-99m: Half-life is 6 hours. It is tagged with sestamibi (cardiolite) or tetrofosmine (myoview). It is injected in two separate injections, one at rest and the second at peak-exercise
- Dual isotope imaging: Use of both thallium-201 and technetium-99m, substantially reduces procedure time. Patient receives thallium-201 at rest and immediately goes for stress test. Technetium-99m is injected at peak exercise and images are obtained 30–60 minutes later.

When patient is unable to perform exercise for whatever reason, physicians use pharmacological agents along with nuclear imaging. There are three agents in common use:

1. Dipyridamole (Persantine): It is a direct vasodilator. It increases coronary flow in normal arteries but much less so in poststenotic artery, thus creating a "steal phenomenon". This is the basis of heterogeneous radiotracer uptake.
   A four-minute intravenous (IV) infusion (0.142 mg/kg) of Persantine is followed by technetium-99m sestamibi and patient is sent for SPECT scan. Persantine does cause headache, nausea, chest pain, hypotension, bronchospasm and dizziness. If needed, these can be reversed by IV aminophylline given as 50–100 mg bolus.
2. Adenosine: It has the same properties as Persantine but has substantially short half-life. It is infused at 5 microgram/kg/min for 6 minutes. Radiotracer is injected after 3 minutes and scans are taken after the procedure. It has same side effects as IV Persantine, which can be reversed by IV aminophylline.
3. Dobutamine: Intravenous infusion at 5 microgram/kg/min, increased every 3 minutes to a maximum dose of 40 microgram/kg/min, Radiotracer is injected, when 85% predicted maximum heart rate is achieved or the maximum dose is reached or if patient experiences unpleasant side effects such as headache, hypotension, ectopy, dyspnea, paresthesia or flushing.

IMAGE INTERPRETATION

- Compare rest and stress images. Make sure they are done in exact same positions



Figs 4A and B: (A) Normal scan (B) Inferolateral ischemia. Abbreviations: HSA, Horizontal short axis; SA, Short axis; VLA, Vertical long axis

- Document fixed defects indicate old MI (Figs 4A and B)
- Document reversible defects and their location indicate ischemia
- Document left ventricular size and function by gated SPECT images
- Over-estimation of defects must be restrained. Breast shadows in women can significantly affect accuracy

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35 CHAPTER

Evaluation of Syncope

Jayant C Bhalerao

DEFINITION

Syncope is defined as a transient, reversible loss of consciousness and postural tone. Vasovagal syncope, also known as neuromediated syncope or neurocardiogenic syncope is the most frequent cause in clinical practice.

Other cardiac causes are severe valvular stenosis, hypertrophic cardiomyopathy, atrial myxoma, high-grade coronary artery disease or high-grade carotid artery disease, Stokes-Adams attacks due to advanced AV block or tachyarrhythmias. Cardiac causes of syncope logically cannot last too long without causing catastrophic consequences.

Prolonged syncope generally occurs in neurological causes like brainstem transient ischemic attacks, seizure disorder, intracranial bleeding, etc.

EVALUATION OF VASOVAGAL SYNCOPE (NEUROMEDIATED SYNCOPE)

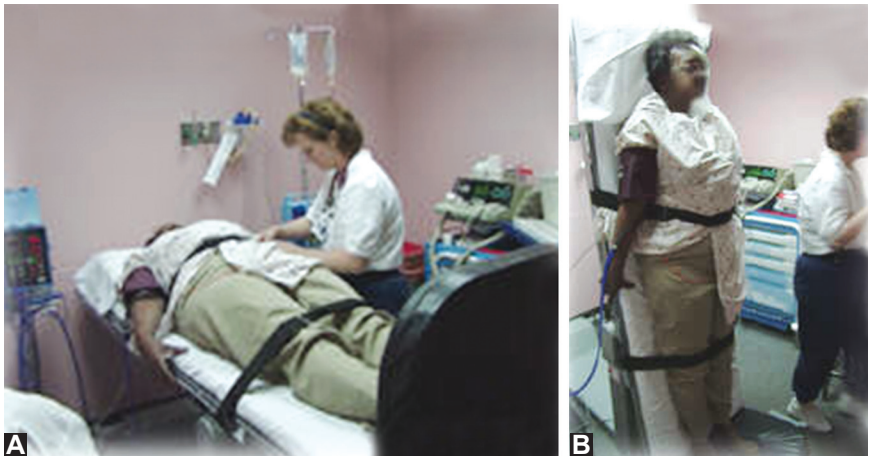
First and foremost, all secondary causes listed above must be excluded. Having done that, we proceed with Tilt Table Test (Figs 1A and B).

Tilt Table Test Protocol

Numerous protocols and drug agents have been published. Physicians follow "American College of Cardiology Expert Consensus Document" (Benditt DG et al., 1996).

Baseline Study

After 30 minutes, supine equilibration period in an overnight fasting state, intravenous fluids are replaced to make sure volume depletion is not the cause of syncope. Vital signs and electrocardiographic rhythm strips are recorded and monitored frequently.



Figs 1A and B: Tilt table test

Patient is rapidly but smoothly tilted up to 70° for 3–45 minutes. Rise in heart rate and blood pressure is normal response. If patient fails to show hypotension and bradycardia, patient is lowered back to supine position and pharmacological provocation is tried using isoproterenol (Isuprel) 1–5 microgram/min for 5 minutes followed by head up tilt position at 60°. Five-minute supine position is recommended between dose-escalation.

PATHOPHYSIOLOGY

Upright position causes displacement of volume from thorax to dependent extremities, thereby lowering the blood pressure and causing reflex tachycardia. Baroreceptors present in aortic arch and carotid arteries are stimulated resulting in afferent signals to brain's vasomotor center. This results in increased catecholamine secretion characterized by rise in blood pressure and heart rate (sympathetic response).

In response, receptors present in inferior-posterior wall of the left ventricle are stimulated by the stretch reflex (Bezold-Jarisch reflex) and carry signals to vasomotor center via vagal afferents.

Normally, these counteracting mechanisms of autonomic regulation work in a smooth proportionate way like an accelerator and a brake in a car.

In patients susceptible for neuromediated syncope, this automatic regulation is jerky and imbalanced resulting in exaggerated sympathetic response followed by an exaggerated parasympathetic response. When parasympathetic response overwhelms the sympathetic response, hypotension and bradycardia results, leading to syncope.

Head-up tilt test exploits this by reducing venous return. Isuprel increases the myocardial contractility and blood pressure thus squeezing the baroreceptors to initiate the Bezold-Jarisch reflex.

INTERPRETATION

- Heart rate response: Normally, heart rate increases by less than 15% of basal level. In abnormal response, there is abrupt drop in heart rate by more than 30% from the peak response
- Blood pressure response: Normally, systolic blood pressure drops up to 20 mm Hg and increase in diastolic blood pressure by about 10 mm Hg. In abnormal case, there is abrupt decrease in blood pressure by over 30% from the peak

Accuracy of head-up tilt test is about 80% (sensitivity and specificity) in diagnosing neuromediated cardiac syncope.

Sound clinical judgment goes a long way in evaluating syncope.

TREATMENT

Beta blockers (non-selective) are the most effective way to treat neuromediated syncope. They block the exaggerated sympathetic activation and thus prevent the cascade of subsequent events.

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CHAPTER 36

Heart Catheterization: Basic Principles

Jayant C Bhalerao

INTRODUCTION

Since 1970, heart catheterization has become an integral part of cardiology. What was considered a taboo, is now commonplace. Take an example of coronary angiography in acute myocardial infarction (MI). It has helped us revolutionized our understanding of hemodynamics, physiology and anatomy in a clinical situation where it can make a big difference in patient care. Many therapeutic interventions such as angioplasty, valvotomy, ablation and pacing, implantable defibrillators, catheter closure of congenital defects, etc. are all the offshoots. More progress has taken place in cardiology in the past 2–3 decades than its entire history.

This book can only highlight some of the fundamentals of this vast subject. No matter how descriptive one gets, you cannot fully understand the nuances of heart catheterization until someone guides and shows how to do it. This is the best example of "*Guru-Shishya*" (Teacher-Pupil) tradition, as we know it. It takes several months to get over the steep learning curve.

RIGHT HEART CATHETERIZATION

Technique

Seldinger Technique

The patient is prepared and draped after an informed consent. Multiple sites that can be easily compressed, such as internal jugular vein or femoral vein, can be used to gain venous entry. After injecting 3–5 cc local anesthetic agent (1–2% lidocaine) a 16 gauge needle is introduced in the vein. Guidewire is then threaded and the needle is removed. Never force the guidewire! It must glide in effortlessly. A dilator, made of hard rubber is then glided over to loosen the tissues. Remove the dilator and thread in the catheter over the guidewire. The guidewire is much longer than the length of the catheter. Make sure physicians always hold on to the end of the guidewire as they slide the catheter in. Once the catheter is in, remove the guidewire. Take care of hemostasis and keep the area clean. Catheter is now in inferior vena cava or superior vena cava

depending on which vein physicians chose to gain entry. Flush the catheter with heparinized saline inflate the balloon and advance it carefully under either fluoroscopy or pressure curve guidance in to the right atrium (RA) then right ventricle (RV) and across the pulmonary valve in the main pulmonary artery (PA) and then one of its branches (Figs 3 to 6). Pressure is measured at

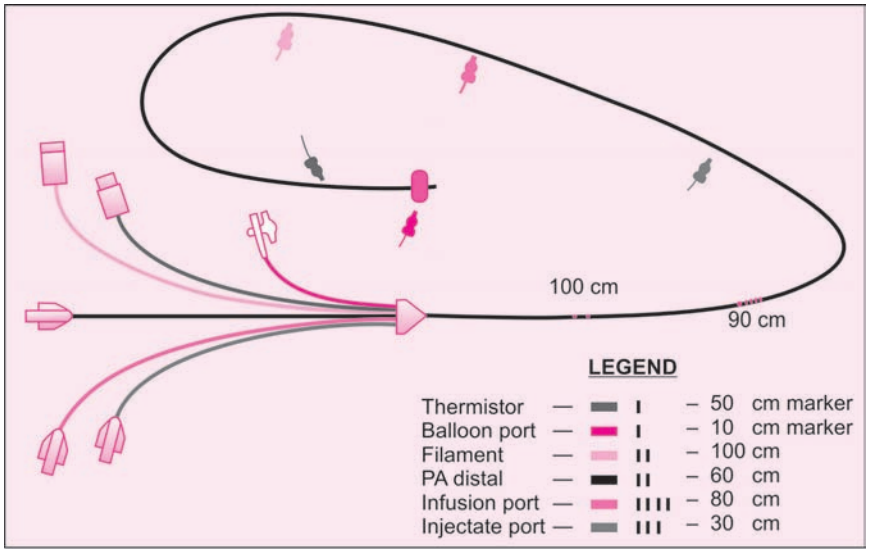


Fig. 1: Swan-Ganz catheter

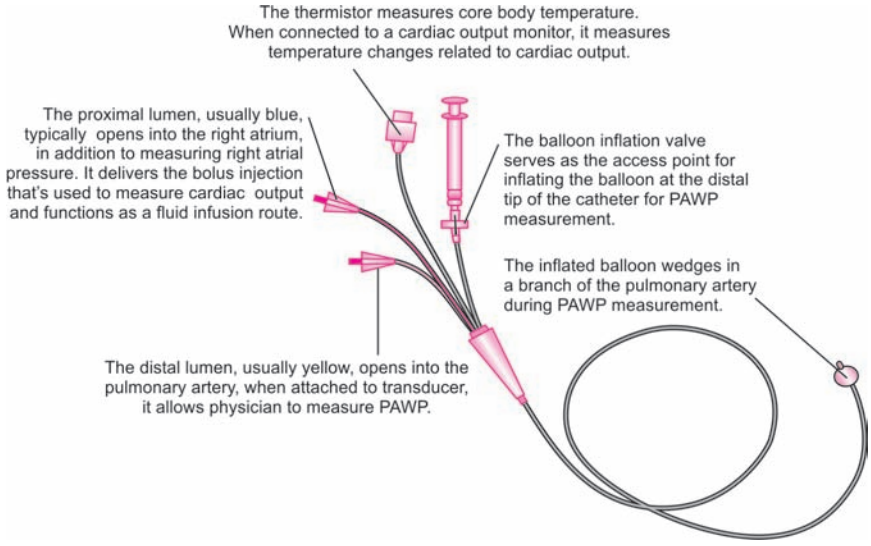


Fig. 2: Swan-Ganz standard thermodilution pulmonary artery catheter for measuring cardiac output, central venous pressure, pulmonary artery pressure and pulmonary capillary wedge pressure (PAWP)

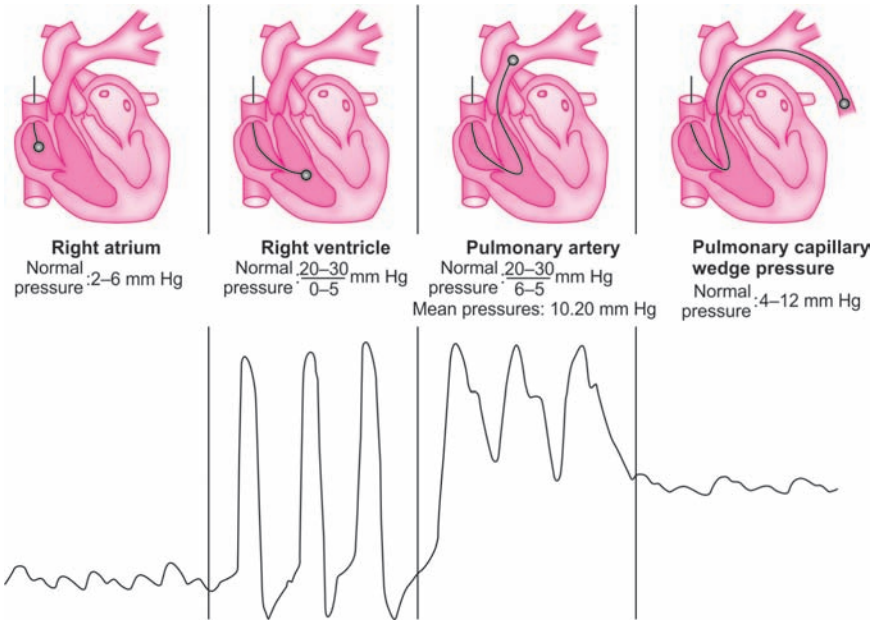


Fig. 3: Characteristics intracardiac pressure waveforms during passage through heart

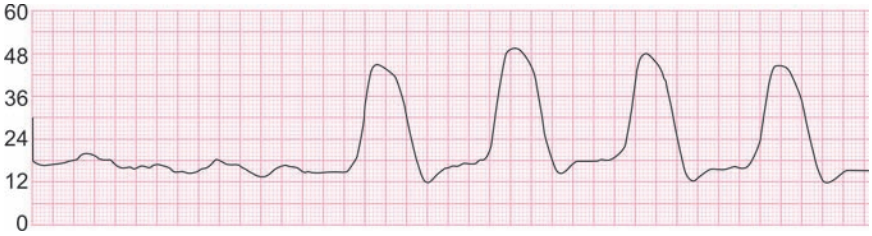


Fig. 4: A tracings showing conversion from central venous pressure to the right atrial pressure waveforms during pulmonary artery catheterization

each chamber. Make sure there is no pressure gradient. Blood samples can be obtained at various levels for O_2 saturation if intracardiac shunt is suspected. Finally, the catheter is advanced (tell it wedges) in the smaller branches of PA to obtain the pulmonary capillary wedge (PCW) pressure which is generally equal to the left ventricular end-diastolic pressure if the mitral valve is normal. Mostly a balloon-tipped catheter is used for right heart catheterization. Once the catheter is wedged, deflate the balloon. By doing so, physicians should get the PA pressure tracing again. Slowly re-inflate the balloon till the catheter wedges again. Never use more than 1.5 cm^3 of air. Overinflation of the balloon may cause rupture of PA and or cause pulmonary infarction.

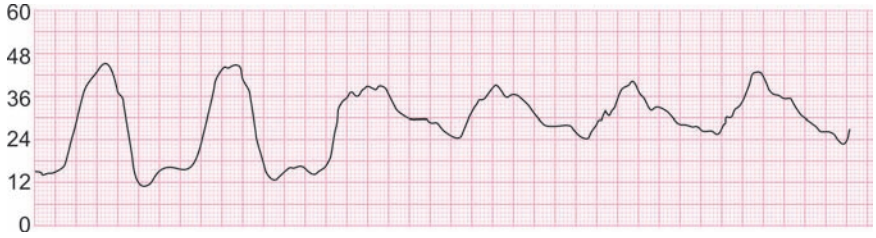


Fig. 5: A tracings showing conversion from right atrial pressure to pulmonary artery pressure waveform during pulmonary artery catheterization

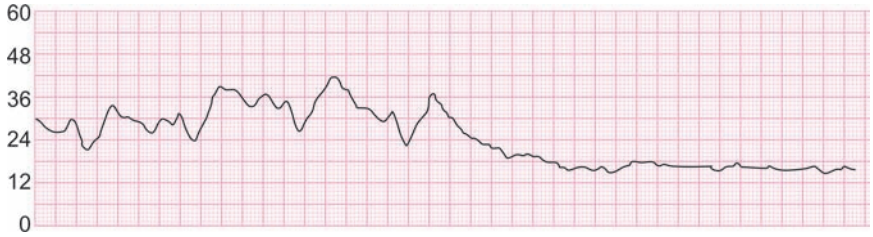


Fig. 6: A tracings showing conversion from pulmonary artery pressure to pulmonary capillary wedge pressure waveform during pulmonary artery catheterization. Over-wedging occurs when tip is distal to optimal position

If the right heart catheter is left in for hemodynamic monitoring, get a chest X-ray to confirm the location of the tip (Fig. 7), and make sure, there is no pneumothorax, etc. If physicians use internal jugular vein, keep the patient in Trendelenburg position and using the carotid artery as a guide, insert the needle at the upper end of the triangle created by two heads of sternomastoid muscles and point inferolaterally towards the ipsilateral nipple. Remember, the internal jugular vein lies anterolateral to the carotid artery. If physicians use the subclavian vein, make absolutely sure that the patient is either in perfect supine position or preferably in Trendelenburg position.

Read the humorous description about the experience of an intern, Dr Atul Gawande, doing this procedure for the first time in Harvard Medical School in his book "Complications: A Surgeon's Notes on an Imperfect Science" in chapter "Education of a knife". If practice of medicine cannot teach humility, author guesses nothing can.

Complications

- Local injury and bleeding
- Pulmonary injury causing infarction, bleeding or pneumothorax
- Infection: Local or septicemia from indwelling catheter

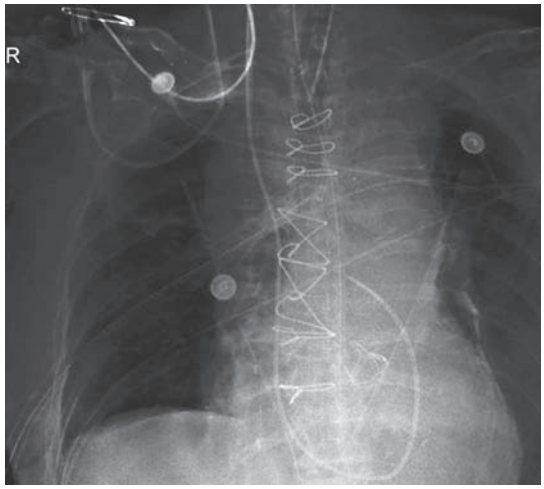


Fig. 7: Chest X-ray showing right heart catheter in right pulmonary artery

LEFT HEART CATHETERIZATION

Introduction

In 1958, Dr Mason Sones from Cleveland Clinic performed the first selective coronary arteriogram. It was performed using brachial artery cut-down. Over the years, preformed Judkins catheters, passed through femoral artery has become far more popular and now hardly anyone uses the Sones's technique. Although over 1.5 million coronary angiograms are performed in the United States every year, one must recognize the fact that this is a risky procedure and must only be performed by highly trained professionals. In the United States, the cardiologist in training program must perform at least 300 such procedures and be board certified in cardiovascular medicine to be able to get hospital privilege for such procedure. Such stringent criteria are necessary to assure patient safety. Today, despite the availability of many diagnostic procedures to diagnose coronary artery disease, coronary arteriogram remains the gold standard. It not only confirms the diagnosis of coronary occlusion but also defines other anatomical details necessary for selecting proper therapy. It has opened the floodgates for various therapeutic interventions, which now defines what cardiology is today.

Besides coronary arteriography, once cardiologists became experts in exploring the arterial side of the circulation, it opened the avenues for confirming severity of valve and congenital heart defects. It became easier to define left ventricle (LV) function with precision never possible before.

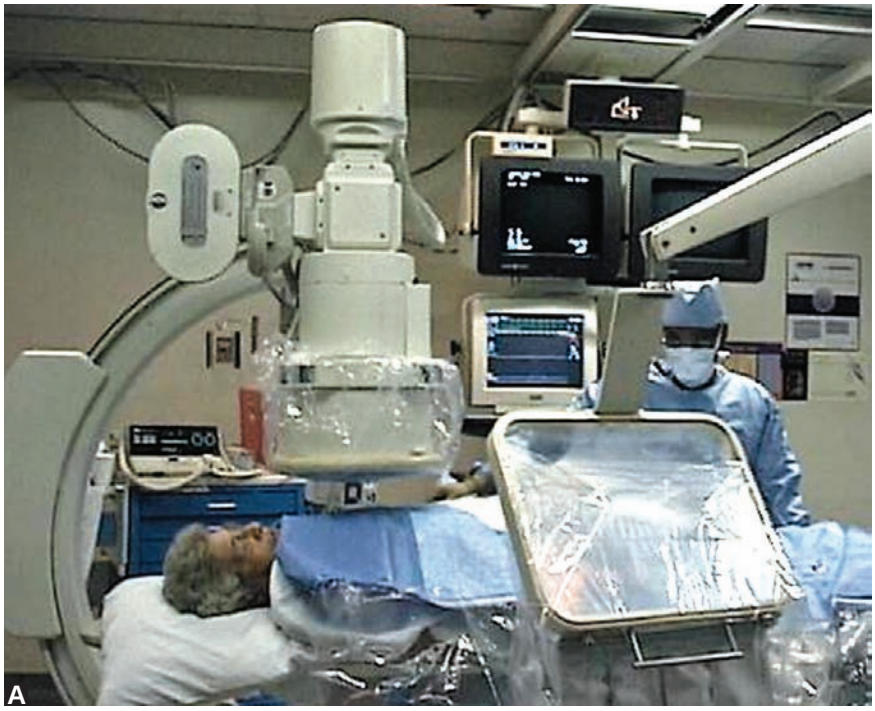
These days, it is lot easier to know when to do coronary angiogram than when not to do them. It does need a lot of good judgment to know the latter.

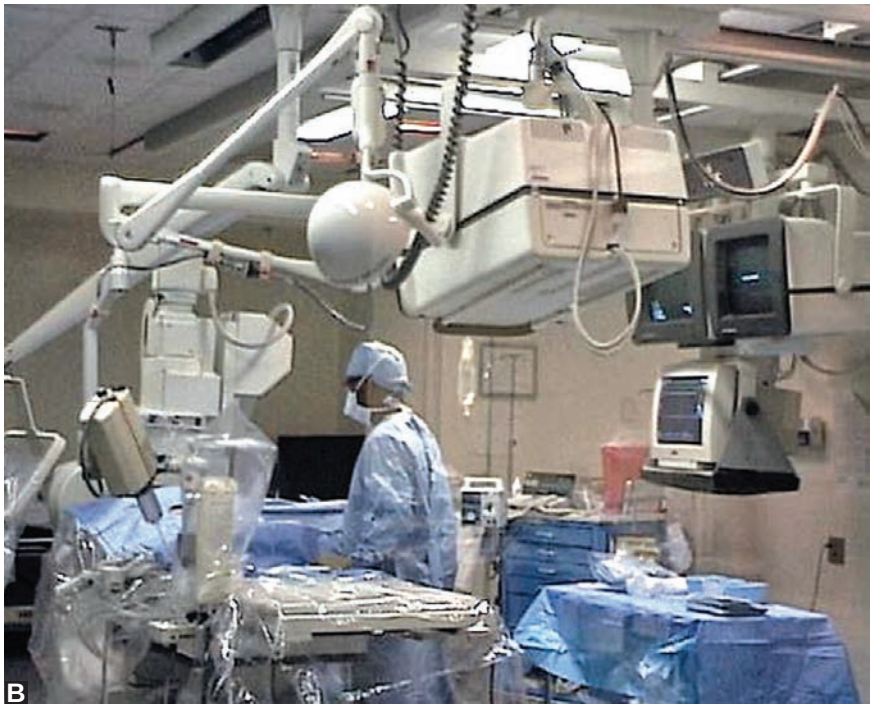
Procedure

- Informed consent must clearly explain to the patient the possibility of death, stroke or heart attack as a direct consequence of this procedure
- Medication: Mild tranquillizer makes the experience tolerable. Aspirin 325 mg postoperatively should be given if angioplasty is planned. Clopidogrel 300 mg postoperatively as a loading dose is generally given if stenting is planned. Metformin must be stopped on the day of the procedure if the creatinine is even slightly elevated (to avoid lactic acidosis). If a protracted procedure is anticipated, insert a Foley catheter before the procedure
- Educate patient about the need to cough when the contrast dye is injected (it helps dye induced bradycardia resolve quickly). Explain to experience hot sensation for few seconds after the dye is injected. Nausea is not uncommon therefore patient is kept *nil per os* (NPO) (nil by mouth) overnight
- Contrast dye: Iodinated contrast dye is commonly used therefore make sure patient is not allergic to iodine. If so, premedicate with prednisone 40 mg postoperatively every 6 hr x 4 doses or intravenous (IV) hydrocortisone 100 mg 6 hr before the procedure along with IV Benadryl 50 mg. It is better to give small quantity of dye to see the response. Patients with renal insufficiency need to be hydrated properly and if possible low-osmolar nonionic dye may be used (very expensive!). If one can avoid doing left ventricular angiogram, do so to minimize the amount of dye used
- Radiation safety is to be followed strictly. Higher cine frames increase radiation hazard, therefore use 30 frames/second than 60 frames/second

Access Site

- Femoral artery: Femoral artery lies exactly in the middle of the groin (i.e. from anterior iliac spine to symphysis pubis). Remember the mnemonic NAVAL = Nerve, Artery, Vein, Adipose tissue and Lymph nodes—starting from lateral to medial
- Point of entry: Two centimeter inferior to the midpoint of inguinal ligament. Under aseptic precaution, procaine 1% or lidocaine 2% is slowly injected. Then, 18 gauge Cook needle is inserted vertically into the artery. Once inside the artery, a 0.035 inch J-tipped guidewire is inserted. Needle is withdrawn. An arterial sheath with dilator is threaded over the guidewire into the arterial lumen. Dilator and guidewire is removed and the sheath is flushed with saline. A 4- or 6-Fr sheath is used for routine cases while 8-Fr sheath is used for acute cases or planned interventions
- Engaging the coronary artery: Typically a Judkins L4 catheter is used to engage left coronary artery. It is first flushed with heparinized saline and passed over a J-tipped guidewire through the sheath. Under fluoroscopic guidance, the catheter is gently advanced in ascending aorta and the guidewire is removed. Catheter is engaged in left coronary ostium with its tip parallel to the lumen of the artery. Left coronary ostium is located posterolaterally just above the aortic valve. After making sure there is no





Figs 8A and B: Cardiac catheterization table and equipment

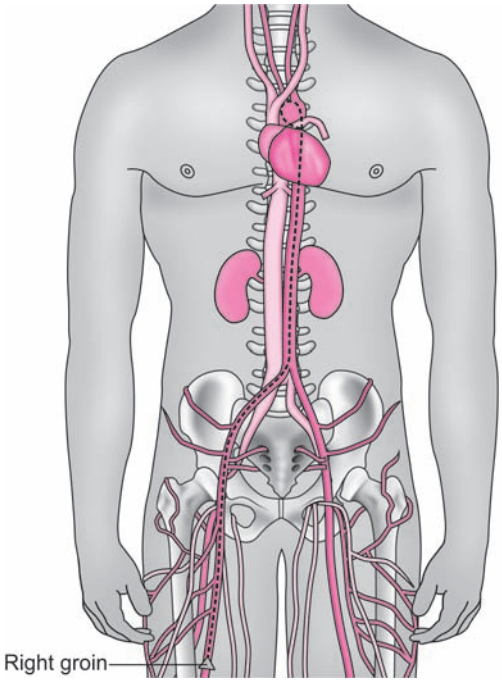


Fig. 9: Cardiac catheterization

air bubble in the syringe about 8–10 cc dye is injected steadily and with adequate force while recording the cine. Multiple views are recorded and the catheter is removed. Right coronary artery (RCA) is visualized by using Judkins R4 catheter. Right coronary ostium is located anteriorly, 2 cm above the aortic valve**.** Cine angiogram is taken in multiple views and the catheter is withdrawn

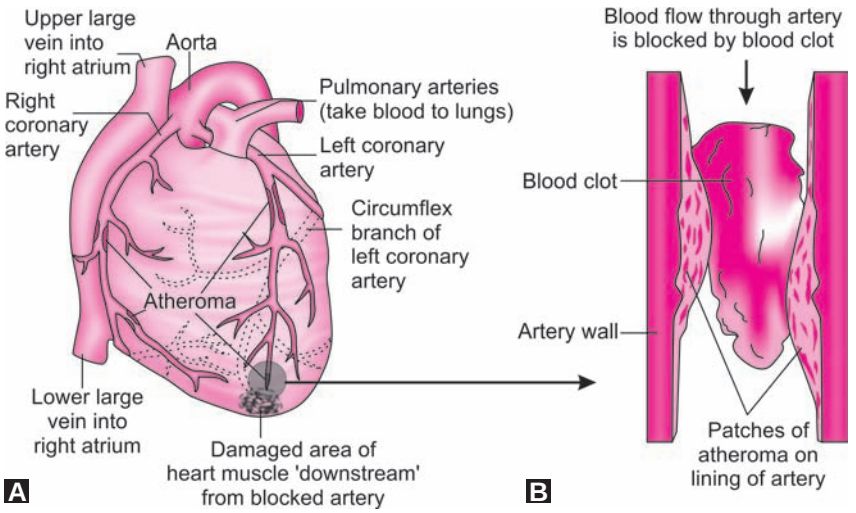
- Left ventriculogram**:** A pig-tail catheter is then inserted over the guidewire and under fluoroscopy advanced in the ascending aorta. While watching the ECG monitor, the catheter is gently pushed to coincide with the R wave (indicating open aortic valve). Once inside the LV cavity, catheter is flushed and pressures are recorded. Left ventriculogram is obtained in right anterior oblique (RAO) and left anterior oblique (LAO) position using about 12–15 cc/sec dye for 3 seconds. Catheter is flushed again and pressure is recorded while pulling the catheter across the aortic valve and the catheter is removed. Steady pressure for 15 minutes at the puncture site and sterile dressing is all that is needed before the patient is wheeled back to his room
- Normal coronary anatomy: Left coronary artery comes off the aortic root posterolaterally as left main coronary artery. It quickly bifurcates in to two large branches namely left anterior descending (LAD) and left circumflex (LCx). LAD travels along the anterior wall of the LV and gives off septal perforator branches and diagonal branches. Distally, it wraps around the left ventricular apex. LCx gives off marginal branches. Some times the LCx is "dominant", meaning it gives off the posterior descending branch.

Usually, the RCA gives off posterior descending artery (PDA) in over 75% cases, in which case it is called the "dominant". RCA gives off right ventricular branch in its mid course and the branch to AV node near the AV groove just before the origin of PDA. In its proximal course, RCA gives off artery to sinus node. Sometimes, the left main artery may trifurcate in to LAD, LCx and intermediate arteries

- Postcatheterization care: If the procedure is long, re-inject local anesthetic agent again. After the sheath is removed, pressure is held with a finger tip directly over the pulse for 20 minutes (about 3 minutes for each French size). Bed rest for 6 hr is then recommended (1 hr for each French size). Various closure devices, such as FemoStop, C-clamp, Angio-Seal, Perclose/Techstar and VasoSeal, can be used if 8-Fr sheath was used.

Complications

- Major complications are death, stroke, myocardial perforation and acute MI. Incidence of these major complications are less than 0.1%. Coronary artery dissection can occur in about 1% cases. Usually, simple observation is all that is necessary. Sometimes, emergency stent placement or bypass surgery may be needed
- Renal failure: Intravenous contrast material is nephrotoxic. Preexisting renal insufficiency, dehydration, diabetes and large amount of dye used are the usual culprits. Proper hydration and using less than 30 cc dye for the entire procedure is helpful.
- Complex arrhythmias and conduction defects
- Vagal reaction causing profound bradycardia and hypotension is transient and responds to IV atropine and adequate sedation



Figs 10A and B: Myocardial infarction. (A) Heart, front view, showing patches of atheroma. (B) Cross section of coronary artery showing patches of atheroma

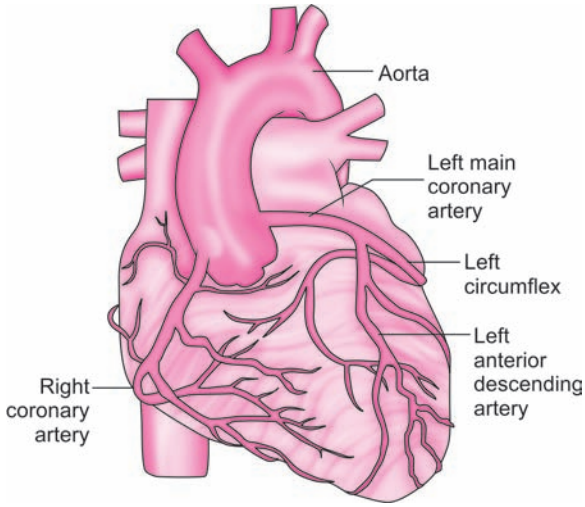


Fig. 11: Illustration of the heart showing coronary arteries. The main left coronary artery, which branches into the left anterior descending artery and the circumflex branch, and the right coronary artery

- Worsening of mechanical problems such as congestive heart failure
- Coronary artery spasm with angina
- Local bleeding, thrombus occlusion, arterial perforation, pseudoaneurysm formation and infection
- Allergic reaction to dye
- Femoral nerve injury

In 99% of the times, the procedure is uneventful and provides information that is fundamentally important to the selection of proper therapy. Judicious selection of patients goes a long ways to minimize untoward side effects.

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CHAPTER 37

Hemodynamic Data, Calculation of Shunts and Valvular Stenosis

Jayant C Bhalerao

NORMAL VALUES AND FORMULAE

Right Atrium Pressure	0–8 mm Hg	
Right Ventricle Pressure	15–30/0–8 mm Hg	
Pulmonary Artery Pressure	15–30/3–12 mm Hg	
Cardiac Output	4–8 L/min	
Cardiac Index	2.5–4.5/L/min/m^2	Cardiac Output/Body Surface Area
Stroke Volume	40–120 cm^3/beat	Cardiac Output/Heart Rate
Systemic Vascular Resistance	770–1,500 dynes sec/cm^2	(Mean Arterial Pressure – Central Venous Pressure) X 80/Cardiac Output
Pulmonary Vascular Resistance	20–120 dynes sec/cm^2	(Pulmonary Arterial Resistance – Pulmonary Capillary Wedge Pressure) X 80/Cardiac Output
Fick cardiac Output	4–8 L/min	(Weight X 3 mL/kg)/ [(AO_2 – VO_2) X 1.36 X Hemoglobin X 10]
Shunt Function	1.5–2.0 Small Defect > 2.0 Large Defect	Qp/Qs

CALCULATION FOR LEFT-TO-RIGHT SHUNT

- Shunt Function = Qp/Qs

- Qp = Systemic Flow – Shunt Flow = O_2 Consumption/[10 X (Pulmonary Vein O_2 – Pulmonary Artery O_2)]
- Qs = O_2 Consumption/[10 X (Arterial O_2 – Mixed Venous O_2)]
- Simplified calculation using saturation only:

Qp/Qs = (Arterial O_2 Saturation – Mixed Venous O_2 Saturation)/(Pulmonary Vein O_2 Saturation – Pulmonary Arterial O_2 Saturation)

In right-to-left shunt, systemic flow is oxygen consumption divided by arterial oxygen content minus pulmonary arterial oxygen content. Pulmonary blood flow is calculated by oxygen consumption divided by pulmonary vein oxygen content minus pulmonary arterial content. A shunt fraction ratio of greater than 1.5 often necessitates closure.

CALCULATION OF AORTIC VALVE AREA

- Planimeter five aortic – Left ventricular gradients and average the area.
- Measure systolic ejection period (SEP) and average the values.
- Convert planimeter area to mean systolic pressure gradient:
  Mean valve gradient (MVG) = Area X Scale Factor/SEP
- Compute aortic valve flow using:
  1000 X Cardiac Output/Heart Rate X SEP
- Compute Valve Area = Valve Flow/K (X) C (X) square root of Left Ventricular Pressure Peak minus Aortic Pressure

Using the Gorlin formula where K = 44.3 and C is an empirical constant that is 1 for semilunar valves and tricuspid valve and 0.85 for mitral valve.

Simplified Aortic Valve Area = Cardiac Output/square root of gradient

Gradient = Peak Left Ventricular Pressure – Peak Aortic Pressure.

This quick formula for valve area differs from Gorlin formula by 18% +/- 13% in patients with bradycardia and tachycardia. If the heart rate is above 90, this number is divided by 1.35 (Fig. 1).

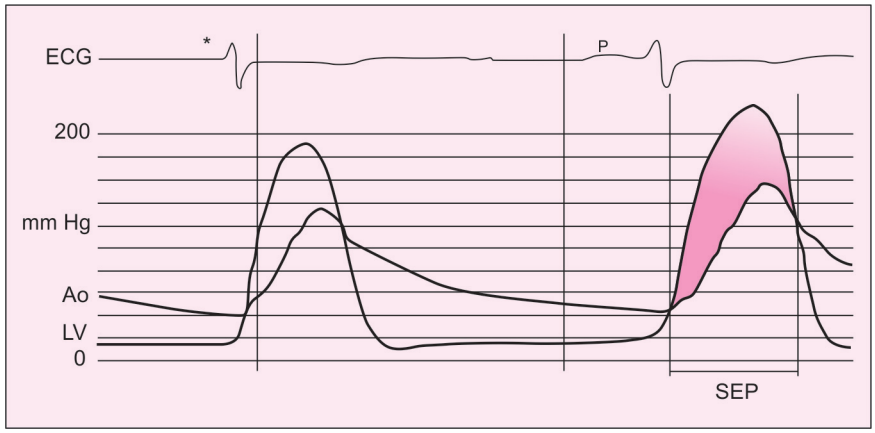

Fig. 1: Pressure in aortic stenosis simultaneously recorded pressures from the left ventricle (LV) and aorta (Ao) in a patient with aortic pressure is greater than that of aorta. The pressure gradient and systolic ejection period (SEP, in sec/beats) are used in the Gorlin formula to calculate the aortic valve area (aortic valve area = cardiac output/[44.3 X SEP X HR X square root of mean gradient). Source: Kern MJ. Cardiac Catheterization Handbook, 2nd edition. St. Louis: Mosby-Year Book; 1995

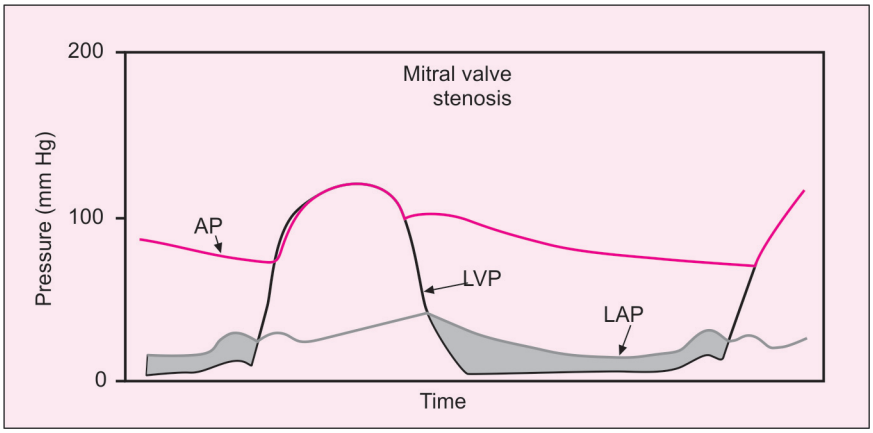

Fig. 2: During ventricular filling (diastole), LAP exceeds LVP (gray area, pressure gradient generated by stenosis). Abbreviations: AP, Aortic pressure; LAP, Left atrial pressure; LVP, Left ventricular pressure

CALCULATION OF MITRAL VALVE AREA

- Planimeter five left ventricle – Pulmonary capillary wedge area
- Measure diastolic filling period (DFP)
- Convert planimetered area to mean diastolic pressure gradient (MVG)
  Where MVG = Area X Scale Factor/DFP
- Compute mitral valve flow using:
  1000 X Cardiac Output/HR X DFP
- Compute mitral valve area using Gorlin formula where mitral valve flow is divided by 44.3 X 0.85 X square root of diastolic pressure difference (Fig. 2)

If your head is spinning after reading these formulae, relax! All cardiac catheterization machines will compute this information and will automatically give a printout of the results.

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CHAPTER 38

Risk Assessment in Noncardiac Surgical Procedures

Jayant C Bhalerao

One of the more common reasons for cardiac consultations is preoperative risk assessment and clearance for surgery and anesthesia. Given the multitudes of surgical procedures with varying degrees of risk levels and given the multitudes of patient profiles, making this decision requires common sense, judgment and deep understanding of cardiac physiology and anatomy. Same set of clinical data may have different significance in two different patients. When a surgeon requests a preoperative evaluation, he or she is not asking physicians to merely rubberstamp his decision or "clear" a patient for surgery, they are expecting three things from a cardiologist:

1. Assess current medical status
2. Assess cardiac risk posed by the procedure
3. Recommend how to decrease the risk

Communicating with all parties (the surgeon, anesthetist and the family) is crucial. It is especially true when the risks are high.

FACTORS THAT PREDISPOSE PATIENT TO HIGH RISK

- Recent myocardial infarction (MI) (less than 3 months)
- Decompensated heart failure
- Unstable angina
- Severe aortic stenosis (valvular or subvalvular)
- Significant arrhythmias
- High-grade carotid artery disease
- Diabetes
- Chronic obstructive pulmonary disease (COPD)
- Severe renal disease
- Large abdominal aortic aneurysm.

Needless to say, patients evaluation must be specifically directed to these above discussed conditions.

In 1977 Goldman L, et al published a scoring system in the New England Journal of Medicine, which was later modified by Engle KA in 1989 (Annals of Internal Medicine). American College of Cardiology and American Heart

Association Task Force Committee published another to provide more efficient approach to this issue. Unfortunately, none of these are user-friendly. Author thinks if physicians weigh the risk posed by the surgical procedure against the backdrop of patient risk profile, they can reach a reasonable consensus. It is not a perfect science. The urgency of a surgical procedure sometimes gives physicians no better choice.

RISKY PROCEDURE

- High risk: Emergency major procedures in elderly frail patients with diffuse atherosclerosis, especially in long drawn-out procedures with large volume shifts
- Low risk: Cataract or breast operations, endoscopic procedures and biopsy procedures.

HOW DO YOU PROCEED?

- Thorough history and physical examination, looking specifically for factors that predispose patients to postoperative morbidity and mortality (see above). Routine laboratory tests, electrocardiogram (ECG) and chest X-ray are mandatory
- Remember, risk of post surgical event is 10 times higher in patients with abnormal thallium study! So, if physicians suspect high risk based on their evaluation, always perform either dobutamine-thallium or adenosine-thallium or dobutamine-echocardiogram to quantitate underlying ischemia (unless it is a life-threatening situation)
- Always get an abdominal ultrasound to rule out large aortic aneurysm
- Always get a carotid ultrasound to rule out high-grade stenosis
- If the situation does not allow the luxury of such testing, and the situation is dire, make sure complete the evaluation when the situation permits in the postoperative period
- Echocardiogram to evaluate left ventricular (LV) function. Use Swan-Ganz catheter to monitor pulmonary capillary wedge pressure if LV function is poor. Large shifts of volume and the surgical stress can easily provoke or aggravate LV failure. Use of transesophageal echocardiogram is getting more popular also
- If the thallium studies indicate high-grade coronary artery disease, preoperative cardiac catheterization may be warranted. It all depends on the time available prior to surgery. If surgery cannot be postponed, it should be considered at a later date.

HOW TO DEAL WITH PACEMAKERS AND IMPLANTABLE CARDIAC DEFIBRILLATORS?

- In patients who are completely pacemaker dependent, use of electrcautery should be as briefly as possible
- Biventricular pacing minimizes the risk of electrocautery

- After the surgical procedure, all pacemakers are reinterrogated to confirm optimum performance
- Implanted defibrillators are programmed to "off" before the surgery and then to "on" after the procedure.

HOW TO DEAL WITH UNCONTROLLED HYPERTENSION?

With availability of so many wonderful anti-hypertension medicines, this is never a big problem.

HOW TO DEAL WITH PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY?

Patients with idiopathic hypertrophic subaortic stenosis (IHHS) [(hypertrophic obstructive cardiomyopathy (HOCM)] do not tolerate tachycardia, decreased volume, inotropic agents and nitrates. Proper communication with anesthesiologist before surgery is needed.

In general, the strategy must be individualized.

Intraoperative MI should be suspected if a patient develops hypotension or LV failure. MI associated with surgical procedures is generally non-ST segment elevation myocardial infarction (STEMI) and mostly occurs within 3 days of surgery. Mortality rate is over 50% in such cases. If suspected, urgent coronary angiography should be considered.

39 CHAPTER

Stem Cell Therapy

Jayant C Bhalerao

BACKGROUND

There is a growing interest in the stem cell therapy to not only palliate but "cure" human diseases. It has become the forbidden fruit of medicine. The more they try to suppress it, the greater is the desire of doctors and patients to explore this therapy. Desperate and preterminal patients want to try it regardless of what the scientific community has to say about it. It is almost like the AIDS epidemic, when patients were revolting against the medical establishment to release drugs even if the clinical trials were incomplete. The US Federal Drug Administration (FDA), the government agency responsible for approval of drug therapy in the USA has taken a cautious approach. Commercial companies are impatient and applying continuous pressure on the government to approve the stem cell therapy even though large, double-blind trials have not been completed. The testimonials from patients with jaw-dropping results in autoimmune diseases, such as multiple sclerosis, psoriatic arthritis and other chronic inflammatory disorders, acts as a strong enticement to others with similar hopeless situation to try this therapy. People want to try it because they have "nothing to loose". This is adding fuel to the fire. People are willing to spend their entire life savings to go to distances to get this therapy. Clinics have opened in South America near the US border like Panama and Guatemala to attract the US patients.

In view of this extreme interest in stem cell therapy to cure human diseases, author feels it is good to get familiar with the basic principles.

INTRODUCTION

Stem cells are the earliest precursors of cell line. These cells can differentiate into various cells such as adipose cells (adipogenic), cartilage (chondrogenic), muscle cells (myogenic), bone (osteogenic), or blood vessel (angiogenic) to name a few. Embryo provides the most potent and prolific stem cells. As the age advances, the quantity and quality of these stem cells decrease significantly. For ethical concerns, embryonal stem cells are not available for research in

the USA. Other sources are umbilical blood, bone marrow and adipose tissue. Adipose tissue derived stem cells are easily obtainable by liposuction. Usually 1 lb fat will give 30 million stem cells which are enough for the treatment. They are just as good as the bone marrow derived stem cells. These autologous stem cells (derived from the patient) can be "expanded" in the laboratory.

Autologous stem cells can be given intravenously, intramuscularly, intra-articularly or intrathecally without any side effects. Rejection is not a problem. Some may get flu-like reaction lasting a day or so. Autologous stem cells have been used extensively in cosmetic surgery and veterinary medicine (horses) for several years without problems.

COMPONENTS OF ADIPOSE TISSUE

The liquid substance derived by liposuction is called "stromal vascular fraction" or SVF. It contains the following:

- Mesenchymal stem cells (MSC)
- Endothelial precursor cells (EPC)
- Immune regulatory cells monocytes and macrophages
- T-regulatory cells (TREG)

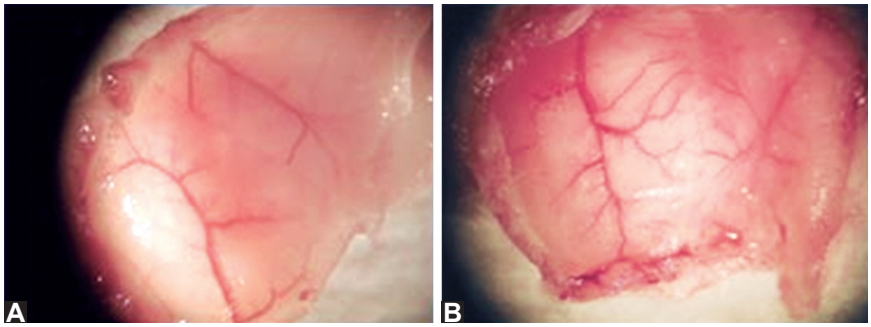
These stem cells have several surface markers. Those cells with phenotype CD34-positive (CD34+) have ability to block the T cell mediated tissue injury and inflammation. These cells block the "clonal expansion" of TREG. *In vitro* "expanded" stem cells have fewer CD34+ phenotype compared to *in vivo* "unexpanded" stem cells. Furthermore, besides this powerful anti-inflammatory property, SVF also has growth factors like IGF-1 and HGF-1 which help in healing process and repair the damaged tissues.

Medical literature is replete with mind numbing examples of "cures" in various autoimmune disorders. Patients covered from head to toe with psoriasis and severe psoriatic arthritis showing complete resolution in 3–6 months, or patients with advanced multiple sclerosis with excruciating and incurable myoclonus and seizures recovering almost completely in 3 months! Internet is full of testimonials from such patients.

Needless to say, cardiologists were equally eager to find such results for their patients with end-stage heart failure and inoperable diffuse coronary artery disease. The recent status of stem cell therapy in heart disease is discussed below.

STEM CELL THERAPY IN HEART DISEASE

Initial reports from Germany 15 years ago showed some spectacular results with intracoronary and/or direct injection of stem cell in the myocardium. Copious growth of collateral arterioles was documented. Unfortunately, human results have been rather disappointing (Figs 1A and B). A recent article from the department of molecular cardiology from the Cleveland Clinic, "Challenges for heart disease stem cell therapy" by Jane Hoover-Plow, et al in Vascular Health and Risk Management 2012:8;99-113 Dove Medical Press Ltd. showed the meta-analysis of 8 randomized trials. It showed that in less than half of the trials, there was only small improvement in cardiac function.



Figs 1A and B: Photographs (A) before and (B) after stem cell therapy in rat mesenteric vessels showing angiogenesis

Although disappointing, the challenges before the researchers are:

- Improve the isolation and identification of stem cells
- Increase the ex-vivo expansion of stem cells
- Increase the delivery effectiveness
- Develop a clearer understanding of mobilization and homing (placement), and
- Improve the stem cell engraftment and survival.

Such is the problem with medical research! Just when physicians think they have reached the destination, they find it was just a mirage! Failures should strengthen our resolve. Keep the hope alive!

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CHAPTER 40

Sudden Cardiac Death and Genomics

Jayant C Bhalerao

BACKGROUND

Close to 5 million people around the world die suddenly of cardiac causes. Maybe high profile athletes in the USA have brought the problem to the forefront. Sudden death in young athletes seems to be increasing, and last year alone 66 young college athletes have dies in the USA. It has been long recognized that sudden death is more common in some families. Chances of sudden death increases ninefold if both parents had died suddenly. A group of conditions have been identified, which has raised a question of a genetic basis. Rapid advances in molecular biology have made it easy to decipher the genome and this tool is being used worldwide to understand the genetic substrate predisposing to sudden death. These patients can be grouped as follows:

- Coronary artery disease, congestive heart failure, dilated and hypertrophic cardiomyopathy constitute 90% of the cases of sudden cardiac death (SCD)
- Ion transport defects like long QT syndromes, Brugada syndrome and arrhythmogenic right ventricular dysplasia constitute less than 10% cases. They have one common denominator. They all have genetic defect, which regulates ion transport in the cardiac myocytes either with calcium or potassium or sodium transport
- Sudden cardiac death in young athletes (SCDY): Over 3,000 cases have been reported in 10 years. Of these, 2,000 were males and 1,000 were African Americans

One problem with genetic defects is that most of the diseases listed above are polygenic. There is high incidence of false positive and false negative results. Sample size is small and at times, the sample contamination is high. There is a bias to report positive study and not others. At any rate, despite these drawbacks, the worldwide race is on to uncover the genetic basis for this dreadful problem.

HOW DO GENES AFFECT SUDDEN CARDIAC DEATH?

- Genes regulate ion transfer in-and-out of the cardiac myocytes. Defect in gene regulation leads to increased arrhythmogenesis
- Genes regulate autonomic nervous system. Defect in autonomic regulation causes loss of R wave variability and T wave alternans, etc. It is known that this is associated with high incidence of SCD

Some cardiac conditions may have monogenic defect:

- Long QT Syndrome: It is an autosomal dominant disorder. Several subtypes are reported. QT-1 syndrome has mutation in the alpha subunit of potassium channel protein KvLQT1, which leads to reduction in the inward potassium current.

  Exposure to drugs like antihistamines, quinalones, erythromycin, antifungal drugs and macrolide antibiotics cause a "Second Hit", where environmental insult is needed for genetic defect to manifest.
- Brugada Syndrome: Defect in sodium channel coded by gene SCN5A.
- Cardiomyopathies like hypertrophic, dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia (ARVD/C) have defect in sarcomeric protein such as beta-myosin heavy chain and cardiac troponin.
- Role of genes in coronary artery disease (CAD): Multitudes of genetic defects have been identified in CAD affecting propensity to atherosclerosis, coronary thrombosis, electrical and autonomic stability, rate of collateral formation and rate of thrombolysis. Seattle Study has identified CPC5 gene, which seems to have protective influence. Brugada syndrome and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) have been discussed in earlier chapter "Ventricular Arrhythmias".

Needless to say, much needs to be done in this difficult problem. Based on our current understanding, to identify and manage these patients and athletes, we propose the following:

- Pre-participation sports screening and physical
- Provider education (doctors and nurses, etc.)
- Raising public awareness and CPR/AED training
- Emergency response protocols
- Medical examiner (autopsy) protocols.

REMEMBER THESE SEVEN CAUSES OF SCD IN YOUNG ATHLETES (SCDY)

1. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)
2. Long QT syndrome
3. Cocaine abuse (causes coronary spasm)
4. Hypertrophic cardiomyopathy
5. Acute myocarditis (viral or diphtheria)

6. Arteriosclerotic coronary artery disease
7. Brugada syndrome

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CHAPTER 41

Application of Genetics and Genomics to Cardiovascular Disease

Janardan D Khandekar

INTRODUCTION

To paraphrase Paul Dudley White, the father of American cardiology, the best way to ensure one's longevity is to choose parents wisely. It is, of course, not possible to choose one's parents, but that statement signifies that family history plays as a major risk factor for heart diseases such as coronary heart disease and sudden death due to arrhythmia. In the near future, the exciting advances in genetics and genomics may also allow physicians to predict, prognosticate and perhaps treat cardiovascular diseases (CV) based on individual risk factors. This, also known as personalized medicine, will be practiced in the not-too-distant future.

Genetics, defined as the study of genes and heredity, was first studied by Gregor Mendel in the mid-nineteenth century through experiments on the color of peas. The Mendelian inheritance, as it called, is caused by a mutation of one gene and leads to clinically manifested diseases. The diseases such as dilated and hypertrophic cardiomyopathy, premature death due to disturbances in cholesterol metabolism, and sudden death due to prolonged QT interval, are dramatic clinical syndromes, but are comparatively rare. More common CV conditions such as hypertension, hypercholesterolemia, and type-2 diabetes, which lead to atherosclerosis, also have a genetic component but are caused by recessive mutations in the genes with small effects.[1,2] These disorders are therefore polygenic and occur as a result of interaction between genetic predisposition along with environmental and behavioral factors, as well as random (stochastic) events (one could also call that "*karma*"). This is also known as complex genetics.

The recent explosion of knowledge of the new biology began in 1953 with discovery of the structure of DNA by James Watson and Francis Crick. This was followed by contributions of hundreds of scientists including some key observations from Nobel Laureate Har Gobind Khorana, have led to greater understanding of genomics, a discipline in genetics that studies genome of various organisms. Observations that the basic structure of DNA has been

maintained over the last five hundred million years, and that various model organisms such as earthworm, yeast (used to make yogurt), fruit fly, zebra fish and mouse share their DNA with humans, have propelled the knowledge of human biology. In 2002, the entire human genome was cloned and approximately 22,000 genes have been identified. This, along with evidence that the function of genes can be altered by the methylation of DNA or alteration in the histone proteins around which DNA is intertwined, determines the propensity to develop diseases (epigenetics). A brief description of the role of genetics and genomics in common CV conditions is provided.

CORONARY ARTERY DISEASE[1]

Several studies have shown genetic changes that predispose individuals for premature coronary artery disease. Studies have identified at least thirteen new loci on DNA associated with coronary artery disease (CAD). The early-onset myocardial infarction has identified strongly with the locus on chromosome 9p21 region (the "p" stands for short arm of chromosome). Specific sites on DNA are also associated with altered coronary lipid metabolism, as well as hypertension.

ARRHYTHMIAS

Prolonged QT interval has been linked with specific genomic markers. The sudden death syndrome has been linked to at least thirteen genes, and there are about 800 mutations that may be implicated in this syndrome. One of the identified mutated genes affects calcium channel and is similar to the one implicated in migraine. Several drugs, such as macrolide antibiotics, ondansetron, and drugs used in gastrointestinal motility disorders also cause prolonged QTc. Similarly, atrial fibrillation and sick sinus syndrome have been linked to specific genetic changes.

The branch of genomics that has potentially immediate application in CV diseases is known as pharmacogenomics. It is well known that medications work only in about 50% of the patients. Factors that influence low-response rate include variation in absorption, metabolism, excretion and sensitivity of target molecules. Metabolism of the drug is affected by genetic makeup of the patient. It has long been shown that genetic variation in cytrochrome *2C19* (Cyp2) and VKORC1 are responsible for the metabolism of warfarin. Further, dosages of warfarin need to be adjusted based on this genetic makeup of a patient. Similarly, cytrochrome *2C19* is also responsible for activating clopidogrel and the particular variant of the gene (*cyp 2 A1)* is a slow metabolizer of clopidogrel to its active form. Thus, patients having this type of genetic variation need to be given double the dose of clopidogrel to get desired effect. In a recent study, application of these genetic studies has shown to impact outcome in acute coronary disease.[3] It is also known that the variation in gene for beta-adrenergic receptor (*ADRB1*) is also associated with altered response to beta-blocker in heart failure. The myopathy that may occur in patients receiving statins has been linked to variant in gene *SLC01B1*. The effect of aspirin is also affected

by genomic changes in its acetylation. There are practical implications to the practicing physicians of these observations.

In summary, the genetics, genomics and other basic science discoveries, such as study of metabolism, is revolutionizing the entire medical field. Just as one studies anatomy and physiology, the study of molecular biology is impacting ability of physicians to take care of patients. The field of genetics and genomics has already made a significant impact in other fields, such as oncology and infectious diseases, and is likely to make a high impact in the field of cardiology. It is important for students, residents and other physicians involved in the field of cardiology to get acquainted with this emerging field.

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Epilogue

The practice of medicine profoundly influences your life in a very personal way. For one thing, it makes you humble. Along the way, we come across the finest of what humanity has to offer—finest teachers, institutions, books, colleagues, and patients.

Ours is the first generation of doctors to face some unprecedented challenges in the form of strangulating litigation climate, mal-influence of insurance, drug and medical equipment and drug companies, defensive medicine, unbridled greed, and ever expanding oppressive bureaucratic regulations. The drumbeats are getting louder. Our collective response will spell what the future generation of doctors would inherit.

Most of our "real" education usually starts after completion of our training. We learn so much from our patients—courage, human suffering, patience, tolerance, hardship and acceptance of things the way they are. It changes us little by little. Path to "*Nirvana*" is tough and requires superhuman efforts.

Besides the countless fine textbooks that we read, we should also try literary works by medical doctors. Some, which have touched the author profoundly, are as follows:

- "Emperor of all Maladies"—a Pulitzer Prize winner by Dr Siddharth Mukherjee, MD, from Harvard University and Columbia University.
- "My own Country", "Tennis Partner" and "Cutting for Stone" by Dr Abraham Verghese, MD, from Stanford University
- "Complications", "Better" and "Check List" by Dr Atul Gawande, MD, from Harvard University.

The author strongly feel that books like these should be a "compulsory reading" for every physician. The author do not think physician can become complete without reading such literary masterpieces. Physician will understand dedication, hard work, empathy, compassion and the relentless pursuit for a better tomorrow. Above all, let this great profession teach physician humility and respect for other lives.

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