Alessandro Capucci
Editor

Clinical Cases in Cardiology

A Guide to Learning and Practice

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Preface

Knowledge in cardiovascular science has expanded widely in the last decades and recent years. The proof of this development is the increasing number of scientific articles published, and the frequent updates of the cardiological guidelines. Cardiology now comprehends a wealth of subspecialties such as hemodynamics, electrophysiology, heart failure management, the study of syncope, and genetics of cardiac diseases, only to mention a few, and each of these subspecialties counts on devoted specialists who focus their attention and skillfulness basically on their specific field only. As a result, learning in the cardiovascular field has become fragmentary, and some diagnostic and therapeutic procedures artificially expand. In other words, in this day and age there is an increasing need of a professional who should be able to follow the patient from the diagnostic to the therapeutic phase, and therefore able to interpret the role and meaning of every subspecialty approach. The figure I am referring to is the clinical cardiologist, who should act as an interface between the patient and the subspecialist, according to patient needs but maintaining the ability to interpret single exam indications and responses, and finally managing indications and contraindications for all the specific therapies. The clinical cardiologist is the one who primarily should take care of the patient by checking indications and results coming from more specialized fields in cardiology.

How is it possible to give adequate academic and professional preparation to such an important medical figure, when a subspecialist is considered so important nowadays and usually collects the majority of the resources devoted to the health system? Specialized scientific articles and texts written for subspecialists are difficult learning tools for a cardiologist who is not dedicated full time to a specific clinical topic, since it is often hard even to follow the reported concepts. The majority of the medical texts are written for subspecialists and contribute to knowledge partition. Moreover, the current trend of doctors in search for medical information goes towards internet, which on one hand may help save time because one goes directly to a specific topic, but on the other, a variety of different facets are missed, which are usually contained in more encompassing and wide-ranging publications.

In this book we thought of a different approach, mainly aimed at reaching the majority of professionals in cardiology. With this book we want to address chiefly young cardiologists, cardiology residents in training, general practitioners, and cardiologists that wish to maintain and improve their clinical mission. Each chapter is devoted to a specific topic of cardiac diseases and is

constructed starting from a clinical case, that is thoroughly discussed, then the description of the current referred knowledge and the guidelines in use.

One of our most important goals while writing this book is to invite the readers to think primarily of the patient they have in front of them, when they have to interpret symptoms and signs. At that stage, a correct and complete anamnesis is mandatory and turns out to be the real basis for patient framing. Second, but not less important, the patient should be visited considering all the semeiotic aspects (not only the cardiological physical exam), then interpreting EKG. At that point, our clinical guess should be correctly addressed and, when needed, we could rely on more specific exams, whose indications, contraindications, adverse events, and possible interpretations we should know well.

This book, by presenting to the reader clinical cases often encountered in the daily practice, has the only goal to describe them and find the correct clinical approach, always reminding the reader that semeiotic and clinical evaluation keep a major role in our medical profession and allow an essential link to the patient's health and psychophysical recovery.

That was our intention and we hope we have achieved our goal.

Ancona, Italy Alessandro Capucci, MD

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Part I

Acute Ischemic Heart Disease

ST Elevation Related to the Site of Coronary Occlusion

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Maria Vittoria Matassini and Matilda Shkoza

1.1 Case Report

A 44-year-old man was referred to our ICU at 1:30 AM from the medical first aid due to intense, prolonged, non irradiated retrosternal pain, insurgent at 00:30 AM while sleeping, and profuse cold sweating. The medical first aid recorded an ECG immediately, at their arrival, that showed sinus rhythm, third-grade AV block, narrow QRS escape rhythm with a heart rate of 33 bpm, ST elevation in the inferior leads (DII, DIII, aVf) with specular ST depression in DI and aVl, and QRS axis of 105°. Blood pressure was 90/50 mmHg. Therapy with salicylic acid 500 mg IV, unfractionated heparin 4000 UI IV and clopidogrel 300 mg per os therapy was administered. The patient was immediately transferred to our ICU for further evaluation and treatment.

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Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: systemic arterial hypertension and dyslipidemia
- Family history: no family history of structural heart disease
- 2005: stab wound in the midsternal area

Allergies

None

Medications

None

Vital Signs

- Temperature: 36.5 °C
- Heart rate: 33 bpm
- Arterial blood pressure: 85/50 mmHg
- Respiratory rate: 20 breaths/min
- Oxygen saturation: 97 %

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Physical Examination

- General appearance: well developed, well nourished, alert but confused, suffering from retrosternal pain, with pallor and cold sweat
- Lungs: dyspnea; clear to percussion and auscultation without rhonchi, wheezing, or diminished breath sounds; presence of bibasilar rales
- Cardiovascular: normal S1 and S2; no S3, S4, or murmurs; regular rhythm; no vascular murmurs
- Abdomen: positive bowel sounds, soft and nondistended, no guarding or rebound, no masses

Routine Laboratory Test

White blood cells 17,000 mmc, total cholesterol 338 mg/dl, triglycerides 853 mg/ml, AST 398 U/L, ALT 117 U/L, LDH 689 U/L, γGT 60 U/L, troponin I highly specific 116 ng/ml, CKMB 222.8 ng/ml, and uric acid 8.4 mg/ml. The remaining laboratory tests were normal.

Instrumental Examination

The ECG at entrance (Fig. 1.1a, b) confirmed the previous one, already described.

A complete echocardiographic examination was performed and showed normal dimensions of the cardiac chambers, reduced systolic left ventricle function (EF 45 %) due to hypokinesia of the inferior and posterolateral wall, normal right ventricular function (TAPSE 21 mm), and mild mitral and tricuspid regurgitation with normal pulmonary artery systolic pressure.

Clinical Course and Therapeutic Management

These findings all together were suggestive for inferior ST elevation acute coronary syndrome complicated by third-degree AV block.

As soon as possible, a transcutaneous pacing and a continuous electrocardiographic, blood pressure, and oxygen saturation monitoring were placed, and the cath lab team was advised. Therapy with crystalloid and dopamine 5 gamma/kg/min infusion was practiced with blood pressure increase to 120/70 mmHg, and morphine was administered for the transcutaneous pacing pain. At 1:45 AM the patient was transferred to the cath lab to perform coronary angiography and to position a temporary pacing via the right femoral vein. The angiography showed right coronary artery dominance with thrombotic occlusion of its middle tract; no other stenosis was present. At 2:05 AM the patient underwent manual thrombus aspiration (EXPORT) and PTCA with medicated self-expanding stent (STENTYS DES 3.5–4.5×17 mm) implantation via the right radial artery. A bolus of abciximab 0.25 mg/kg was administered, and the patient was shifted to prasugrel with a loading dose of 60 mg administered in the cath lab. The residual stenosis was <20 % and TIMI flow was 3. Continuous unfractionated heparin infusion was administered during the 12 h following the procedure. The transvenous pacing was removed 48 h later being the patient again in stable sinus rhythm. Continuous electrocardiographic monitoring during the first 6 days did not show any dangerous tachyarrhythmia or bradyarrhythmia. Therapy with ASA 100 mg od, prasugrel 10 mg od, atorvastatin 80 mg od, losartan 12.5 mg od, and pantoprazole 40 mg od was started since the first day. Metoprolol tartrate 25 mg bid was added the second day. The patient was transferred to our semi-intensive cardiology unit on the third day and then discharged on the seventh day with a follow-up visit, ECG, and echocardiography programmed 2 months later. Therapy at discharge was ASA 100 mg od, prasugrel 10 mg od for 12 months, atorvastatin 80 mg od, losartan 12.5 mg od, pantoprazole 40 mg, and metoprolol tartrate 25 mg bid.

1.2 ST Elevation Myocardial Infarction (STEMI)

Definition and Epidemiology

The last ESC guidelines published in 2012 define "acute myocardial infarction" (AMI) as the evidence of myocardial necrosis (elevation of cardiac biomarkers, typical ECG alterations,

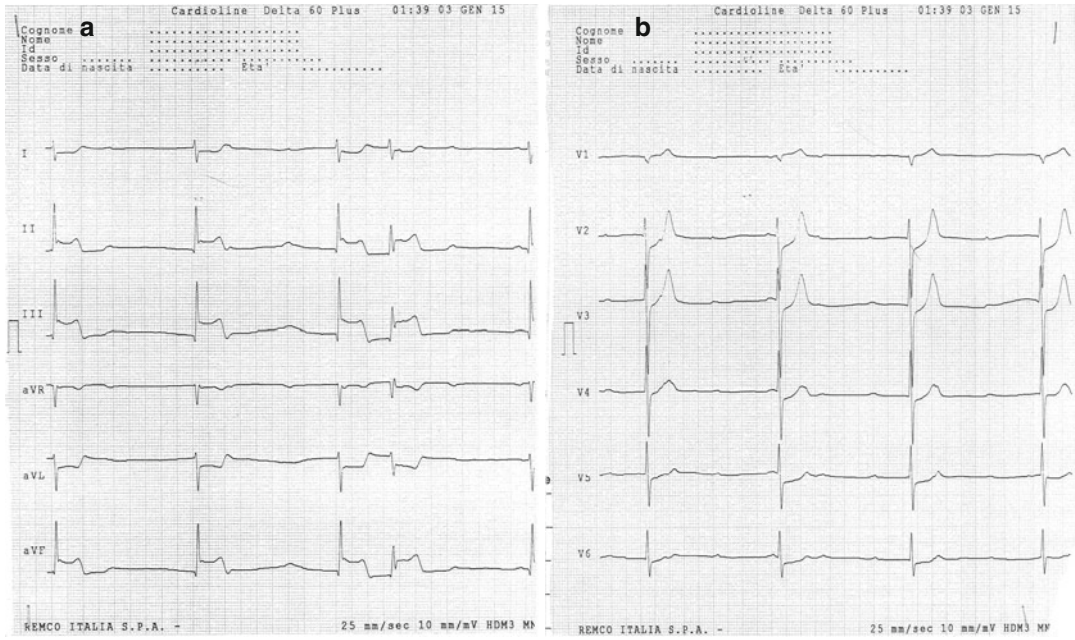

Fig. 1.1 (**a**, **b**) Patient ECG: sinus rhythm, third-grade atrioventricular block, narrow QRS escape rhythm with a heart rate of 33 bpm, ST-segment elevation in the inferior leads (DII, DIII, aVf) with specular ST-segment depression in DI and aVl, QRS axis of 105°

imaging alterations, or autopsy evidence) in the presence of a clinical setting suggestive for myocardial ischemia [1].

Acute myocardial infarction with ST elevation (STEMI) is a clinical syndrome characterized by the typical symptoms of myocardial ischemia with electrocardiographic ST elevation (persistent for more than 20 min) and following release of cardiac biomarkers [2].

Coronary artery disease (CAD) is the most common cause of death in the whole world. In 2012, 7.4 million people in Europe (which is 13.2 % of all deaths) died from CAD [3].

At present, up to 25–40 % of AMI presentations are STEMI ones [4–7]. The incidence of STEMI hospital admissions is different among countries that belong to ESC [8]. In the last decades there has been a STEMI incidence decrease despite an NSTEMI incidence increase. In the Sweden registry, which is probably the most comprehensive STEMI registry, an incidence of 66 STEMI/100,000/year, similar to those of other countries like the Czech Republic [9], Belgium [8], and the USA [10], has been reported.

The in-hospital mortality of unselected STEMI patients varies from 6 to 14 % [8]. Ejection fraction, the Killip class, age, time delay to treatment and mode of treatment, prior myocardial infarction history, renal dysfunction, diabetes mellitus, and diseased coronary artery number are all factors that influence mortality. Hospitals with a high clinical volume and high rate of invasive procedures have lower mortality rates [11]. STEMI mortality significantly decreased thanks to a frequency care increase [5, 7].

Pathology and Pathophysiology

Pathology

The causes of STEMI are different, but they can be divided into two principal groups:

- Coronary atherosclerosis complicated by coronary thrombosis, the main one
- Non-atherogenic forms that are rare such as arteritis, trauma to coronary arteries, coronary mural thickening with metabolic disease or

intimal proliferative disease, emboli to coronary arteries, congenital coronary artery anomalies, myocardial oxygen demand–supply disproportion, hematologic, and miscellaneous [12]

We will focus our attention on the first cause of STEMI, the coronary atherosclerosis.

A previous classification based on ECG evolution divided patients with MI into two groups: patients with a Q-wave infarction, very often considered a transmural infarction, and patients with a non-Q-wave infarction. Currently, a new classification based on pathophysiology divides patients into other two groups: those with STEMI related to an acute thrombotic occlusion of an epicardial coronary artery and those with NSTEMI/unstable angina, due to stenosis of a coronary artery without occlusive thrombi. When there is a chronic total occlusion of the coronary artery, patients do not always have an MI because of collateral blood flow development and other factors.

The most important element on AMI's physiopathology is the atherosclerotic plaque. The plaque evolution is an active process lasting years that consists in intima lipoprotein accumulation, lipoprotein oxidation and glycation, intima leukocyte migration, foam cell development, intima smooth cell migration with consequent extracellular matrix accumulation, atherosclerotic plaque growth, and a fibrofatty lesion formation with a lipid core surrounded by an acellular fibrous capsule. Cytokines and effector molecules like hypochlorous acid and superoxide anion play an important role in this process.

During this natural evolution, high-risk plaques can undergo plaque disruption [13, 14] that is induced by stressors like intramural blood pressure, coronary vasomotor tone, and tachycardia. So, thrombogenic substances are exposed with secondary activation and aggregation of platelet; moreover, thrombin generation is promoted with subsequent thrombus formation. There is seasonal and circadian variation of some of these key physiologic variations, and that is why STEMI happens more frequently in the winter early morning hours and following natural disasters [15].

Anatomically, two major types of MI can be detected: transmural infarcts characterized by the presence of a full ventricular wall thickness myocardial necrosis and nontransmural or subendocardial MI with necrosis involvement of the subendocardium or intramural myocardium or both. In the first case, there is a completely occlusive thrombus of an epicardial coronary artery that subtends the infarct area with a typical ST-segment elevation. The transmural necrosis can cause a full wall thickness vital myocardial loss and subsequent fibrosis that is evidenced by Q-wave evolution in the leads overlying the infarcted zone. In a few number of patients, there is not a Q-wave evolution but an R-wave height reduction.

There is a specific correlation between the coronary artery occluded, the myocardial area developing necrosis, and the ECG derivation that shows an ST elevation (Fig. 1.2).

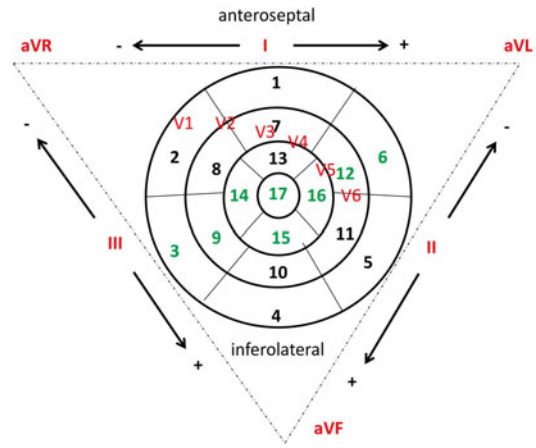

Fig. 1.2 Schematic representation of left ventricle segments, Einthoven's triangle with electrocardiogram derivations. LAD supplies segments nr 1, 2, 6, 7, 8, 12, 13, 14, 15, 16, and 17; LCX supplies segments nr 4, 5, 6, 10, 11, 12, 15, 16, and 17; RCA supplies segments nr 3, 4, 9, 10, 11, 14, 15, 16, and 17. Areas of shared perfusion between LAD, LCX, and RCA are shown in green. The infarct artery can be deduced identifying the leads with ST-segment elevation and correlating these with the segments that these leads explore and so with coronary arteries that supply these segments. For example, ST segment elevated prominently in leads exploring segments 1, 2, 7, 8, 13, 14, and 17 which means that the occluded vessel is the LAD. LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex

The earliest myocardial ultrastructural changes occurring within the first 20 min are reversible. Changes become irreversible after 20 min up to 120 min of ischemia [16]. After 6–12 h of necrosis onset, myocardium gross alteration can be identified. So, in the first 30 min after ischemia onset, myocardial injury is reversible; subsequently, a progressive viability loss occurs and usually completes at 6–12 h. That is the reason why the reperfusion therapy benefits are greatest when patients are treated early.

Generally, the right ventricle is less involved by infarction. It is interested in approximately 50 % of patients with transmural infarct of the inferoposterior wall and posterior portion of the septum [17]. The right ventricle shows an excellent recovery of systolic function once reperfusion is restored [18].

Pathophysiology

When a coronary artery is occluded, immediate myocardial contractile alteration occurs. There are four sequential patterns of abnormal contraction:

- Dyssynchrony (adjacent segments do not contract at the same time)
- Hypokinesia (reduced contraction)
- Akinesia (cessation of contraction)
- Dyskinesia (the segment expansion is paradoxical)

As an acute compensation of these alterations, a hyperkinesia of the normal myocardium segments usually firstly develops. It results from sympathetic nervous system activity increase and Frank–Starling mechanism and lasts up to 2 weeks.

If ischemic injury involves >15 % of the myocardium, the systolic–diastolic function of the LV becomes depressed, and a decline of cardiac output, stroke volume, and blood pressure occurs. End-systolic volume and end-diastolic pressure increase and diastolic dysfunction appears. The degree of end-systolic volume increase has been shown to be an important predictor of STEMI mortality [19]. If ischemic injury involves >25 % of the myocardium, clinical heart failure becomes typical, and if the myocardial loss is >40 %, cardiogenic shock appears.

Improvement is possible thanks to the recovery of the stunned (reversibly injured) myocardium after revascularization, but in some patients the infarcted LV may dilate causing LV remodeling. This can be a compensatory mechanism restoring a normal stroke at the expense of a reduced ejection fraction; however, dilation elevates afterload (Laplace's law) that depresses LV stroke volume and increments the consumption of myocardial oxygen, intensifying myocardial ischemia. The infarct size, patency of the related coronary artery, and renin–angiotensin–aldosterone system (RAAS) influence LV remodeling. For this reason, LV remodeling can be reduced by an antagonist of RAAS. Even aldosterone inhibitors reduce collagen deposition and decrease ventricular arrhythmia development [20].

Clinical Features

Symptoms

The typical STEMI discomfort is a prolonged (more than 20 min), constricting, oppressing, or compressing pain of variable intensity. It has a retrosternal location and often radiates to the ulnar side of the left arm, or rarely both arms; to the neck, jaw, and shoulders; and rarely to the epigastrium or interscapular region. In some patients, frequently those with an inferior STEMI, the location is the epigastrium simulating abdominal disorders. In these patients nausea and vomiting may occur due to vagal reflex activation or LV receptor stimulation. Symptoms like cold perspiration, palpitations, profound weakness, dizziness, and a sense of imminent death may be present.

In some cases there is an atypical presentation of STEMI-like atypical location of the pain or dyspnea, syncope, profound weakness, or acute indigestion. Some patients are wholly asymptomatic, and STEMI can be unrecognized and discovered in a subsequent routine electrocardiographic examination. These patients have a similar prognosis of symptomatic ones.

In up to half of STEMI patients, a precipitating factor like reduced oxygen supply to the

myocardium (hypotension, hypoxemia, pulmonary embolism, etc.) or increased myocardial oxygen demands (aortic stenosis, fever, agitation, tachycardia, emotional stress, unusually heavy exercise) can be identified.

Physical Examination

STEMI patients may appear anxious and agitated. Heart rate varies from bradycardia to tachycardia/tachyarrhythmia, and blood pressure varies from hypotension (patient with right ventricle involvement or cardiogenic shock or low blood pressure acute heart failure) to normotension and even to hypertension due to adrenergic activation.

Fever is present in most patients and resolves within 4–5 days. It is a nonspecific response to tissue necrosis.

Patients with cardiogenic shock or right ventricular infarction infarct have elevated jugular pressure.

Carotid pulse in STEMI patients may be small due to reduced stroke volume. When LV failure develops, rales are audible.

The Killip classification is a prognostic classification dividing STEMI patients according to the presence and severity of heart failure signs:

- Class I: no rales or third sound
- Class II: rales in <50 % of pulmonary field with or without third sound
- Class III: rales in >50 % of pulmonary field (pulmonary edema)
- Class IV: cardiogenic shock

A third and/or fourth sound may be heard in STEMI patients with severe LV dysfunction that determines elevation of LV filling pressure. When the fourth sound is heard, a corresponding presystolic pulsation is present. Additional systolic murmur (transient/persistent) due to mitral regurgitation as a result of mitral valve apparatus dysfunction may be audible. Along the left and right sternal border, a holosystolic, prominent murmur, accompanied by a thrill, is audible in the presence of interventricular septum rupture. Pericardial friction rubs can be present especially in patients with large infarctions [21]. They are audible along the left sternal border in the first 2 weeks and most commonly on the second or third day.

Diagnosis

The diagnosis of STEMI starts from symptom assessment: history of chest pain lasting at least 20 min or more; not responding to nitroglycerine is typical.

The confirmation of diagnosis must be completed as soon as possible with a 12-lead ECG, also considering the addition of posterior (V7–V8–V9) or right leads (V4R–V5R, V6R) in patients with high suspicion, respectively, of posterior or right ventricle infarction.

If available, a continuous ECG monitoring should be initiated in all patients to detect life-threatening arrhythmias and allow defibrillation if required.

The diagnostic electrographic sign is a new ST-segment elevation measured at the J point in two contiguous leads with the following thresholds: ≥0.25 mV in men below the age of 40 years, ≥0.2 mV in men over the age of 40 years, or ≥0.15 mV in women in leads V_2–V_3 and/or ≥0.1 mV in other leads [1]. According to leads involved by ST elevation, the localization of the ischemia is as follows:

- Anterior MI: V1–V6
- Septal MI: V1–V4
- Lateral MI: I, aVL, V5, V6
- Inferior MI: II, III, aVF
- Posterior MI: V7–V8–V9 (high R in V1–V3 with ST depression V1–V3)
- Right ventricle MI: V1, V4R–V5R–V6R

Although not frequently seen, an earlier sign of ischemia could be the presence of hyperacute T waves; later, the ECG alterations evolve in ST elevation in those leads that register the electrical activity of the ischemic myocardium. ST elevation typically presents a concave configuration but over time becomes more pronounced, more convex, and rounded upward. In the absence of reperfusion strategies, the natural evolution of ECG is as follows: the ST gradually returns to

isoelectric baseline, there is a reduction of R-wave amplitude with the development of Q waves, and T waves become inverted. The ECG changes usually may take place from few weeks to several hours from presentation.

Moreover, the initial ECG presentation of acute coronary syndrome could be represented by new or presumed new left bundle branch block (LBBB) [1].

The electrocardiographic diagnosis could be more difficult in some categories of patients:

- Patients with preexistent LBBB: in the presence of intraventricular conduction delay, the diagnosis could be suspected in the presence of concordant ST elevation with QRS or in case of marked ST abnormalities. Two signs are highly specific: Cabrera's sign, a prominent notching in the ascending limb of S wave in leads V3–V4, and Chapman's sign, a notching in the ascending limb of R wave in V5–V6 [22]. A scoring system has been developed from the GUSTO-1 trial called Sgarbossa's criteria [23] but not providing diagnostic certainty.
- Patients with paced rhythm: in case of clinical strong suspicion, the diagnosis should be confirmed by angiography; reprogramming of the pacemaker with the appearance of intrinsic rhythm and the evaluation of ischemic ECG changes may be considered when feasible.
- Patients with isolated posterior myocardial infarction: the involvement of the inferobasal portion of the heart may appear as an isolated ST depression ≥0.05 mV in leads V_1 through V_3. The documentation of ST elevation ≥0.05 mV in the posterior chest wall leads should be treated as STEMI.
- Patients with left main coronary obstruction: the typical ECG signs are aVR ST elevation and inferolateral ST depression; the presence of ST depression in eight or more surface leads together with ST elevation in aVR and/or V1 suggests ischemia due to multivessel disease or left main coronary artery obstruction.

The following steps are not necessary for the diagnosis; however, they complete the clinical picture of patients with ACS: blood sampling for troponin determination and echocardiography for differential diagnosis and for the assessment of the involved myocardium, left ventricular function, and mechanical complications.

Therapy

The following recommendations are based on currently accepted European guidelines [1].

Initial therapy of patients with acute coronary syndrome with ST elevation is represented as follows:

- Oxygen administration in the presence of hypoxia or acute heart failure.
- Relief of pain and anxiety: IV opioids are very useful, although they must be used with caution for their potential side effects, such as respiratory depression, nausea, vomiting, hypotension, and bradycardia.

The following steps of treatment are related to some crucial aspects: the first one is time from symptom onset and the second one, the availability of a primary PCI center.

Patients with a diagnosis of STEMI within 12 h from symptom onset should be considered for mechanical or pharmacological reperfusion strategy, as soon as possible. Moreover, reperfusion therapy should be taken into account in the presence of ongoing ischemia even if the onset of pain dates back more than 12 h. Primary PCI may also be done in stable patients presenting 12–24 h after symptom onset.

In case of reperfusion strategy, the choice between mechanical and pharmacological methods depends on the availability of a primary PCI center with an experienced team or the time needed to reach the PCI center. PCI strategy is preferred to fibrinolysis when there is a primary PCI hospital or when the transfer to a PCI center could be realized within 120 min from symptom onset. In the other cases, fibrinolysis should be undertaken and followed by consideration of rescue PCI in case of treatment failure or by consideration of routine angiography in all stable patients within 3–24 h.

In case of mechanical reperfusion, only the culprit lesion should be treated with PCI and stenting [24]. Primary multivessel revascularization in addition to the supposed culprit lesion is indicated in case of cardiogenic shock or persistent ischemia, after the culprit lesion treatment [1, 25, 26]. In case of multivessel disease, staged multivessel PCI could be considered as recent meta-analysis showed improvement in short- and long-term survival and reduction of repeated PCI [27]. However, other randomized trials should confirm the benefits of staged multivessel PCI in STEMI.

Primary Percutaneous Coronary Intervention: Pharmacotherapy

The main stones of therapy in acute coronary syndrome are represented by antiplatelet and anticoagulant drugs.

1. Antiplatelet therapy consists of a combination of two antiplatelet agents: the first option is aspirin, both oral and IV, if patients are unable to swallow, and the second one is an adenosine diphosphate (ADP) receptor blocker. For a long time, clopidogrel has been the only and preferred ADP blocker, while in the last years new antiplatelet agents such as prasugrel and ticagrelor have been studied [28, 29] and currently accepted in guidelines and widely used in common clinical practice. Prasugrel and ticagrelor present a more rapid onset of action and higher efficacy when compared to clopidogrel. Therefore, clopidogrel is preferably used when prasugrel or ticagrelor is either not available or contraindicated. Table 1.1 summarizes the main features of old and new antiplatelet agents.

   The glycoprotein IIb/IIIa (GP IIb/IIIa) antagonists are the most recent additions to the antiplatelet agents available that are given intravenously. Currently, three GPIIb/IIIa antagonists are available: abciximab, eptifibatide, and tirofiban. The role of these agents is debated: in the era of potent oral antiplatelet agents, the upstream use is uncertain; moreover, if bivalirudin is chosen as an anticoagulant, its use does not add further benefits. On the other side, if UFH or enoxaparin is administered, the association of GPIIb/IIIa antagonists remains debatable. Current guidelines suggest the administration of GP IIb/IIIa inhibitors for bailout therapy if there is angiographic evidence of a massive thrombus, slow or no reflow, or thrombotic complication.
2. Anticoagulant therapy in primary PCI-treated patients may be achieved with unfractionated heparin (UFH), enoxaparin, and bivalirudin, with the aim to reduce acute vessel thrombosis risk. Anticoagulants should be started as soon as possible and stopped at the end of PCI procedure, except in the presence of other conditions that require prolongation of anticoagulants, such as atrial fibrillation or mechanical valve or left ventricular thrombosis.

   Bivalirudin is a direct thrombin inhibitor, nowadays, recommended by European guidelines over unfractionated heparin and a GP IIb/IIIa blocker (Ib) [1]. As previously reported, when bivalirudin is preferred, addition of GP IIb/IIIa blockers does not add adjunctive benefits, and bivalirudin alone is associated with lower bleeding rates and reduced mortality [32].

   Enoxaparin (with or without routine GP IIb/IIIa blocker) may be preferred over unfractionated heparin with a class II of indication, level B; finally, unfractionated heparin with or without routine GP IIb/IIIa blocker must be used in patients not receiving bivalirudin or enoxaparin (I, C) [1].

Fibrinolysis

Fibrinolysis must be considered when mechanical revascularization is not available in recommended timelines [1]. Prehospital treatment with fibrinolytic drugs by emergency medical personnel is strongly suggested, when feasible: the benefits from fibrinolytic therapy are higher in the first 3 h from symptom onset and then rapidly decline [33]. The delay from first patient contact and initiation of fibrinolysis should be within 30 min to improve treatment efficacy, in both hospital and prehospital settings.

There are many absolute and relative contraindications to fibrinolysis, as reported in Table 1.2.

A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin-specific agents).

Aspirin and clopidogrel must be administered to treated patients. Parenteral anticoagulation is

Table 1.1 Old and new antiplatelet agent for acute coronary syndrome

	Clopidogrel	Ticagrelor	Prasugrel
Trial	CURE [30], PCI-CURE [31]	PLATO [28]	TRITON-TIMI 38 [29]
Class	Thienopyridine	Nucleoside analog	Thienopyridine
Doses	300–600 mg loading dose + 75 mg maintenance dose	180 mg loading dose + 90 mg maintenance dose bis in die	60 mg loading dose + 10 mg maintenance dose
Mechanism of action	Irreversible inhibition of P2Y12 subtype of ADP receptors on the platelet surface	Reversible and noncompetitive binding of P2Y12 subtype of ADP receptors on the platelet surface	Irreversible inhibition of P2Y12 subtype of ADP receptors on the platelet surface
Metabolism	Prodrug activated through hepatic metabolism by cytochrome P450 enzymes Genetic variability in enzyme function affects drug efficacy	No metabolism for activation	Prodrug with intestinal, serum, hepatic metabolism (cytochrome P450 enzymes)
Onset of action	Within 2 h	Within 30 min	Within 30 min
Excretion	Renal (50 %), biliary (46 %)	Biliary	Renal (~68 %), biliary (~27 %)
Side effect		Dyspnea Ventricular pauses Increased rate of bleedings	Increased rate of bleedings
Contraindications	Hypersensitivity Active bleeding Significant liver impairment Cholestatic jaundice	Hypersensitivity Active bleeding History of intracranial hemorrhage Moderate to severe hepatic impairment Concomitant use of strong CYP3A4 inhibitors	Hypersensitivity Active bleeding Prior stroke/transient ischemic attack Moderate to severe hepatic impairment
	Use with caution in patients at high risk of bleeding or with significant anemia	Use with caution in patients at high risk of bleeding or with significant anemia	Not recommended in patients aged ≥75 years or in patients with lower body weight (<60 kg) Use with caution in patients at high risk of bleeding or with significant anemia

recommended until revascularization (if performed) or for the duration of hospital stay, from at least 48 h up to 8 days. Enoxaparin is preferred over UHF.

Patients treated with fibrinolysis must be transferred to a PCI-capable center: stable patients should be studied within 3–24 h. Rescue PCI is indicated in case of treatment failure (<50 % ST-segment resolution at 60 min), recurrence of ST-segment elevation, or recurrent ischemia. Also patients with heart failure or cardiogenic shock must undergo angiography [1].

Arrhythmia Management in Acute Phase

Arrhythmias are very frequent in the acute phase of STEMI, and every kind of arrhythmia could be seen [1].

Table 1.2 Contraindications to fibrinolysis

Absolute	Previous intracranial hemorrhage, known cerebrovascular lesion or intracranial neoplasm, ischemic stroke within the last 6 months, aortic dissection, recent major trauma/surgery/head injury, gastrointestinal bleeding within the past month, known bleeding disorder, noncompressible punctures in the past 24 h
Relative	Poorly controlled hypertension (Pas > 180 mmHg or Pad > 110 mmHg), transient ischemic attack in the last 6 months, current use of anticoagulant therapy, pregnancy or within 1 week postpartum, advanced liver disease, infective endocarditis, active peptic ulcer, prolonged or traumatic resuscitation

As occurred in our patient, inferior myocardial infarction is frequently associated with bradyarrhythmias, from sinus bradycardia to atrioventricular (AV) blocks. Sinus bradycardia, first-degree AV block, and second-degree AV block type I usually do not require specific treatment; in case of symptoms or severe hypotension, IV atropine should be administered, and if not effective, temporary pacing should be started. All medications interfering with electrical conduction should be withheld. Second-degree, type II, and third-degree atrioventricular blocks usually need temporary pacing, especially if concomitant hypotension or heart failure is present.

AV blocks developing during inferior infarction are usually supra-Hisian and reversible with the restoration of coronary perfusion, and they carry a good prognosis. The ECG shows an escape rhythm with narrow QRS. In case of anterior MI, the presence of an AV block underlines the existence of an extensive necrosis, interesting electrical conduction ways; the block is usually infra-Hisian with a low escape, wide QRS rhythm. A new bundle branch block or a new hemiblock should be highly monitored because they often precede a complete AV block.

Atrial fibrillation is also very common in STEMI patients, especially in the presence of heart failure [34]. Anticoagulation should be started if not contraindicated, and effective rate control achieved in order to reduce myocardial oxygen demand. In case of hemodynamic instability or ongoing ischemia, urgent electrical cardioversion is indicated, while pharmacological cardioversion could be achieved with amiodarone in stable patients with recent arrhythmia onset. For further details on atrial fibrillation management, see Chap. 20.

Ventricular arrhythmias (VA) vary from ventricular premature beats to non-sustained and sustained ventricular tachycardias (VT) to ventricular fibrillation. The prevalence of ventricular arrhythmias has been investigated in the fibrinolytic era [35] and, later, in the primary percutaneous coronary intervention era [36]: VA remain fairly common even if the real incidence may be underestimated because MI resulting in prehospital sudden cardiac death could have not been considered in evaluating studies.

Ventricular premature beats and non-sustained VT are really common in the first days from MI. Treatment is not recommended [1] unless non-sustained VT causes hemodynamic instability.

Sustained monomorphic VT are often not tolerated, especially in the presence of worse left ventricular dysfunction; moreover, they may produce ischemia and degenerate in ventricular fibrillation.

In hemodynamically unstable patients, electrical cardioversion is mandatory. In stable VT, diagnosis and treatment should be prompt because of the risk of rapid deterioration of clinical and hemodynamic conditions. If the patient is stable, IV amiodarone, sotalol, or lidocaine could be attempted, even if conversion rates are low.

For polymorphic VT and ventricular fibrillation, the first therapy consists of immediate defibrillation [37]. If polymorphic VT develop in the setting of bradycardia, a temporary pacing at higher rate should be started.

For further details in the management of ventricular arrhythmias and long-term risk evaluation for sudden death, see Chap. 18.

Long-Term Therapies for ST-Segment Elevation Myocardial Infarction

Long-term management of patients with acute coronary syndrome with ST elevation consists of lifestyle changes, risk factor control, and long-term drug therapy.

Lifestyle changes are mainly represented by interruption of smoking, diet and weight control, and regular physical activity. Blood pressure should be regularly controlled with the following target: systolic pressure <140 mmHg.

If available, exercise-based rehabilitation is strongly recommended; different studies showed positive effects of cardiac rehabilitation in terms of mortality, reinfarction, and quality of life [38]. Rehabilitation also favors achievement of a better risk factor control and correct titration of accepted therapy, as beta-blockers.

Aspirin therapy is indicated indefinitely after STEMI, or if not tolerated, clopidogrel should be used. The combination of dual antiplatelet therapy is recommended for up to 12 months after STEMI, with a minimum of 1 month for patients receiving PCI and bare-metal stents and 6 months for patients receiving PCI and drug-eluting stent. Dual antiplatelet therapy should be maintained up to 1 year in patients with STEMI who did not receive a stent.

Oral beta-blockers must be introduced during hospital stay and continued thereafter in all patients without contraindications. High-dose statins early after admission are indicated in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol concentrations. A target value of <70 mg of LDL cholesterol must be reached, and regularly a lipid profile must be assessed.

Angiotensin-converting enzyme, or if not tolerated angiotensin receptor blocker, is indicated in patients with an impaired ejection fraction (EF < 40 %), with heart failure in the early phase, and with diabetes. However, they may be considered in all STEMI patients for their modest effect on mortality.

Finally, aldosterone antagonists should be considered for patients with at least mild left ventricular dysfunction (EF ≤ 40 %) and heart failure or for diabetic patients, provided that no renal failure or hyperkalemia is present.

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Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)

2

Marco Marchesini, Marco Morelli, and Luca Piangerelli

2.1 Case Report

A 66-year-old man with no previous cardiovascular disease was admitted to the emergency department for worsening chest pain and dyspnea. The patient referred the presence of intermittent chest pain a month ago mainly at rest. No history of fever was present.

Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: type II diabetes mellitus, systemic hypertension, and mild renal failure
- Family history: no family history of structural heart disease
- 2013: hospital admission for interstitial pneumonia complicated by respiratory failure

Allergies

None

Medications

Ramipril 5 mg, atorvastatin 20 mg, pantoprazole 20 mg, and insulin

Vital Signs

- Temperature: 36.5 °C
- Heart rate: 95 bpm
- Arterial blood pressure: 150/80 mmHg
- Respiratory rate: 15 breaths/min
- Oxygen saturation: 99 %

Physical Examination

- *General*: alert, awake, and oriented; restless
- *Neck*: no jugular venous distention, no lymphadenopathy, no carotid bruits
- *Cardiovascular*: regular and tachycardic rhythm, apical soft proto-mesosystolic murmur (2/6 at the Levine scale)
- *Lungs*: no rales, rhonchi, or wheezes to auscultation, normal percussion
- *Abdomen*: no hepatomegaly or splenomegaly, no ascites, no masses, normal bowel sounds in

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all four quadrants, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness
– *Extremities*: no cyanosis or clubbing, no peripheral edema

Routine Laboratory Tests

– *Complete blood count*: normal
– *Cholesterol* (*total*, *HDL*, *LDL*) *and TG*: total 280 mg/dl, LDL 150 mg/dl
– *Hepatic function* (*GOT*, *GPT*, *γ-GT*, *ALP*, *total bilirubin*, *amylase*, *lipase*): normal
– *Thyroid function* (*TSH*, *FT3*, *FT4*): normal
– *Renal function* (*creatinine*, *BUN*): creatinine 1.5 mg/dl (eGFR 65 ml/min/1.73 mq)
– *Serum electrolytes*: potassium 4.5 mEq/l, sodium 139 mEq/l
– *Biomarkers*: troponin I 5.4 ng/ml, BNP 80 pg/ml, C-reactive protein 0.2 mg/dl, glycosylated hemoglobin 81 mmol/l

Instrumental Examination

An ECG performed at patient's admission revealed a right bundle branch block with left anterior hemiblock and ST depression (>0.1 mv) in V3-6 and DII-avF with ST elevation in aVR (Fig. 2.1).

Echocardiography: moderate concentric hypertrophy (LV mass/BSA 135 g/m^2, relative wall thickness 0.45) with preserved LV global function (estimated ejection fraction of 56 %) and hypokinesia of the middle and apical anterior wall; normal dimension and function of the right ventricle (TAPSE 20 mm, FAC area 40 %); impaired relaxation of the left ventricle (E/A < 0.75, E/E' < 10); mild mitral and tricuspid regurgitation; systolic pulmonary artery pressure of 35 mmHg

Chest x-ray showed the absence of pulmonary congestion, lobe consolidation, or bronchograms.

Clinical Course and Therapeutic Management

Clinical, instrumental, and laboratory data allowed us to make diagnosis of SCA-NSTEMI: ECG changes (ST depression >0.05 in more than two contiguous leads), rise in cardiac biomarker levels, and normal left ventricle global function with regional hypokinesia – no signs of myopericarditis.

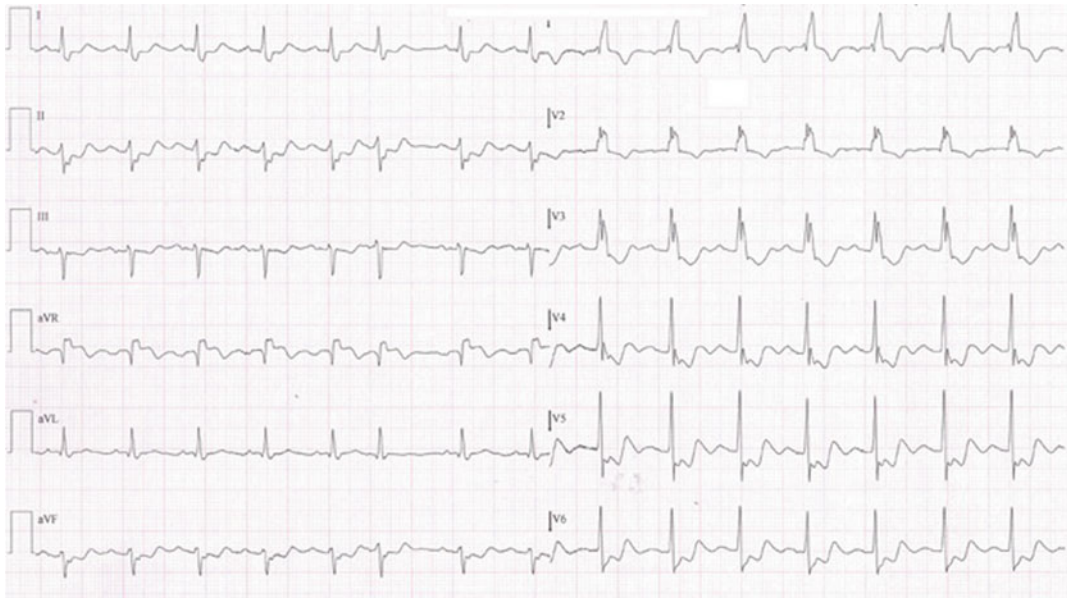

Fig. 2.1 ECG of patients during chest pain

According to guidelines, the patient was assessed with established risk scores for prognosis and bleeding (GRACE 120, intermediate risk; CRUSADE 30, low risk of bleeding). Antiplatelet therapy with aspirin and ticagrelor (P2Y12 inhibitor) with a loading dose of 300 mg and 180 mg, respectively, and anticoagulant therapy with fondaparinux 2.5 mg/die were started. Intravenous nitrate treatment and beta-blocker therapy (metoprolol 2.5 mg ev.) were administered due to persistent angina and tachycardia. ACE inhibitor (ramipril 5 mg) was continued, and high-dose statin therapy (atorvastatin 80 mg) was initiated.

The patient remained asymptomatic in the subsequent hours despite an increase in cardiac biomarkers (troponin I 15 ng/ml) at the laboratory analysis (6 h after patient admission). Given a GRACE score of 120, an ECG suggesting a left main or multivessel coronary artery disease (ST depression in many leads with ST elevation in avR) and the presence of high-risk criteria (significant rise in troponin) an early invasive strategy was performed. Thus, the patient underwent a coronary angiography (<24 h) that showed triple-vessel disease with a SYNTAX score >22 (Fig. 2.2).

Considering the clinical status (asymptomatic patient, progressive lowering in cardiac biomarkers: Tn I 10 ng/ml 12 h after patient admission) and the unfavorable coronary anatomy (SYNTAX score >22), the patient was sent for coronary artery bypass grafting (CABG, class I A). Ticagrelor was then discontinued, and CABG was performed 5 days later without procedural or bleeding complications. The patient was then transferred on day 12 to a postsurgery rehabilitation center with a progressive improvement in functional capacity and subsequently dismissed after 7 days. The therapy at discharge was dual-antiplatelet therapy (aspirin 100 mg and ticagrelor 90 bid), ramipril 5 mg, atorvastatin 80 mg, metoprolol 50 mg bid, pantoprazole 20 mg, and insulin therapy.

2.2 Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)

Definition and Epidemiology

Coronary artery disease (CAD) is one of the major causes of deaths and morbidity in developed countries with a prevalence that increases with age [1]. Nearly 17.3 million deaths in 2013 worldwide were related to cardiovascular disease [2]. Acute coronary syndrome (ACS) represents one of the most frequent and life-threatening clinical presentations of CAD and is related to plaque rupture or an ischemic imbalance between myocardial oxygen supply and demand. The extensive use of high-sensitive troponin assay may have led to more diagnosis of myocardial infarction (MI) hiding a possible reduction in the incidence of MI [3]. According to the most recent guidelines [4], the term myocardial infarction should be used in

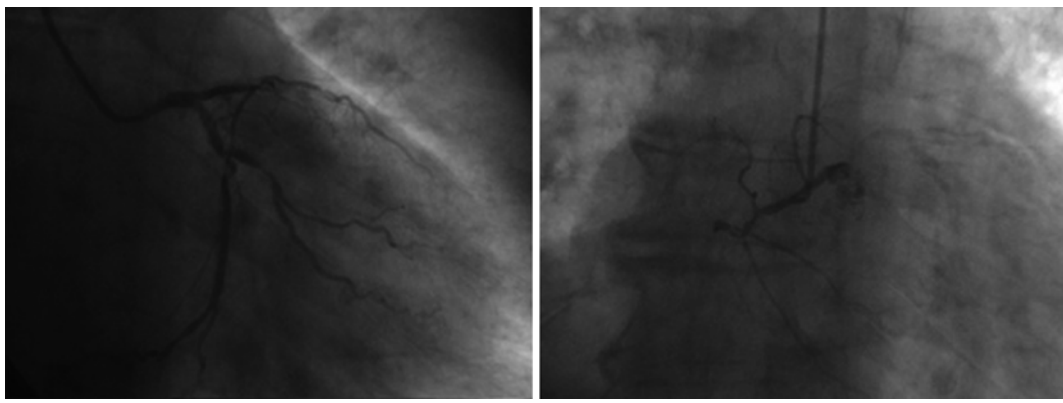

Fig. 2.2 Coronarography showing multivessel disease

the presence of symptoms of ischemia and/or rise in cardiac biomarkers (troponin I or T values above the 99th percentile upper reference limit) with the following criteria: ST-segment or T-wave changes, imaging evidence of loss of viable myocardium or regional motion abnormalities, and intracoronary thrombus by angiography or autopsy. Two different clinical presentations may be encountered based on electrocardiogram (ECG) findings and pathophysiology:

- Myocardial infarction with persistent (>20 min) ST elevation (see Chap. 1).
- Myocardial infarction without persistent ST elevation includes ST-segment depression >0.05 mV in two contiguous leads, T-wave inversion >0.1 mV in two contiguous leads, pseudo-normalization of T wave, or no ECG changes [4]. Two types of non-ST-elevation ACS are recognized: NSTEMI or unstable angina (UA) based on the evaluation of cardiac biomarkers.

In the last years, it has been observed an increase in the rate of non-ST-elevation myocardial infarction (NSTEMI) in relation to ST-elevation myocardial infarction (STEMI) with an annual incidence of ~3 per 1,000 inhabitants [5]. Hospital mortality is higher between STEMI patients, while in the long term death rates are consistently larger in NSTEMI [6]. NSTEMI patients are often older with significant comorbidities. These data suggest the need of significant efforts both in the acute phase and in long-term management to ensure better outcomes.

Pathophysiology

Atherosclerosis is a multifocal disease caused by lipid accumulation that affects large-sized and medium-sized arteries [7]. CAD is a dynamic process that leads to a progressive reduction in the vessel size due to plaque formation. NSTEMI is due to complete or partial occlusion of a coronary artery or a mismatch between oxygen supply and demand. ACS is generally precipitated by a plaque rupture or erosion with acute thrombosis or vasoconstriction leading to a sudden and critical reduction in blood flow. Inflammation plays a determinant role in plaque erosion and subsequent thrombus formation. Rarely ACS may be caused by other mechanisms such as arteritis, trauma, dissection, congenital abnormalities, or drug abuse [8].

Diagnosis

The diagnosis of NSTE is complex and more difficult than STEMI due to less obvious signs and a wider differential diagnosis. Risk stratification should be evaluated during the diagnostic phase guiding the revascularization and treatment strategy.

Clinical Presentation

The more frequent symptom of ACS is retrosternal chest pain irradiating to the left arm or to the neck sometimes described as retrosternal pressure or heaviness. Dyspnea, diaphoresis, or nausea is often associated. Atypical presentation is common in older patients, women, and patients with diabetes and may lead to a missed diagnosis [9]. Exacerbation of symptoms during physical exertion and reduction at rest is common. Relief of pain after administration of nitrates is also quite specific. UA is characterized by the presence of new-onset angina, post-MI angina, or crescendo angina. The presence of risk factors should be carefully evaluated as it significantly increases the probability of CAD diagnosis. The most common risk factors are male sex, family history of CAD, older age, peripheral artery disease, diabetes mellitus, renal failure, previous cardiovascular disease, and dyslipidemia.

Physical Examination

Physical examination shall evaluate the presence of NSTEMI complication such as heart failure with pulmonary or systemic congestion and establish the presence of precipitating factors (i.e., anemia). Extracardiac (pneumonia, pneumothorax, costochondritis) and nonischemic (valvular disease, pericarditis) causes of chest pain may also be excluded.

Electrocardiogram

A 12-lead resting ECG must be obtained in 10 min after the first medical contact. Additional ECG must be obtained if the patient presents symptoms at (3 h) 6-9-24 h and immediately during symptoms [8]. Comparison with previous ECG recordings is recommended especially in patients with known ST alterations (i.e., left ventricular hypertrophy). A completely normal ECG does not exclude the presence of ACS. Typical ECG findings are ST-segment depression or T-wave inversion in at least two contiguous leads.

Cardiac Enzymes

Cardiac troponins are the reference markers of MI because they are more specific and sensitive than other markers [10]. The initial rise in troponins occurs in approximately 4 h and may remain elevated up to 2 weeks. The diagnostic cutoff is a value exceeding the 99th percentile of normal reference population with an assay with an imprecision of <10 % [4]. High-sensitivity assays have been introduced with higher sensitivity and specificity. A single normal test is not sufficient to exclude ACS in the presence of suggestive symptoms and may be repeated. Relevant changes in troponin levels are also important because they allow to make differential diagnosis between a relevant number of possible non-ACS-related troponin elevations (Table 2.1).

Table 2.1 Possible causes of troponin rise

Chronic or acute renal failure
Congestive heart failure
Hypertensive crisis
Arrhythmias
Pulmonary embolism
Myocarditis
Stroke or subarachnoidal hemorrhage
Aortic dissection
Cardiac contusion, ablation, cardioversion
Takotsubo cardiomyopathy
Infiltrative disease (i.e., amyloidosis)
Drug toxicity
Sepsis or respiratory failure
Rhabdomyolysis

Imaging

Noninvasive Imaging

Echocardiography is the tool of choice due to its availability and feasibility. Left and right ventricular systolic function may be assessed and represents a relevant prognostic factor. New-onset regional wall hypokinesia or akinesia is also a typical finding that suggests myocardial ischemia. Echocardiography may also exclude other causes of chest pain such as aortic dissection, pulmonary embolism, aortic stenosis, pericarditis, or hypertrophic cardiomyopathy.

Stress echocardiography and nuclear myocardial perfusion are II° level tests that may lead to myocardial ischemia diagnosis especially in low-risk patients. Multidetector computed tomography (CT) permits visualization of coronary arteries and may be useful in excluding other causes of chest pain such as aortic dissection or pulmonary embolism. Different studies reported high negative predictive value of this technique in intermediate-risk patients [11].

Invasive Imaging

Coronary angiography remains the gold standard as it provides relevant diagnostic informations. Timing of angiography should be evaluated on the basis of risk assessment. It is recommended to prefer radial approach when feasible because it has lower risk of hematomas and bleeding [12]. Angiograms should be obtained after and before the use of nitrates to exclude the vasoconstriction due to ACS. In ambiguous lesions, intravascular ultrasound (IVUS) of fractional flow reserve (FFR) may help in the correct evaluation of stenosis and treatment strategy.

Risk Stratification and Treatment Strategy

To date two alternative approaches have been validated for the treatment of acute coronary syndromes (ACS) without ST-segment elevation (NSTE-ACS), such as unstable angina (UA) and acute myocardial infarction without ST elevation (NSTEMI). The two strategies differ in the timing for cardiac catheterization.

The first option is the early invasive strategy, meaning that the patient is quickly sent to the cath lab for coronary angiography, followed by the eventual PCI or surgical revascularization based on the angiographic results.

The second option, called conservative strategy, consists in medical therapy alone for the initial treatment, reserving cardiac catheterization only to those who have recurrent ischemia or other high-risk features.

Conservative Strategy Versus Invasive Strategy

Currently, the results of these alternative strategies have been analyzed in several randomized trials. A meta-analysis in which seven studies were included showed a significant benefit offered by the early invasive strategy in terms of reduction of 2-year mortality from all causes and myocardial infarction (MI), with no increase in adverse periprocedural events. Patients who have most benefited from an early invasive strategy were those with abnormal troponin values and high-risk features.

These results have been translated into the European Society of Cardiology (ESC) NSTEMI Guidelines published in 2011 that recommend a routine invasive strategy in almost the totality of patients with NSTEMI while highlighting the crucial role of risk stratification.

NSTEMI Patients: Indications in the Light of the Most Recent Guidelines

Although, for ethics and safety reasons, patients with UA/NSTEMI at *very high risk* (refractory angina, severe heart failure, electrical and/or hemodynamic instability) were excluded from randomized clinical trials, it is universally accepted that these patients must be sent within 2 h to the cath lab for an urgent invasive strategy, regardless of risk stratification and the values of troponin (class I, level of evidence C).

Based on randomized clinical trials, patients at *high risk* who have a GRACE score >140 or with at least one of the primary high-risk criteria must be treated with an early invasive strategy, within 24 h from the first medical contact (class I, level of evidence A). Among all other patients with UA/NSTEMI, those who have at least one secondary high-risk criterion or recurrent symptoms should be treated with an invasive strategy within 72 h (class I, level of evidence A).

- *Primary high-risk criteria*:
  - (a) Relevant increase and fall of troponin
  - (b) Dynamic changes of the ST segment and/or T wave
- *Secondary high-risk criteria*:
  - (a) Diabetes mellitus
  - (b) Renal impairment (eGFR <60 mL/min/1.73 m^2)
  - (c) Reduced left ventricular ejection fraction (<40 %)
  - (d) Early postinfarction angina
  - (e) Recent angioplasty (PCI)
  - (f) Previous bypass surgery (CABG)
  - (g) Intermediate- to high-GRACE-risk score (108–140)

From this, it is clear that by definition NSTEMI ACS with elevation of myocardial necrosis markers should be treated with an invasive strategy within 72 h, since the elevation of troponin alone is considered a primary high-risk criterion. Therefore, a conservative strategy is now restricted to a narrow subgroup of patients: basically not to those who have a NSTEMI, but only to patients with unstable angina (then with negative troponin) and without recurrent symptoms.

Moreover, even among patients with UA, only those without high-risk characteristics should be approached with a conservative strategy, that is, nondiabetics, those with normal global contractile function of the left ventricle, those who have not been subjected in the past to PCI or CABG, and those with a GRACE risk score <108. In this small group of patients (low risk and without recurrent symptoms), a noninvasive assessment of inducible ischemia is recommended (class I, level of evidence A), which must be performed before hospital discharge. Coronary angiography

should be performed only if the results of noninvasive tests are positive for inducible ischemia.

Revascularization Strategies

In approximately one-third of patients, angiography will reveal single-vessel disease, allowing ad hoc PCI of the culprit lesion in most cases. In a multivessel disease, the choice has to be made between culprit-lesion PCI, multivessel PCI, CABG, and a combined (hybrid) revascularization [13, 14]. The distribution of PCI versus CABG in patients with multivessel disease suitable for revascularization is approximately 80 % versus 20 % [15]. The revascularization strategy in patients with multivessel CAD should be determined early by the Heart Team and based on the patient's clinical status, as well as the severity and distribution of the CAD and the characteristics of the lesion. The SYNTAX score has proven to be strongly predictive of death, myocardial infarction, and TVR [16]. Culprit-lesion PCI is usually the first choice in most patients with NSTE-ACS and multivessel disease; however, there are no prospective studies comparing culprit-lesion PCI with early CABG. In stabilized patients with multivessel disease and a high SYNTAX score (>22), particularly when there is no clearly identified culprit lesion, a strategy of urgent CABG should be preferred. The strategy of multivessel PCI rather than culprit-lesion PCI has not been evaluated in an appropriate randomized clinical trial. In a large database including 105,866 multivessel CAD patients with NSTE-ACS, multivessel PCI was compared with single-vessel PCI and was associated with lower procedural success but similar in-hospital mortality and morbidity [17]. Complete revascularization at the time of the index procedure did not result in lower mortality rates over 3 years, as compared with a staged procedure strategy. However, incomplete revascularization appears to be associated with more 1-year adverse event rates. In the ACUITY trial, CABG was compared with PCI among patients with multivessel disease [15]. PCI-treated patients had lower rates of stroke, myocardial infarction, bleedings, and renal injury and similar 1-month and 1-year mortality but significantly higher rates of unplanned revascularization at both 1 month and 1 year. However, only 43 % of CABG patients could be matched, and there was a strong trend for a higher rate of major adverse cardiac events (MACE) at 1 year with PCI, compared with CABG (25.0 % vs. 19.5 %, respectively; p 0.05).

Culprit-lesion PCI does not necessarily require a case-by-case review by the Heart Team, when the procedure needs to be performed ad hoc after diagnostic angiography particularly in case of continuing or recurrent ischemia, hemodynamic instability, pulmonary edema, recurrent ventricular arrhythmias, or total occlusion of the culprit coronary artery requiring urgent revascularization. For all other scenarios, revascularization should be discussed in a multidisciplinary setting. After culprit-lesion PCI, patients should be discussed by the Heart Team, in the context of functional evaluation of the remaining lesions, patients' comorbidities, and individual characteristics.

Medical Therapy: The Importance of Balancing the Ischemic and Hemorrhagic Risk

The therapeutic management of NSTEMI includes the use of anti-ischemic and antithrombotic drugs in combination to coronary revascularization. The timing and intensity of these therapeutic interventions must be individualized for each patient in light of both the ischemic and the bleeding risk, since most of the antithrombotic therapies increase the risk of bleeding. Risk assessment is an ongoing process that must begin with the first medical contact, until discharge from the hospital, because it can change the therapeutic strategy at anytime.

Among the main ischemic risk factors, age and the presence of other comorbidity (anemia, diabetes, etc.) have the greatest prognostic impact. Other factors consist in the characteristics and mode of onset of pain (being worse angina at rest and/or relapsing) and hemodynamic conditions. Other prognostic factors recognized and to which attention should be paid are the electrocardiographic changes and the elevation of a series of biomarkers such as troponin, C-reactive protein (CRP), and the N-terminal fragment of the atrial natriuretic peptide (NT-proBNP).

From the integration of all these risk factors, several risk scores have been developed, among which the best known are the TIMI risk score and the Global Registry of Acute Coronary Events (GRACE) score. The TIMI risk score is the most used in the past due to its simplicity, but its discriminating power is significantly lower than that of the GRACE score, basically because it does not take into account parameters of crucial importance as hemodynamics. In contrast, the GRACE score includes the heart rate (HR), blood pressure (BP), and the presence of heart failure, in addition to classical risk factors such as age, any prior MI or previous PCI, creatinine values, myocardial-specific enzymes, and ST changes on ECG. Therefore, it provides a more accurate estimate of the risk both on admission and at discharge. The calculation can be made online at http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html.

To date, GRACE score remains the only ischemic risk score considered in the ESC Guidelines. At the same time, it is crucial to perform an evaluation of the bleeding risk during the prognostic stratification. The CRUSADE bleeding score is a score that is used to predict the risk of major bleeding in light of eight parameters; patients with an increased risk of bleeding are women, diabetics, and those with low hematocrit, with low values of creatinine clearance, with signs of heart failure, with low (or too high) blood pressure, with high heart rate, and with history of other vascular disease.

A score <21 identifies patients at very low risk, between 21 and 30 configures a low risk, between 31 and 40 the risk is moderate, between 41 and 50 the risk is high, and >50 configures a very high risk. The calculation can be made online at http://www.crusadebleedingscore.org. The execution of both scores is recommended by the ESC Guidelines in class I, level of evidence B.

Anti-ischemic Agents

- Oxygen insufflation: (4–8 L/min) if oxygen saturation is <90 %.
- Nitrate treatment (sublingual, oral, or intravenous) is indicated to relieve angina and/or in patients with signs of heart failure (I; C).
- Morphine 3–5 mg intravenously or subcutaneously, if severe pain.
- Patients who are taking chronic beta-blocker therapy, admitted with ACS, should be continued on beta-blocker therapy if not in Killip class III (I; C).
- Oral beta-blocker treatment is indicated in all patients with LV dysfunction without contraindications (I; B).
- Calcium channel blockers are recommended for symptom relief in patients already receiving nitrates and beta-blockers (dihydropyridine type) and in patients with contraindications to beta-blockers (benzothiazepine or phenylethylamine type) (I; B).
- Calcium channel blockers are recommended in patients with vasospastic angina (I; C).
- Intravenous beta-blocker treatment at the time of admission should be considered for patients in a stable hemodynamic condition (Killip class <III) with hypertension and/or tachycardia (IIa; C).
- Nifedipine or other dihydropyridines are not recommended unless combined with beta-blockers (III; B).

Oral Antiplatelet Agents

- ASA: loading dose of 150–300 mg, maintenance dose of 75–100 mg daily (I; A).
- P2Y12 inhibitor should be added to aspirin and maintained over 12 months (I; A).
- Ticagrelor (180-mg loading dose, 90-mg twice daily maintenance dose) is recommended for all patients at moderate-to-high risk of ischemic events (I; B). Contraindications: previous hemorrhagic stroke, II° or III° degree atrioventricular block, sick sinus syndrome, bradycardia, syncope, and anticoagulant therapy.
- Prasugrel (60-mg loading dose, 10-mg daily maintenance dose) is recommended for patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI (I; B). Contraindications: previous stroke or TIA, oral anticoagulant therapy, trauma or recent surgery, age >75 years, and low body weight <60 kg.

- Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel (I; A). A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option (I; B). Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used (IIb; B).
- A proton pump inhibitor (PPI; preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal hemorrhage or peptic ulcer and appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, age >65 years, anticoagulants, or steroids therapie) (I; B).
- In patients pretreated with P2Y12 inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischemic events, should be considered (IIa; C). Ticagrelor or clopidogrel should be considered to be (re)started after CABG surgery as soon as considered safe (IIa; B).

GP IIb/IIIa Receptor Inhibitors

Among patients who are already treated with DAPT, the addition of a GP IIb/IIIa receptor inhibitor (abciximab, tirofiban, eptifibatide) for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low (I; B).

Anticoagulants

Anticoagulation is recommended for all patients (I; A).

- Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favorable efficacy-safety profile (I; A). If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) should be added at the time of PCI (I; B). It is contraindicated in severe renal failure (CrCl <20 mL/min).
- Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available (I; B). Dose reduction to 1 mg/kg once dialysis is indicated in the case of severe renal failure (CrCl <30 mL/min).
- If fondaparinux or enoxaparin is not available, UFH with a target aPTT of 50–70 s is indicated (I; C). UFH infusion is recommended when CrCl is <30 mL/min or eGFR is <30 mL/min/1.73 m^2 with most anticoagulants (fondaparinux <20 mL/min).

In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge (I; A).

Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated (IIa; C).

Crossover of heparins (UFH and LMWH) is not recommended (III; B).

Treatment of Anemia and Hyperglycemia

Treatment of elevated blood glucose should avoid both excessive hyperglycemia (>180–200 mg/dL) and hypoglycemia (<90 mg/dL) (I; B).

Blood transfusion may have deleterious effects, so it is recommended only in the case of compromised hemodynamic status or hematocrit <25 % or hemoglobin level <7 g/dL (I; B).

Secondary Prevention

Beta-blockers are recommended in all patients with reduced LV systolic function (LVEF <40 %) (I; A).

ACE inhibitors/ARB are indicated within 24 h in all patients with LVEF <40 % and in patients with heart failure, diabetes, hypertension, or CKD, unless contraindicated (I; A).

ACE inhibitors/ARB are recommended for all other patients to prevent recurrence of ischemic events, with preference given to agents and doses of proven efficacy (I; B).

Aldosterone blockade with eplerenone is indicated in patients after MI who are already being treated with ACE inhibitors and beta-blockers and who have an LVEF <35 % and either diabetes or heart failure, without significant renal dysfunction (serum creatinine >2.5 mg/dL for men and >2.0 mg/dL for women) or hyperkalemia (I; A).

Statin therapy with target LDL-C levels <70 mg/dL initiated early after admission is recommended (I; B).

Patients with NSTE-ACS and severe LV dysfunction should be considered after 1 month for device therapy (CRT and/or ICD) in addition to optimal medical therapy (IIa; B).

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Part II

Mimicking Ischemic Heart Disease

Pericarditis

3

Alessia Urbinati and Marco Flori

3.1 Case Report

A 43-year-old man was admitted to our cardiology department, reporting a progressive chest pain which referred to the neck and left shoulder within the last 7 days.

Medical History and Cardiovascular Risk Factors

- Previous medical history showed acute pericarditis 2 months ago and was treated with ibuprofen 600 mg PO bid for 10 days.
- Smoking (ten cigarettes a day) for 10 years.

Allergies

Dust

Medications

None

Vital Signs

- Temperature: 36 °C
- Heart rate: 82 bpm
- Arterial blood pressure: 140/80 mmHg
- Respiratory rate: 12 breaths/min
- Oxygen saturation: 99 %

Physical Examination

- *General*: alert, awake, and oriented. Well developed and well nourished
- *Neck*: no jugular venous distention
- *Cardiovascular*: Regular rate and rhythm, S1 and S2 are normal, mild systolic murmur at the apex, pericardial friction rub, no gallops, point of maximal intensity non-displaced and non-sustained, no hepatojugular reflux
- *Lungs*: clear to auscultation
- *Abdomen*: no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no hepatosplenomegaly
- *Extremities*: no cyanosis or clubbing, no peripheral edema

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Laboratory Tests Performed

- *Complete blood count*: normal
- *Cholesterol* (*total*, *HDL*, *LDL*) *and TG*: normal
- *Hepatic function* (*GOT*, *GPT*, *γ-GT*, *ALP*, *total bilirubin*, *direct and indirect*): normal
- *Thyroid function* (*TSH*, *FT3*, *FT4*): normal
- *Renal function* (*creatinine*, *BUN*): normal
- *Serum electrolytes*: potassium 4.4 mEq/l, sodium 141 mEq/l.
- *Cardiac biomarkers* (*troponin*, *CK-MB*): *normal*
- *Markers of inflammation* (*CRP*, *ESR*): *CRP 1.3 ng/ml*, *ESR normal*
- *Serologic testing for antinuclear antibody and rheumatoid factor*: negative
- *Mantoux test*: *negative*

Instrumental Examination

The first ECG (Fig. 3.1) revealed sinus rhythm with a heart rate of 85 bpm, normal atrioventricular conduction, incomplete right bundle branch block, and ST elevation in all leads but aVR.

Cardiac echocardiography (Fig. 3.2) showed circumferential pericardial effusion and normal dimensions and function of the cardiac chambers, mild mitral regurgitation, and mild inferior vena cava (IVC) dilatation that collapses with inspiration. No signs of cardiac tamponade.

The thoracic CT and the clinical history showed no signs of malignancy.

After 3 days, ECG findings changed (Fig. 3.3).

Final Diagnosis

Recurrent idiopathic acute pericarditis.

The patient was treated with colchicine in combination with nonsteroidal anti-inflammatory drugs (NSAID).

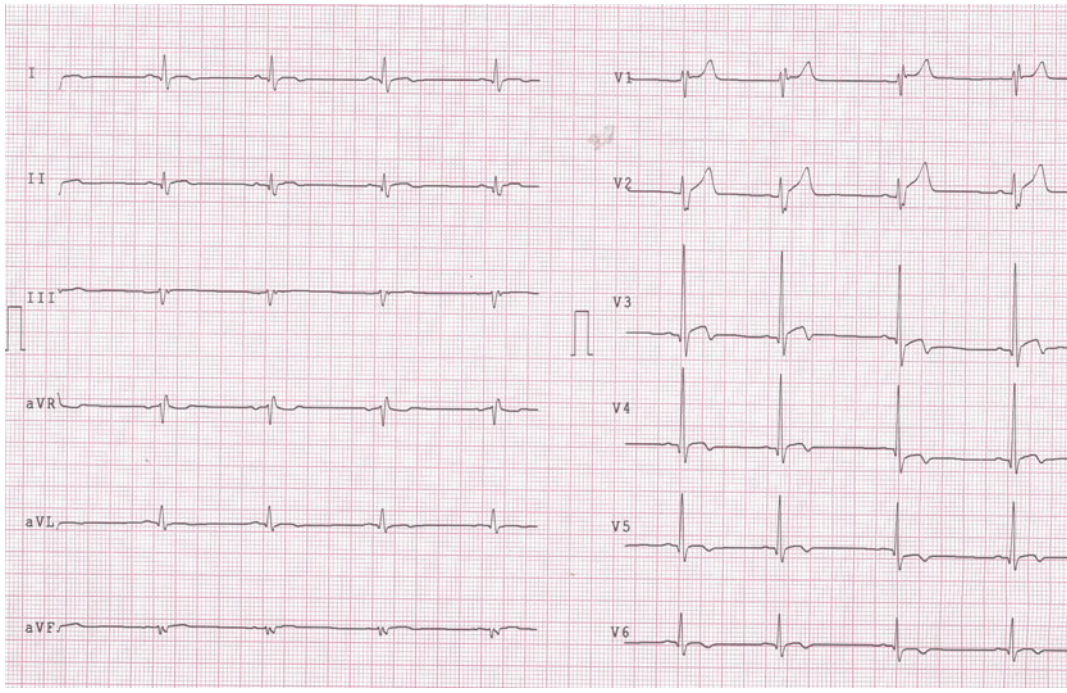

Fig. 3.1 Rest ECG showing diffuse ST elevation

3.2 Pericarditis

Pericarditis is an inflammation of the pericardium, often with fluid accumulation. Pericarditis can be acute, chronic (defined as persistent after 6 months), and recurrent. Acute pericarditis is a common disorder with an annual incidence of 27.7 new cases per 100,000 inhabitants in Europe [1]. Nevertheless, this disease may occur as an isolated entity or manifestation of an underlying factor. Acute pericarditis is diagnosed in about 5 % of patients hospitalized to the emergency department with nonischemic chest pain [2]. In developed countries, acute pericarditis is idiopathic in 85–90 % of cases [3].

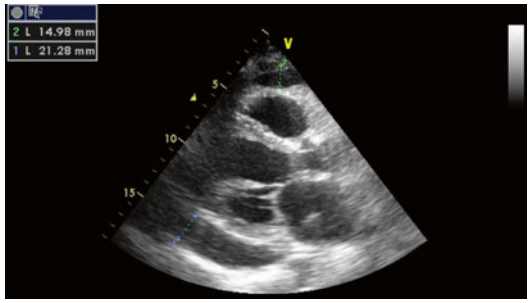

Fig. 3.2 Two-dimensional transthoracic echocardiogram showing the parasternal long-axis view. A moderate-sized pericardial effusion is present posteriorly

Etiology of Acute Pericarditis

- Idiopathic
- Infectious
  - Viral
  - Bacterial
  - Tuberculous
  - Fungal
  - Parasites
- Neoplastic disease
- Acute myocardial infarction (early pericarditis): within 1 or 3 days after a heart attack
- Dressler syndrome

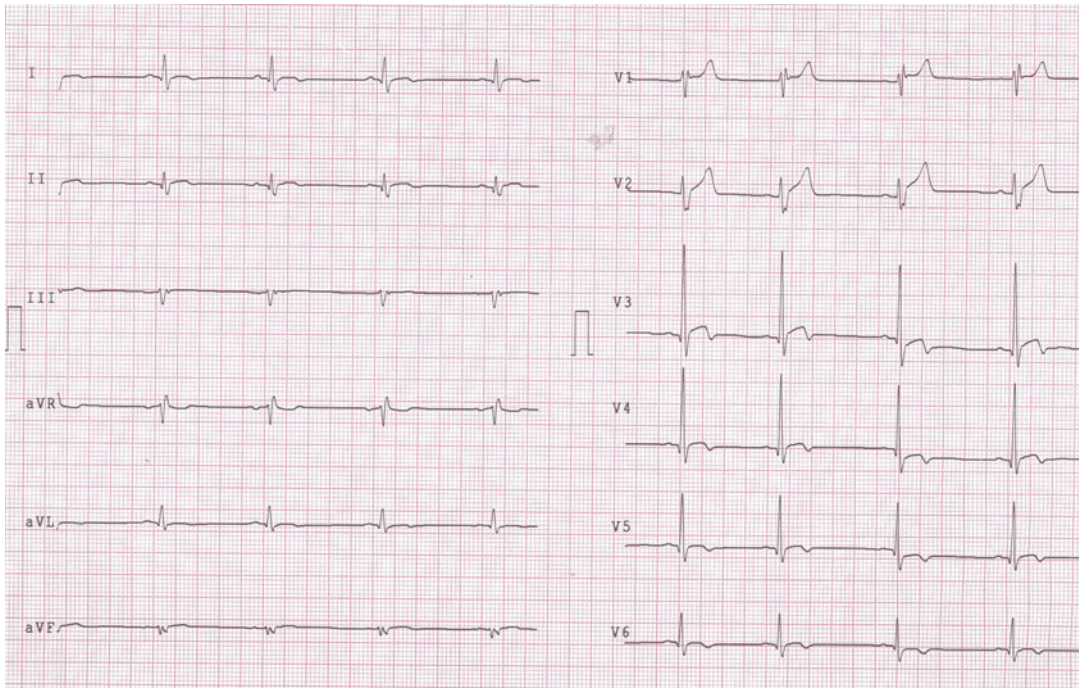

Fig. 3.3 Control ECG showing T-wave inversion in DI, aVL, V3, V4, V5, and V6

- Autoimmune disorders
- Uremia
- Myocarditis
- Trauma (severe injury to the chest)
- Radiotherapy (especially in breast cancer and lung cancer patients)
- Cardiac surgery
- Adverse drug reaction (such as penicillin and chemotherapy medicines)

Clinical History and Examination

Patients with pericarditis usually report a prodrome of fever, gastrointestinal disorders, or myalgias. Typically, pericarditis comprises chest pain, ECG alterations, and laboratory signs of inflammation [4]. Absence of common inflammation markers (erythrocyte sedimentation rate and C-reactive protein) could be present in up to 20 % of cases, especially in the initial stage of the disease and with previous anti-inflammatory therapies [5]. Assessment of vital sign is important. The presence of hypotension, dyspnea, reduced cardiac tones, and signs of elevated venous tone (jugular distension, liver tenderness) may indicate cardiac tamponade, which requires an urgent treatment. Chest pain is usually of abrupt onset, stabbing or sharp, and substernal but may be radiated to arms, neck, or jaw. Chest pain is more intense in supine position and lighter in prone position. Pericardial rubs are due to the friction of inflamed pericardial layer and fibrin, auscultated usually in patients leaning frontward, at the left sternal border, throughout the whole cardiac cycle. The rub of pericarditis might be transient, and it is important for the clinicians to auscultate the heart repeatedly [6].

Electrocardiogram might be normal during pericarditis. Further, pericardial effusion can lead to a decrease in the amplitude of the QRS voltage, while the P waves are less frequently affected [7]. Nonetheless, it must be considered that low QRS voltage is a weak predictor of pericardial effusion and the correlation between the decrease in QRS amplitude and the amount of fluid is poor [8]. The etiology of changes in repolarization during pericarditis is still debated. Typical ECG alterations are divided into four stages [9]:

- Stage 1: ST elevation in all standard leads except aVR and V_1 with upward concavity. Elevation of more than 0.5 mV is uncommon.
- Stage 2: ST segment returns to the baseline and T-wave amplitude decreases.
- Stage 3: Inversion of T waves, usually not too deep.
- Stage 4: Return to normal.

Depending on the time of presentation, some stages might be absent, and different stages might be present in different leads at the same time. Therefore, ST elevation and T-wave inversion can be observed simultaneously in different leads, but their coexistence in the same lead is uncommon, and it should suggest an acute coronary syndrome. A typical alteration in ECG, during pericarditis, is PR segment depression $\geq$0.5 mV compared to TP segment: these findings are usually an early alteration, and it is shown in almost 80 % of cases.

Chest radiography is useful to exclude secondary causes of chest pain (pneumonia, pneumothorax, traumatism) and might show enlarged heart in case of pericardial effusion.

Echocardiography has a pivotal role for the assessment of the cardiac function and presence and quantification of pericardial effusion. A large pericardial effusion with diastolic collapse of the right atrium, respiratory variation of mitral inflow (decrease in E wave of >20 % during inspiration), and dilated inferior vena cava with reduced collapsibility may suggest cardiac tamponade.

Differential Diagnosis

Acute pericarditis is usually benign but should be promptly distinguished from the other life-threatening conditions. Ruling out an acute coronary syndrome (ACS) is of utmost importance.

Table 3.1 Different characteristics of pericarditis and acute coronary syndrome

		Acute pericarditis	Acute coronary syndrome
Clinical history and examination	CV risk factors	Not correlated	Correlated
	History of fever or GI disorders	Frequent	No
	Chest rubs	Frequent	No
	Chest pain	Hitching/stabbing; reduced leaning frontward	Heaviness/constriction; no correlation with movements
ECG	ST elevation	Diffuse, upward concavity	Localized with specular ST depression
	PR depression	Frequent	No
	T-wave inversion	Diffuse, uncommon with concomitant ST elevation/depression	Diffuse/localized; ST elevation/depression may coexist
Echocardiography	Kinetics	Normal[a]	Focal kinetic defect
	Pericardial effusion	Frequent	Rare, may be present in cardiac rupture
Laboratory	Troponin	Negative[a]	Positive; negative in UA
	Inflammation markers	Usually elevated	Usually normal

CV cardiovascular, *GI* gastrointestinal disorders, *UA* unstable angina
[a]May be altered with concomitant myocarditis

Assessment of cardiovascular risk factors and previous heart diseases may help in the diagnosis. Different characteristics of acute pericarditis and ACS are shown in Table 3.1. Pneumothorax, acute pulmonary embolism, and acute aortic syndrome are other causes of acute chest pain with high mortality if undiagnosed and have to be excluded. Other conditions that may simulate pericarditis are respiratory disorders (pneumonia, bronchitis, asthma), musculoskeletal diseases, herpes zoster, anxiety, and others, but ECG and cardiac biomarker alterations are rare in these conditions.

Therapy and Prognosis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line therapy in acute pericarditis. High-dose aspirin, ibuprofen, or indomethacin may be used for 1–3 weeks, but no single NSAID appears to be more effective than the other [2]. Colchicine has shown to be safe and effective in reducing recurrences [10]. Pericarditis symptoms respond promptly to corticosteroid therapy. Nonetheless, corticosteroids are associated with increased recurrences and should only be used when other therapies have shown to be ineffective. Concurrently, rest and avoidance of demanding physical activity help to minimize the symptoms.

When pericardial effusion is present and clinical examination and echocardiography suggest hemodynamic impairment of cardiac function (cardiac tamponade), pericardiocentesis should be considered.

Prognosis of acute pericarditis depends on etiology and comorbidities. Conditions such malignancy, uremia, and HIV have the worse prognosis. Viral or idiopathic pericarditis is usually a benign condition with very low mortality.

Relapsing pericarditis is one of the most challenging complications of acute pericarditis, and no optimal treatment for this disorder of the pericardium has been definitively established. One or more recurrences arise up to 30 % of patients after an initial episode of acute pericarditis, usually within the first 18 months. Findings are similar to the initial episode, including pleuritic chest pain, diffuse ST-segment elevation, and elevated serum markers of inflammation [11]. Recurrences must be differentiated from episodes of chest discomfort with the patient reminiscent of prior pericardial pain but no other sign of recurrence (no elevation of inflammatory markers, no ECG alterations, pericardial rubs, or pericardial effusion).

In the absence of specific clinical trials, NSAIDs should be the first-line therapy of recurrences with a prolonged administration for 2–4 weeks. Colchicine associated to NSAIDs has shown to reduce episodes of recurrent pericarditis of additional 50 % [12]. If refractory pericarditis is present, corticosteroid therapy should be considered using lower effective dose for their side effects in long-term therapies. Immunosuppressors (methotrexate, azathioprine) have shown symptom improvement in a small number of patients not respondent to steroids. Finally, few data of pericardiotomy in continuous relapsing pericarditis showed variable efficacy with some patients reporting complete remission but others continuing to be plagued with ongoing symptoms [13].

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Intracranial Bleeding

4

Alessia Urbinati and Michela Brambatti

4.1 Case Report

A 40-year-old man was admitted to the emergency room after a 2.5 m fall from a scaffold. He showed signs of impaired consciousness and a scalp wound localized in the left tempofrontal region. Personal pathological history was unknown. The neurological evaluation revealed a Glasgow Coma Scale (GCS) score of 10: eye response = 3 (eye opening to verbal command), motor response = 6 (obeys command), and verbal response = 1 (no verbal response). The patient, after tracheal intubation for airway protection, underwent head computed tomography (CT) scan, which revealed bifrontal and left temporal subcortical-cortical bleeding with subarachnoid hemorrhage (Fig. 4.1). Subsequent chest x-ray, abdominal ultrasound, and chest-abdominal CT revealed no further traumatic injuries.

Vital Signs

- Heart rate: 80 bpm
- Blood pressure: 108/80 mmHg
- Oxygen saturation: 98 %

Physical Examination

- *General*: traumatic scalp wound 4 cm

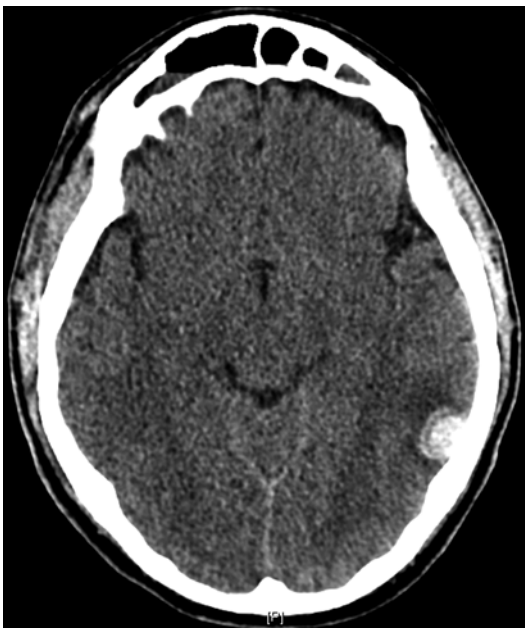

Fig. 4.1 Brain axial CT showing left temporal focal bleeding

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- *Neurological*: mental status was impaired. Pupil exam showed pupil asymmetry <1 mm and no dilatation or constriction; pupils were reactive to light and accommodation bilaterally. No alterations in deep tendon reflexes.
- *Cardiovascular*: regular rate and rhythm, S1 and S2 normal, no murmurs, rubs, or gallops, and no hepatojugular reflux.
- *Lungs*: no signs of respiratory effort on inspection. No wheezes, no crackles or stridor, and no bronchial or vesicular breath sounds on auscultation over the lung fields bilaterally.
- *Abdomen*: no lesions or signs of trauma. No pain or rebound on light and deep palpation, no organomegaly, and normal bowel sounds in all four quadrants.

Routine ECG was performed after the hospitalization, showing sinus rhythm, normal atrioventricular conduction, incomplete right bundle branch (RBBB), and no alterations in repolarization.

Laboratory Exams on Admission and Other Tests

Exams (including high-sensitivity cardiac troponin) were unremarkable except for a mild leukocytosis of 14,500/mm^3.

After 2 days in the hospital, the patient had a control CT of the brain that showed an increased size of the left temporal subarachnoid hemorrhage, with minimum brain compression and appearance of posterior subcortical-cortical bleeding. The patient was clinically stable, but ECG changed dramatically and showed sinus tachycardia; normal atrioventricular conduction; ST elevation in DII, DIII, aVF, V4, V5, and V6; and ST depression in aVR, aVL, V1, V2, and V3 (Fig. 4.2).

Fast echocardiography was performed, revealing no cardiac contractile abnormalities. Blood sample showed a rise in troponin level: 0.16 ng/ml.

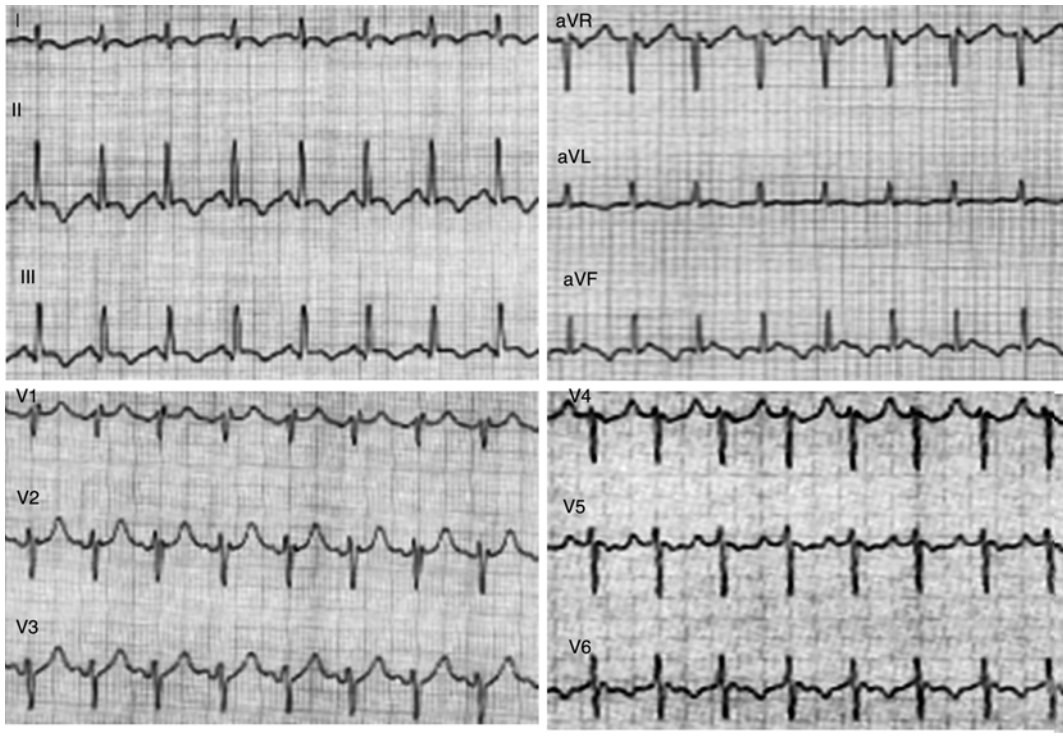

Fig. 4.2 Rest ECG showing incomplete right bundle block and normal repolarization

What Are the Possible Causes for ST Elevation?

- Acute ST-segment elevation myocardial infarction (STEMI)
- Coronary spasm
- Pericarditis
- Left ventricular aneurysm
- Brugada syndrome
- Left bundle branch block
- Left ventricular hypertrophy
- Early repolarization
- Drugs (e.g., cocaine, digoxin, quinidine, tricyclics, and many others)
- Electrolyte abnormalities (e.g., hyperkalemia)
- Neurogenic factors (e.g., stroke, hemorrhage, trauma, tumor, etc.)
- Metabolic factors (e.g., hypothermia, hypoglycemia, hyperventilation)

What Are the Possible Causes of Increased Troponin Level?

- Acute coronary syndrome
- High blood pressure in lung arteries (pulmonary hypertension)
- Blockage of a lung artery by a blood clot, fat, or tumor cells (pulmonary embolus)
- Congestive heart failure
- Myocarditis
- Prolonged exercise
- Trauma that injures the heart
- Weakening of the heart muscle (cardiomyopathy)
- Long-term kidney disease

In a setting of acute coronary syndrome and ST elevation, the patient has been promptly treated with metoprolol and acetylsalicylic acid intravenous and a percutaneous coronary angiography was urgently performed which showed just a non-critical stenosis (<30 %) of the right coronary artery. In the following 48 h, ST elevation gradually resolved, and waves were inverted in DII, DIII, aVF, V4, V5, and V6 (Fig. 4.3). A repeated head CT scan revealed a partial reduction of the encephalic bleeding. The patient was extubated and transferred to a spoke intensive care unit.

4.2 ECG Correlation and Intracranial Bleeding

ECG Abnormalities

In patients with acute cerebrovascular events, especially intracranial hemorrhage (ICH) and ischemic stroke, electrocardiographic repolarization abnormalities are frequently observed regardless of the presence or absence of previous cardiac diseases. Repolarization abnormalities warrant attention as they increase the vulnerable period during which an extrasystole is more likely to result in ventricular tachycardia or fibrillation. Repolarization abnormalities thus may explain the higher risk of arrhythmias and sudden death following acute neurological disorders [1–4].

The exact incidence of ECG abnormalities is still unclear but ranges from 50 to 98 % and includes QT prolongation, T wave inversion, prominent U wave, ST segment elevation or depression, peaked P waves, and transient pathological Q waves [1]. A typical, but not pathognomonic, pattern is characterized by "giant T waves," abnormally wide T waves of increased amplitude (mostly negative than positive); elevation or depression of the ST segment is less frequent [4].

However, as in our case, these ST changes are particularly important since they may simulate acute myocardial ischemia and therefore mislead physicians in the initial diagnosis. In fact, unconscious patients with ICH and ST segment elevation may be misdiagnosed with acute myocardial infarction and could be incorrectly treated with antiplatelet and anticoagulative drugs with devastating consequences. Also, in the setting of cerebrovascular events, changes in ST segment have

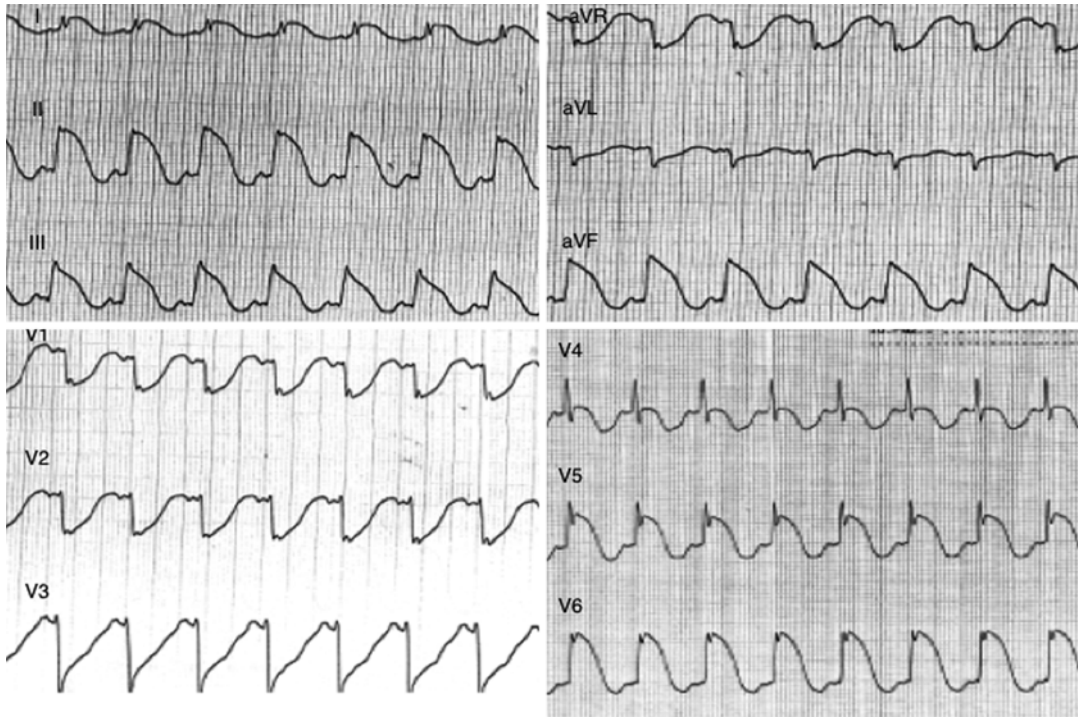

Fig. 4.3 Control ECG showing ST elevation in DII, DIII, aVF, V4, V5, and V6 and ST depression in aVR, aVL, V1, V2, and V3

generally the same polarity of T wave, and rarely, ST elevation is diffuse simulating acute pericarditis.

The ECG abnormalities usually reverse after the neurological clinical recovery.

Arrhythmias

In a prospective study, serious arrhythmia in the first 72 h after admission with acute stroke was detected in 25 % of 501 patients [5]. The risk for cardiac arrhythmia was highest during the first 24 h of care and declined with time during the first 3 days. In previous series, cardiac arrhythmias were detected in 6–25 % of patients after stroke [6, 7].

Atrial fibrillation is the most common cardiac arrhythmia accounting for nearly 60 % of all events of arrhythmia [5]. However, transient atrial fibrillation is more common among patients with ischemic stroke than with ICH; in this latter setting, atrial fibrillation occurs more frequently among patients who have developed brainstem or peri-insular hematomas [8].

As a consequence of repolarization abnormalities, especially with prolonged QT interval, malignant ventricular arrhythmias, including ventricular tachycardia, torsades de pointes, and ventricular fibrillation, may also be observed [9]. So, it is very important to check for QTc prolongation and to select drugs that do not prolong QT interval.

Mechanisms Leading to ECG Abnormalities

The mechanism through which cerebrovascular events lead to these ECG abnormalities is still unknown; however, autoptic findings reported that over 50 % of patients had cardiac muscle contraction band necrosis. The most plausible hypothesis suggests that ECG changes result as a consequent alteration of the autonomic nervous system control on cardiac electrophysiology that

results in catecholamine release at the terminal nerve at the cardiac myocyte [2, 3]. Increase of adrenergic stimulus increases myocardial oxygen demand, reduces coronary perfusion time, and also has a direct cardiotoxic effect with generalized spasm of the coronary arteries. Some evidence suggests also that sympathetic stroke-related activity causes calcium overload in ventricular myocytes and consequently arrhythmias. Furthermore, the type and location of the cerebrovascular event may correlate with the type of arrhythmia as each cerebral hemisphere seems to have a different influence on cardiac functions. Indeed, injury of the right insula may cause bradycardia and vasodepressor effects, while the left insular region may pose a higher risk for tachycardia and hypertension [10, 11].

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Takotsubo Cardiomyopathy

5

Giulia Pongetti and Azzurra Fabbrizioli

5.1 Case Report

A 65-year-old woman presented to the emergency room for chest pain developed after a car accident, where she was involved, persistent for at least 30 min. The pain did not decrease by changing position. It consisted of a retrosternal pressure or heaviness ("angina") radiating to the neck, accompanied by dyspnea and palpitations.

Medical History and Cardiovascular Risk Factors

- Familiar history of ischaemic cardiovascular disease
- Current smoker (about ten cigarettes per day)
- Arterial hypertension
- Dyslipidemia
- Anxious depressive syndrome
- She doesn't refer any other previous cardiovascular disease

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Allergies

No allergy was referred by the patient.

Social History

- She has two sons in good health. At present, she is menopausal and retired.
- She drinks a glass of wine once in a while.
- She walks for about 3 km three times a week.

Medications

- Sertraline 50 mg/day at 8:00 am
- Valsartan 160 mg/day at 8:00 am

Vital Signs

- Temperature: 36 °C
- Heart rate: 110 bpm
- Blood pressure: 160/100 mmHg
- Respiratory rate: 18 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %

Physical Examination

- *General*: agitated, alerted, awake, and oriented
- *Head*, *eyes*, *ears*, *nose*, and *throat*: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and

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accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection.
- *Neck*: supple, no jugular venous distension, no lymphadenopathy, and no carotid bruit.
- *Cardiovascular*: regular heart rate, protodiastolic gallop with S3 added, apical holosystolic murmur 2/6, no rubs, no hepatojugular reflux, and capillary refill less than 2 s.
- *Lungs*: no rales on auscultation, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal upon percussion.
- *Abdomen*: plan, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant on percussion, soft, nondistended/nontender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly.
- *Extremities*: no cyanosis or clubbing. No peripheral edema.
- *Neurological*: no focal deficit.
- *Psychiatric*: normal affect, no hallucinations, normal speech, and no dysarthria.
- *Skin*: intact, no rashes, no lesions, and no erythema.

Routine EKG at Rest

Sinus tachycardia at 120 bpm, normal atrioventricular conduction (PR 120 ms), complete right bundle branch block (QRS 140 ms), ST segment depression from V1 to V6 with inverted T waves, and QTc interval of 460 ms (Fig. 5.1).

Routine Laboratory Tests

- Complete blood count: normal
- Renal function: creatinine 0.8 mg/dl (normal)
- Hepatic function (GOT, GPT, y-GT, ALP, total bilirubin, direct and indirect): normal
- Electrolytes: Na 137 mEq/L and K 4.1 mEq/L (normal)
- Fasting blood glucose: 156 mg/dl
- Troponin I: 0.13 ng/ml (n.v. <0.08 ng/ml)
- CK-MB: 1.7 ng/ml (n.v. <5 ng/ml)
- BNP 92 pg/ml (n.v. <100 pg/ml)
- Inflammation index: VES 25 mm/h (n.v. <27 mm/h;) and CRP 0.5 mg/dl (n.v. <0.6 ng/ml)
- D-dimers: 180 ng/ml (n.v. <230 ng/ml)

Chest X-Ray

Normal heart size and volumes. No bone fractures and no signs of trauma or dissection of the major mediastinal vessels. Absence of pulmonary congestion, pleural effusion, or signs of pneumothorax (not shown).

What Are the Possible Causes of Chest Pain in This Patient?

- *Myocardial disease*
  - Acute coronary syndromes without persistent ST elevation (NSTE-ACS) or unstable angina (UA)
  - Myocardial infarction secondary to an ischemic imbalance for rise of blood pressure or tachycardia
  - Coronary spasm
  - Cardiac contusion
  - Stress cardiomyopathy (Takotsubo syndrome)
  - Myocarditis, pericarditis, and myopericarditis
- *Valvular heart disease*
  - Severe aortic stenosis
  - Severe aortic regurgitation
- *Aortic disease*
  - Traumatic aortic injury
- *Thoracic trauma and/or fractures*
- *Pulmonary disease*
  - Pneumothorax
  - Pulmonary embolism

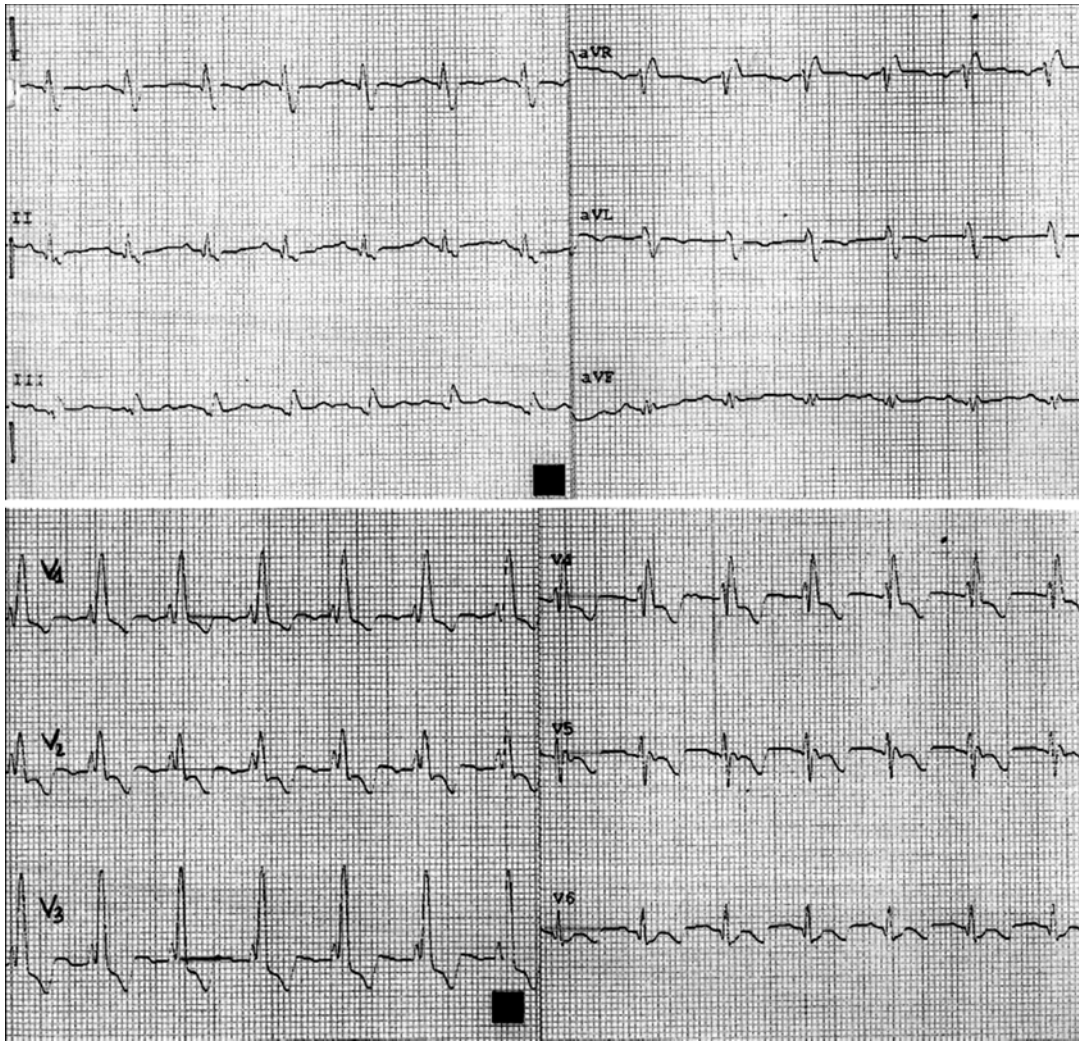

Fig. 5.1 EKG at rest while the patient was symptomatic

A pulmonary embolism is unlikely for the low pretest probability (the patient has never suffered previous pulmonary embolism or deep vein thrombosis; she didn't have previous surgery, trauma, long immobilization, or cancer; and she never used hormone replacement therapy). Furthermore, the normal D-dimer level excludes this affection with high sensitivity.

Pneumothorax and thoracic fractures can be excluded because physical examination and chest x-ray were normal.

The EKG shows ST segment depression in anterior leads which ruled out coronary spasm, usually characterized by ST elevation (Prinzmetal angina) although it may consider a possible posterior ST elevation with anterior ST depression as a mirror image.

A phlogistic damage (myocarditis, myopericarditis) is unlikely because the EKG modifications are not typical and not widely represented in all the EKG leads; moreover, the patient didn't report flu or gastrointestinal disease, and the laboratory tests did not show clear signs of a phlogistic state.

The chest pain referred by the patient was quite typical for "angina" or also could suggest an aortic damage caused by car accident. An echocardiography was done to evaluate those possible diagnostic alternatives.

Echocardiography

The aortic valve is trileaflet. Slight enlargement of the left atrium (LA diameter M-mode = 4.2 cm; area 4 c = 22 cm^2). Mild functional mitral regurgitation caused by displacement of the papillary muscles. Normal right atrium (area 4 c = 12 cm^2). Right ventricle also normal in size and function. Normal tricuspid valve. Mild tricuspid regurgitation centrally directed (PASP = 35 mmHg). Normal pulmonic valve. The interatrial septum is normal. The left ventricle is slightly hypertrophic (LV mass index 97 g/m^2) with apical and mid-left ventricular dilatation; moderate reduction of systolic global function for complete akinesis of the apical and mid-segments and compensatory basal hyperkinesis. The ejection fraction measured with Simpson's biplane method was 40 %. Normal pericardium and aorta (aortic root dimension = 3.0 cm; ascending aorta = 3.2 cm; aortic arch = 3.3 cm; thoracic aorta = 2.9 cm; abdominal aorta = 2.0 cm). The inferior vena cava was not dilated. Pseudonormal diastolic pattern with increased filling pressure (E/A 1.1, E/E' 16, E dec time 170 m/s) (Fig. 5.2).

Conclusion

- Severe valvular disease, hypertrophic cardiomyopathy, pericardial effusion, and rupture of the wall or septum were ruled out.
- Aortic root and aortic isthmus diameters were normal without any intimal flap or thrombus along the aortic wall. A traumatic aortic injury (TAI) was also unlikely because of features of the car accident suffered by the patient.
- The echocardiography findings showed moderate reduction of systolic function for apical and mid-left ventricular dilatation and akinesia with compensatory basal hyperkinesis compatible with ischemic injury. This pattern of wall motion abnormality ("apical ballooning") is quite typical for stress cardiomyopathy (Takotsubo-like), but also an AMI cannot be excluded without a coronary angiography.

While the patient has been prepared for coronary angiography, he has been treated with:

- Initial loading dose of aspirin (300 mg)
- Initial loading dose of ticagrelor (180 mg)
- Fondaparinux 2.5 mg/day
- Perindopril 2 mg/day
- Atorvastatin 80 mg/day
- Bisoprolol 2.5 mg/day

Coronary Angiography and Left Ventriculography

A coronary angiography was performed within 24 h from admission showing right coronary dominance and absence of significant coronary artery stenosis (Fig. 5.3).

The left ventriculography showed complete apical and mid-ventricular akinesis with systolic

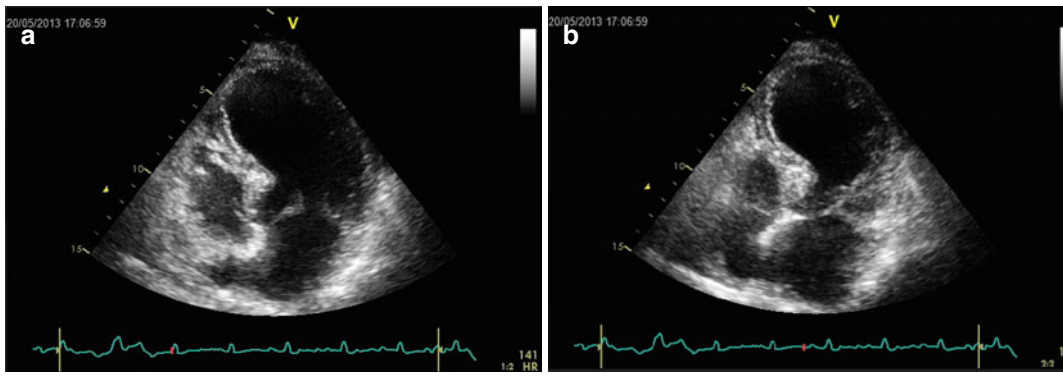

Fig. 5.2 Echocardiographic picture recorded at rest during systole (**a**) and during diastole (**b**); typical LV ballooning during systole is visible, characterized by complete akinesis in the apical to mid-segments circumferentially of the left ventricle with relative compensatory hypercontractility in the basal segments

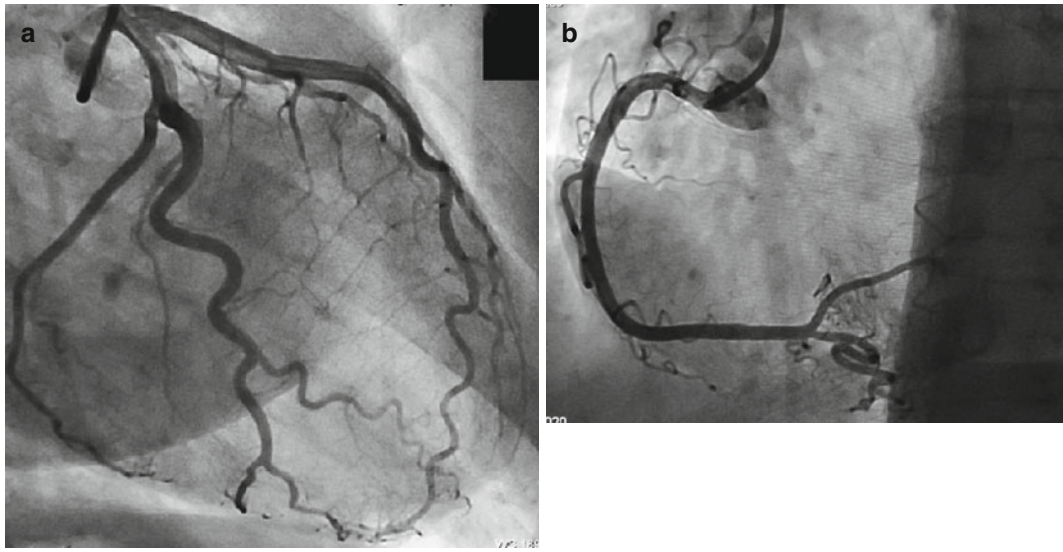

Fig. 5.3 Coronary angiography of left coronary artery (**a**) and right coronary artery (**b**); right coronary dominance and absence of significant coronary artery stenosis are shown

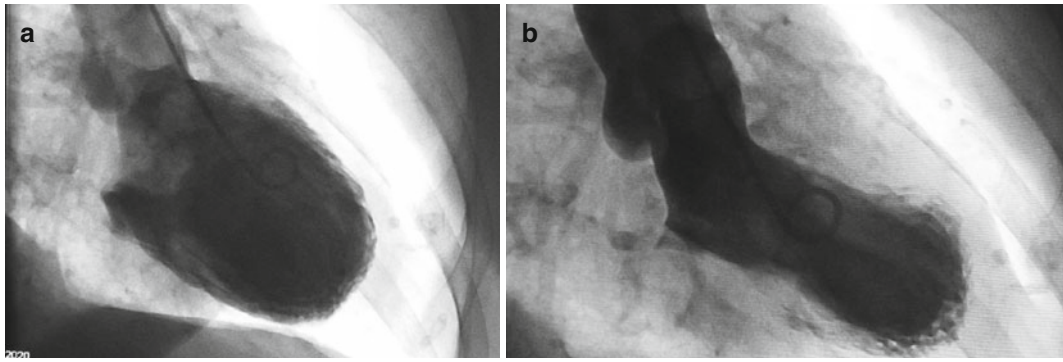

Fig. 5.4 Left ventriculography recorded during diastole (**a**) and systole (**b**); complete apical akinesis and mid-ventricular akinesis are shown, with systolic "apical ballooning" and moderate systolic dysfunction

"apical ballooning" and moderate systolic dysfunction. No spasm was recorded (Fig. 5.4).

Conclusion

- Absence of significant culprit coronary artery stenosis or intracoronary thrombosis
- "Apical ballooning" pattern

Final Diagnosis

The clinical presentation that mimics an acute myocardial infarction triggered by emotional stress (car accident) with modest EKG changes at presentation and with low plasma levels of cardiac biomarkers, disproportionate with the severity of ventricular dysfunction, could suggest the diagnosis of Takotsubo cardiomyopathy. This diagnosis is confirmed by findings on imaging (echocardiography and ventriculography) of transient apical- to mid-ventricular ballooning with compensatory basal hyperkinesis, without coronary stenosis.

Subsequent blood tests have shown normalization of cardiac biomarkers (max values: troponin I 2.45 ng/mL, CK MB 6.7 ng/mL), and echocardiography has displayed progressive recovery of contractile function until complete normalization.

Subsequent EKGs performed during hospitalization showed the typical evolution described in TC with new onset of negative and deep T waves and marked QTc interval prolongation and then slow and complete regression of these abnormalities after about 15 days.

EKG Performed at Day 3

Sinus rhythm at 65 bpm, normal atrioventricular conduction (PR 120 ms), complete right bundle branch block (QTS 140 ms), and normal ST segment with deep inverted T waves from V1 to V6 and DI, DII, AVL, and AVF (QTc interval of 624 ms) (Fig. 5.5).

The patient was discharged with the following therapy:

- Aspirin 100 mg/day
- Perindopril 2 mg/day
- Atorvastatin 40 mg/day
- Bisoprolol 5 mg/day

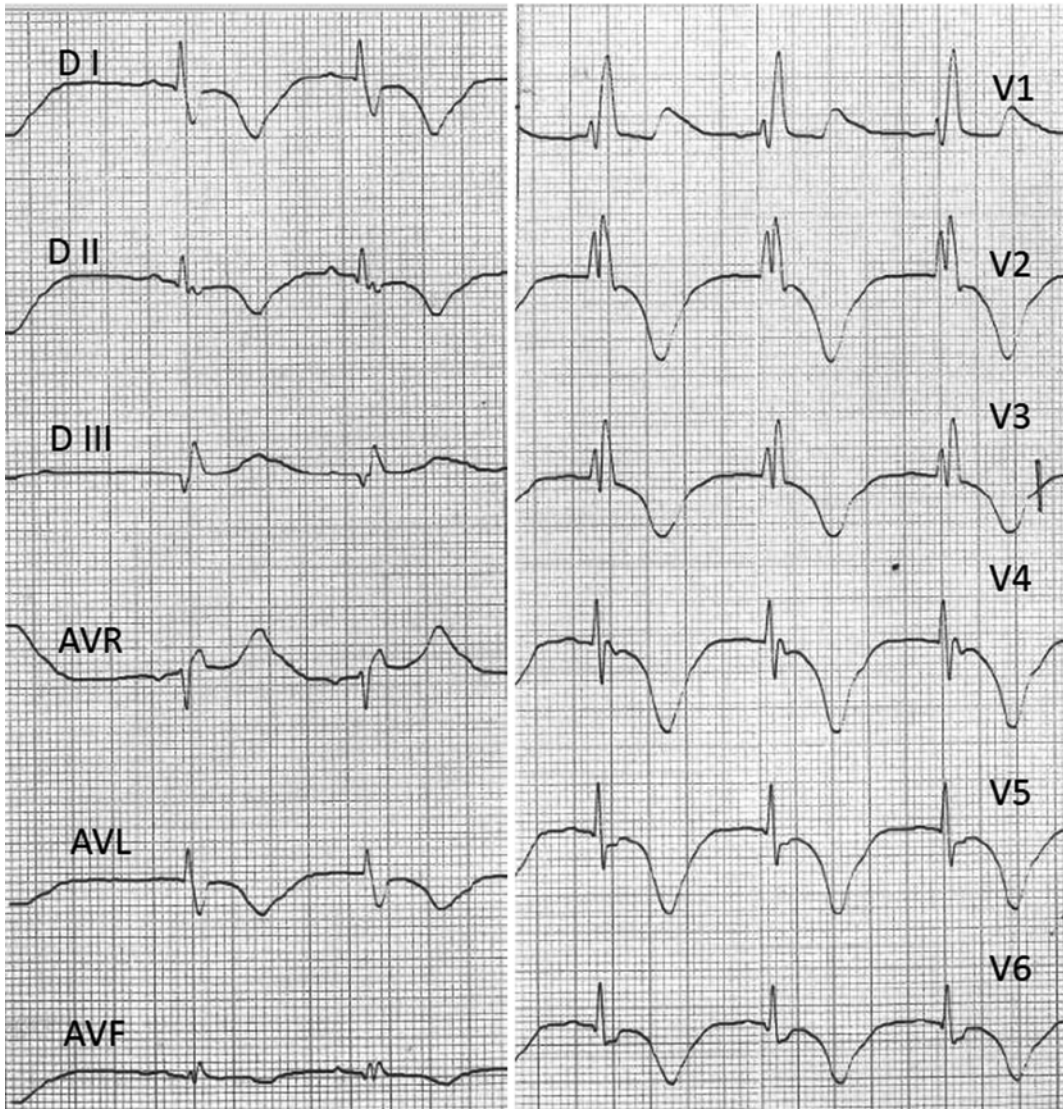

Fig. 5.5 EKG at rest during the third day of hospitalization while the patient was asymptomatic

5.2 Takotsubo Syndrome

Definition

Takotsubo syndrome (TS) is a reversible cardiomyopathy, first described in 1990 by Sato et al. in Japan [1], also known as "apical ballooning syndrome" or "stress cardiomyopathy," since it has become increasingly recognized worldwide.

It is characterized by signs and symptoms of acute myocardial infarction (AMI) but without demonstrable coronary artery stenosis.

Epidemiology

TS accounts for about 1–2 % of all cases of suspected AMI [2, 3].

It typically occurs in postmenopausal elderly women (average age 68 years); men account for a minority of cases (4–13 %), and rarely also children or young adults may be affected [4].

Pathogenesis

The exact pathogenesis of Takotsubo cardiomyopathy (TC) is still unknown, but various hypotheses have been suggested and discussed over the years.

- *Coronary artery spasm or transient acute artery thrombosis* [3, 5]: These hypotheses have been actually withdrawn because the typical "apical ballooning" is incongruent to a singular coronary artery supply region. The hypothesis of a multivessel coronary spasm would not explain the discrepancy between severe ventricular dysfunction and the only slightly increased levels of cardiac enzymes and why the recurrence could present different myocardial localization in the same patient or why some patients show the "apical sparing" variant [3].
- The long-lasting ST segment elevation in Takotsubo patients challenges strongly the hypothesis of a transient thrombosis which usually presents rapid resolution of ST segment elevation [6].
- Finally, the histological changes usually observed in TC (coagulative myocytolysis and myofibrillar degeneration) are different from those observed in ischemic disease (coagulative necrosis) [6].
- *Coronary microvascular dysfunction*: This hypothesis has been initially proposed based on findings of a diminished coronary flow reserve [7] and on a significant improvement of myocardial perfusion during adenosine infusion in patients with TC but not with STEMI [8]. However, other trials didn't confirm the "slow flow" phenomenon in many Takotsubo patients, so they supposed that this impairment of microcirculation could be a possible consequence of the myocardial dysfunction caused by TC itself [9].
- *Catecholamine toxicity*: Some authors found markedly elevated catecholamine levels in patients with TC, suggesting that these might be the main pathogenic factor [10]; however, many subsequent studies have not uniformly shown elevated plasma catecholamine levels in TC patients [11]. So it is likely that circulating catecholamines are somehow involved in the pathogenic process but not the only ones responsible.
- *Cardiac sympathetic disruption*: Recently a new hypothesis has been proposed regarding the disruption of local cardiac sympathetic nerve endings with local release of norepinephrine into the myocardial tissue, which could damage it and lead to the systolic dysfunction; moreover, it seems that the characteristic circular pattern of ventricular wall motion abnormality follows the cardiac sympathetic supply system [12].

Clinical Features

The clinical features of TS are usually completely superimposable with those of an acute myocardial infarction (AMI).

- *Symptoms*: acute and prolonged anginal chest pain, described like retrosternal pressure or heaviness, sometimes radiating to the left arm or

neck. When present, a typical aspect useful for diagnosis is that the chest pain usually occurs after mental or physical stress, such as the unexpected death of a relative or friend or receiving news of serious diagnosis or having a great fright [13]. However, recently an international meta-analysis (COUNTS study) has shown that these stressors have a limited impact occurring in about only 36 % of patients [14]. In men, physical stress rather than emotional stress is much more associated with the occurrence [4].

- Dyspnea, nausea, and diaphoresis can accompany chest pain.
- *Comorbidities*: A high number of patients affected by TS present cardiovascular risk factors like hypertension (54 %), dyslipidemia (32 %), diabetes mellitus, obesity, and history of smoking, similar to that seen in patients with AMI [14]. Moreover, it has been noted that sometimes TS can occur in patients affected by comorbidities that are usually associated with an excess of catecholamine systemic production like obstructive pulmonary disease, sepsis, thyroid (thyrotoxicosis), or neurological disease (cerebrovascular accidents, subarachnoid haemorrhage, etc.) [3], malignancy, or psychological disorders (22 %) [14].
- *12-Lead EKG*: During the acute phase, it usually shows ST segment depression or transient/persistent ST segment elevation in anterior leads, perfectly mimic king acute myocardial infarction [15–18]. Sometimes it can show also T-wave inversion or Q waves. In subsequent days, the EKG abnormalities follow a distinctive time sequence [19].
- *Cardiac biomarkers*: Troponin, creatinine kinase, and BNP are usually increased.
- *Echocardiography*: It plays a central role during diagnostic process because it shows a typical pattern of wall motion abnormality: complete akinesis or hypokinesis in the apical to mid-segments circumferentially of the left ventricle with relative compensatory hypercontractility in the basal segments (LV ballooning during systole). During left ventriculography, this particular systolic left ventricular shape is more evident and explains the reason why this syndrome has this particular name: it resembles a typical pot (called exactly "Takotsubo") used for a long time in Japan to capture octopuses, which has a round bottom and a narrow neck.
- Other patterns of wall motion abnormality have been reported less frequently, involving the basal-mid segment (apical sparing variant or "inverted Takotsubo") or the right ventricle. Typically, the wall motion abnormality involves regions which are incongruent to a particular coronary artery supply; instead during an AMI, it is more common to find these hypokinetic/akinetic areas supplied by a particular coronary artery.

Clinical Course and Complications

Clinical course of TC is usually characterized by the progressive lowering of chest pain and gradually complete resolution of the wall motion abnormality after some days; less frequently it needs some weeks or months, but differently from AMI, there aren't permanent areas of hypokinesis/akinesis of the left ventricle motion.

- *EKG evolution*: The EKG abnormalities show a slower progression than during AMI, with a specific evolution: gradually during the first hours from symptom onset, there is the complete resolution of ST segment elevation/depression. Negative T waves usually occur after 24–72 h and then gradually deepen progressively during the days/weeks following [20]. Abnormal Q waves could be seen in precordial leads, but these are transient in most patients and generally resolve within a few days to several weeks.
- QTc interval becomes prolonged (>500 ms) progressively as the negative T wave deepens, and this could favor life-threatening ventricular arrhythmias such as torsades de pointes and ventricular fibrillation [18].
- After some weeks, there is usually the complete restoration of the ECG pattern prior to the acute event [15].
- *Recurrences*: These may occur with a rate range from 0 to 15 % after the first episode

and may show the typical apical ballooning or even different patterns of wall motion abnormalities [21].

- *Acute complication*: Despite the most common general favorable course, the in-hospital death ranges from 0 to 8 % because of possible acute complications [22]. Congestive heart failure is one of the most common acute complications (approximately 3–46 %) occurring more frequently in patients with right ventricular involvement [22].
- As already mentioned, during the acute and subacute phases, corrected QT (QTc) interval is markedly prolonged (usually >500 ms), and this is a potential risk factor for life-threatening arrhythmias such as torsades de pointes and ventricular fibrillation that could require external defibrillation [23]. Bradycardia, hypokalemia, hypomagnesemia, and the use of antiarrhythmic drugs may favor arrhythmias when there is QTc prolongation, so they have to be quickly corrected. The reversible nature of the cardiomyopathy suggests that the use of systematic device implantation after a ventricular arrhythmias isn't recommended at the moment.
- Apical thrombosis may occur during the acute phase when the wall motion abnormalities are more evident, due to low blood flow within the apical segment. This could become a potential source of emboli especially when the resolution of the apical akinesis/dyskinesis occurs [24]. Prophylactic anticoagulation therapy should be considered to prevent apical thrombosis and embolic events until the resolution of the "apical ballooning."
- Hypotension occurs frequently and can result from LVOT obstruction associated with basal hypercontractility, complicated by systolic anterior movement of the mitral valve anterior leaflet and mitral regurgitation.
- Cardiogenic shock and ventricular rupture are rare complications described in literature.

Diagnosis

There is yet no consensus on the diagnostic criteria for TC: researchers at the Mayo Clinic proposed first diagnostic criteria in 2004, which have been modified recently (2008) and included [25, 26]:

1. Transient hypokinesis, dyskinesis, or akinesis of the left ventricular midsegments, with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
3. New ECG abnormalities (either ST segment elevation or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma or myocarditis.

Patients were assigned this diagnosis when they satisfied all these criteria.

Japanese investigators have recently presented diagnostic guidelines [27].

There is not a single shared diagnostic test so TC is currently a diagnosis of exclusion.

Furthermore in addition to clinical features, EKG, and echocardiography abnormalities, coronary angiography is mandatory to exclude coronary plaque rupture (culprit lesion) which would need angioplasty and stent implantation or multivessel epicardial coronary spasm. Most patients have angiographically normal coronary arteries or mild atherosclerosis (considering advanced age and several coronary risk factors). In fact, many authors have attempted to find unique ECG criteria capable of distinguishing between Takotsubo and STEMI patients during the acute phase, but actually no criteria have been found, and ECG keeps a limited diagnostic role [18, 20].

Cardiac magnetic resonance is a suitable method to establish TC diagnosis. It allows to evaluate the global systolic function and the area of wall motion abnormalities; moreover, it shows the area of myocardial edema, which is a typical finding in TC, inflammation, and fibrosis. Contrary to myocardial infarction or myocarditis, there aren't areas of delayed enhancement because in TC there isn't an irreversible damage [28, 29].

Treatment

Medical treatment remains empirical.

During the acute phase, therapy must be individualized depending on the hemodynamic situation.

In stable conditions, patients are often treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers to prevent excessive sympathetic activation [13]. To reduce the risk of thromboembolism, patients with marked apical ballooning should be treated with anticoagulant therapy until the contractility of the apex is improved, unless there is a definite contraindication [24].

In hemodynamically unstable patients, early administration of intra-aortic balloon pump counterpulsation should be considered in addition to cardiopulmonary circulatory support and continuous venovenous hemofiltration. There is controversy on the use of cardiac stimulants because of increasing circulating catecholamines. For patients with severe LV outflow tract obstruction, treatment with β-blocker and volume expansion should be considered to reduce the obstruction and increase the cardiac filling.

There is no consensus regarding long-term management of TC [30], although it could be reasonable to treat patients with β-blockers and ACE inhibitors during the ventricular recovery period; however, no data support the continuous use of these drugs for the prevention of recurrence and improvement of survival rate [21]. Physicians may consider stopping those drugs after normalization of left ventricular function normalization.

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Early Repolarization Pattern

6

Azzurra Fabbrizioli and Giulia Pongetti

6.1 Case Report

A 38-year-old black man was admitted to the emergency medical service (EMS) for some episodes of acute chest pain, started some days ago, exacerbated by deep inspiration and different movements and positions. The pain was intermittent, not irradiated and not accompanied by other symptoms, and was independent of physical exercise or food consumption.

The patient didn't refer flu or recent infection neither traumatic events during the previous weeks.

He has been admitted from EMS to our department for further investigation.

Medical History and Cardiovascular Risk Factors

- Smoker (18 cigarettes/day).
- No familiar history of ischemic cardiovascular disease.
- About 6 months ago, the patient had been hospitalized in another hospital for an episode of acute chest pain developed after intense physical activity. The myocardial biomarkers weren't elevated. He underwent coronary angiography, which showed normal coronary artery anatomy and absence of significant stenoses or thrombus. He has been discharged with Cardioaspirin and beta blockers, but he stopped consumption autonomously after some weeks.
- Migraine from some years.

Allergies

None

Medications

None

Vital Signs

- Temperature: 36.7 °C
- Heart rate: 60 bpm
- Blood pressure: 135/70 mmHg

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- Respiratory rate: 16 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %
- Glasgow Coma Scale (GCS): 15

Physical Examination

- *General*: no acute distress, alert, awake, and oriented. Well developed and well nourished.
- *Head, eyes, ears, nose, throat*: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, no conjunctival injection.
- *Neck*: supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit.
- *Cardiovascular*: Regular rate and rhythm, S1 and S2 are normal; no murmurs, rubs or gallops; point of maximal intensity nondisplaced and nonsustained; no hepatojugular reflux; and capillary refill less than 2 s.
- *Lungs*: no rales, rhonchus, or wheezes, no egophony, no alterations in tactil fremitus, and normal percussion.
- *Abdomen*: mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, nondistended/nontender, no rebound or guarding, no costovertebral angle tenderness, no hepatosplenomegaly.
- *Extremities*: no cyanosis or clubbing. Mild peripheral edema.
- *Neurological*: cranial nerves II through XII intact, no focal deficit.
- *Psychiatric*: normal affect, no hallucinations, normal speech, no dysarthria.
- *Skin*: intact, no rashes, and no lesions.

What Are the Possible Causes of Acute Chest Pain in a Young Man?

- Cardiac causes
  - Acute coronary syndrome (ACS)
  - Myocarditis/pericarditis
  - Cardiomyopathy
  - Valvular disease
- Pulmonary causes
  - Pneumothorax
  - Pneumonia/pleuritis
  - Pulmonary infection
  - Pulmonary embolism
- Vascular causes
  - Aortic dissection
  - Aortic aneurysm
- Gastrointestinal causes
  - Esophageal spasm
  - Esophagitis
  - Peptic ulcer

A pulmonary disease is unlikely because the chest pain was not accompanied by other suggestive symptoms like dyspnea, temperature, shortness of breath, tachypnea, fatigue, tachycardia, or hypotension and lung physical examination was normal. However, a chest x-ray was performed, and it showed normal heart size and volumes, no pulmonary congestion or pleural effusion, and no signs of pneumothorax.

A severe valvular disease is unlikely according to the absence of significant cardiac murmurs during physical examination, the clinical features of chest pain, and the lack of other symptoms like dyspnea, tachycardia, or fatigue. The chest pain could be also explained by gastrointestinal disorder like esophagitis or peptic ulcer, and a complete esophagogastroduodenoscopy (EGDS) could be required to exclude that possible cause of symptoms.

Owing to these observations, an EKG was recorded, and an echocardiogram and routine laboratory tests were performed.

EKG

Sinus rhythm, heart rate of 60 bpm, normal atrioventricular conduction (PQ 200 ms), cardiac electrical axis +15°, normal intreventricular conduction, ST-segment elevation about 2 mm in V2–V4 and about 0.5–1 mm in V5–V6, flat T wave in D2, aVF. QTc 400 ms (Fig. 6.1).

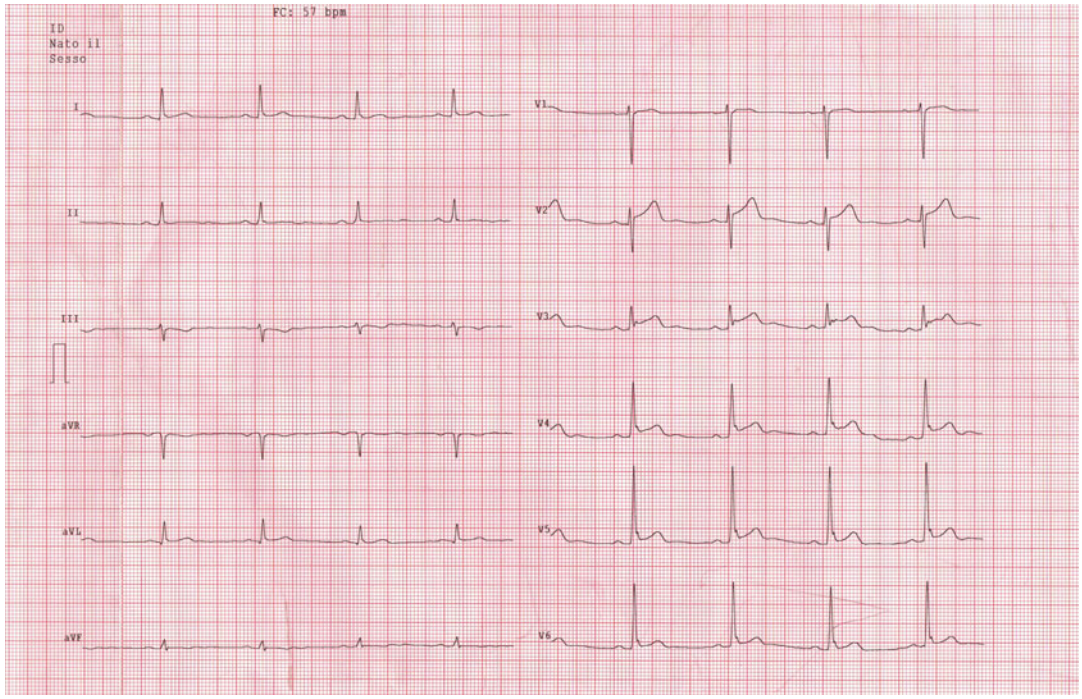

Fig. 6.1 EKG at rest while the patient was asymptomatic

Echocardiography (Not Shown)

Normal both atria size (LA diameter M-mode = 3.6 cm; area 4c = 18 $cm^{2.}$ RA area 4c = 16 cm^2). Normal size and wall thickness of the left ventricle (iLVEDV 42 ml/m^2), which shows a preserved systolic function (ejection fraction with Simpson's method 0.67). Normal size and global function of the right ventricle (TAPSE 23 mm).

Normal morphology of the cardiac valves; mild tricuspid regurgitation and normal systolic pressure gradient (PASP = 25 mmHg). Normal size of the aortic root (24 mm) and of the proximal ascending aorta (28 mm); normal size of the aortic arch (26 mm) and the descending thoracic aorta (22 mm) in the explored segments too. The inferior vena cava has also a normal size (12 mm) and physiological collapsing during inspiration. Normal diastolic pattern without increased filling pressure (E/A 0.9, E/E' 6, E dec time 210 m/s).

Absence of pericardial effusion.

Conclusion: normal echocardiographic findings for a 38-year-old man.

Routine Laboratory Tests

- *Complete blood count*: normal.
- *Cholesterol (total, HDL, LDL) and TG*: normal.
- *Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect)*: normal.
- *Thyroid function (TSH, FT3, FT4)*: normal.
- *Renal function (creatinine, BUN)*: normal.
- *Electrolytes (Na+, K+, Ca++, Mg++, Cl−)*: normal.
- *Fasting blood glucose*: 102 m/dl (5.67 mmol/L).
- *Troponin I-hs*: *0.012 ng/ml (n.v < 0.055 ng/ml)*
- *Inflammation index*: *VES 35 mm/h (n.v < 27 mm/h), CRP 0.2 mg/dl (n.v <0.6 ng/ml)*
- *D-dimers*: *150 ng/mL (n.v. < 280 ng/mL)*

The echocardiographic findings are completely normal, so we can rule out cardiomyopathies and any severe valvular disease as previously supposed.

Similarly, the aortic size is normal, and there are no signs of acute aortic dissection (intimal

flap) or intramural hematoma. Furthermore, the biomarkers are normal (D-dimer and troponin), and the symptoms referred by the patients are not typical of acute aortic syndrome. Moreover, he didn't present any cardiovascular risk factor, with the exception of the smoking habit. He did not have any familial history of arterial disease.

The EKG recorded while the patient was asymptomatic showed ST-segment elevation in precordial leads (V2–V6), with positive T wave and a concave pattern, without any reciprocal ST-segment changes in the other leads.

The Most Common Causes of ST-Segment Elevation in a Young Man

- Acute coronary syndrome with ST-segment elevation (ACS-STEMI) with or without possible coronary spasm
- Myocarditis/pericarditis
- Early repolarization pattern
- Acute pulmonary embolism
- Hyperkalemia
- Brugada syndrome
- Acute aortic dissection

The first hypothesis we have to exclude is ACS-STEMI. Even though there was an ST-segment elevation in more than one precordial lead, it should be ≥0.25 mV when measured at the J point in a man under 40 years. Moreover, the upward concavity is not typical of STEMI; the limb leads showed an essentially normal repolarization pattern, and there were no reciprocal EKG changes. By considering also normal echocardiography and laboratory results and the clinical history (previous recent coronary angiography was completely normal), we excluded the ACS hypothesis.

The EKG pattern in possible coronary spasms is also different because in addition to the ST-segment modification the R wave may become taller and the S wave may decrease in amplitude or disappear in the leads in which the ST elevation is observed (see Chap. 1).

The repolarization abnormalities in our patient were not typical of an acute pulmonary embolism, which is usually characterized by sinus tachycardia, or other atrial arrhythmias, complete or incomplete right bundle branch block, "pulmonary P wave," ST-segment abnormalities, and/or inverted T wave in right precordial leads. Clinical signs and symptoms and the normal D-dimer level highly contribute to exclude pulmonary embolism.

There were no peaked T waves ("tended") in right precordial leads as we could expect during hyperkalemia; moreover, the laboratory tests ruled out any electrolyte abnormality.

The EKG pattern was also not typical of Brugada type 1 pattern (ST-segment elevation ≥2 mm descending with an upward convexity, inverted T wave in at least one right precordial lead); the clinical history was also negative for syncope or tachyarrhythmic episodes.

Acute pericarditis could be more likely, especially according to chest pain, early recurrence, and its characteristics. Usually in this pathology, the ST-segment elevation is diffuse in all the leads and little pronounced; QRS complex generally shows a reduction in amplitude, and PR can be depressed in many leads. In myocarditis, the most common EKG finding is diffuse T wave inversion, whereas ST-segment displacement is less common. The absence of flu during the days/weeks before, the normal values of the logistic index at the laboratory tests together with the absence of pericardial effusion or wall motion abnormalities made those hypotheses unlikely.

Final Diagnosis

According to the clinical history, echocardiographic findings, and laboratory tests, we concluded that the EKG abnormalities were due to an early repolarization pattern.

An exercise testing was performed showing a complete normalization of the ST-segment elevation during exercise with a slow and progressive return during recovery (Fig. 6.2). That confirmed our diagnostic hypothesis.

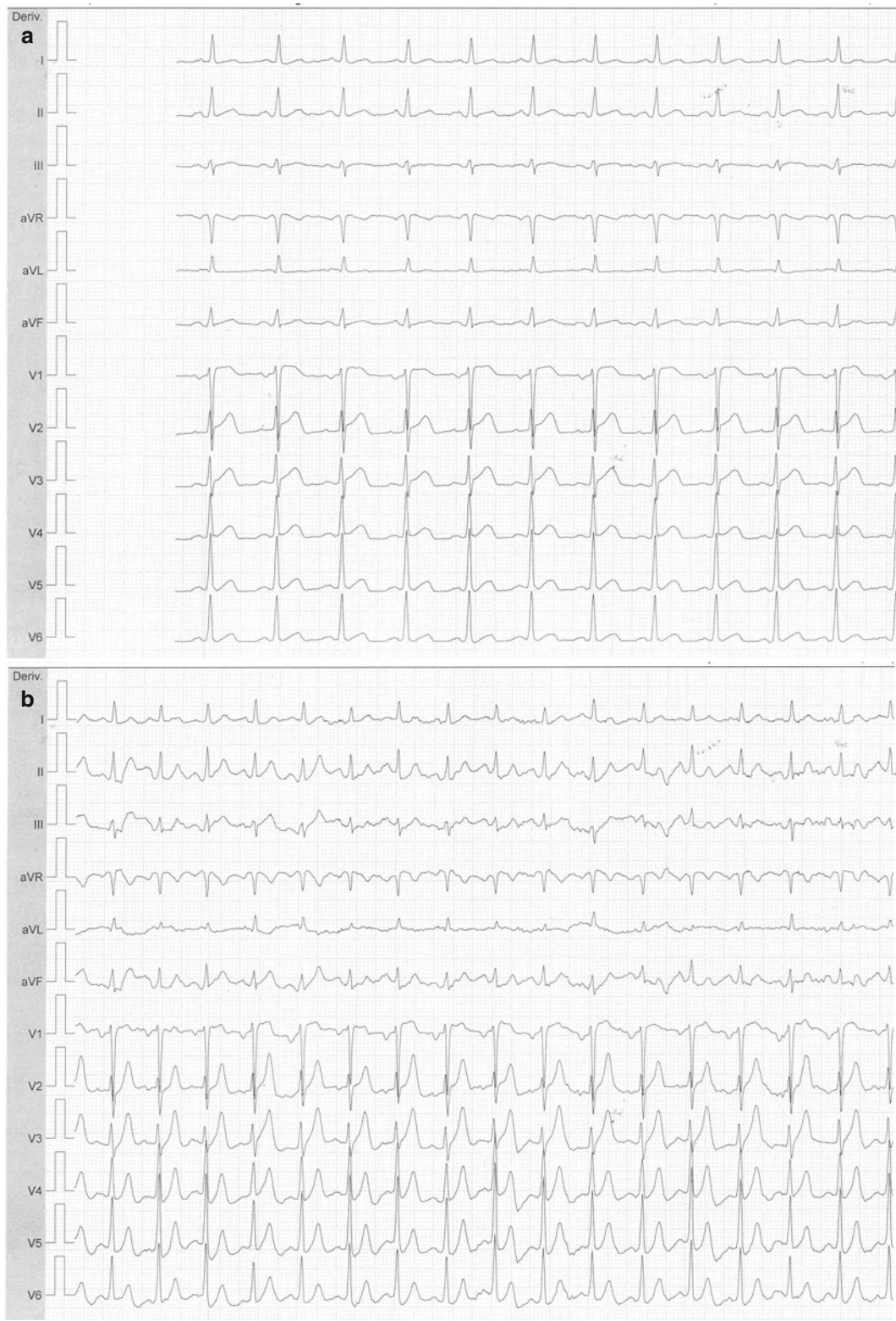

Fig. 6.2 EKG recorded during exercise testing showing the ER pattern at rest (**a**), normalization of the ST-segment elevation during exercise (**b**); slow return to the baseline and then progressive return of the ER pattern (**c**, **d**)

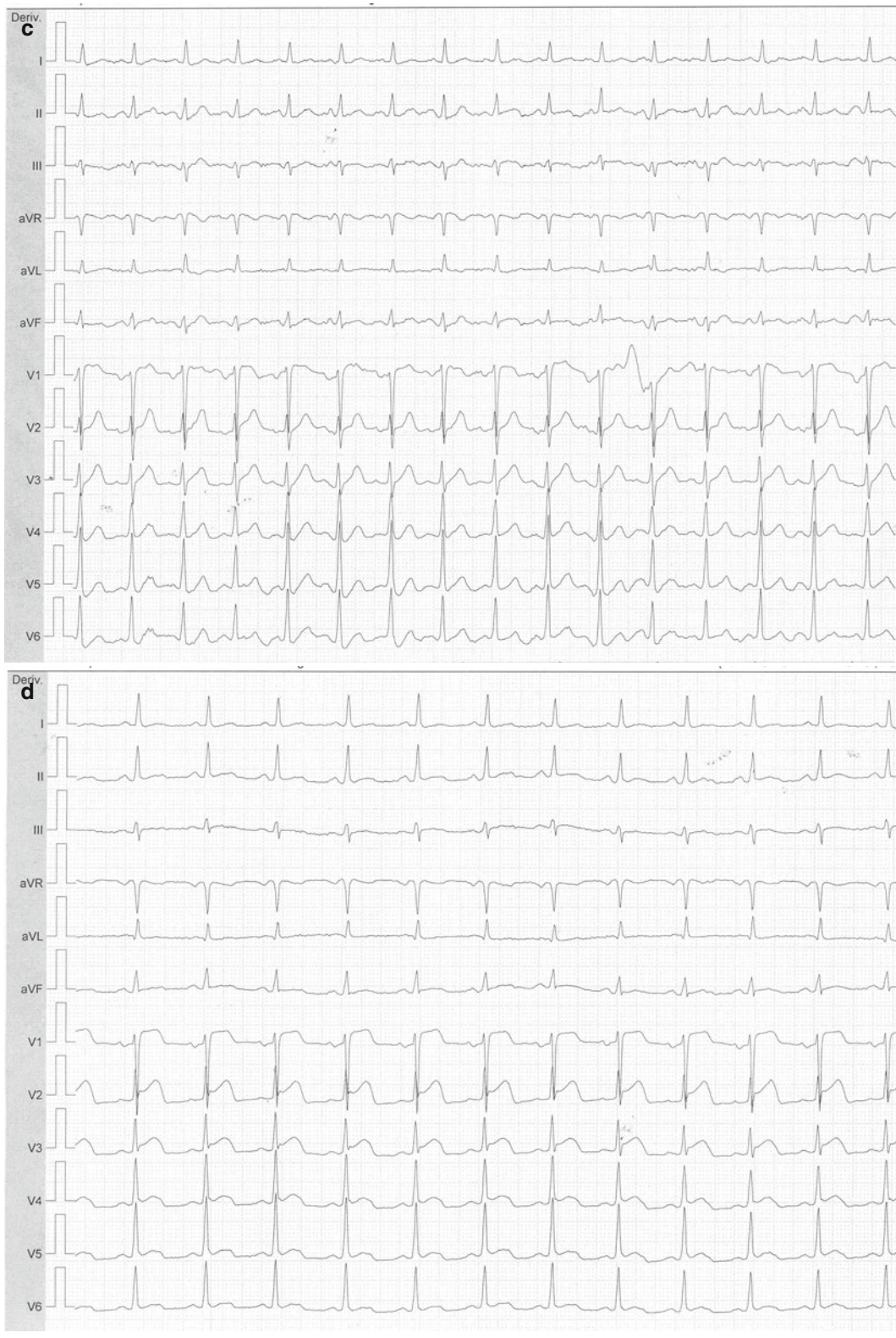

Fig. 6.2 (continued)

This EKG pattern is more frequent in black men and does not require any pharmacological treatment.

There is no common agreement if different ER patterns (commonly separated in benign and malignant forms, *see below*) are associated with a higher risk of SCD. Nevertheless, our patient's EKG showed a benign pattern because the ST-segment elevation was present only in precordial leads, with upper concavity, and the T waves were large and positive. There was a J wave in some leads (V4–V5–V6), but it was little and did not show significant modifications. The complete repolarization pattern remained stable during the hospitalization period without significant changes at rest. Moreover, the patient did not present proarrhythmic conditions and did not refer familiar history of SCD. So he could be safely discharged.

However, for completing diagnostic evaluation, we decided to perform an EGDS, which showed a grade B gastroesophageal reflux disease *(Los Angeles classification)* with some mucosal breaks that did not extend between the tops of the two mucosal folds. Proton pump inhibitor therapy has been prescribed, and a gradual decrease of the chest pain was observed during the following days. Finally, the patient was discharged suggesting an additional gastroenterological reassessment in the next weeks after full therapy.

6.2 Early Repolarization

The early repolarization (ER) pattern is a particular EKG aspect first described in 1936 by Shipley and Hallaran as a normal variant of repolarization [1]. Subsequently, a new classification proposed by Haissaguerre et al. [2] defined ER pattern as the J point elevation associated with a slurring (deflection in the R-wave descent) or a notching (positive deflection with a secondary r′ wave) on the terminal portion of QRS, called J wave, associated with ST-segment elevation or a horizontal/descending ST segment.

Epidemiology

ER affects the general population from 6 to 13 % [2–4] and is more frequent in men (75 %) and young athletes [4] and may disappear with aging [5]. It is more common in black people [2, 5].

Electrocardiographic Features

The ER EKG pattern is characterized by J point elevation ≥1 mm in at least two contiguous leads (the J point is the junction between the end of the QRS complex and the ST segment) often associated with J wave, also called Osborn wave [6], that is a rare deflection similar to a P wave, situated at the end of the QRS complex and usually visible both in precordial and limb leads. It is a typical finding during hypothermia, but may be present also during hypercalcemia or in Brugada syndrome [5]. His amplitude can increase with vagal tone [7, 8]. Actually, the presence of ST-segment elevation is not necessary for ER EKG diagnosis. Anyway, the ST-segment elevation is characterized by upward concavity, more frequently in precordial leads without any reciprocal depression. It is usually <2 mm (rarely > 5mm) in precordial leads (usually V4–V6) but may also be present in inferior or lateral leads. In some cases, the J point elevation is associated with horizontal/descending ST segment.

QT interval is always normal. The ER pattern is intermittent and therefore not constant in all the recorded EKG.

Pathogenesis

The electrophysiological mechanism underlying the ER pattern is the presence of a voltage gradient between the epicardium and endocardium.

Some epicardial regions have a faster repolarization during phase 1 of the action potential than the endocardial regions, due to an increased repolarizing current or a decreased depolarizing current. The more common ionic current involved in this modifications seems to be the K± current

(Ito), which starts the repolarization phase [10, 11]. In this way, there is a voltage gradient between the epicardium and endocardium which produces the J wave on the surface EKG. When this voltage gradient occurs later in the action potential, it is responsible for the ST-segment elevation.

Differential Diagnosis of ST-Segment Elevation

One of the key points about ER is to discriminate this "benign" condition from other disorders presenting ST-segment elevation and requiring specific medical treatment.

- *ACS-STEMI*: the diagnosis of ACS-STEMI is clinical and electrocardiographic. The typical ischemic EKG changes usually show ST-segment elevation ≥0.25 mV in men below the age of 40 years and ≥0.2 mV in men over 40 years or ≥0.15 mV in women, when measured at the J point in at least two contiguous leads, and reciprocal changes. The lack of reciprocal changes (without changes except aVR) and the isolated ST-segment elevation reduce the positive predicted value for STEMI; anyway, it can be useful in the comparison with previous EKG and the evaluation of symptoms, cardiovascular history, echocardiography, cardiac biomarkers, and serial EKG monitoring.
- Acute Pericarditis: the typical EKG modifications during an acute pericarditis are diffuse concave ST-segment elevation with positive T waves and no reciprocal ST-segment depression (except in aVR and V1). In about 50 % of cases, PR segment depression may be visible which usually occurs in all leads except aVR and V1, and it is pathognomonic of acute pericarditis.

  To achieve the right diagnosis of acute pericarditis, the comparison with previous EKG is useful, considering symptoms, presence of pericardial rubbings, pericardial effusion, positive cardiac biomarkers, and serial EKG monitoring to evaluate the typical time modification.
- *BRUGADA SYNDROME*: in Brugada type 1 pattern, there is typical coved J wave- ST segment elevation ≥2 mV and an inverted T wave in at least one right precordial lead [11]. The J wave may be accentuated by increased vagal tone and fever and may be unmasked by the class I antiarrhythmic drugs (flecainide, ajmaline, and procainamide) [11, 12].

Exercise Test

Exercise or isoproterenol test may cause regression of the ST-segment elevation, presumably as a result of a diminished difference between ventricular action potential durations during sympathetic stimulations. This phenomenon may be clinically useful to diagnose ER pattern in patients with low suspect of acute myocardial infarction or acute pericarditis [9].

Clinical Features and Risk Stratifications

The main question about early repolarization is its possible relation to an arrhythmic risk eventually causing sudden cardiac death (SCD) in young subjects.

A first report in 1984 showed an association between an ER pattern and ventricular fibrillation (VF) [13]. More recently in 2008, Haissaguerre et al. demonstrated in a large study that ER pattern is six times more common in patients who suffered previous VF than in matched controls; moreover, these patients have more likely an increased risk of recurrent SCD [2].

In particular, it seems that the ER pattern in inferior leads is the one with the most increased arrhythmic risk of SCD, especially when the J point is >2 mm (three-fold risk increased), as demonstrated in a control study with over 10,000 patients, followed for 30 years [4].

In 2011, Tikkanen et al. analyzed the different electrocardiographic phenotypes in ER and their long-term outcome, distinguishing between benign and malignant forms. In the benign

pattern, the ST segment and the T waves have a temporary stability, and T waves are generally large, positive, and concordant with the ST-segment deviation from V2 to V4. In this patient, the ER pattern is not a mortality risk factor, also if situated in inferior leads.

On the other hand, the malignant pattern is characterized by a notched J wave, a horizontal/descending ST elevation, and T waves discordant to their respective ST-segment deviation. The ST/T waves' morphology may change in 24 h, particularly during the night. This pattern seems to be associated with an increased risk of all-cause mortality [14]. These data have been confirmed by a recent meta-analysis where the ER pattern associated with high SCD risk is present in <0.3 % of the general population [4, 15]. It is a common agreement that large and dynamic J waves are more prevalent in patients with idiopathic VF. Anyway, the risk of VF in general population is 0.03 % (3/10,000), and the higher risk ER pattern may increase ten times SCD (30/10,000) [16]. There are, moreover, some proarrhythmic conditions like acute ischemia, electrolytic disturbances, or depressed ventricular function which may trigger VF and unmask an ER malignant pattern [9, 17].

There is no consensus regarding the pharmacological therapy for VF in these patients; amiodarone or quinidine have been empirically used in a clinical context [18].

For patients resuscitated from SCD, it is mandatory to implant an ICD (implantable cardioverter-defibrillator) whenever all the possible reversible proarrhythmic triggers have been excluded [19].

There are no clear recommendations for primary prevention in asymptomatic patients, and at the moment, any pharmacological therapy and/or stopping physical activity is not recommended even at competitive level.

Patients with syncope and an ER pattern at rest EKG should undergo common diagnostic evaluation usually done for unexplained loss of consciousness.

Currently, the ER pattern is still an object of study.

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Part III

Heart Failure and Resynchronization Therapy

Acute Heart Failure and Pulmonary Edema

7

Andrea Romandini and Simone Maffei

7.1 Case Report

A 64-year-old man was admitted to the emergency room for acute dyspnea. The patient reported fatigue and dyspnea for minimum efforts during the days before. He reported no recent pathological findings.

Medical History and Cardiovascular Risk Factors

- Type 2 diabetes mellitus.
- 2013: access to the emergency room for asthenia and dizziness; on that occasion, high levels of glucose were found.

Allergies

None

Social History

He used to smoke about 30 cigarettes/day some years ago.

Home Medications

Rosuvastatin 20 mg at 9.00 p.m., metformin 850 mg at 12.00 a.m and at 8.00 p.m.

Vital Signs

Temperature: 36.5 °C
Heart rate: 126 beats per minutes
Blood pressure: 170/100 mmHg
Respiratory rate: 22/min
Oxygen saturation while breathing in ambient air: 92 %

Physical Examination

General: alert, awake, and oriented but slightly agitated
Neck: slight jugular venous distention, no lymphadenopathy, and no carotid murmur
Cardiovascular: early diastolic gallop with S3 and, systolic murmur 2/6 at the mesocardium without radiation to the armpit, neck, or carotid vessels

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Lungs: breath sounds diffusely decreased, in particular at the lung bases, and rales up to medium shots bilaterally

Abdomen: plain, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, nondistended/nontender, no rebound or guarding, no costovertebral angle tenderness, hepatomegaly up to 2 cm from the costal margin, no splenomegaly, and Giordano and Murphy signs negative

Neurological: negative cerebellar test, cranial nerve intact, no focal deficit, and reflections normoexcitable

Psychiatric: normal

Skin: pale, cold, and sweaty with cyanosis of the extremities

Routine Laboratory Tests

- Complete blood count: leukocytosis with neutrophilia (WBC 10.760/mmc, 91.20 % neutrophils), hemoglobin 13.5 g/dl, and platelets 248,000/mmc
- Inflammatory markers: ESR 29 mm/h and CRP 0.6 mg/dl
- Hepatic function: GOT normal, GPT with slight increase (61 U/l), γ-GT 121 U/l, and ALP, total bilirubin (direct and indirect), and coagulation normal
- Normal renal function (creatinine 0.82 mg/dl, BUN 38 mg/dl, eGFR 92.8 ml/min/1.73 m^2)
- Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- Fasting blood glucose: 179 mg/dl
- Myocardial necrosis markers: normal CK-MB and Hs-TnI 0.059 ng/ml (n.v. 0–0.055)
- BNP: 744 pg/ml
- Thyroid function: normal TSH and fT4 and fT3 2.10 pg/ml (n.v. 2.2–4.2 pg/ml)

The blood gas analysis performed in ambient air showed pH = 7.41, pO_2 = 58 mmHg, pCO_2 = 40 mmHg, and p/F = 276. ECG showed a sinus tachycardia (heart rate was 126 beats per minutes), normal atrioventricular and intraventricular conduction, and nonspecific alterations of ventricular repolarization.

Chest X-Ray

X-ray showed signs compatible with acute pulmonary edema.

What Are the Possible Causes of Worsening Acute Dyspnea and Orthopnea in This Patient?

There are several causes that may acutely unbalance the left ventricle function. There may be cardiac, extracardiac, or iatrogenic triggers; however, dyspnea can also be related to diseases affecting primarily the lungs. These are the possible causes in this patient:

- Acute myocardial infarction
- Hypertensive crisis
- Arrhythmias
- Acute myopericarditis
- Lung diseases (bacterial pneumonia)
- ARDS
- Pulmonary embolism
- Valvular disease (acute mitral regurgitation)

The patient was apyretic and CRP was negative, although there was a mild leukocytosis with neutrophilia.

EKG

EKG was negative for ischemic alterations, and hs-troponin I was minimally altered with normal CK-MB.

According to these data, acute myocardial infarction, bacterial pneumonia, arrhythmias, and acute myopericarditis were initially excluded as possible causes of dyspnea. The patient was then treated with furosemide bolus and infusion of nitroglycerin to reduce high blood pressure initially encountered. A CPAP (continuous positive

airway pressure) was positioned and was set a FiO_2 of 50 % and PEEP (positive end-expiratory pressure) of 10 cmH_2O. The patient showed marked improvement in dyspnea, and blood gas analysis showed a significant increase in pO_2 ($pO_2 = 58$ mmHg → 139 mmHg). This favorable response to treatment could make us exclude a noncardiogenic acute pulmonary edema (ARDS), which is characterized by severe hypoxemia refractory to increased FiO_2 and reduced lung compliance.

Echocardiography

An echocardiography was also recorded: "tricuspid aortic valve with normal valve opening; standard size of the aortic root and ascending aorta with mild ectasia of the aortic arch. Mild left atrial enlargement (44 ml/m^2). Normal right ventricle size and systolic function (TAPSE 22 mm). Slightly dilated left ventricle with severe reduction of systolic global function (EF 25 %) and diffuse hypokinesia; modest pericardial effusion more evident close to the right sections and conditioning initial atrial collapse. No significant gradients. Mild mitral insufficiency, mild tricuspid regurgitation with high pulmonary arterial pressure (60 mmHg). Inferior vena cava dilated and hypo-collapsing." Echocardiogram ruled out the presence of significant valvular disease and dysfunction and dilatation of the right sections but showed severe left ventricular dysfunction associated with mild pericardial effusion. At this diagnostic–therapeutic point, an underlying ischemic heart disease or a myopericarditis could not be excluded.

Coronary Angiography

An invasive coronary angiography documented the absence of hemodynamically significant stenosis, and an eco-color-Doppler of the lower limbs excluded the presence of a deep vein thrombosis (to rule out thromboembolic pulmonary disease).

Therapy

After resolution of the acute phase, a specific therapy for heart failure was given to the patient (ACEI, beta-blockers, potassium sparing), and in a few days, a good cardiovascular compensation was restored (demonstrated also by the gradual reduction of BNP: 744 pg/ml → 250 pg/ml). The absence of a compatible clinical history, the slightest movement of hs-troponin (0.059 ng/ml → 0.061 ng/ml → 0.033 ng/ml), and the constant negativity of inflammatory markers made the myopericarditis an unlikely cause of the acute pulmonary edema. We thought the hypertensive crisis was the cause of acute heart failure.

Final Diagnosis

The final diagnosis was "hypertensive crisis complicated by acute pulmonary edema in patients with hypokinetic-dilated cardiomyopathy without hemodynamically significant stenosis" After 2 months, the patient was asymptomatic and in good hemodynamic compensation. A new echocardiogram showed the absence of pericardial effusion and an improvement in ejection fraction (EF: 25 % → 39 %).

7.2 Definition and Clinical Classification of Acute Heart Failure Syndromes (AHFSs)

According to the latest European Society of Cardiology (ESC) guidelines, heart failure (HF) can be defined as "an anomaly of cardiac structure or function impairing heart's ability to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues despite normal filling pressures or at the expense of increased filling pressures" [1]. The clinical manifestations of heart failure result from the impaired forward cardiac output (forward failure) and/or elevated venous pressure related (backward failure) to the failing heart. The clinical syndrome of HF may result from disorders of any aspect of cardiac

function including pericardial disease, myocardial disease, endocardial disease, valvular heart disease, arrhythmias and conduction disorders, congenital heart disease, high output state, or volume overload state. These patients may present with reduced or preserved left ventricular (LV) systolic function. LV ejection fraction (LVEF) is considered important in classification of patients with HF because of differing patient prognosis and response to therapies and because most clinical trials selected patients based on LV ejection fraction (LVEF). For this reason, patients with HF are broadly categorized (with some difference among major international guidelines) in HF with preserved EF (normal or mildly reduced LVEF and LV not dilated) and HF with reduced EF (LVEF usually ≤35–40 %). An episode of acute heart failure or acute heart failure syndrome (AHFS) is usually defined as a rapid or gradual onset (or change) of symptoms and signs of heart failure (HF) requiring immediate medical attention (unplanned hospitalization or office room visit). Patients with AHFS are generally classified into those presenting with HF for the first time (de novo AHF) and those with worsening chronic HF.

Pathophysiology of AHFS

Regardless of the underlying cause or superimposed precipitating factor, pulmonary and systemic congestion (due to increased left- and/or right-side heart filling pressures), with or without low cardiac output, is the unifying finding in the broad spectrum of hemodynamic models in AHFS [2, 3]. Congestion and not low cardiac output is the main cause for AHFS [4–7].

High left-side filling pressure results in pulmonary hypertension (pulmonary congestion) with increased pulmonary capillary wedge pressure (PCWP) that preceded the subsequent clinical congestion with pulmonary interstitial and alveolar edema.

High right-side filling pressure results in systemic venous hypertension (systemic congestion) with increased central venous pressure (CVP) leading to jugular vein distension and often subsequent peripheral edema and gradual body weight gain [8]. Volume overload is only one of the possible hemodynamic perturbations that may explain the elevated filling pressure. Additional pathophysiologic mechanisms are afterload mismatch (increased afterload) and abnormal end-ventricular diastolic pressure (related to ventricular diastolic dysfunction/abnormal compliance and valvular regurgitation). Pulmonary congestion, with or without associated systemic signs, may be the results of two different pathways. The cardiac (central) pathway is the mechanism by which a low cardiac output (usually an acute decrease induced by a variety of precipitant mechanisms including ischemia, arrhythmia, inflammatory activation or progression of underlying HF process induced by progressive myocardial dysfunction) leads to a further neurohormonal activation, lower renal perfusion (cardiorenal syndrome), and fluid accumulation with systemic congestion (overload fluid retention) [9, 10]. The vascular (peripheral) pathway is related to increased vascular stiffness/resistance with acute afterload mismatch impairing systolic performance and resulting in redistribution of fluid from systemic to pulmonary circulation rather than in general fluid retention [2, 9, 10]. Venous volume mobilization of the splanchnic circulation has also been proposed as complementary mechanism [11]. Although in most cases both pathways are active during an AHF event, the magnitude of one pathway may predominate in each patient and is usually suspected according to AHF initial clinical presentation.

Precipitants of Acute Heart Failure

Approximately 80 % of acute decompensated heart failure (ADHF) patients have a worsening of chronic heart failure. In such patients with preexisting HF, one or more identifiable exacerbating factors not necessarily related to the evolution of the underlying HF disease can be often identified (up to 70 %) (Table 7.1). Detection and treatment of precipitating factors is necessary both for acute management of an episode of AHF and prevention of its recurrence.

Table 7.1 Precipitants of acute heart failure

Precipitants and causes of acute heart failure syndromes (AHFSs)	
Rapid deterioration	Gradual deterioration
Rapid arrhythmias	Arrhythmias
Acute coronary syndromes (ACSs)	Infections (including endocarditis)
Mechanical complications of ACS	Exacerbation of COPD/asthma
Acute pulmonary embolism	Anemia
Hypertensive crisis	Renal failure
Cardiac tamponade	Use of drugs that increase Na^+ retention (steroids, NSAIDs, etc.)
Additional acute CV disorders (acute aortic dissection, myocarditis)	Nonadherence with HF medications or diet regimen (including alcohol abuse)
Peripartum cardiomyopathy	Poor controlled hypertension
Acute mechanical valve dysfunction	Endocrine abnormalities

Modified and reproduced with permission from McMurray et al. [1]

Table 7.2 Common physical findings in HF

Possible physical findings in heart failure
More specific
Third heart sound (S3)
Jugular venous distension
Hepatojugular reflux
Laterally displaced apical impulse
Cardiac murmurs
Less specific
Pulmonary rales
Decreased breath sounds at lung bases (pleural effusion)
Peripheral edema and ascites
Hepatomegaly
Tachycardia
Tachypnea
Irregular rhythm (ectopic beats or atrial fibrillation)
Muscle wasting (cachexia)

Data from McMurray et al. [1]

Clinical Profiles at Presentation

The two major classes of symptoms in HF are those due to volume overload (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, gastrointestinal symptoms) and those due to a reduction in CO (fatigue and weakness). The most common are dyspnea and fatigue. Dyspnea (at exertion or at rest) is related to complex physiological mechanisms involving both pulmonary venous congestion and a buildup of lactic acid by working muscle increasing the ventilatory response to exercise. On the other hand, low cardiac output state often results in fatigue and weakness due to reduced skeletal muscle perfusion or atrophy. Elevated systemic venous pressures like those occurring in volume overload or right ventricular dysfunction states are responsible for abdominal discomfort (liver congestion and abdominal ascites), anorexia, and peripheral edema. Common physical findings are summarized in Table 7.2. The most common clinical findings are dyspnea (approximately 90 %), rales, and peripheral edema (65 %).

On the basis of typical clinical and hemodynamic characteristics, AHF patients may present with one of several distinct clinical profiles considering that some overlap between groups may exist [8]. The main clinical profiles and relative features are summarized in Table 7.3.

Another classification scheme has been previously proposed (Forrester classification) and is based on the severity of disease at presentation rather than on the cause of HF [12, 13]. It is a simple strategy to classify patients into specific hemodynamic profiles that may be helpful to guide the initial management strategy. Accordingly, a patient presenting with AHFS may be classified into one of the four specific hemodynamic profiles based on the absence or presence of signs of congestion (wet or dry) and the adequacy of peripheral perfusion (warm or cold): warm and dry, warm and wet, cold and dry, and cold and wet.

Clinical Assessment and Diagnosis of AHF

Traditionally, the diagnosis of HF is a clinical diagnosis combining characteristic symptoms with physical findings, and still today no single

Table 7.3 Common clinical profiles in AHFS

Clinical profiles	Common clinical features
Hypertensive (SBP >160 mmHg)	In many patients, LVEF is preserved (normal CI); relative rapid onset; prevalent pulmonary oversystemic congestion
Normal or high-normal blood pressure	Usual in patients with worsening HF (normal or low CI); gradual onset; mild-to-moderate systemic congestion associated
Low blood pressure (SBP <90 mmHg)	Usual in patients with advanced or end-stage HF disease (severe reduced LVEF with low CI); many patients may have a low cardiac output with signs of organ hypoperfusion; intravascular depletion due to aggressive diuretic therapy may play a role (ensure preload optimization); gradual onset
Flash pulmonary edema	Related to sudden rise in left-side filling pressure (with low or normal CI) induced by acute precipitating factors (e.g., hypertensive crisis); rapid onset with respiratory distress
Cardiogenic shock	Often complicated acute life-threatening condition inducing low CO state (acute MI, fulminant myocarditis, acute valve dysfunction); rapid onset usually; evidence of signs of hypoperfusion (altered mental status, cold skin, oliguria/anuria, etc.)
ACS and AHFS	May be present in up to 25 % patients with ACS; rapid or gradual onset (depending on severity of underlying LV dysfunction); possible resolution after efficacious myocardial revascularization
Isolated right-sided HF	Related to increased right-side filling pressure due to RV dysfunction or pulmonary hypertension (if rapid-onset CI is usually low); onset may be rapid (e.g., RV infarct, acute pulmonary embolism) or gradual (e.g., cor pulmonale, primary pulmonary hypertension, cardiac mass/tumors); evidence of systemic (peripheral edema, hepatomegaly) over pulmonary congestion
Perioperative AHFS	Usually related to volume overload or myocardial injury during cardiac surgery; rapid or gradual onset
High-output failure	Related to conditions associated with high CI (septic shock, anemia, thyrotoxicosis, Paget's disease, pregnancy); patients usually present tachycardia, warm extremities, variable degree of pulmonary and systemic congestion

Data from Gheorghiade et al. [2]

tests can absolutely establish its presence or absence. Unfortunately, signs and symptoms of HF often overlap with those of other common medical conditions (especially with chronic lung disease), and those more specific are also less common (like orthopnea and paroxysmal nocturnal dyspnea) or less reproducible (third heart sound and jugular venous distension) so that several ancillary tests, also contributing to determine mechanisms underlying the AHF, are usually needed to support the clinical diagnosis of AHF.

A chest radiography should be performed initially because it may aid in diagnosis of HF as well as in ruling out other differential diagnoses (e.g., pneumonia). Findings suggestive of HF include cardiomegaly (cardiac-to-thoracic width ratio above 50 %), upper zone vascular redistribution (cephalization), interstitial edema with Kerley B-lines, alveolar edema, and pleural effusions. Radiographic evidence of signs of pulmonary congestion in a patient with dyspnea makes the diagnosis of heart failure more likely; however, the absence of radiographic pulmonary congestion does not exclude diagnosis of AHF. Patients with chronic heart failure, despite AHF symptoms and elevated PCWP, may have few radiographic signs because of enhanced lymphatic drainage. Electrocardiography (ECG) is not useful for diagnosis but offers possible clues to identify both specific treatable precipitating factors of AHF (acute myocardial ischemia and arrhythmias) and also possible etiology of HF (e.g., Q wave in ischemic cardiomyopathy).

Laboratory tests (blood chemistry and hematological tests) are useful to guide initial therapy, to detect reversible cause of HF (e.g., hypocalcemia, thyroid dysfunction) and comorbidities (anemia), and to obtain prognostic information.

Serial monitoring of myocardial necrosis biomarkers (troponin) is recommended initially for diagnostic (exclude acute coronary syndrome) and prognostic purpose. Troponin elevation in acute HF does not necessarily indicate the presence of an acute coronary syndrome. A significant number of patients with AHFS have increased levels of troponin as a result of myocardial injury during AHF episode resulting from ischemic injury and myocyte apoptosis. Such troponin elevation is associated, however, with poor long-term prognosis.

Measurement of natriuretic peptide (NP) levels is helpful especially when the diagnosis is in question. Natriuretic peptides (BNP and NT-proBNP) are a family of hormones released in increased amounts from myocytes (especially ventricular) secondary to myocardial stretch and elevated end-diastolic filling pressure as occurs in AHFS. Increased NP levels are indicators of both the presence and severity of illness. Accordingly, European guidelines recommend measurement of NP levels both to exclude alternative causes of dyspnea and to obtain prognostic information. Patient presenting with acute onset or worsening of symptoms suggestive of HF with a plasma BNP level <100 pg/ml or NT-proBNP <300 pg/ml is unlikely to have AHFS. For patients presenting in nonacute way (slow onset of symptoms), a lower exclusion NP cutoff point should be used to avoid "false-negative" diagnosis (35 pg/ml for BNP and 125 pg/ml for NT-proBNP). Results of NP tests should be always interpreted in the context of all available clinical data and should not be used in isolation to diagnose HF. A variety of conditions associated with myocardial stretch even in the absence of AHF can still be associated with NP elevation (e.g., atrial fibrillation, pulmonary hypertension, and pulmonary embolism). In addition, NP levels are falsely increased in renal failure and tend to be lower in obese patients.

An initial bedside transthoracic echocardiography is recommended both to support the diagnosis of AHFS and to determine its etiology through an assessment of cardiac anatomy and function (left and right ventricular systolic function and wall motion, diastolic function, valvular function, and pulmonary artery pressure). The TD-derived E/Ea parameter is being used to noninvasively estimate LV filling pressures. In addition, especially for those with hypotensive AHFS, echocardiographic assessment of inferior vena cava (IVC) diameter and its respiratory variation aid to determine the patient volume status.

AHFS Management

The main goal of short-term therapy (hours to days) for AHFS has been to achieve the lowest left ventricular filling pressure possible without decreasing cardiac output (especially renal perfusion), increasing heart rate, or further activating neurohormones because these factors have been associated with a worse prognosis [2]. The physician's challenge is that many of the current medications that improve hemodynamics and symptoms may have potential deleterious effect on such variables [8].

Currently, the use of available pharmacological agents for the acute management of AHFS is largely empirical. None of the employed agents would meet today's standards for approval based on evidence for clinical efficacy and safety. However matter, no major clinical practice guidelines include any therapeutic class I, level-of-evidence A recommendations for the pharmacological treatment of AHFS [1].

Evaluation and management of AHFS include three main phases: the initial or early phase (stabilization phase), the in-hospital phase, and the discharge phase. The main goals of each phase are summarized in Table 7.4.

Initial Management Strategy

After treatment of life-threatening conditions, improving hemodynamics and correlated symptoms are the key goals in early management. This requires a basic understanding of pathophysiologic mechanisms underlying an episode of acute HF and how potential overt precipitants adversely affect the cardiovascular system. These conditions and all HF precipitants should be targeted

Table 7.4 Phases of AHFS management

AHF management	
Phases	Goals
Early stabilization phase	Ensure resuscitative supports and appropriate timely interventions to treat life-threatening conditions eventually associated with AHFS (such as hypoxia, unstable arrhythmias, STEMI, acute mechanical valve dysfunction) Establish diagnosis Determine patient clinical profile to align initial treatment Begin initial treatment to improve congestive symptoms, cardiac filling pressure, and/or CO Identify and treat reversible precipitating factors adversely affecting the CV system
In-hospital phase	Start in-hospital monitoring (BP, HR, O_2 saturation, fluid balance, weight, laboratory tests) Monitor signs/symptoms of congestion for careful uptitration of decongestive therapy Establish a proper workup to detect and treat specific underlying cardiac abnormalities or comorbidities that cause or contribute to HF progression (e.g., CAD, valvular disease, arrhythmias, ventricular dyssynchrony, systemic or pulmonary arterial hypertension) Initiation/uptitration of evidence-based therapy for chronic HF according to guidelines (beta-blockers, ACE inhibitors, ARBs, MRA antagonists, electrical devices)
Discharge phase	Ensure patient "dry weight." Congestive signs and symptoms should be reassessed (both at rest and during activity) and natriuretic peptide levels measured Perform transition to oral diuretics Assess functional capacity (6-min walking test) Establish postdischarge planning

and treated for optimal results. Aligning treatment decision to initial patient clinical profile can yield to treat specific subgroups of patients with more tolerable therapies.

Taking the above consideration in mind, according to recommendations from ESC 2012 Guidelines [1], early management of acute pulmonary edema/congestion includes an initial intravenous bolus of loop diuretics at time of presentation (usually furosemide 40 mg i.v. or 2.5 time the total outpatient oral loop diuretic dose) and eventually an i.v. vasodilator if SBP >110 mmHg (class of recommendation II, level B) or an i.v. inotropic agent if SBP <85 mmHg (class of recommendation II, level of evidence C) as adjunctive therapy. Of note, in the American Guidelines (AHA 2013) on heart failure, no specific cutoff values exclude the use of a vasodilator, but its use is advocated generally in the absence of symptomatic hypotension. Subsequently, patients should be reevaluated (within 1 h) for adequate response. Response to treatment includes reduction in dyspnea and adequate diuresis (>100 ml/h urine production in first 2 h), accompanied by an increase in oxygen saturation and usually reduction in respiratory rate and heart rate. In the absence of adequate response, all clinical-laboratory parameters should be reassessed (ECG, echocardiogram with hemodynamic measures, and principle laboratory tests) and several options considered. The most common cause of inadequate response is, however, poor response to the diuretic regimen utilized. Strategies to enhance diuretic efficacy will be discussed below in this chapter. AHF patients unresponsive to diuretic pharmacological therapy may be eventually considered for transient venovenous ultrafiltration (UF) that allows mechanical extracorporeal removal of plasma water. In patients with persistent hypotension (low CO) despite initial vasoactive therapy, other conditions like acute ischemic mechanical complications, severe valve dysfunction (particularly aortic stenosis), or alternative diagnoses (e.g., pulmonary embolism) requiring primary intervention rather than palliation of consequences should be reconsidered. Pulmonary artery catheterization may be sometimes useful in such unresponsive patients especially to ensure that hypotension is not due to inadequate LV filling pressure enabling more tailored vasoactive therapy (both inotropes and vasopressors). Finally, in unresponsive patients with persistent hypotension or cardiogenic shock with a rapid deterioration, a short-term mechanical circulatory support (including intra-aortic balloon pump and ECMO)

may be considered as a "bridge to decision therapy."

Approximately 80 % of patients are hospitalized with worsening of HF. For those with new-onset HF who stabilize after initial management, a chronic HF should be considered, and they should be treated according to recommendation of current guidelines. Initiation or implementation of evidence-based pharmacological therapies for chronic heart failure such as beta- blockers, ACE inhibitors, aldosterone-blocking agents, ARB, and electrical device should occur soon during this phase after stabilization. This topic will be extensively addressed in the chapter on chronic heart failure. For the acute setting, it is important to underline that the outpatient oral HF medications should be always carefully reviewed at admission. Generally, HF therapy should be continued at same doses during an AHFS episode unless the patient has hypotension or contraindications (such as hyperkalemia and severe renal failure for ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists) that may require dose reduction or complete withholding. Several reports have shown that continuation of HF medical therapy with ACE inhibitors (or angiotensin receptor antagonists) and with beta-blockers for most patients is usually well tolerated and results in better outcomes [14, 15].

Ventilation

Oxygen supplementation should be titrated in order to keep the patient comfortable achieving arterial oxygen saturation above 90 %; caution is required in patients at risk of CO_2 retention. In the presence of significant respiratory distress, noninvasive positive-pressure ventilation (CPAP or BiPAP) may be immediately considered to relieve dyspnea and to improve hypoxia, metabolic disturbance, and hemodynamic parameters (reduced LV wall stress and cardiac work) in the absence of contraindications (hypotension, vomiting, depressed consciousness, pneumothorax).

Previous studies and meta-analysis support the use of noninvasive ventilation (NIV) in cardiogenic pulmonary edema showing that besides respiratory and metabolic improvement, its early use can also prevent the need for endotracheal intubation. However, in the recent Cardiogenic Pulmonary Oedema trial (3CPO), no differences other than an improvement in dyspnea were seen in the rates of death or intubation between patients treated with NIV compared to standard oxygen therapy [16]. Currently, according to ESC guidelines, NIV should be considered in such dyspneic patients generally when SBP is not below 85 mmHg (class of recommendation IIa, level of evidence B).

Opiates

Opiates such as morphine sulfate may be beneficial in pulmonary edema because it is thought to induce mild venodilatation (thereby reducing preload) and reduce anxiety and distress associated with dyspnea.

Despite wide empiric use, small previous trial raised concern about the safety of morphine, because its use has been associated with increased need for invasive ventilation and greater in-hospital mortality [17, 18]. At present, according to the latest European guidelines, an i.v. opiate, along with antiemetic medication, may be considered in particularly restless and distressed patients to relieve anxiety and improve breathlessness. Patients should be carefully monitored because opiates can induce respiratory depression.

Diuretic Therapy

Diuretics are the mainstay of therapy in managing congestion in ADHS. Although safety and efficacy of diuretics have not been established in randomized controlled trials, long observational experience has shown their efficacy in relieving congestive symptoms. By reducing intravascular volume, diuretic therapy in ADHF lowers CVP and PCWP reducing pulmonary and peripheral edema often increasing forward-stroke volume and CO. In addition, when given intravenously, loop diuretics may act as vasodilators (principally

venodilators) with additional benefit on renal and pulmonary congestion. Despite the demonstrated efficacy in managing congestion, the use of aggressive diuretic regimens may be associated with neurohormonal activation, worsening renal function, electrolyte abnormalities, and arrhythmias and so with adverse clinical outcomes [19, 20].

Current guidelines recommend administering the lowest dosage in order to achieve and maintain euvolemia avoiding volume depletion and dehydration.

Loop diuretics have the most rapid onset and most powerful effect. In acute setting, like AHFS, intravenous rather than oral administration is recommended because of greater drug bioavailability and more rapid onset of action. Diuretic dosing should be individualized and titrated according to patient status and initial response. Considering the bolus therapy, usually the diuretic effect begins within 30 min with a peak at 1–2 h [21]. Common suggested initial doses of intravenous loop diuretics are 40 mg for furosemide, 0.5–1 mg for bumetanide, and 5–10 mg for torsemide in patients who are not receiving loop diuretics [22]. In patients who have been already taking a loop diuretic, the dose should be almost equal or greater (i.e., 2.5 times) than the maintenance oral dose (in ESC guidelines, the greater dose is advocated) [1]. As discussed above, poor response to the diuretic is a common cause of inadequate response to initial therapeutic approach in AHFS. Now a widely accepted definition of diuretic resistance in HF is still lacking. In HF patients, the diuretic dose–response curve may be shifted downward and to the right because of a reduction in both renal drug delivery and natriuretic response. So higher doses are required to achieve a given diuretic response, and the maximal effect may be bunted [23]. Once a single effective dose has been determined, it should be administered multiple times per day (two or three times) according to the magnitude of diuresis needed. If there is little or no response, experts recommend dose doubling at 2 h intervals as needed (until effective diuresis is demonstrated) up to the maximum effective doses (ceiling doses over which no further diuresis will be achieved). Suggested maximum effective doses of loop diuretics in heart failure and renal insufficiency have been previously described [22]. Regarding the use of furosemide, in patients with HF and normal renal function, suggested maximal intravenous doses are 40–80 mg, but in the presence of renal insufficiency, larger staring doses may be required up to 160 or 200 mg in moderate and severe renal impairment, respectively. Doses of 250 mg or above should be given by infusion over 4 h.

From a pharmacokinetic and pharmacodynamic perspective, there are potential benefits of continuous infusion versus intermittent bolus. Continuous infusion results in more constant delivery of diuretics to the tubule with increased diuresis probably minimizing intermittent periods of the known postsodium retention effect. After a starting loading dose, suggested starting infusion rate of loop diuretics varies with the level of renal function (GFR or creatinine clearance). For furosemide, suggested doses are 10 mg/h with a GFR > 75 ml/min, 10–20 mg/h with a GFR 25–75 ml/min, and 20–40 mg if GFR < 25 ml/min. If an adequate response has not occurred within 1h, a loading dose should be repeated and then the infusion rate uptitrated [22].

However, existing data still does not allow definitive recommendations for clinical practice because even in a recent trial, no clear benefit or harms with intermittent bolus versus continuous infusion strategy have been demonstrated [24].

Several strategies can be tried to overcome such diuretic resistance especially during in-hospital phase. A common method for treating diuretic resistance is the sequential nephron blockade by adding a thiazidic or thiazide-like diuretic (DCT diuretics) [25, 26]. Metolazone and hydrochlorothiazide are the most common molecules used in combination with loop diuretics. Many clinicians prefer metolazone, a thiazide-like diuretic, because it has a longer half-life and a preserved efficacy in advanced renal failure (GFR below 20 ml/min) [27]. However, such combination therapy is associated with significant increase in adverse effect especially when high doses of DCT diuretics are used compared to either therapy alone [28].

It is advisable to start with lower dose of DCT diuretic (hydrochlorothiazide 12.5–25 mg or metolazone 2.5–5 mg) and maintain a daily regimen for a short period with careful monitoring of electrolyte balance and fluid depletion [29].

Additional Strategy to Enhance Diuresis

Dopamine infusion at low doses (≤3 μg/kg/min) may selectively activate dopamine receptors (DA1 and DA2) resulting in renal vasodilation and increasing renal blood flow. However, a significant benefit of standard use of dopamine has not been confirmed in recent randomized studies [30]. Although there is uncertainty, in the latest 2012 ESC guidelines, it is advocated to start infusion with low dose of dopamine (at 2.5 mcg/kg/min) in patients with poor response to diuretic regimen.

Salt and fluid restriction is another strategy that has also been commonly used during initial management of AHF patients, although as noted in recent European guidelines no firm evidence exists to support this practice. By reducing sodium load at the nephron, postdiuretic sodium retention may be reduced, especially when sodium intake is high. Generally, it is common to restrict sodium intake <2 g/day and fluid intake <1.5–2.0 L/day [1].

Ultrafiltration

AHF patients unresponsive to diuretic therapy may be considered for venovenous ultrafiltration (UF). UF allows mechanical extracorporeal removal of plasma water across a semipermeable membrane in response to a transmembrane pressure gradient (convective transfer). Venovenous UF is performed at bedside via a central or peripheral vascular access using a transportable UF console. With slow continuous UF usually performed in HF patients, the amount of ultrafiltrate created is small (2–4 ml/min) and does not require replacement with substitution fluid. Compared to hypotonic urine output achieved with loop diuretics, the ultrafiltrate (or volume removed) is isotonic to plasma and therefore removed more sodium (and less potassium). In addition, UF allows a better control of plasma water removal rate that can be tuned to match the putative refilling rate from the interstitium (approximately 15 ml/min) avoiding intravascular depletion and the vicious cycle of further neurohormonal activation [31].

Intravenous Vasodilators

By reducing both preload and afterload and therefore cardiac filling pressure, vasodilators may have beneficial hemodynamic effects in ADHS by reducing pulmonary congestion and usually increasing CO. The mechanisms for increased CO include left and right ventricular afterload reduction, improved diastolic ventricular properties, reduced mitral regurgitation, and eventually reduction in myocardial ischemia.

Currently approved intravenous vasodilators in clinical practice are organic nitrates such as nitroglycerin (NTG) and isosorbide dinitrate (ISDN), inorganic nitrates such as sodium nitroprusside (SNP), and nesiritide (currently not available in many European countries).

Despite that nitrates have been used to relieve symptoms and improve hemodynamic acute HF for many years, their use is still based on limited evidence primarily from small, single-center studies [32]. Currently, the use of intravenous vasodilators is recommended (class II and level of evidence B) to relieve symptoms and to reduce pulmonary congestion in patients in AHFS with intact blood pressure. In the latest 2012 ESC guidelines [1], their use is advocated only in patients with a BP greater than 110 mmHg, compared to ACCF/AHA guidelines where their use is limited only in the presence of symptomatic hypotension. Suggested intravenous doses of vasodilators in AHFS are indicated in Table 7.5.

Among organic nitrates, the most widely used is NTG. At low modest doses, intravenous NTG acts primarily through venodilatation, while at higher doses (>40 mcg/min) the effect of arteriolar dilatation begins to be apparent [33]. However,

Table 7.5 Doses of intravenous vasodilators in AHFS

Suggested intravenous vasodilator doses in AHFS	
Agent	Doses
Nitroglycerine	Start with 10–20 mcg/min and then increase up to 200 mcg/min
Isosorbide dinitrate	Start with 1 mg/h and then increase up to 10 mg/h
Nitroprusside	Start with 0.3 mcg/kg/min and then increase up to 5 mcg/kg/min

Modified and reproduced with permission from McMurray et al. [1]

despite a graded dose–response curve, a variable interindividual response exists also related to baseline levels of systemic vascular resistance. A process of careful uptitration is always needed to avoid sudden BP reduction or hypotension. A significant drawback for intravenous nitrate particularly with NTG is the phenomenon of tachyphylaxis that may occur in 15–30 % of patients within 24 h probably related to strong counter-regulatory neurohormonal activation that leads to sodium and water retention [34].

Sodium nitroprusside (SNP) is the sodium salt of a complex molecule that breaks down in the blood interacting with oxyhemoglobin and directly releasing NO and cyanide into circulation. SNP is a potent vasodilator with the faster onset of action (within 60–90 s). Its short half-life (approximately 2 min) facilitates early establishment in the intensive care unit of an individual patient's optimal level of vasodilation. Even low doses produce an equivalent venous and arteriolar dilatation resulting in balanced vasodilation of both sides of the circulation [35]. Because SNP can cause significant hypotension, it is usually used in intensive care settings even with invasive arterial monitoring. It is postulated that SNP may potentially increase the risk of a coronary steel phenomenon: as opposed to nitroglycerin's preferential effect on larger conductance vessels, SNP dilates smaller resistance vessels creating a low-pressure system distal to occluded vessels that diverts critical pressure-dependent flow from ischemic areas [36]. The clinical significance of these observations is uncertain, and the true incidence of clinically significant coronary steal remains unknown.

Inotropes and Vasopressors

Despite the hemodynamic benefits in the short-term management, positive inotropic agents have not demonstrated improved outcomes in patients with HF in both hospital and outpatient settings. Rather, data from some registries and post hoc analyses of RCT suggest an increased morbidity and mortality with inotrope use in HF. In fact, as opposed to hemodynamic benefits, inotropes may cause sinus tachycardia and precipitate myocardial ischemia and arrhythmias [37–39].

In AHFS, the use of intravenous inotropic agents may be helpful to improve CO in patients with severe LV dysfunction with hypotension (PAS < 85 mmHg) and/or low-output syndrome. In such patients, the marginal systemic perfusion may limit institution and adequate response to the other pharmacological treatment like diuretics. On the other hand, at the cost of increasing afterload and decreasing cardiac output, drugs with arterial vasoconstriction action (e.g., norepinephrine or dopamine at high doses) may be a temporizing measure to redistribute CO from extremities to vital organs, and their use is restricted to patients with persistent hypoperfusion despite optimization of cardiac filling pressure and the concomitant use of inotropes. The use of inotropic/vasopressor agents will be addressed in the chapter on the management shock. In the 2102 ESC guidelines, the use of inotropes is in class IIa of recommendation, level of evidence C, and the use of vasopressor in class IIb, level of evidence C [1].

Calcium sensitizers such as levosimendan are a new category of inotropic agents that exert positive inotropic effects by increasing the affinity of troponin C for calcium. Levosimendan exertion also has a vasodilatory effect by blocking adenosine triphosphate-dependent potassium channels in the vascular smooth muscle cells. Such inotropic and vasodilator effects may result in increased CO and reduced filling pressures in AHF patients. Compared to the classic inotropic

agents, calcium sensitizers have two major pharmacodynamic advantages: first, increase in contractile force occurs without increasing calcium loading that is associated with enhanced myocardial oxygen consumption, increased heart rate, and arrhythmias; second, the inotropic effect is not attenuated by concomitant treatment with beta-blockers. At present, the real risk/benefit ratio of levosimendan in AHFS is still debated in light of less favorable outcomes observed in a recent study compared to placebo [40]. Currently, levosimendan is approved in Europe as a second-line agent for severe low-output HF refractory standard therapy, and according to ESC guidelines its use may be considered (recommendation class IIb, level of evidence C) especially in patients with chronic beta-blocker therapy to overcome the beta-blockade effect.

Thromboembolism Prophylaxis

Several mechanisms like increased systemic venous pressure, low cardiac output, and procoagulant blood changes may increase the risk of venous thromboembolism in patients with HF. For this reason, in the absence of contraindication to anticoagulation, thromboembolism prophylaxis (e.g., LMWH) is currently recommended when HF patients are hospitalized (if not already anticoagulated) to reduce the risk of deep vein thrombosis and pulmonary embolism (recommendation class I, level of evidence A) [1].

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Chronic Heart Failure

8

Simona Masiero and Marco Morelli

8.1 Case Report

A 67-year-old man came to the emergency room of our hospital for worsened exertional dyspnea, orthopnea, increased fatigue during ordinary activities, swollen ankles and reduced urine output. He was affected by chronic nonischemic dilated cardiomyopathy. He reported on a progressively worsening of symptoms in the previous 15 days and a weight gain of about 6 kg.

Medical History and Cardiovascular Risk Factors

- In 2007 the patient underwent to the first hospitalization for heart failure with a diagnosis of nonischemic hypokinetic dilated cardiomyopathy (confirmed by a coronary catheterization). Since then he started a therapy with loop diuretic, beta-blocker, ACE inhibitor, and aldosterone antagonist.
- Since 2007 nowdays he underwent to several hospital admissions for acute exacerbation of heart failure.
- In 2013 a CRT-D has been implanted because of low ejection fraction (EF 25 %), LBBB (left bundle branch block), and persistent symptoms in NYHA functional class III despite optimized medical therapy. The ambulatory device follow-up highlighted some episodes of sustained ventricular tachycardia treated with overdrive or shock and episodes of atrial fibrillation. For these reasons he started a therapy with amiodarone and VKA (vitamin K antagonist: warfarin) therapies.
- Chronic renal failure.
- Hypertension.
- Benign prostatic hypertrophy.

Medications

Furosemide 50 mg at 8:00 am, metolazone 5 mg at 6:00 pm on alternate days, spironolactone 25 mg at 8:00 pm, metoprolol 25 mg at 8:00 am and 25 mg at 8:00 pm, warfarin according to INR, amiodarone 200 mg at 1:00 pm, dutasteride 0.5 mg at 8:00 am, and tamsulosin 0.4 mg at 8:00 pm. Allopurinol 150 mg ore at 8:00 pm and pantoprazole 20 mg ore at 7:00 am

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Vital Signs

- Temperature: 36.4 °C
- Heart rate: 70 bpm
- Blood pressure: 110/60 mmHg
- Respiratory rate: 20 breaths per minute (mild tachypnea)
- Oxygen saturation while breathing ambient air: 93 %

Physical Examination

- General: fatigued, short of breath, alert, awake, and oriented; well developed and well nourished
- Head, eyes, ears, nose, and throat: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- Neck: supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- Cardiovascular: regular rate and rhythm, laterally and down displaced apical impulse, S1 and S2 normal, S3 present (gallop rhythm), 3/6 systolic murmur at the cardiac apex and mesocardium, and no hepatojugular reflux
- Lungs: rales at auscultation at the bases bilaterally, mild wheezing, no rhonchi, no alterations in tactile fremitus, and normal percussion
- Abdomen: mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, and no hepatosplenomegaly
- Extremities: no cyanosis or clubbing; mild peripheral edema of the ankles
- Neurologic: cranial nerves II through XII intact and, no focal deficit
- Psychiatric: normal affect, no hallucinations, normal speech, and no dysarthria
- Skin: intact, no rashes, no lesions, and no erythema

Which Are the Possible Precipitants for Heart Failure Decompensation?

- Inadequate dose/adherence to prescribed therapies
- Noncompliance with dietary restrictions (sodium and/or liquids, etc.)
- Acute myocardial ischemia
- Worsened valvular heart disease
- Arrhythmias (bradyarrhythmias or tachyarrhythmias)
- Exacerbation of chronic obstructive pulmonary disease with or without pneumonia
- Infections (pneumonia, influenza, etc.)
- Renal dysfunction
- Endocrine disorders (diabetes mellitus, hypo-/hyperthyroidism)
- Anemia
- Medications (nonsteroidal anti-inflammatory drugs, drugs with negative inotropic effect such as calcium channel blockers)

EKG

A routine EKG at rest was performed (Fig. 8.1).

Report: sinus rhythm, heart rate 72 bpm with atrium-driven biventricular pacing, QRS duration 160 msec.

Despite correct biventricular pacing (axis directed upper right), the QRS complex is wide. Several lead configurations have been tried assessing EKG and echocardiographic findings in order to find the best stimulation without success.

Routine Laboratory Tests

- Complete blood count: normal
- Cholesterol (total, HDL, LDL) and TG: normal
- Hepatic function (GOT, GPT, γ-GT, ALP, bilirubin): slight increase in transaminases

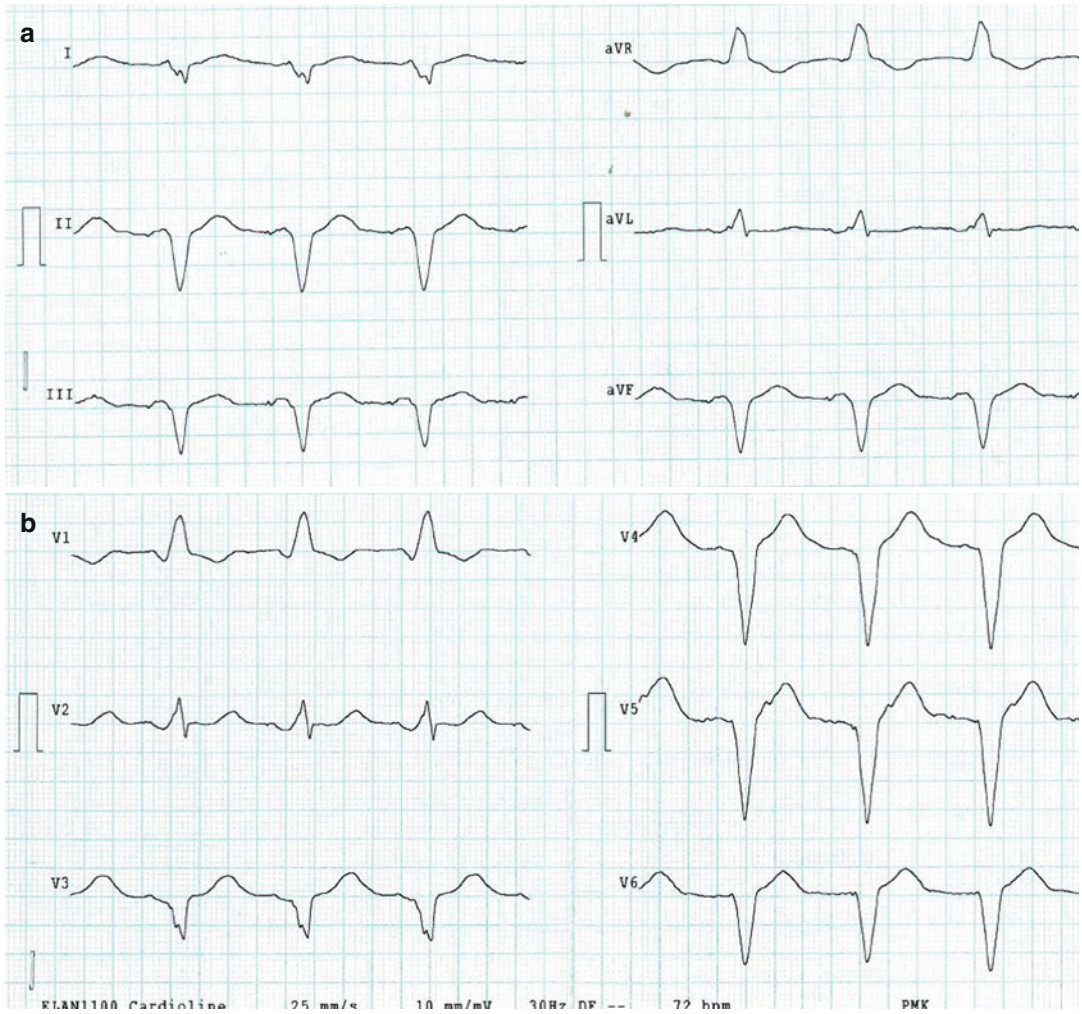

Fig. 8.1 (**a**, **b**) Routine EKG at rest. Despite correct biventricular pacing (axis directed upper right), the QRS complex is wide. Several lead configurations have been tried assessing EKG and echocardiographic findings in order to find the best stimulation without success

- Thyroid function (TSH, FT3, FT4): normal
- Renal function: creatinine 1.7 mg/dl (estimated glomerular filtration rate with the Cockcroft–Gault equation (GFR-CG) = 50 ml/min → moderate chronic kidney disease), BUN 55 mg/dl
- Electrolytes: mild hyponatremia 134 mEq/l and hypokalemia 2.1 mEq/l
- Fasting blood glucose: 194 m/dl (10.78 mmol/L)
- HbA1c: 6.8 % (50.8 mmol/mol)
- TnI-hs and CK-MB: normal
- BNP: 1,100 pg/ml

Chest X-Ray

A chest X-ray was performed too (Fig. 8.2). Cardiac shadow was slightly enlarged for an increase of cardiac transverse diameter. A left-sided pleural effusion was seen obliterating the costophrenic recess associated with a bilateral hilar enlargement with widespread bronchovascular marking and interstitial pulmonary congestion was presence of right ventricular and atrial leads and coronary sinus lead.

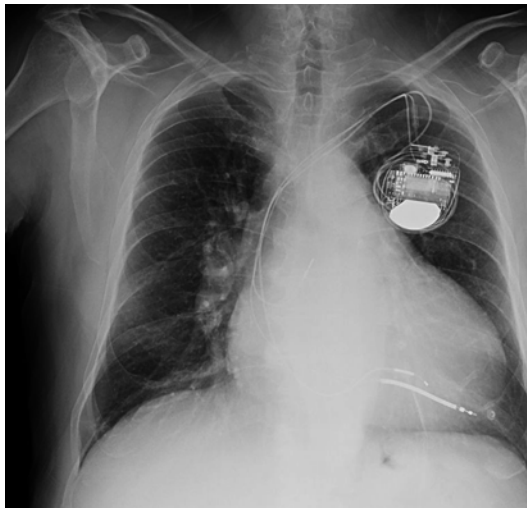

Fig. 8.2 Chest X-ray. The cardiac shadow is slightly enlarged due to an increase of cardiac transverse diameter. A left-sided pleural effusion obliterates the costophrenic recess and is associated with a bilateral hilar enlargement with widespread bronchovascular marking and interstitial pulmonary congestion. The presence of right ventricular and atrial leads and coronary sinus lead

Echocardiography

In order to complete the diagnostic process at admission, an echocardiography was performed.

- The left ventricle was severely dilated (indexed left ventricular end-diastolic volume (iLVEDV) 167 ml/m^2) with severe reduction of systolic function (ejection fraction measured with Simpson's biplane method = 25 %; stroke volume = 29.4 cc; cardiac output = 2.1 l/min; cardiac index = 1 l/m^2) and restrictive diastolic pattern. Moreover, filling pressures were increased (*E*/*E*' = 16).
- Right ventricle was slightly dilated and hypokinetic (basal diameter "RVD1" = 42 mm; tricuspid ring excursion "TAPSE" = 14 mm).
- Severe dilatation of both atria (LA diameter M-mode = 53.5 cm; RA area A4C = 34 cm^2).
- No pericardial effusion.
- The inferior vena cava was dilated without inspiratory collapse.
- The aortic valve was trileaflet and sclerotic.
- The mitral ring was dilated with moderate valvular regurgitation.
- There was evidence of massive tricuspid regurgitation with pulmonary hypertension (estimated PAPs of about 60 mmHg).

Clinical Course and Medical Therapy

- Furosemide: 40 mg t.i.d. (three times a day) intravenous boluses
- Slow-release potassium chloride: 1,200 mg b.i.d. (bis in die) per os
- Canrenoate potassium: 100 mg o.d. (once daily) intravenous boluses
- Saline 0.9 % continuous infusion 40 cc/h + KCl 40 mEq
- Dobutamine (250 mg/50 ml): 2 μg/kg/min continuous infusion
- Dopamine (200 mg/50 ml): 2 μg/kg/min continuous infusion
- Metoprolol: 25 mg b.i.d. per os
- Ivabradine: 5 mg b.i.d. per os
- Amiodarone: 200 mg o.d. per os
- Warfarin: according to INR
- Tamsulosin: 0.4 mg o.d. per os
- Dutasteride: 0.5 mg o.d. per os
- Pantoprazole: 20 mg o.d. per os

C-PAP therapy was administered (PEEP 7.5 mmHg, FiO2 0.5) with intermittent cycles of about 2 h.

After 48–72 h there was a significant loss of fluids supported by good diuresis. The patient reported improvement in dyspnea, and we observed a consistent reduction of ankle edema. The inotropic support was gradually discontinued. The laboratory tests showed a progressive increase of potassium values and reduced levels of BNP. The chest X-ray showed a reduced degree of pulmonary congestion, and the echocardiogram showed stable EF (0.25) associated with a small increase in cardiac index (1.3 ml/min/m^2) and a slight reduction of the PAPs (50 mmHg).

Once the patient reached an acceptable grade of compensation, he was proposed for the implantation of a left ventricular assist device as

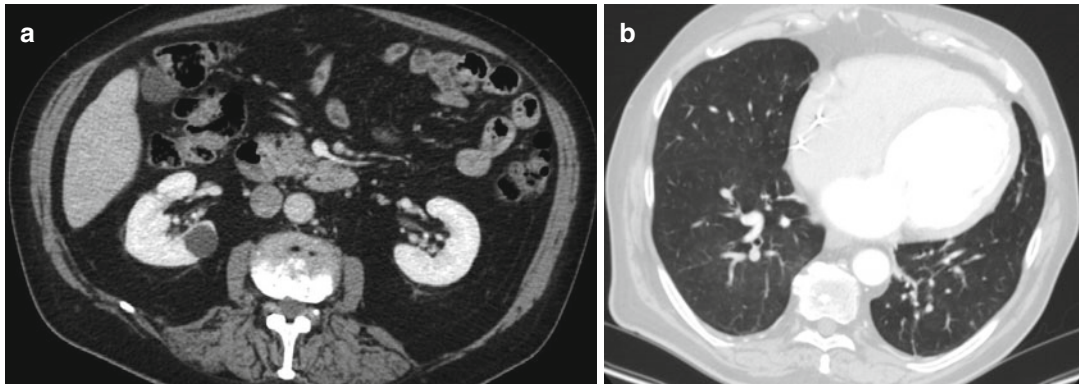

Fig. 8.3 (**a**, **b**) Chest–abdomen CT with contrast, with completely normal appearance

destination therapy. For this purpose the patient underwent to a new coronary angiography and chest–abdomen CT with contrast which were completely normal (Fig. 8.3a, b).

In order to perform a complete evaluation before the left ventricular assist device implant, we performed a right heart catheterization which showed:

- Normal pressures in the right atrium, right ventricle, pulmonary artery, and wedge
- Slight increase in total pulmonary resistance
- Arteriolar resistance at the upper limit of normal

By the investigations carried out during the hospitalization, the patient has been judged suitable for LVAD as a destination therapy and added to the waiting list at a referral center for the implant.

Until the LVAD implant, on top therapy to chronic heart failure including loop diuretic, aldosterone antagonist, ACE inhibitor, and beta-blocker, the patient underwent cyclic intravenous inotropic therapy.

8.2 Heart Failure

Definition

Heart failure (HF) can be clinically defined as a syndrome in which patients have typical symptoms (e.g., breathlessness, ankle swelling) and signs (e.g., elevated jugular venous pressure, pulmonary crackles) resulting from an abnormality of cardiac structure or function [1].

Chronic heart failure (CHF) can be caused by several types of cardiac dysfunction and is most commonly due to left ventricular dysfunction. An isolated right ventricular (RV) dysfunction is very rare, and generally RV involvement is secondary to left ventricular (LV) dysfunction.

Demonstration of an underlying cardiac cause is essential to diagnose HF as the precise pathology determines the specific treatment used. More recently, CHF has been classified into two categories: HF due to LV dysfunction even called HF with reduced ejection fraction (HF-REF or systolic heart failure) and HF where only a diastolic dysfunction is detectable called HF with preserved ejection fraction (HF-PEF or diastolic heart failure). 1 HF-REF is the best understood type of HF in terms of pathophysiology and treatment and is the focus of this chapter.

Furthermore, HF can present either as a chronic condition or acutely, occurring de novo, or as a decompensation of CHF. The purpose of this chapter is to cover CHF, while acute heart failure is discussed in another section of this book.

Epidemiology

CHF prevalence is 1–2 % of the population, and the prevalence increases to approximately 15 %

in the elderly [2]. At least half of patients with HF have a low EF, and approximately 50 % of patients with significant LV systolic dysfunction have no symptoms or signs of heart failure. HF occurs more frequently in male rather than female sex.

Etiology

The causes of CHF are listed in Table 8.1. There is a geographical variation regarding the etiology of CHF. In Western countries two-thirds are secondary to ischemic disease, and other important contributors are hypertension, valve disease, and alcohol. Rheumatic disease still remains the most common cause of CHF in the developing countries, while Chagas disease is frequent in South America.

Pathophysiology

Left ventricular dysfunction is associated with hemodynamic, autonomic, neurohumoral, and immunological changes.

The term "systolic dysfunction" refers to a decrease in myocardial contractility and consequently a decrease in cardiac output. Signs and symptoms of HF are due in part to compensatory mechanisms utilized by the body in an attempt to adjust for a primary deficit in cardiac output. Many of the processes involved in sustaining HF are maladaptive which means that they were originally designed to maintain blood pressure and vital organ perfusion.

Table 8.1 Causes of chronic heart failure

Coronary artery disease
Hypertension
Valve disease
Congenital heart disease
Infective: viral myocarditis, Chagas, HIV, Lyme disease
Alcohol
Toxins: anthracyclines or trastuzumab
Deficiencies: beriberi, thiamine
Hemochromatosis
Idiopathic
Familiar
Peripartum
Tachycardia induced
Infiltrative states: amyloid, sarcoid, endomyocardial fibrosis, hypereosinophilic syndrome
High output: AV fistulae, Paget's disease

Changes in Hemodynamics

Decrease of cardiac output leads to an increase of:

- Left ventricular end-diastolic pressure
- Pulmonary capillary wedge pressure

Based on the Frank–Starling law, the initial increase of left ventricular end-diastolic pressure is initially compensated by an increase of contractility, but as the increase persists, the myocardium fails and cardiac output drops.

Neurohumoral Changes

Neurohumoral adaptations, such as activation of the renin–angiotensin–aldosterone and sympathetic nervous systems by the low-output state, can contribute to maintenance of perfusion of vital organs in two ways:

- Maintenance of systemic pressure by vasoconstriction, resulting in redistribution of blood flow to vital organs
- Restoration of cardiac output by increasing myocardial contractility and heart rate and by expansion of the extracellular fluid volume

The principal neurohumoral systems involved in the response to HF are the sympathetic nervous system, the renin–angiotensin–aldosterone system (RAAS), and antidiuretic hormone [3, 4, 5]. One of the first responses to a decrease in cardiac output is activation of the sympathetic nervous system, resulting in both increased release and decreased uptake of norepinephrine at adrenergic nerve endings. The effects of high circulating concentrations of epinephrine and norepinephrine include:

- Increase in heart rate, blood pressure, and myocardial oxygen demand
- A toxic damage on the myocardium leading to cell apoptosis
- A downregulation of beta-1 receptors in the heart

The decrease of cardiac output leads to a reduction of renal afferent arteriolar blood flow causing secretion of renin and, subsequently, production of angiotensinogen and angiotensin I. The angiotensin I is then converted by the ACE present in the lung to angiotensin II. There is also evidence that angiotensin II can be synthesized locally at a variety of tissue sites including the kidney, blood vessels, adrenal gland, and brain [6].

Angiotensin II increases aldosterone release, inducing systemic and renal vasoconstriction. Furthermore, angiotensin II can act directly on myocytes and in the myocardium to promote pathologic remodeling as myocyte hypertrophy, re-expression of fetal protein isoforms, myocyte apoptosis, and alterations in the interstitial matrix. Aldosterone-mediated effects are sodium and water retention and hypokalemia resulting in pulmonary and peripheral edema and increased afterload. Activation of the carotid sinus and aortic arch baroreceptors by the low cardiac output in heart failure leads to enhanced release of antidiuretic hormone and stimulation of thirst. Elevated levels of ADH may contribute to the increase in systemic vascular resistance in HF via stimulation of the V1A receptor, which is found on vascular smooth muscle cells, and also promote water retention via the V2 receptor by enhancing water reabsorption in the collecting tubules. The combination of decreased water excretion and increased water intake via thirst often leads to a fall in the plasma sodium concentration. The degree of hyponatremia is an important predictor of survival in these patients.

The Natriuretic Peptide System

The increased LV and left atrium wall stretch due to raised left ventricular end-diastolic pressure leads to secretion of the natriuretic peptide hormones. The types of natriuretic peptide hormones which circulate in high concentration in HF are:

Brain natriuretic peptides

- BNP, the active peptide
- NT-proBNP, the inactive N-terminal fragment

Atrial natriuretic peptides (ANP and NT-ANP)
These peptides cause:

- Natriuresis
- Vasodilatation
- Offset in the activation of RAAS

Plasma ANP levels rise early in the course of the disease and have been used as a marker for the diagnosis of asymptomatic left ventricular dysfunction.

All these processes are responsible for sodium and water retention and a progressive depression of myocardial function. The last step of this fall is an adverse remodeling of the left ventricle involving myocyte hypertrophy, death, and fibrosis.

Diagnosis

Clinical Symptoms and Signs

The three most common symptoms and signs of HF are:

- Breathlessness
- Fatigue
- Peripheral edema

Breathlessness is induced by exercise, and only in case of advanced heart failure, it appears at rest. Symptoms that are more specific (i.e., orthopnea and paroxysmal nocturnal dyspnea) are less common, especially in patients with milder form of HF and who are, therefore, insensitive [7, 8].

Many of the symptoms of HF are nonspecific and do not, therefore, help discriminate between HF and other problems.

Symptoms are used to assign NYHA class to patients as listed in Table 8.2.

Table 8.2 Since many of the symptoms of HF are non-specific and do not, therefore, help discriminate between heart failure and other problems, patients are usually assigned an NYHA class

New York Heart Association functional classification based on the severity of symptoms and physical activity	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations
Class VI	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

Physical signs can be related to the presence of either fluid retention or poor cardiac output. They usually include:

- Elevated jugular venous pressure
- Orthopnea
- Hepatojugular reflux
- Third heart sound (gallop rhythm)
- Laterally displaced apical impulse
- Cardiac murmur
- Peripheral edema (ankle, sacral, scrotal)
- Wheezing, pulmonary crepitations
- Weight gain (>2 kg/week)
- Reduced air entry and dullness to percussion at lung bases (pleural effusion)
- Tachycardia
- Bloated feeling, irregular pulse
- Tachypnea (>16 breaths/min)
- Hepatomegaly
- Ascites
- Palpitations
- Tissue wasting (cachexia)

To diagnose HF both of the following criteria should be present:

- Symptoms and/or signs of heart failure
- Cardiac dysfunction at rest

The presence of cardiac dysfunction must be proved to make the diagnosis of heart failure.

As stated in the current guidelines 1, investigations that should be considered in *all patients* are:

- A 12-lead ECG, to determine heart rhythm, heart rate, QRS morphology, and QRS duration and to detect other relevant abnormalities. HF is rare in the presence of a normal ECG. The predictive value of the ECG is >90 %.
- Measurement of natriuretic peptide (BNP, NT-proBNP) to exclude alternative causes of dyspnea. If the value is within a normal range, HF is very unlikely. Natriuretic peptide measurement has an extremely high negative predictive value (>98 %).
- A chest radiograph (X-ray), to detect/exclude certain types of lung disease (e.g., cancer, asthma/COPD). It may allow also to identify pulmonary congestion/edema. A normal X-ray does not exclude a diagnosis of heart failure.
- Transthoracic echocardiography is the key exam in the diagnostic process of HF. It allows to evaluate cardiac structure and function, to measure LV ejection fraction, and to understand the cause of cardiac dysfunction.
- Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/total iron blood capacity) and thyroid.
- A complete blood count to detect anemia, which may be a cause or effect of CHF.

Furthermore, only in case of clinical suspicions, the following investigations can be considered 1:

- Coronary angiography in patients with angina pectoris to evaluate the coronary anatomy
- Myocardial perfusion/ischemia imaging (echocardiography, CMR, SPECT, or PET) in patients thought to have CAD and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischemia or viable myocardium
- Exercise testing to detect reversible myocardial ischemia or as part of the evaluation of patients for heart transplantation and mechanical circulatory support, to aid in the prescription of exercise training, and to obtain prognostic information
- CMR imaging: recommended to evaluate cardiac structure and function, to measure LVEF, and to characterize cardiac tissue, especially in subjects with inadequate echocardiographic images or where the echocardiographic findings are inconclusive
- Left and right heart catheterization as part of evaluation process for heart transplantation or mechanical circulatory support, to estimate right and left heart function and pulmonary arterial resistance

Management

The goals of HF therapy are clinical relief of symptoms and a reduction in the risk of morbidity (including the rate of hospitalization) and mortality.

Management of HF begins with an accurate assessment of the underlying etiology, contributing factors, and severity of the syndrome. This is followed by a therapeutic regimen aimed at the following factors as well as addressing underlying and concurrent cardiovascular disease.

Treatment should address systemic contributing factors (e.g., thyroid dysfunction, infection, uncontrolled diabetes), as well as comorbidities such as chronic obstructive pulmonary disease and sleep apnea.

Recommendations for lifestyle modification are:

- Cessation of smoking
- Restriction of alcohol consumption
- Salt restriction (<2 g/day in patients with symptomatic HF)
- Fluid restriction (1.5–2 L/day) in patients with refractory HF, particularly those with hyponatremia
- Weight reduction in obese subjects
- Daily weight monitoring recommended to detect fluid accumulation
- Appropriate preventative care including pneumococcal vaccination and annual influenza vaccination

Review of Drugs

The drugs that now form the cornerstones in the management of HF are:

- Diuretics
- Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor antagonists (ARBs)
- Beta-adrenoceptor antagonists
- Mineralocorticoid receptor antagonist (MRA)
- Nitrate plus hydralazine
- Digoxin

Loop Diuretics

Loop diuretics are generally introduced first for fluid control in patients in overt HF. The goal is relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. In general loop diuretic therapy is based on furosemide, bumetanide, or torasemide. The aim is to use the

minimum dose necessary to render the patient euvolemic. The most common side effects are renal dysfunction, hypokalemia, hyponatremia, hyperglycemia, and gout.

The usual starting dose in outpatients with HF is 20–40 mg of furosemide or its equivalent. Subsequent dosing is determined by the diuretic response. In patients who are volume overloaded, a reasonable goal is weight reduction of 1.0 kg/day. If a patient does not respond, the diuretic dose should initially be increased to find the single effective dose, rather than giving the same dose twice a day.

Intravenous diuretics (either as a bolus or a continuous infusion) are more potent than their equivalent oral doses and may be required for unstable or severe disease.

Some patients can develop a "loop diuretic" resistance if they are treated for a long time. In this category of patients, it is useful to add a thiazide diuretic (i.e., metolazone 2.5–5 mg/day) instead of increasing the dose of loop diuretics (i.e., >80 mg b.i.d. furosemide) to block differing sites in the nephron and overcome the resistance.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists

ACE inhibitors or, if not tolerated, ARBs are typically initiated during or after the optimization of diuretic therapy. ACEi and ARBs were first used because of their vasodilatory effect in the treatment of HF. It was subsequently understood that their beneficial effects arise above all from the antagonism of the rennin–angiotensin system.

These drugs are now first-line agents for all patients with HF, and unless there are contraindications, their use should be considered mandatory in all patients. It has been proved that they reduce both mortality and morbidity in large randomized clinical trials with a relative risk reduction of 20–25 %.

ACEi and ARB must be used with caution in patients with significant renal dysfunction; moreover, ACEi can induce cough (5–10 %) and angioedema. ARB can be used in case of ACEi intolerance.

These drugs are usually started at low doses and then titrated. ACEi and ARBs with proven clinical efficacy in HF based on randomized clinical trials with their suggested dosing are listed in Table 8.3.

Table 8.3 Suggested dosage for ACEi and ARBs with proved clinical efficacy for HF based on randomized clinical trials

ACE inhibitors	**Starting dose (mg)**	**Target dose (mg)**
Captopril	6.25 t.i.d.	50 t.i.d
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandolapril	0.5 o.d.	4 o.d.
ARB	**Starting dose (mg)**	**Target dose (mg)**
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan	50 o.d.	150 o.d.

Beta-Adrenoceptor Antagonists

Beta-adrenoceptor antagonists are also mandatory in patients with HF. Beta-blockers are initiated after the patient is stable on ACE inhibitors, again beginning at low doses with titration to trial goals as tolerated. The beta-blocker trials in HF were carried out in patients receiving therapy with an ACE inhibitor; thus, the improvement in survival is additive to that induced by ACE inhibitors [9, 10]. They unequivocally reduce both mortality and morbidity in clinical trials with a 35 % relative risk reduction on average. They can be used in patients with COPD but are contraindicated in patients with significant reversible airway obstruction. Furthermore, they should be used with caution in patients with peripheral vascular disease even if there is not an absolute contraindication.

Drugs with proven efficacy in clinical trials and the approved doses are listed in Table 8.4.

Table 8.4 Beta-blockers with proven efficacy in clinical trials and approved dosages

Beta-blocker	Starting dose (mg)	Target dose (mg)
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25–50 b.i.d.
Nebivolol	1.25 o.d.	10 o.d.
Metoprolol succinate (CR/XL)	12.5/25 o.d.	200 o.d.

Mineralocorticoid Receptor Antagonist (MRA)

Spironolactone and eplerenone, which compete with aldosterone for the mineralocorticoid receptor, prolong survival in selected patients with HF as demonstrated in randomized controlled trials [11].

MRAs are recommended to treat HF in patients who have NYHA functional class II and a left ventricular ejection fraction (LVEF) ≤30 % or NYHA functional classes III to IV and an LVEF <35 %, who can be carefully monitored for serum potassium and renal function. MRAs are also recommended for patients post ST elevation myocardial infarction who are already receiving therapeutic doses of ACE inhibitor, have an LVEF ≤40 %, and have either symptomatic HF or diabetes mellitus and who can be carefully monitored for serum potassium and renal function. The serum potassium should be <5.0 mEq/L and estimated glomerular filtration rate should be ≥30 mL/min per 1.73 m. The endocrine side effects of spironolactone result from nonselective binding to androgen and progesterone receptors; eplerenone has greater specificity for the mineralocorticoid receptor and therefore has a lower incidence of endocrine side effects (1 versus 10 % in clinical trials). Although eplerenone is associated with fewer endocrine side effects than spironolactone (i.e., painful gynecomastia), this advantage must be weighed against the marked difference in cost between the two drugs. It may be reasonable to begin with spironolactone (25–50 mg/day) and switch to eplerenone (25 and after 4 weeks 50 mg/day) if endocrine side effects occur. It is essential that serum potassium and creatinine be checked 1–2 weeks after starting spironolactone or eplerenone and periodically thereafter. Patients with poor renal function are particularly at risk for hyperkalemia. For these reasons they should be used with caution in elderly.

Table 8.5 Approved dosages for mineralocorticoid receptor antagonists

MRA	Starting dose	Target dose
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	25–50 o.d.

The approved doses are listed in Table 8.5.

Other Drug Options

Ivabradine

It should be considered for patients in NYHA II–IV heart failure with a heart rate ≥70/min in sinus rhythm and LVEF ≤35 % despite treatment with evidence-based doses of:

- ACEi (or ARB)
- Beta-blocker
- MRA

It may be also considered for patients in NYHA II–IV heart failure with a heart rate ≥70/min in sinus rhythm and LVEF ≤35 % who are unable to tolerate beta-blockers (true asthmatics).

Hydralazine Plus Nitrates

In African-American population the addition of hydralazine plus oral nitrate therapy is recommended for patients with persistent NYHA classes III–IV and LVEF <40 % despite optimal therapy including a beta-blocker, ACEi (or ARB), MRA (if indicated), and diuretics. Although the evidence of benefit is stronger in blacks, the addition of hydralazine plus oral nitrate may be considered in non-blacks who have persistent NYHA class II or IV despite optimal conventional therapy.

Digoxin

Digoxin is given to patients with HF and systolic dysfunction to control symptoms (such as fatigue, dyspnea, and exercise intolerance) and to patients with atrial fibrillation to control the ventricular rate. As demonstrated in the DIG trial, 12 digoxin therapy was associated with a significant reduction in hospitalization for HF but no benefit in terms of overall mortality. Digoxin is indicated in patients with left ventricular systolic dysfunction (LVEF <40 %) who continue to have NYHA functional class II, III, and IV symptoms despite appropriate therapy including an ACE inhibitor, a beta-blocker, an aldosterone antagonist if indicated, and an additional diuretic if necessary for fluid control. The usual daily dose of digoxin is 0.125 mg or less, based upon renal function. Based upon the data from the DIG trial, the recommended serum digoxin concentration is maintained between 0.5 and 0.8 ng/mL.

It is a useful drug in patients with atrial fibrillation to reach an adequate rate control. It should be avoided in patients with ventricular arrhythmias.

Device Therapy

Device therapy in heart failure addresses two potential consequences of left ventricular dysfunction:

- Malignant arrhythmias that can lead to sudden death
- Ventricular dyssynchrony

Prevention of sudden death is an important goal in HF because heart failure is a pro-arrhythmogenic condition arising from combination of structural heart disease and electrolyte imbalance. Ventricular arrhythmias, from premature ventricular beats to ventricular fibrillation, occur in 80 % of patients with heart failure and cardiomyopathy. Up to 50 % of heart failure deaths are sudden cardiac death, usually arrhythmic.

Implantable Cardiac Defibrillators

Implantable cardiac defibrillators (ICDs) have revolutionized the management of heart failure. An ICD is an advanced form of pacemaker that can detect and treat arrhythmias. Several types of ICDs can be implanted: a single bipolar lead placed in the right ventricular apex or a dual-chamber device with a further atrial lead to improve detection of atrial from ventricular arrhythmias. ICDs use the following criteria to distinguish ventricular tachycardia or fibrillation:

- Rate detection zone.
- Rate stability based on the principle that ventricular tachycardia is a stable rhythm without a significant inter-beat variation.
- Sudden onset: ventricular arrhythmias usually have a sudden onset.

According to the current guidelines 1, recommendations for the use of ICDs in patients with HF are resumed in Table 8.6.

Resynchronization Therapy

Resynchronization therapy aims to address the problem of ventricular dyssynchrony in HF. Dyssynchrony is a complex phenomenon which occurs at three different levels:

- Electrical dyssynchrony considered as an intra- or interventricular conduction delay usually manifested as a left ventricular bundle branch block.
- Structural dyssynchrony results from disruption of the myocardial collagen matrix impairing and electrical conduction and mechanical efficiency.
- Mechanical dyssynchrony manifests as regional wall motion abnormalities leading to increased workload and stress, paradoxical septal wall motion, presystolic mitral regurgitation, and reduced diastolic filling times.

Cardiac resynchronization (CRT) typically uses leads in the right atrium, right ventricular

Table 8.6 Current guideline recommendations for the use of ICDs in patients with HF [1]

Recommendations	Recommendation class	Recommendation level
Secondary prevention An ICD is recommended in a patient with a ventricular arrhythmia causing hemodynamic instability, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death	IA	A
Primary prevention An ICD is recommended in a patient with symptomatic HF (NYHA classes II–III) and an EF ≤35 % despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death	IA	A
(i) Ischemic etiology and >40 days after acute myocardial infarction	IA	
(ii) Nonischemic etiology	IB	B

apex, and coronary sinus. CRT functioning will be discussed more in detail in a separate section of this book.

Based on the current guidelines 1, the current indications for CRT implant are listed in Table 8.7.

8.3 Management of Refractory HF

Although the majority of patients with heart failure due to systolic dysfunction respond to optimal medical therapy, some patients do not improve and usually experience rapid recurrence of symptoms. These patients have symptoms at rest and often require repeated prolonged hospitalizations. Specialized strategies are generally considered for these patients, including:

- Continuous or cyclic intravenous positive inotropic therapy with dobutamine or levosimendan
- Mechanical circulatory support
- Cardiac transplantation

Mechanical Circulatory Support

Mechanical circulatory support is a collection of technologies that can be used to offer short-or long-term ventricular assistance for patients with heart failure. They can be classified as follows:

Extracorporeal ventricular support (useful for a short-term time support)

- Intra-aortic balloon pump
- Pulsatile ventricular assist device (VAD)
- Non-pulsatile VAD

Extracorporeal membrane oxygenation (ECMO) → useful for a short-term time support

Intracorporeal ventricular assist devices → useful for a long-term time support

- Pulsatile VAD
- Non-pulsatile VAD
- Total artificial heart

The intentions to use these devices are resumed in Table 8.8.

Short-term devices are used in general in patients with acute heart failure or cardiogenic shock as BTD, BTR, or BTT, while long-term devices are generally reserved as BTT, or in some countries, as Italy, they are approved as DT. Continuous-flow VADs are by far the most commonly used long-term devices.

Cardiac Transplantation

Cardiac transplantation is the final intervention for patients who remain symptomatic despite optimal medical and device therapy. The patient selection

Table 8.7 Current indications for CRT implant

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy		
LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of 120 ms, LBBB QRS morphology, and an EF 35 %, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death	I	A
Non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of 150 ms, irrespective of QRS morphology, and an EF ≤35 %, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death	II	A
Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy		
LBBB QRS morphology CRT, preferably CRT-D, is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30 %, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death	I	A
Non-LBBB QRS morphology CRT, preferably CRT-D, should be considered in patients in sinus rhythm with a QRS duration of 150 ms, irrespective of QRS morphology, and an EF 30 %, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death	II	A

Table 8.8 Terms describing various uses of mechanical circulatory support (MCS)

Bridge to decision (BTD)	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated
Bridge to candidacy (BTC)	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation
Bridge to transplantation (BTT)	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available
Bridge to recovery (BTR)	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS
Destination therapy (DT)	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation

for transplantation is very restrictive; indeed patients have to be able to face the major cardiac surgery and the massive immunosuppressive regime. Cardiac transplantation "is not a cure" but is "the last chance" even because 1 year mortality is approximately 17 % with a median survival of 10.9 years.

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Cardiogenic Shock

9

Maria Vittoria Matassini, Luca Piangerelli, and Matilda Shkoza

9.1 Case Report

A 60-year-old man with a known dilated valvular cardiomyopathy was admitted to the emergency department (ED) for worsening dyspnea and fatigue. The patient and his wife referred the onset of dyspnea a week before, firstly exercise related and then at rest. The patient also referred weight gain (4 kg in 5 days) despite usual food consumption and water restriction and decrease in urine output within the last day.

His vital signs were 80/45 mmHg and 125 beats per minute and his oxygen saturation was 89 %.

Few minutes after his arrival in the ED, while waiting for medical visit, patient's condition rapidly deteriorated with further desaturation and hypotension. He required prompt intubation and mechanical ventilation. Inotropic support with dopamine was started, and the patient was immediately transferred to our ICU for further evaluation and treatment.

Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: dyslipidemia and type II diabetes mellitus.
- Family history: no family history of structural heart disease.
- 1999: diagnosis of severe mitral regurgitation due to rheumatic valvular disease. Concomitant diagnosis of left ventricular dilatation and moderate left ventricular systolic dysfunction (LVEF 40 %).
- 2000: hospital admission for acute pulmonary edema during atrial fibrillation episode with rapid ventricular response. After the acute phase, the patient underwent an echocardiographic evaluation that confirmed severe mitral regurgitation together with the increase in systolic pulmonary artery pressure (PAP 55 mmHg), severe left atrial enlargement, and moderate to severe left ventricular systolic dysfunction (LVEF 38 %). A coronary angiography did not reveal any coronary disease.

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The patient was evaluated and accepted for mitral valve surgery.
- 2001: mitral valve replacement with mechanical prosthesis. Surgical atrial fibrillation ablation was ineffective.
- 2006: hospital admission for hypotensive acute heart failure with renal and hepatic impairment treated with IV diuretics and inotropes. The echocardiogram revealed correct prosthesis function but further worsening of left ventricular function (FEVS 30 %). The patient referred an NYHA class III. The patient was discharged on optimal medical therapy with indication to a follow-up visit after 3 months.
- 2007: cardiac resynchronization therapy with defibrillator (CRT-D) implantation.
- 2010–2013: frequent hospital admissions for acute heart failure. An evaluation for heart transplantation was proposed, but the patient refused.

Allergies

None.

Medications

Furosemide 125 mg in the morning + 75 mg in the evening, ramipril 2.5 mg o.d., bisoprolol 3.75 mg o.d., spironolactone 100 mg o.d., atorvastatin 20 mg o.d., and metformin 500 mg b.i.d.

Vital Signs

- Temperature: 36 °C
- Heart rate: 125 bpm
- Arterial blood pressure: 85/55 mmHg
- Respiratory rate: 16 breaths/min
- Oxygen saturation: 98 %

Physical Examination

- *General:* intubated, sedated; cold sweats and pallor
- *Neck:* jugular venous distention, no lymphadenopathy, no carotid bruit
- *Cardiovascular:* irregular and tachycardic rhythm, apical soft proto-mesosystolic murmur (2/6 at Levine scale)
- *Lungs:* decreased tactile fremitus and dullness to percussion at right pulmonary basis, bilateral medio-basal rales
- *Abdomen:* moderate hepatomegaly, no splenomegaly, no ascites, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness
- *Extremities:* cold, mild cyanosis, peripheral edema

Laboratory Tests

White blood cells 8800/mmc, hemoglobin 10.5 g/l, hematocrit 32 %, platelets 138,000/mmc, creatinine 2.4 mg/dl, blood urea nitrogen 112 mg/dl, AST 288 U/L, ALT 204 U/L, γGT 110 U/L, total bilirubin 2.1 mg/dl with direct bilirubin of 1.6 mg/dl, INR 4.2, uric acid 9.4 mg/ml, potassium 4.8 mEq/l, sodium 134 mEq/l, magnesium 1.2 mg/dl, blood glucose 254 mg/dl

Arterial Blood Gas Analysis

Before orotracheal intubation and mechanical ventilation: pH 7.28, PO_2 55 mmHg, PCO_2 52, lactate 6.7 mmol/L with decreased serum bicarbonate (HCO_3 18 mmol/L)

Instrumental Examination

The ECG (Fig. 9.1) revealed atrial fibrillation with rapid ventricular response (130 bpm).

The echocardiographic examination showed severely dilated left ventricle (LV end-diastolic volume of 280 ml, LV end-diastolic diameter 78 mm), impaired LV function with an estimated ejection fraction (EF) of 20 % because of global hypokinesia, correct function of the mitral prosthesis with a mild intraprosthetic regurgitation, right ventricle dilatation and dysfunction (TAPSE 12 mm, FAC area 25 %), and severe tricuspid regurgitation with

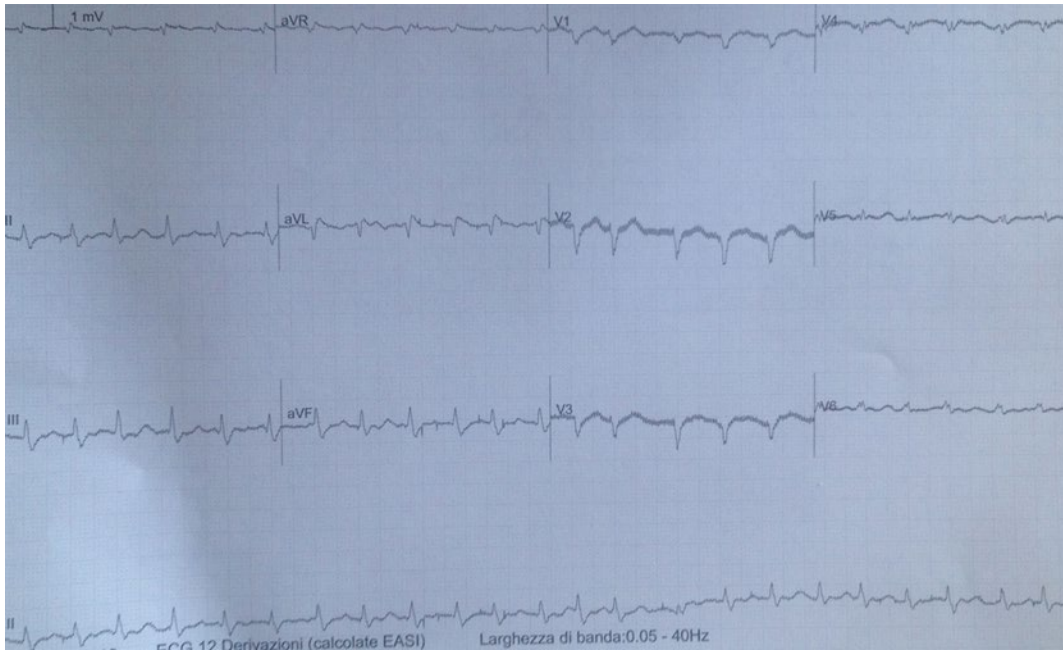

Fig. 9.1 ECG showing atrial fibrillation with rapid ventricular response

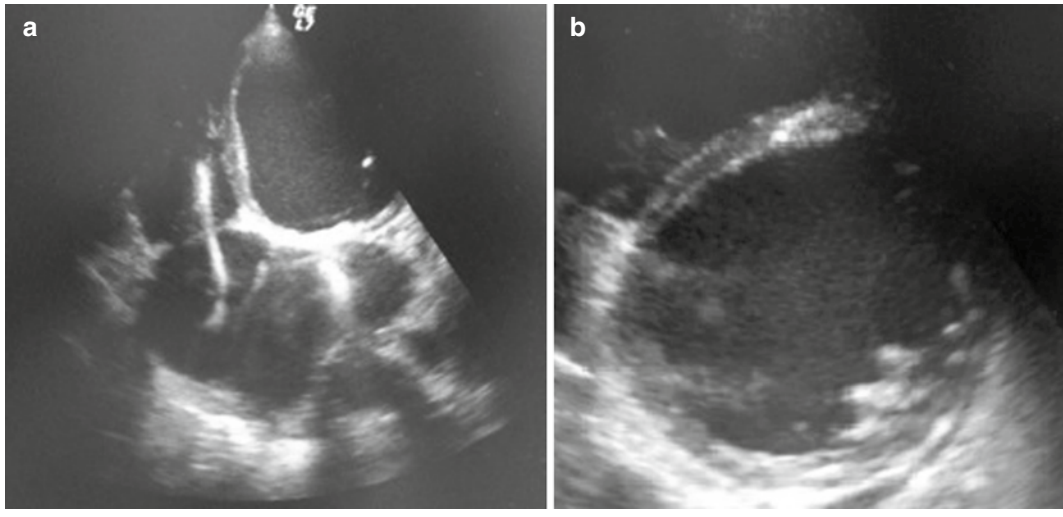

Fig. 9.2 Echocardiographic images: apical four-chamber view (**a**) and parasternal short axis at papillary level (**b**) showing chamber dilation, mitral valve prosthesis, and presence of lead in right chambers

systolic pulmonary artery pressure of 50 mmHg (Fig. 9.2). The cardiac output and the cardiac index as estimated by echocardiography were, respectively, 2.8 l/min and 1.3 l/min/m^2.

Urgent chest radiography was performed showing pulmonary vascular congestion with alveolar infiltrates and right moderate pleural effusion.

Clinical Course and Therapeutic Management

The patient underwent insertion of a radial arterial catheter for invasive measurement of blood pressure and arterial blood gas testing, insertion of central venous catheter at right subclavian site

for drug infusions, measurement of central venous pressure and blood sampling, and determination of central venous oxygen saturation.

Clinical, instrumental, and laboratory data (hypotension <90 mmHg, tissue hypoperfusion with increase in arterial lactate and renal and hepatic impairment, cardiac index of 1.3 l/min/m^2) allow us to make the diagnosis of cardiogenic shock in a patient with advanced heart failure.

Inotropic support with dopamine (5 mcg/kg/min) was continued, and also adrenaline was started at a dose of 0.05 up to 0.08 mcg/kg/min because of persistent hypotension, increase in arterial lactate (7.8 mmol/l), and oliguria.

Continuous infusion of loop diuretics (furosemide, 500 mg/24 h) was started with progressive improvement in diuresis. Intravenous digoxin was administered in the acute phase for AF rate control, and unfractionated heparin was introduced. Insulin infusion was started to correct hyperglycemia and on the following days switched to bolus insulin injection.

The patient's clinical status gradually improved, with normalization of arterial lactate on day 2 and also the central venous oxygen saturation (from baseline 56–63 % on day 2). On day 5, pulmonary congestion significantly improved and the patient was extubated. The patient was gradually weaned from inotropes until interruption on day 7. Therefore, an echocardiography was repeated confirming severe left ventricular dysfunction (FEVS 25 %) and mild to moderate right ventricle dysfunction (TAPSE 15 mm, FAC area 32 %), reducing pulmonary artery pressure (35 mmHg).

A beta-blocker and an angiotensin-converting enzyme inhibitor were started on day 8 and uptitrated (ramipril 2.5 mg o.d., bisoprolol 3.75 mg o.d.). Loop diuretics were switched from IV to oral administration (furosemide 125 mg b.i.d., spironolactone 100 mg o.d.). Oral digoxin was continued to achieve a better rate control. Oral anticoagulation was reintroduced on day 9. Laboratory tests showed improvement of kidney and hepatic function (creatinine 1.4 mg/dl, total bilirubin 1.3 mg/dl, normalization of AST, ALT, and γGT).

Cardiac rehabilitation was started on day 12 with progressive improvement of functional capacity.

Considering the end-stage HF despite optimal pharmacological and device treatment and the recent episode of cardiogenic shock, the possibility to an evaluation for advanced treatment options, as heart transplant or left ventricular assistive device implantation, was offered to the patient who agreed, and a visit in a national reference hospital was therefore planned. The patient was discharged on day 25.

9.2 Cardiogenic Shock

Definition and Epidemiology

Cardiogenic shock (CS) is a complex clinical condition characterized by inadequate end-organ perfusion due to the inability of the heart to provide adequate flow. The tissue hypoperfusion, if prolonged, could result in end-organ damage and finally in multiorgan failure. Cardiogenic shock is a fatal condition if not early diagnosed and treated. The in-hospital mortality approaches 50 % and is related to the severity of hemodynamic impairment, the promptness of diagnosis, and the type of management (medical therapy, mechanical support) [1]. Mortality decreased significantly during the last years because of the wide use of revascularization.

The diagnosis of CS results from multiparametric evaluation and could be made in the presence of:

- Hypotension defined as systolic blood pressure ≤90 mmHg or when vasopressors are required to maintain SBP ≥90 mmHg or mean arterial pressure is 30 mmHg lower than baseline
- Evidence of organ hypoperfusion: resting tachycardia, altered mental status, oliguria, poor capillary refill, cold/diaphoretic extremities
- A reduction in cardiac index (<1.8 L/min/mq without support or <2.2 l/min/mq with support) with evidence of increase in pulmonary capillary wedge pressure (>18 mmHg)

Any cause of severe left or right ventricle dysfunction may cause cardiogenic shock; however,

acute coronary syndrome (ACS) with left ventricular failure is mostly involved. The incidence of CS complicating ACS is approximately 7 % in ST elevation myocardial infarction (STEMI) and 2.5 % in non-STEMI [2]. In those patients presenting with ACS and CS, mechanical complications as ventricular septal or free wall rupture and papillary muscle rupture should be suspected and searched.

Other less frequent causes are acute myopericarditis, stress-induced cardiomyopathy, acute valvular regurgitation or prior severe valvular disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, drugs and medications, arrhythmias, and traumatic cardiac injury.

Cardiogenic shock due exclusively to right ventricle involvement represents only 5 % of cases, and it is characterized by a similar mortality to LV shock [3].

In the ischemic setting, CS could be present acutely or could develop later, within the first days. It seems that later CS is associated with a higher mortality than earlier development of CS [4].

Different risk factors for CS in ischemic patients have been recognized: anterior STEMI, multivessel disease, advanced age, female sex, previous diagnosis of diabetes and hypertension, prior cardiovascular disease, heart failure at admission, systolic blood pressure <120 mmHg, heart rate >90 bpm, and presence of left branch block [5, 6].

Pathophysiology

Systemic perfusion and blood pressure are related to cardiac output (CO) and systemic vascular resistance (SVR):

$$\text{MAP}\left(\text{mean arterial pressure}\right)=\text{CO}\times\text{SVR}$$
$$\text{SVR}=8\eta L/\pi r^4$$
$$\text{CO}=\text{SV}\times\text{HR}$$

η = viscosity, L = vessel length, r = vessel radius, SV = stroke volume, HR = heart rate

The stroke volume depends on the preload, afterload, and myocardial contractility as explained by the Frank–Starling and Hill mechanisms. The initial response to a decrease in blood pressure is mediated by arterial baroreceptors that cause an enhancement in sympathetic activity (via IX and X cranial nerves) with a consequent increase in HR, myocardial contractility, and SVR. More slowly acting mechanisms are the activation of renin/angiotensin/aldosterone system and fluid retention. The reduction in tissue perfusion leads to a reduced oxygen delivery with a shift to anaerobic metabolism and an increase in lactate levels with a possible consequent metabolic acidosis.

Cardiogenic shock (CS) may be precipitated by different cardiac and extracardiac causes as listed below:

- Cardiomyopathies: acute myocardial infarction (MI) involving >40 % of the left ventricular myocardium or dilated cardiomyopathy with cardiac pump failure.
- Arrhythmias: supraventricular arrhythmias may cause cardiogenic shock through an impairment of left ventricular filling. Bradyarrhythmias or ventricular tachycardia/fibrillation may reduce or abolish CO due to an ineffective cardiac contraction.
- Mechanical: valvulopathies (mitral or aortic regurgitation) or intracardiac shunt.
- Extracardiac: any condition that causes a significant reduction in preload or acute increase in afterload (i.e., cardiac tamponade, pulmonary embolism, tension pneumothorax, constrictive pericarditis).

The CS pathophysiology is very complex with differences from patient to patient. Cardiogenic shock evolves through different stages that represent a physiologic continuum from an initially compensated status (pre-shock or shock impending) till multiorgan failure.

Regardless of the precipitating cause, the main feature consists of a reduction of cardiac output with consequent hypotension, unable to maintain an adequate systemic perfusion (Fig. 9.3). The reduction of blood pressure triggers the activation of compensatory mechanisms through sympathetic system and renin/angiotensin/aldosterone system with consequent tachycardia,

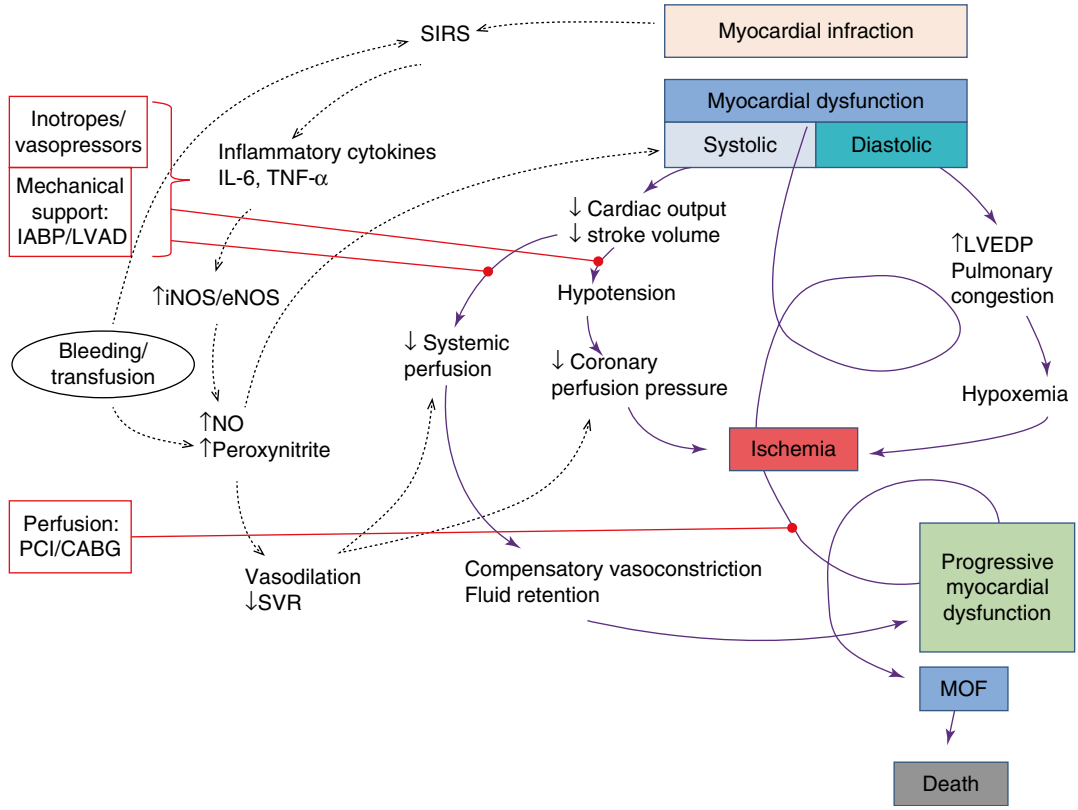

Fig. 9.3 Concept of CS pathophysiology. This is the "downward spiral," induced by left ventricle (LV) systolic dysfunction that leads to reduced stroke volume and cardiac output with consequent hypotension. Coronary blood flow is therefore reduced with ischemia and further myocardial dysfunction. Even diastolic dysfunction with increased left ventricular end-diastolic pressure (*LVEDP*) and pulmonary edema leads to hypoxemia and consequent ischemia. The reduced systemic perfusion activates compensatory mechanisms that cause vasoconstriction and fluid retention, increasing left ventricle after- and preload and aggravating myocardial dysfunction. The systemic inflammatory response syndrome (*SIRS*) characterized by cytokine (interleukin-6 (*IL-6*) and tumor necrosis factor (*TNF*)) production and consequent endothelial and inducible nitric oxide synthase (*eNOS*, *iNOS*) activation leads to nitric oxide (*NO*) and peroxynitrite production that causes reduced systemic vascular resistance (*SVR*) with vasodilatation and further myocardial depression. Bleeding complications and subsequent transfusions have a negative role in the shock spiral. If there is not a prompt intervention with treatment options shown in red (inotropes/vasopressors, mechanical support with intra-aortic balloon pumping (*IABP*) and left ventricular assist device (*L-VAD*), reperfusion by percutaneous coronary intervention (*PCI*) or coronary artery bypass (*CABG*)), the vicious circle leads to multiorgan failure (*MOF*) and death

increased contractility, a marked systemic vascular resistance (SVR) elevation increasing LV afterload, and fluid retention with increase in preload. These compensatory mechanisms in the long term become maladaptive and result in a further marked reduction in tissue perfusion. Hypotension, vasoconstriction, tachycardia, and increased myocardial contractility reduce myocardial perfusion and increase myocardial oxygen demand, exacerbating ischemia.

Pump failure causes diastolic dysfunction with increased ventricular diastolic pressure that further reduces coronary perfusion pressure, worsening ischemia. The increased ventricular diastolic pressure increases left atrial pressure which may cause pulmonary congestion leading to hypoxia, further exacerbating myocardial ischemia. Ischemia worsening aggravates myocardial dysfunction and begins a vicious cycle that leads to progressive

end-organ hypoperfusion with multiorgan failure (MOF) and death when not interrupted (Fig. 9.3). Reduced systemic perfusion leads to anaerobic metabolism and consequently to lactic acidosis that further depresses myocardial function.

Some patients do not have elevated SVR, suggesting that the compensatory vasoconstriction is not universal, and moreover, a systemic inflammatory response may be involved [7], contributing to myocardial dysfunction and hypotension (via vasodilatation). In fact, in the presence of myocardial infarct, cytokines (interleukin-6 (IL-6), tumor necrosis factor (TNF)) that activate inducible nitric oxide synthase (iNOS) are released, leading to increased levels of nitric oxide (NO) with consequent vasodilatation and worsening hypotension [8]. Nitric oxide and superoxide lead to peroxynitrite production that impairs myocardial contractility [9]. The inflammatory mediators lead to microcirculatory abnormalities like regional heterogeneity in blood flow which plays a very important role in organ failure pathogenesis. In fact data shows that IL-6 levels correlate with organ failure and mortality [10].

Even if severe LV failure is the principal cause of CS, other factors, here below listed, may contribute to hypotension:

- Hypovolemia due to bleeding with a hemorrhagic shock superimposition or due to diuretic therapy
- Septic shock superimposition
- Severe preexistent valvular heart disease like critical aortic stenosis or new-onset valvular disease like severe mitral regurgitation
- Important bradycardia that causes low cardiac output and hypotension in patients with reduced LV function due to acute MI
- Atrial arrhythmias with rapid ventricular response or ventricular tachycardia
- Drugs lowering blood pressure (nitrates, beta-blocker, calcium antagonists, ACE inhibitors, diuretics, and morphine)

These factors should be promptly detected and, when possible, corrected.

Diagnosis

The diagnostic evaluation during cardiogenic shock must not delay resuscitation if needed and must be conducted at the same time. Diagnostic efforts should be made to recognize the stage of pre-shock to prevent loss of the compensatory mechanisms and progression to shock and multiorgan dysfunction.

Medical History and Physical Examination

Medical history may be collected from the patient or relatives in case of advanced shock. The presence of cardiovascular risk factors or the history of chest pain may suggest acute myocardial infarction (MI). Additional information about comorbidities or allergies should be recorded.

Cardinal findings on physical examination are:

- Hypotension: defined as absolute (PAS <90 mmHg or PAM <65 mmHg) or relative ($\Delta P > 30$ mmHg). Prominent and persistent hypotension (>30 min), despite volemic correction, may require inotropes to ensure adequate systemic perfusion.
- Oliguria: decreased urine output (diuresis <0.5 mg/kg/h), consequence of renal hypoperfusion related to reduced cardiac output and blood redistribution to other vital organs.
- Cool and clammy skin: compensatory vasoconstriction to redirect blood flow to vital organs, causes cold, mottled, or diaphoretic skin.
- Altered mental status: ranges from agitation to delirium and coma.

Dyspnea, chest pain with tachycardia, and tachypnea are often present. On cardiac auscultation, gallop rhythm or new murmurs may be found. Pulmonary congestion with diffuse crackles is also a typical finding but may lack in about one-third of patients at presentation [11]. Jugular venous distension and hepatomegaly are clinical signs related to an increased preload, especially during right ventricular failure. A capillary refill time >2 s is a frequent finding and should be

associated with low mixed venous oxygen saturation.

Electrocardiogram

Electrocardiogram (ECG) suggests the diagnosis of acute MI in the presence of ST-T alterations. Supraventricular and ventricular tachy- or brady-arrhythmias may cause shock and can be diagnosed by ECG monitoring. Shocked patients usually present sinus tachycardia.

Echocardiogram

Echocardiography may confirm the diagnosis of cardiogenic shock, showing marked depression of left or right ventricular function with low stroke volume and elevated filling pressures. It is also useful in evaluating cardiac chambers, regional wall motion, the pericardium, and valves: it could detect causes or contributing factors as regional wall motion abnormalities, the presence of cardiac tamponade, or severe mitral or aortic regurgitation. In acute MI, echocardiogram should be repeated to exclude the presence of mechanical complications as ventricular septal, free wall, or papillary muscle rupture [12]. Transthoracic echocardiography (TTE) is the first step, but transesophageal echocardiography (TEE) should be used when TTE images are suboptimal especially in patients with mechanical ventilation.

TTE plays also a role as a less invasive tool for evaluating hemodynamic parameters with Doppler-based methods. Small ventricles ("kissing ventricles") usually suggest the use of fluid challenge, while a dilated and hypokinetic right ventricle should be related to pulmonary embolism.

Hemodynamic Monitoring

Hemodynamic monitoring through a pulmonary artery catheter adds further details in the diagnosis, establishing cardiac output, pulmonary artery occlusion pressure (PCWP), systemic vascular resistance, and continuous mixed venous oxygen saturation (SvO_2) [13]. These parameters are also helpful in guiding inotropic/vasopressor therapy or fluid resuscitation and in assessing mechanical ventilation settings [14]. Pulmonary artery catheterization has never shown to improve patient's outcomes in clinical trials [2, 3, 15]. The diagnosis of cardiogenic shock is confirmed in the presence of a reduced cardiac index (<2.2 l/min with inotropic support or <1.8 without therapy), an increased PCWP (>15–18 mmHg), and/or a reduction in SvO_2/$SvcO_2$ (<70 % and <65 %, respectively). A fall in SvO_2 is suggestive for a reduced oxygen delivery or an increase in oxygen consumption and may reflect inadequate tissue perfusion even in a pre-shock stage. According to guidelines [12], an invasive hemodynamic monitoring is recommended in a patient with persistent hypotension refractory to pharmacological treatment with uncertain left filling pressures.

Laboratory Evaluation

Laboratory tests are useful in identifying causes of shock and in evaluation of organ failure. Basic chemistry tests, complete blood count, liver and renal function tests, amylase and lipase, and arterial blood gas should be evaluated. Cardiac biomarkers (troponin T/I, CK-MB) are useful in the diagnosis of acute MI and correlate with infarction extension. Arterial or venous lactates complete the picture because an increased serum lactate level may correlate with a reduced oxygen delivery with a shift to anaerobic metabolism. Elevated lactate serum levels (>1.5 mmol/l at admission, >1 mmol/l after 24 h) are also associated with increased mortality [16].

Coronary Angiography

Coronary angiography should be performed early in patients with suspected acute MI. Revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is also recommended without any delay in patients with cardiac pump failure related to an ischemic cause [12].

Differential Diagnosis

The differential diagnosis for shock may be challenging and must be focused on underlying causes of inadequate tissue perfusion.

1. *Hypovolemic shock* – hypovolemic shock is related to an intravascular volume loss due to hemorrhage or third-space loss with a reduced preload that leads to a reduction in CO and an increase in systemic vascular resistance to maintain adequate perfusion. Dry mucous and decreased jugular and central venous pressure with low PCWP are typical findings.
2. *Distributive shock* – distributive shock is related to vasodilatation with a consequent drop in SVR. The CO is increased as a compensatory mechanism, while the PCWP may be low or normal. Possible causes of distributive shock are sepsis or systemic inflammatory response syndrome, anaphylaxis, neurogenic disease, and toxic problems.
3. *Cardiogenic shock* – as discussed previously, cardiogenic shock is related to a cardiac pump failure and may be divided in to four categories in relation to etiology.
4. *Combined shock* – different mechanisms contribute to generate shock (i.e., septic shock may coexist with a cardiac pump failure due to myocardial stunning related to sepsis).

Management

The initial approach consists of:

- Identification of patients with high risk to develop CS (they should be transferred to the nearest tertiary center)
- Early diagnosis (before a frank hypotension is being manifested) with a consequent rapid stabilization
- Identification/treatment of reversible causes

Invasive blood pressure, heart rate, rhythm, and oxygen saturation should be continuously monitored. Right heart catheterization is not routinely recommended, but it can be very useful in a subgroup of patients (persistently hypotensive patients or patients with uncertain LV filling pressure) to guide optimal treatment decisions.

The principal therapeutic targets in these patients are:

- MAP >65 mmHg in order to restore tissue perfusion and to prevent multiorgan dysfunction (MOF)
- Systemic vascular resistances: 800–1000 dyn/s/cm^{-5}
- CI >2.5 l/min/m^2
- FC <110 bpm
- SVO_2 >65 %
- Lactate <2 mmol/l

These parameters should be monitored every 90 min.

Reversible causes should be detected and treated emergently, for instance, revascularization in acute coronary syndromes, surgery for mechanical complications of MI or acute valvular disease, and pericardial drainage in tamponade.

In patients with evidence of ACS (ongoing ischemia, persistent ST elevation, new LBBB), early revascularization with either PCI or CABG must be considered. In the SHOCK trial, CS patients treated emergently with PCI or CABG had an improved long-term survival than patients who did not or underwent revascularization later [17]. The CS is the only situation in which an emergency multivessel revascularization can be performed [17, 18]. Fibrinolysis should be considered when PCI or CABG is not available [19]. Indications for antiplatelet/antithrombin therapies are similar to those in STEMI patient without CS (see Chap. 1).

When a reversible underlying cause is not present, the medical management role is primarily supportive, serving as a bridge to mechanical circulatory support, heart transplantation, or recovery, because there is lack of evidence that the medical management alone improves survival.

Even if there are only a few clinical trials with discording results, sympathomimetic inotropic and vasopressor agents are the mainstay of the medical first-line therapy. These agents interact with specific receptors (Table 9.1) and activate adrenergic pathways, increasing myocardial

contractility and modifying vascular tone. The principal inotropes and vasopressors that we commonly use in CS are (Table 9.2):

Dobutamine: It is predominantly a β-adrenergic agonist with a β1/β2 ratio of 3:1. It increases HR, SV, and CO with a modest decrease in blood pressure and SVR [20]. It also has a mild α1-adrenergic agonism, and this is the reason why vascular resistance decrease does not persist at higher doses. These beneficial effects are limited by myocardial oxygen consumption increase that worsens myocardial ischemia, precipitates tachyarrhythmias, and increases mortality. The ESC guidelines recommend dobutamine and dopamine as the first-line inotropic therapy in CS.

Epinephrine (adrenaline): It is a potent agonist of all adrenoreceptors. Its use results in HR, SV, CO, and coronary blood flow increase. At low doses, a passive pulmonary vessel stretching accommodates CO increase, but at high doses, it determines a pulmonary vascular resistance increase and so a right ventricle afterload increase. Even adrenaline increases myocardial oxygen consumption due to increase in HR and stroke work. It has metabolic effects like increased plasma glucose and lactate concentration. The lactate concentration increase seems not to be harmful.

Norepinephrine (noradrenaline): It is a potent α-agonist that also stimulates β1 receptors, with an increase in blood pressure, SVR, and SV. Like adrenaline, it increases right ventricle afterload. Either cerebral circulation or coronary circulation is protected to a certain extent from these vasoconstrictor effects due to the relative paucity of the vascular adrenoreceptors, while pulmonary, renal, splanchnic, and cutaneous blood flow is not spared. The ESC guidelines recommend noradrenaline as second-line therapy in CS patients.

Dopamine: It has a dose-dependent action. At low doses (≤2 γ/kg/min), it activates dopaminergic receptors with splanchnic and renal vasodilatation. At medium doses (5–10 γ/kg/min), it activates β1 receptors with HR and CO increase. At intermediate doses (2–5 γ/kg/min), either dopaminergic or β1 receptors are stimulated. At high doses, it predominates α-adrenergic action with

Table 9.1 Location and response of adrenergic receptors

Receptor	Location	Activity
α1	Vascular smooth muscle Heart	Contraction Increase force of contraction
α2	Vascular smooth muscle	Contraction
β1	Heart	Increase force of contraction Increase AV nodal conduction velocity
β2	Smooth muscle (vascular, bronchial, GI, and GU)	Relaxation
D	Vascular smooth muscle	Relaxation

AV node atrioventricular node, *GI* gastrointestinal, *GU* genitourinary

Table 9.2 Inotropes and vasopressors used in CS

Medication	Receptor/mechanism	Doses	BP	HR	CO	SVR
Dobutamine	β1 > β2 > α	2–15 γ/kg/min	↓	↑	↑↑	↓
Milrinone	PDE II inhibitor	0.375–0.75 γ/kg/min	↓↓	↑	↑↑	↓↓
Levosimendan	Ca sensitizer	0.05–0.2 γ/kg/min	0	0	↑↑	↓↓
Epinephrine	β1 = β2 > α	0.01–0.03 γ/kg/min, max 0.1–0.3 γ/kg/min	↑	↑	↑↑↑	↓
Norepinephrine	α > β1 > β2	0.01–0.03 γ/kg/min, max 0.1 γ/kg/min	↑↑	0 or ↓	0	↑↑
Dopamine	Moderate dose β	5–10 γ/kg/min	↑↑	↑	↑↑	0 or ↓
Dopamine	High dose α	10–20 γ/kg/min	↑↑	↑↑	↑	↑↑
Phenylephrine	α1	60–60 γ/min	↑↑	↓	↓	↑
Vasopressin	V1	0.01–0.04 units/min	↑↑	0	0	↑↑

BP blood pressure, *CO* cardiac output, *HR* heart rate, *SVR* systemic vascular resistance

vasoconstriction and increase in SVR that may cause a CO decrease. De Backey et al. showed in a subgroup analysis that in CS patients dopamine increased 28-day mortality rate compared with norepinephrine, but in this study dopamine doses in CS patients are not specified, and this may be a reasonable explanation of these results because high-dose dopamine causes a CO decrease [21].

Milrinone: It inhibits phosphodiesterase-3 and prevents cyclic adenosine monophosphate (cAMP) degradation that activates protein kinase A which results in increased calcium influx into the cardiomyocyte with increased contractility. In the smooth muscle, elevated cAMP causes relaxation (vasodilatation) because it inhibits myosin light-chain kinase. Milrinone has a similar cardiovascular profile to dobutamine. In fact it increases HR, SV, and CO and decreases mean blood pressure, SVR, and pulmonary artery resistances, reducing preload and afterload and consequently ventricular wall stress. Although milrinone affects hemodynamics, the OPTIME-CHF trial did not show a difference in days of hospitalization between decompensated heart failure patients treated with 48 h administration of milrinone and placebo. In this study, there was not an increase in in-hospital mortality in the milrinone group [22]. Actually milrinone is recommended only for refractory CS patients.

Levosimendan: It is a calcium-sensitizing agent that binds troponin C, at systolic calcium concentrations, and prolongs myosin–actin interaction due to troponin I inhibition. So levosimendan does not increase cellular calcium concentration and consequently does not impair diastolic function and cardiac rhythm. It has phosphodiesterase III inhibitory effects and causes blood pressure decrease. Levosimendan has an active metabolite so its inotropic effects continue even after infusion is stopped. The SURVIVE study did not show a 180-day mortality rate through short-term levosimendan and dobutamine infusion in acute decompensated heart failure [23], but deaths in the first weeks were significantly fewer in the levosimendan group. There are only few data (limited to case reports) on the role of levosimendan in CS patients. The ESC guidelines recommend levosimendan infusion to reverse beta-blocker effects if the last ones are thought to contribute to hypotension.

Phenylephrine: It is an α1-selective agonist that causes an increase in SVR and blood pressure and a reflex bradycardia that determines a decrease in CO. This is the reason why its utilization in CS is very rare.

Vasopressin: It activates V1 vascular smooth receptors and causes vasoconstriction. In refractory CS, vasopressin has been utilized, increasing MAP without effects on CI, pulmonary capillary wedge pressure, or urine output [24].

Assessment and optimization of cardiac filling pressure enhance hemodynamic improvement in CS. Hypovolemia should be treated with intravenous fluid replacement, and this should be guided by PCWP, systemic arterial pressure, arterial oxygen saturation, central venous pressure (target value 8–10 mmHg if there is no right ventricle (RV) dysfunction, 10–12 mmHg if RV dysfunction), and cardiac output measurement.

When hypervolemia with pulmonary and peripheral edema is present, diuretics (loop diuretics or combining loop with thiazide diuretic when patient becomes resistant to the first ones) should be used.

Actually the intra-aortic balloon pumping (IABP) may be considered in patients with acute myocardial infarction complicated by CS. The evidence does not support the IABP routine use because the IABP SHOCK II trial did not show a 30-day mortality difference between the IABP and control groups in patients with CS complicating MI, probably due to high rate of patient shift from the control to the IABP group [25].

In patients with refractory shock, LV mechanical device may be considered. The percutaneous circulatory support devices can be distinguished in four categories:

- Mechanical left ventricle support that unloads LV pressure (IABP)
- Mechanical left ventricle support that unloads LV volume (TandemHeart and Impella Recover 2.5 l/min or 4 l/min)
- Mechanical biventricular support (combination of right and left ventricle support)
- Mechanical biventricular support with membrane oxygenation (ECMO)

Oxygen or mechanical respiratory support is indicated according to clinical and blood gas asset.

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Cardiac Resynchronization Therapy and Possible Dysfunctions

10

Laura Cipolletta and Michela Brambatti

10.1 Case Report

A 65-year-old man had been diagnosed with congestive heart failure (HF) due to dilated cardiomyopathy in 2013. He had been in chronic AF since 2012. He was referred to the hospital with worsening HF in May 2014; however, his HF symptoms remained New York Heart Association (NYHA) class III despite the administration of appropriate medical therapy. So he was referred to our clinic for cardiac resynchronization therapy (CRT).

Medical History and Cardiovascular Risk Factors

- No cardiovascular risk factor; he had a family history of idiopathic dilated cardiomyopathy.
- 2013: diagnosis of nonischemic dilated cardiomyopathy

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Allergies

None

Medications

Bisoprolol 5 mg, valsartan 40 mg b.i.d., furosemide 40 mg t.i.d., spironolactone 50 mg q.d., warfarin according to INR values

Vital Signs

- Temperature: 36 °C
- Heart rate: 76 bpm
- Arterial blood pressure: 130/75 mmHg
- Respiratory rate: 14 breaths/min
- Oxygen saturation: 96 %

Physical Examination

- General Appearance: Well developed, well nourished, alert, and cooperative
- Lungs: Clear to auscultation and percussion, several little rales at basal pulmonary fields, without rhonchi, wheezing, or diminished breath sounds
- Cardiovascular: Normal S1 and S2. S3, no S4, and 2/6 mitral systolic murmurs. Irregular

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rhythm. No peripheral edema, cyanosis, or pallor. Warm and well-perfused extremities
- Abdomen: Positive bowel sounds. Soft, non-distended. No guarding or rebound. No masses

Routine laboratory test were normal (hemoglobin 12.2 g/dl, white blood cells 7240/mmc, creatinine 1.3 mg/dl, potassium 3.8 mEq/l, sodium 138 mEq/l, magnesium 1.8 mg/dl).

Instrumental Examination

His 12-lead electrocardiogram (ECG) showed complete left bundle branch block with a QRS width of 167 ms. The chest X-ray showed a severely enlarged cardiac silhouette.

Two-dimensional echocardiography revealed a severely impaired left ventricular (LV) function with a low LV ejection fraction (LVEF) of 28 % assessed according to the modified Simpson method. The patient also had a severely dilated left atrium with an anteroposterior diameter of 55 mm and left atrial volume of 45 mL/m^2 .

Clinical Course and Therapeutic Management

A CRT defibrillator (CRT-D) for primary prevention of sudden cardiac death was implanted in this high-risk patient in May 2014. Due to the patient's long-standing AF and severely dilated left atrium, we decided not to implant an atrial lead, which resulted in VVI biventricular pacing (Fig. 10.1). The interventricular interval was determined at 0 ms guided by echocardiography.

Although the patient's heart failure symptoms improved from NYHA classes III to II and biventricular pacing achieved a success rate of 95 %, multiple episodes of high heart rate AF were detected by the device one month after CRT-D implantation, and oral amiodarone therapy consisting of 200 mg once daily for 5 days per week was started. Three months after the initiation of amiodarone therapy in September 2014, the patient's heart failure symptoms worsened and blood samples showed an elevated plasma brain natriuretic peptide (BNP). His ECG revealed atrial fibrillation with spontaneous QRS (Fig. 10.2).

Since his heart failure symptoms were refractory to medical management, repeated

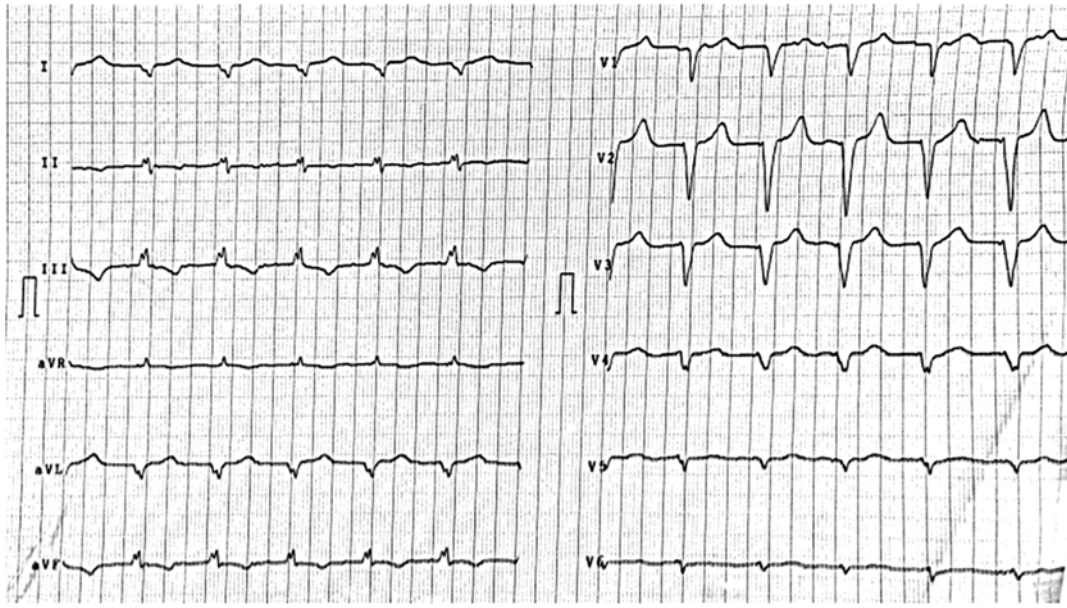

Fig. 10.1 12-lead ECG in atrial fibrillation with biventricular pacing

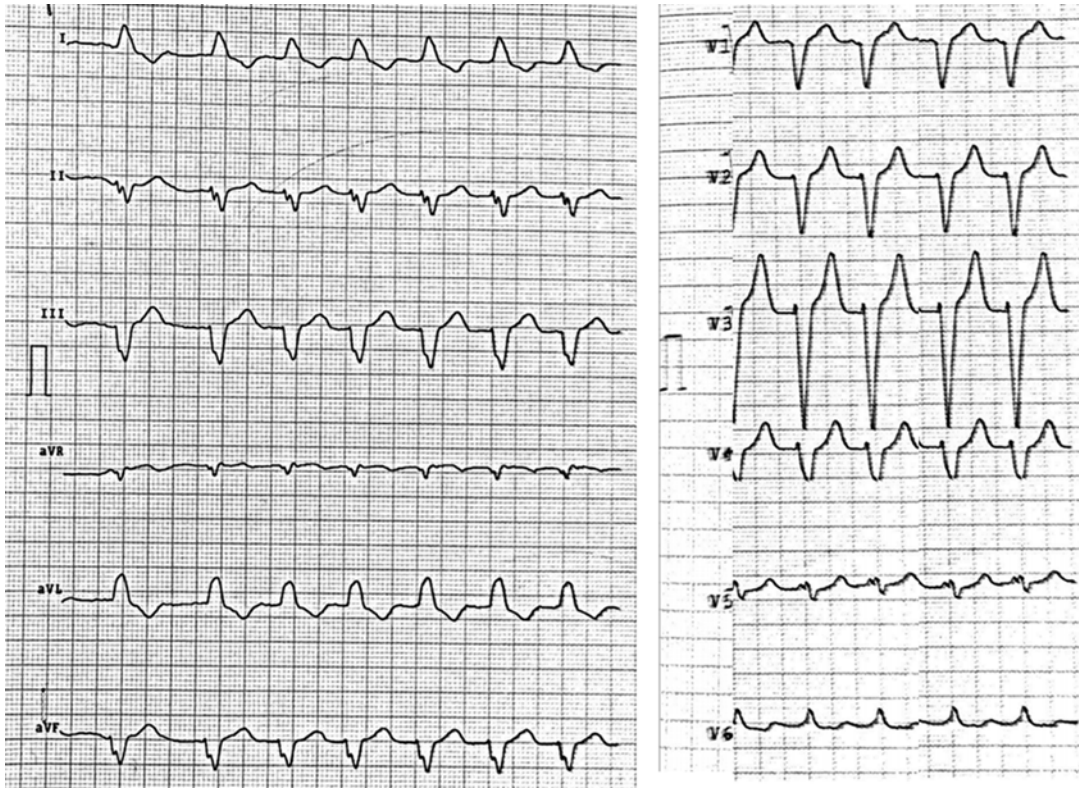

Fig. 10.2 12-lead ECG in atrial fibrillation with spontaneous QRS

echocardiography was performed that revealed an increased left atrial diameter to 58 mm and a volume of 46 mL/m^2 despite mild improvement of the LVEF. The hypothesis of the worsening clinical condition was that the exacerbation of HF was due to high-rate AF or to displacement of left ventricular (LV) lead; therefore, a chest X-ray was performed and the imaging confirmed the LV lead displacement (Fig. 10.3a, b). Figure 10.4a, b represents the coronary sinus angiography during the reimplantation of new LV pacing lead. Two months after the repositioning of biventricular pacing, echocardiography demonstrated an increase in the LVEF from 28 to 38 % and a reduction in the left atrial diameter from 58 to 56 mm and the left atrial volume from 46 to 45 mL/m^2 compared with the values examined in December 2014.

The patient's clinical course was satisfactory, and his plasma BNP level decreased to 504 pg/mL 2 months after the repositioning of the LV lead.

10.2 Cardiac Resynchronization Therapy (CRT)

Definition

Cardiac resynchronization therapy (CRT) is a specific type of pacemaker therapy that aims to restore or improve ventricular contraction by pacing both the right ventricle (RV) and the left ventricle (LV). Indeed, in addition to the right lead, an extra catheter is usually implanted via the coronary sinus to pace the LV, most commonly at the latest activated LV segment. This may be carried out with or without the use of an implantable cardioverter defibrillator (ICD), a device required in patients at risk for ventricular arrhythmias [1].

Left bundle branch block (LBBB) is an electrocardiographic sign of electrical dyssynchrony and, in association with poor LV function, is an independent risk factor for

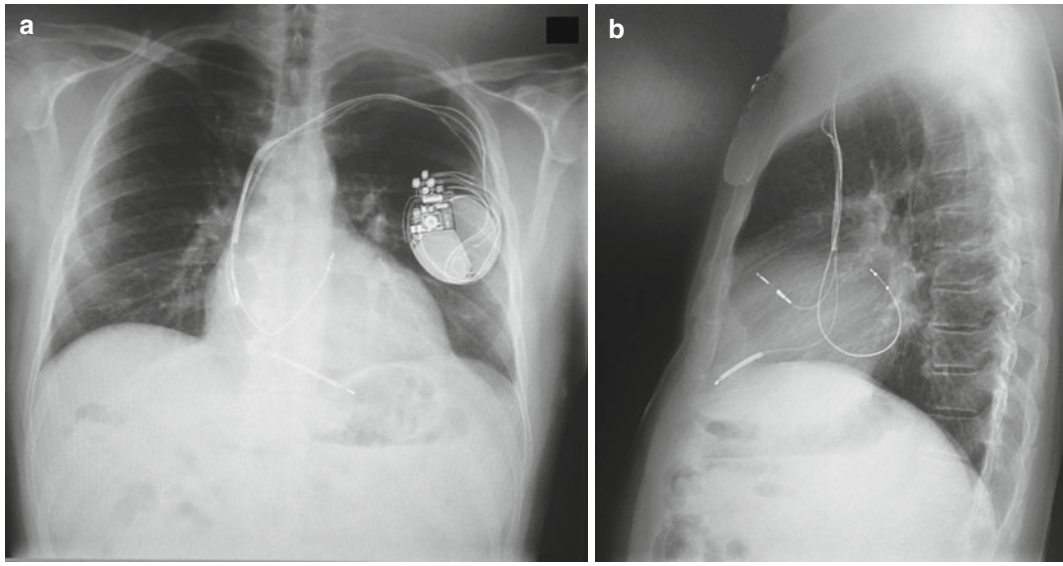

Fig. 10.3 (**a**) Posteroanterior chest X-ray showing the left ventricular lead displacement. (**b**) Latero-lateral chest X-ray confirming the left ventricular lead displacement

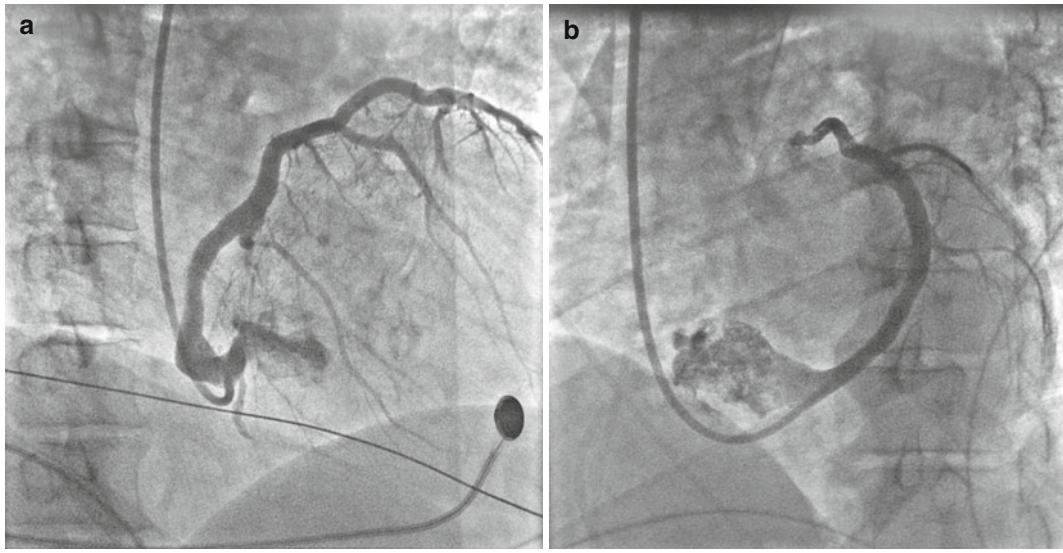

Fig. 10.4 (**a**) Coronary sinus angiography on right anterior oblique projection. (**b**) Coronary sinus angiography on left anterior oblique projection

mortality [2]. LBBB often correlates with mechanical dyssynchrony also called interventricular delay, a nonphysiological timing of LV and RV contraction. There may also be abnormal contraction of individual segments of the LV, causing intraventricular delay. In an HF patient, the inter- and intraventricular dyssynchrony can further worsen the pump function of a failing LV. CRT, through the reestablishment of a more physiological ventricular activation, improves cardiac performance and reduces HF symptoms and also determines a reverse remodeling of the LV along with mortality and hospitalization reduction [3–7].

CRT is usually set in DDD or DDDR mode if the patient is in sinus rhythm. Atrial events trigger an atrioventricular interval that should be long enough in order to allow the optimal atrial contribution to ventricular filling but short enough to allow ventricular pacing for most of the time. As specified in the ESC guidelines [1], the goal of CRT should be to achieve BiV pacing as close to 100 % as possible since the reduction in mortality and hospitalization is strongly associated with an increasing percentage of BiV pacing. In addition, CRT pacing often results in a QRS complex that is narrower than the native QRS complex because of fusion between the two paced signals.

Clinical Trials

CRT has been clinically evaluated in more than 4000 patients in randomized controlled trials (Table 10.1). Early studies were positive in terms of morbidity, including improvements in quality of life, functional status, and exercise capacity. Finally, the large trial COMPANION [3], along with the CARE-HF trial [4], provided the demonstration of mortality benefit in HF patients, defined as LVEF <35 %, QRS duration ≥120 ms, and NYHA functional class III or ambulatory class IV HF. Recently, three major randomized trials [MADIT-CRT [5], RAFT [6], and REVERSE [7]] have demonstrated that CRT can provide functional improvement and decrease the heart failure events in patients with reduced LVEF and NYHA class I or II HF and QRS ≥120 or 130 ms. CRT-D has also been shown to decrease the mortality rate for patients with class II but not class I HF. Further subgroup analyses of data from MADIT-CRT, REVERSE, and RAFT trials demonstrated that a CRT implant in patients with a QRS duration ≥150 ms yielded a greater survival benefit compared to a QRS duration of 120 ms. Also meta-analyses using aggregate data from randomized trials confirmed that CRT was effective in reducing adverse clinical events in patients with baseline QRS duration ≥150 ms and proposed that CRT might not reduce events in patients with a QRS <150 ms [8].

Indications

The 2013 European Society of Cardiology (ESC) guidelines [2] on cardiac pacing and CRT included the following indications for CRT in:

1. Chronic HF patients in sinus rhythm with left ventricular ejection fraction (LVEF ≤35 %):
   - NYHA functional class II, III, or ambulatory IV despite adequate medical treatment and LBBB with QRS duration >150 ms (Class I with level of evidence A).
   - NYHA functional class II, III, or ambulatory IV despite adequate medical treatment and LBBB with QRS duration 120–150 ms (Class I with level of evidence B).
   - NYHA functional class II, III, or ambulatory IV despite adequate medical treatment and non-LBBB with QRS duration >150 ms (Class IIa with level of evidence B).
   - NYHA functional class II, III, or ambulatory IV despite adequate medical treatment and non-LBBB with QRS duration 120–150 ms (Class IIb with level of evidence B).
   - CRT is not recommended in patients with chronic HF and QRS duration <120 ms.
2. Chronic HF patients with permanent atrial fibrillation:
   - NYHA functional class II, III, or ambulatory IV despite adequate medical treatment, LVEF ≤35 %, and QRS duration ≥120 ms, provided that a biventricular pacing as close to 100 % as possible can be achieved (Class IIa with level of evidence B). Otherwise, atrioventricular junction ablation should be added in case of incomplete biventricular pacing (Class IIa with level of evidence B).
   - In patients with uncontrolled heart rate who are candidates for atrioventricular junction ablation, CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control (Class IIa with level of evidence B).
3. Chronic HF patients with conventional pacemaker indication:
   - Upgrade from conventional pacemaker or ICD is indicated in patients with LVEF

Table 10.1 Summary of major studies of CRT

Trials	Patients, no.	NYHA class	LVEF, %	QRS, ms	Primary end points	Secondary end points	Main findings
COMPANION [3]	1520	III or IV	21	159	(1) All-cause mortality or hospitalization	(2) All-cause mortality and cardiac mortality	CRT-P/CRT-D reduced (1) and (2)
CARE-HF [4]	813	III or IV	25	160	(1) All-cause mortality or hospitalization	(2) All-cause mortality	CRT-P reduced (1) and (2)
REVERSE [7]	610	I or II	27 ± 7	153	(1) HF clinical composite score	(2) LVESVi, (3) HF hospitalization, (4) all-cause mortality	Primary end point NS CRT-P/CRT-D reduced (2) and (3) but not (4)
MADIT-CRT [5]	1820	I or II	24 ± 5	162	(1) HF or death	(2) All-cause mortality (3) LVESVi	CRT-D reduced (1) and (3) but not (2)
RAFT [6]	1798	II or III	23 ± 5	158	(1) All-cause mortality or HF hospitalization	(2) All-cause mortality, (3) cardiac mortality, (4) HF hospitalization	CRT reduced (4)

≤35 % and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment (Class I with level of evidence B).

- De novo CRT should be considered in patients with reduced EF and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF.

Definition of "Nonresponders"

Despite advances in procedural expertise and experience, about one-third of patients currently do not respond to CRT [2]. There is a lack of a universally accepted definition to classify a patient as responder or nonresponder to CRT. Typically, clinical trials evaluate event-driven outcome such as HF hospitalizations and mortality as primary clinical determinant of response to CRT and measures of cardiac function and functional status as secondary end points. In real life, patients' overall well-being is a more significant outcome. Also, taking into account that HF is a progressive disease, the prevention of the progress of the illness should be considered as a benefit deriving from CRT and thus a positive response to CRT therapy.

However, in order to avoid implantation-related complications and additional costs, CRT nonresponders should be accurately identified. Several factors have been shown to influence the efficacy of CRT, including chronic renal insufficiency, hemodynamic abnormalities such as precapillary pulmonary hypertension, and ischemic HF [9, 10]. Patients with ischemic HF represent a challenge because coronary disease is progressive, and upcoming ischemic events may be non-associated to CRT response. In particular ischemic patients with extensive scar, usually measured by MRI, have been demonstrated to a lower response rate to resynchronization therapy. End-stage HF patients, including those who are inotropic dependent, appear to have a poor response rate as well. With regard to sex differences, women appear to have a more favorable response from CRT than men, particularly in patients with LBBB and even at a QRS duration less than 150 ms. Contrarily, no significant interaction between age and CRT effect was found [11].

10.3 CRT Malfunctions

Biventricular pacing systems are susceptible to similar system malfunctions of other types of pacemakers; however, in patients with CRT,

long-term complications are more frequent than in single- or dual-chamber pacemaker/ICD systems since these patients have advanced heart failure and implantation is more difficult [12].

Infections

Infection risk of CRT averages between 1 and 3 % yearly and is associated with prolonged hospitalization stay and increased cost. This risk is increased by some factors such as renal failure, device failure, device replacements, malnutrition, prolonged therapy with steroids, diabetes mellitus, device size, and re-interventions. The most common germ in infections related to devices is the *Staphylococcus* (72–95 %). In cases of latent infection, the most responsible microorganism results to be the coagulase-negative *Staphylococcus epidermidis*. The infection can be evident several years after the implant. In most patients with CRT infection, the complete system including all leads should be explanted, although there is a major risk related to the lead burden and the underlying condition of the patient.

Loss of Capture

Non-capture is defined as the release of an atrial or ventricular pacing stimulus without capture. The left ventricular lead of CRT system is separated from the myocardium by the vein wall and by any epicardial fat that may coat the vein. When loss of capture occurs, the capture threshold of the left ventricular lead may be higher than values measured at the implantation procedure. In modern CRT devices, the right and left ventricular leads can be assessed independently if loss of capture is suspected. Widening of the QRS complex or a more elusive change in QRS morphology may be a sign of loss of capture of LV lead. However, only pacemaker interrogation will confirm the issue or a chest X-ray in presence of a significant displacement.

Phrenic Stimulation

Phrenic nerve (PN) stimulation occurs in approximately 15 % of CRT patients and can limit biventricular pacing. The left phrenic runs on the anterior wall and can be irritated by anterolateral, lateral, or posterolateral epicardial stimulation of the LV; the diaphragm can be directly stimulated by electrocatheters placed in posteroinferior areas of the same LV. The occurrence of phrenic nerve stimulation after LV lead implant may be a sign of LV lead migration, in some cases without significant changes in the chest X-ray [12]. The growing use of quadripolar left ventricular leads is overcoming the problem.

Oversensing

Oversensing is defined as the detection of an inappropriate electrical signal. Ventricular oversensing may result in inhibition of ventricular pacing and loss of CRT. In a BiV pacing system, oversensing of atrial activity on the ventricular channel results in ventricular inhibition and loss of CRT, as well as in misdiagnosis of ventricular tachyarrhythmias.

Mechanical Lead Failure

All major malfunctions, including loss of capture, undersensing, and oversensing, can be associated with a rupture in lead insulation or conductor failure. A marked drop in the measured stimulation impedance is a sign of lead insulation break, while a significant increase in impedance conductor is a sign of lead fracture.

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Part IV

Cardiomyopathy

Hypertrophic Cardiomyopathy

11

Marco Marchesini and Erika Baiocco

11.1 Case Report

A 57-year-old man presented to the emergency room complaining palpitations that started suddenly few hours before, during a moderate walking. Palpitations were accompanied by dyspnea and mild dizziness. Symptoms lasted for about 10 min, forcing the patient to rest. The episode interrupted abruptly and spontaneously, and the patient did not remember if heartbeat was regular during the episode. He never had arrhythmias before and he denied syncope or angina.

The patient presented completely asymptomatic to the emergency room.

Medical History and Cardiovascular Risk Factors

- The family history revealed that his mother was affected by hypertrophic cardiomyopathy (HCM). There was not any case of sudden cardiac death in the family.
- At 20 years old, HCM was incidentally diagnosed during a sport screening and since preparticipation screening and since then he was regularly followed up.
- He was a smoker.

Allergies

None

Medications

Verapamil 80 mg BID

Vital Signs

Temperature: 36.3 °C
Resting heart rate: 58 bpm
Blood pressure: 125/90 mmHg
Respiratory rate: 18 breaths per minute
Oxygen saturation while breathing in room air: 99 %

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Physical Examination

The patient appeared in good clinical condition.

At physical examination, the relevant findings were the following:

Cardiovascular: Apical precordial impulse was forceful but not displaced laterally. Regular rate and rhythm; S1 and S2 were normal with an adjunctive S4. Systolic ejection late-peaking murmur was best heard between the apex and left sternal border without radiation to the neck, and it was increased by Valsalva maneuver. Mild diastolic decrescendo murmur was detected in Erb auscultator focus.

Lungs: No rales at auscultation neither rhonchi nor wheezes bilaterally.

Abdomen: Plain and tractable; no hepatosplenomegaly.

Extremities: No lower limb edema.

Routine Laboratory Tests

Complete blood count: normal
Cholesterol (total, HDL, LDL) and TG: normal
Fasting blood glucose: 78 m/dl (4.33 mmol/L)
Hepatic function (GOT, GPT, γ-GGT, ALP, total bilirubin, direct and indirect): normal
Thyroid function (TSH, FT3, FT4): normal
Renal function (creatinine, BUN): normal
Electrolytes (Na+, K+, Ca++, Mg++, Cl−): normal

EKG

A routine EKG at rest was performed (Fig. 11.1).

The initial EKG showed sinus rhythm at 58 bpm, normal atrioventricular conduction (PR interval 160 s), normal QRS duration (0.08 s), absent Q wave,

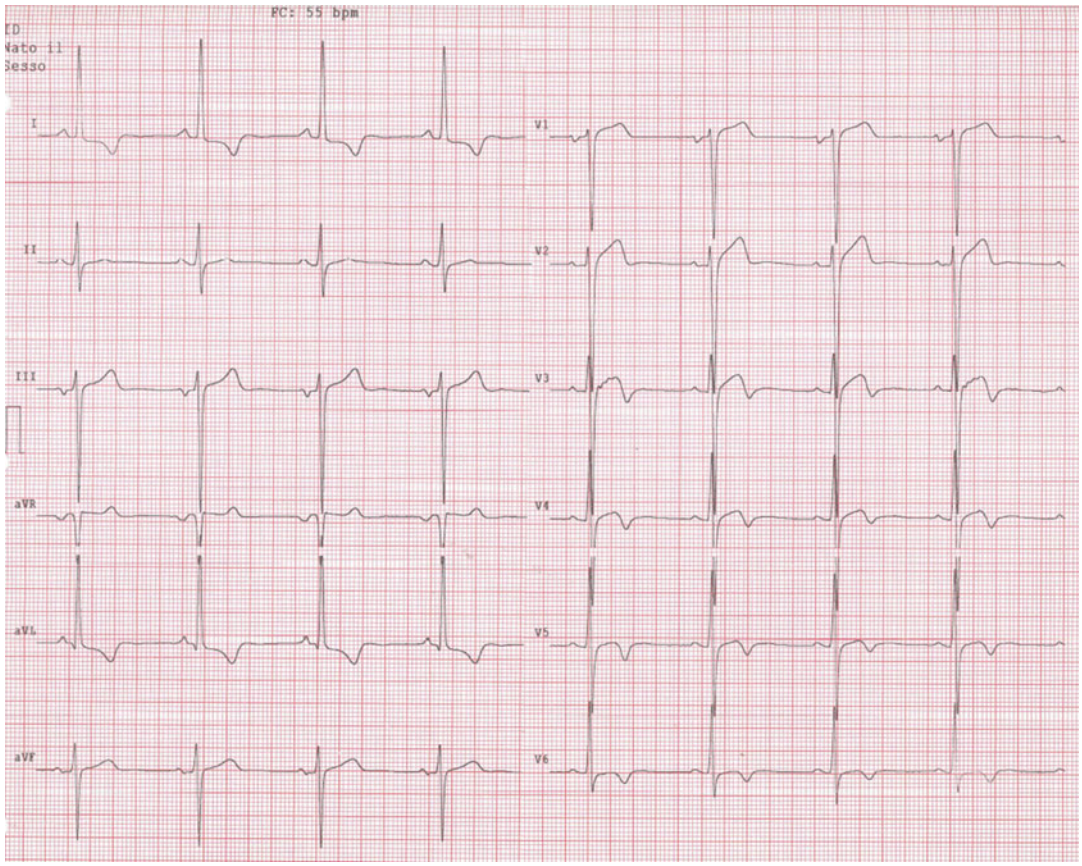

Fig. 11.1 12-lead ECG

and horizontal QRS axis (+15°). Increased amplitude and duration (>0.04 s) of the terminal negative portion of P wave in V1. High-voltage QRS complexes. T-wave inversion in the left precordial leads, reciprocal ST-segment elevation, and tall T wave in the right precordial leads. ST-segment depression and T-wave inversion in lead I and aVL.

The Sokolow diagnostic criteria for left ventricular hypertrophy (LVH) were satisfied: R wave in V_6 + S wave in V_1 >3.5 mV.

Asymmetrical configuration of inverted T waves suggested a nonischemic origin.

Conclusion: sinus rhythm, normal conduction, possible left atrial enlargement, and left ventricular hypertrophy with secondary anomalies of repolarization

We hypothesized that the described palpitations were provoked by a hyperkinetic arrhythmia (supraventricular or ventricular), and we explored the different secondary causes of arrhythmic events:

- Hyperthyroidism
- Fever
- Anxiety
- Anemia
- Use of medications containing stimulant, caffeine, or nicotine
- Strenuous exercise, poor training

He did not report any specific stress condition or recent changes in his lifestyle. He was walking slowly, when the arrhythmia occurred, which therefore can be excluded a physiologic activity response and poor training. According to physical examination, fever was excluded, and the laboratory tests did not show any anemia and thyroid dysfunction.

The most probable cause of symptoms was spontaneous arrhythmia.

Transthoracic Echocardiography (TTE)

A TTE showed (Figs. 11.2, 11.3, and 11.4):

- Left ventricular volumes at lower normal limits (iLVEDV 35 mL/m^2) with massive

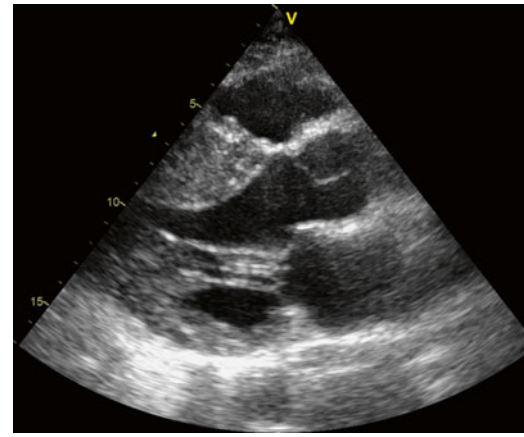

Fig. 11.2 Parasternal long-axis view shows septal hypertrophy

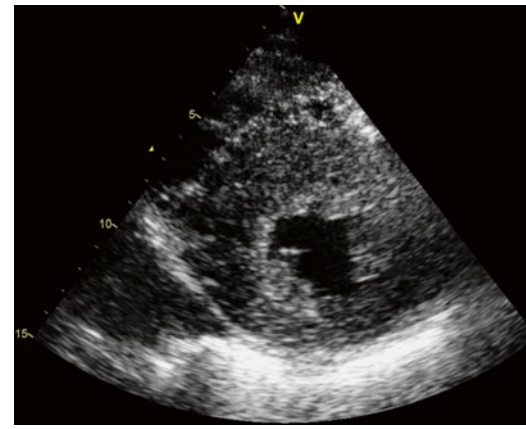

Fig. 11.3 Parasternal short-axis ventricle view

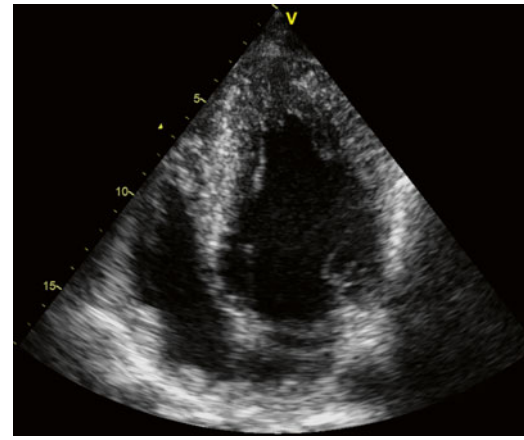

Fig. 11.4 Apical four-chamber view

asymmetrical hypertrophy with septal wall thickness that reached 35 mm; the posterior wall was 15 mm with a septum to posterior wall ratio of 2.4.
- Ejection fraction with the biplane Simpson method was 65 % without regional wall motion abnormalities.
- Diastolic dysfunction grade II with normal estimated filling pressure (E/E' 6).
- Severe left atrial enlargement (LA diameter 55 mm, iLAV >40 mL/m2).
- Systolic anterior motion (SAM) of the anterior mitral valve leaflet, without LVOT obstruction at rest, but with mild flow acceleration during Valsalva (peak gradient 15 mmHg).
- Normal size and function of right atrium and ventricle.
- Normal aortic tricuspid valve with mild central regurgitation
- Normal tricuspid and pulmonic valves.
- Normal dimension of inferior vena cava (IVC) with >50 % inspiratory collapse.
- No pericardial effusion.

According to ESC guidelines, HCM is defined as *a wall thickness >15 mm in one or more LV myocardial segments, as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR), or computed tomography (TC)), that is not explained solely by chronic loading conditions.*

Echocardiographic findings were suggestive of hypertrophic cardiomyopathy: the patient had no history of hypertension or valve disease with elevated afterload. Infiltrative cardiomyopathy was excluded, because the ventricular thickening is usually concentric with characteristic pattern of granular sparkling and different degrees of pericardial effusion.

In a patient with HCM, a sustained episode of palpitation lasting more than few minutes is often caused by supraventricular arrhythmias, especially in the presence of left atrium enlargement; atrial fibrillation is the most common arrhythmia in this population. In our patient, we could not exclude the hypothesis of a ventricular origin, particularly because the symptoms associated with palpitation (dyspnea and dizziness) could point to a hemodynamic distress that is often related to sustained ventricular tachycardias.

In adult patients with HCM, most recent data report on an annual incidence of cardiovascular death near 1–2 % with sudden cardiac death being (SCD) the most common.

Major clinical features associated with an increased risk of SCD are:

- Young age
- Non-sustained ventricular tachycardia (NSVT)
- Maximum left ventricular wall thickness
- Family history of sudden cardiac death
- Syncope
- Left atrial diameter
- Left ventricular outflow tract obstruction
- Exercise blood pressure drop

The patient had no family history of SCD and denied syncope, but the risk assessment comprised also of a 24-h ambulatory ECG and an exercise test.

Exercise Testing with Treadmill

Exercise testing was terminated for asthenia and muscular weakness at a heart rate corresponding to 93 % of maximal heart rate predicted for age. Neither symptoms nor ST-segment depression or elevation occurred. During exercise, arrhythmias were not detected except for two isolated polymorphic ventricular ectopic beats (VE) and one VE couple. Systolic blood pressure and heart rate response were normal.

24-h Ambulatory ECG

24-h ambulatory ECG was performed to detect atrial or ventricular arrhythmias. The total number of beats analyzed was 82,105. Sinus rhythm at average heart rate of 64 bpm, with minimum of 50 bpm and a maximum of 95 bpm. Two hundred fifty total ventricular ectopic (VE) beats of different morphologies with six VE couples and one

NSVT (four beats at 150 bpm). Forty-three total supraventricular ectopic beats with one short run of 12 beats. No significant pauses.

NSVT is defined as ≥3 consecutive ventricular beats at ≥120 bpm lasting <30 s, so only one episode was detected.

In the absence of sustained arrhythmia, the electrophysiological study (EPS) is not specifically recommended.

Clinical Course

According to HCM guidelines, ICD implantation should be considered in patients with an estimated risk of SCD ≥6 % and a life expectancy of >1 year, and it may be considered in patients with an estimated risk between ≥4 and <6 %, while it is not recommended in patients with an estimated risk <4 % unless they have clinical features that are of proven prognostic importance.

Our patient's estimated risk of sudden cardiac death at 5 years was 5 % (intermediate), based on severe cardiac hypertrophy and NSVT; that supported the indication for ICD implant in primary prevention.

The patient was informed about his SCD risk and the necessity of an ICD implant. He was made also aware on the risk of inappropriate shocks, implant complications, and the social and occupational implications of an ICD implant.

According to young age, primary prevention indication, good AV conduction, and patient's preference, we scheduled a subcutaneous ICD (S-ICD) implantation.

At the preimplantation screening test, the patient presented the anatomical and electrocardiographic features ideal for a suitable subcutaneous sensing. An S-ICD was then implanted without complications.

Chest X-Ray

Chest X-ray was performed the day after implantation (Figs. 11.5 and 11.6).

Conclusion: Correct position of the implanted S-ICD system

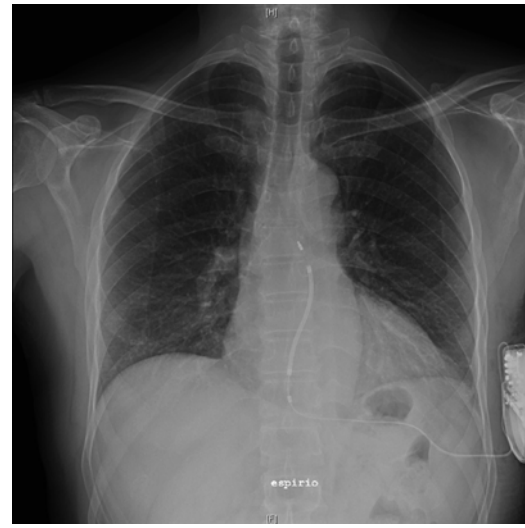

Fig. 11.5 Chest X-ray anterior-posterior (AP) projection

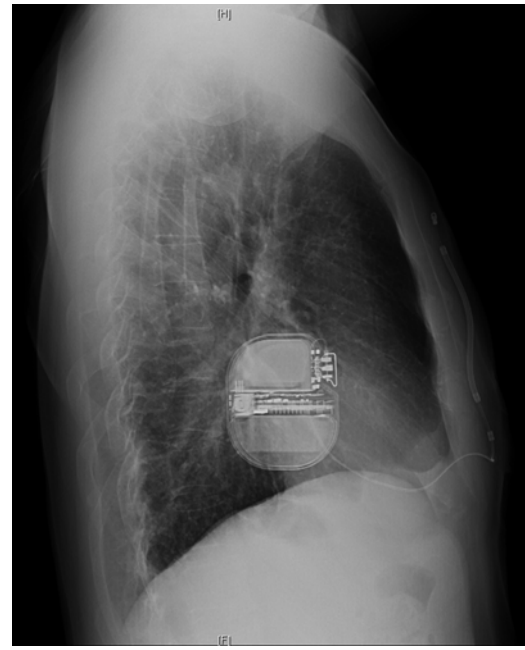

Fig. 11.6 Chest X-ray lateral view

Therapy and Discharge

Because the episode of prolonged palpitation was his first and an S-ICD was implanted, we decided not to give antiarrhythmic therapy and maintained the calcium channel blockers (verapamil) in order to control LVOT gradient.

Moreover, at discharge, the patient was advised to abstain from competitive athletic activity and strenuous physical exertion and was given clinical and echocardiographic follow-up appointments.

11.2 Hypertrophic Cardiomyopathy

Introduction and Epidemiology

The most recent expert consensus on cardiomyopathies has adopted a new classification system no more based on primary or secondary involvement of the heart but in which cardiomyopathies are defined by specific morphological and functional phenotypes as they present for the first time to the observer: mainly hypertrophic, dilated, arrhythmogenic cardiomyopathy and restrictive phenotype. Only in the second time, cardiomyopathies are grouped into familial/genetic and nonfamilial/nongenetic subtypes, irrespective of the presence of extra-cardiac disease [1, 2, 3].

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions. Many are the secondary causes of hypertrophy (in particular left ventricular hypertrophy) that should be considered in differential diagnosis:

1. Athlete's heart
2. Hypertensive cardiomyopathy
3. Valve diseases imposing increased afterload (mainly aortic stenosis)
4. Isolated basal septal hypertrophy in elderly people

Moreover hypertrophic phenotype (variable grade and distribution of ventricular wall thickening) could represent a common picture of different pathologic conditions such as infiltrative disorders due to inborn errors of metabolism (e.g., Pompe disease, Fabry disease) or deposition of anomalous misfolded proteins (different types of amyloidosis). Other genetic causes could be mithocondrial diseases, neuromuscular disorders (Friedreich's ataxia), or malformative syndromes like Noonan or LEOPARD [4].

The true hypertrophic cardiomyopathy is a genetic disease with an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. In general, patients with a sarcomere protein mutation present earlier and report a higher prevalence of family history of HCM and sudden cardiac death (SCD) than those without a mutation. They also tend to have more severe hypertrophy, microvascular dysfunction, and myocardial fibrosis.

Incidence

A number of studies worldwide report a prevalence of HCM in the range of 0.02–0.23 % in adults. In pediatric registries, the prevalence of HCM in children is unknown, but population-based studies report an annual incidence of 0.3–0.5 per 100,000. Most studies report a small male preponderance, while the prevalence in different racial groups is similar.

Diagnosis and Definition

- In an adult, HCM is defined by a wall thickness ≥15 mm in one or more LV myocardial segments—as measured by any imaging technique such as echocardiography, cardiac magnetic resonance imaging (CMR), or computed tomography (CT)—that is not explained solely by loading conditions.
- In children as in adults, the diagnosis of HCM requires a LV wall thickness more than two standard deviations greater than the predicted mean z-score.
- The clinical diagnosis of HCM in first-degree relatives of patients with unequivocal disease (LVH ≥15 mm) is based on the presence of otherwise unexplained increased LV wall

thickness ≥13 mm in one or more LV myocardial segments.

Variants

A particular variant is apical hypertrophic cardiomyopathy (AHCM) that is a rare form of HCM, which usually involves the apex of the left ventricle and rarely involves the right ventricular apex or both. Historically, this condition was thought to be confined to the Japanese population, but it is also found in other populations. Of all the HCM patients in Japan, the prevalence of AHCM was 15 %, whereas in the USA and Europe, the prevalence was only 3 %. The diagnostic criteria for AHCM included demonstration of asymmetrical LV hypertrophy, confined predominantly to the LV apex, with an apical wall thickness ≥15 mm and a ratio of maximal apical to posterior wall thickness ≥1.5. In contrast with the common variant of HCM, up to 54 % of patients with AHCM are symptomatic. This entity should be well known because of its difficult recognition (the apical position of hypertrophic segments represents a limitation for a routine 2D echocardiography) and its high prevalence of complications such as atrial fibrillation, myocardial infarction, apical aneurysm, embolic events, and congestive heart failure [5].

Differential Diagnosis

Genetic and nongenetic disorders causing hypertrophic phenotype can present with lesser degrees of wall thickening (13–14 mm); in these cases, the diagnosis of true HCM requires evaluation of other features including family history, noncardiac symptoms and signs, electrocardiogram (ECG) abnormalities, laboratory tests, and multimodality cardiac imaging. In any situation, the age of presentation is a fundamental clue to the differential diagnosis. Severe (maximal thickness more than 30 mm or equivalent in children) and concentric ventricular hypertrophy in a child, adolescent, or young adult should rise suspicion of metabolic or storage disorders, in particular Pompe disease in the infantile period and Danon disease in adolescent males. Different degrees of concentric hypertrophy with left ventricular systolic impairment is a clue to infiltrative diseases, because the hypokinetic end-stage phases of a true HCM more often pass through a dilation of left ventricle.

A New Diagnostic Tool: Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) is particularly useful for characterizing the presence, location, and extent of LV hypertrophy, which can be limited to one or two left ventricle (LV) segments. In those cases, CMR offers a superior visualization and a higher diagnostic accuracy respect to 2D echocardiography, particularly when the only segments involved are the basal anterolateral free wall or the apex.

Recent study showed that diffuse hypertrophy, involving >50 % of the left ventricle and 8 or more segments, is present in 54 % of patients with HCM, whereas only 10 % of patients present with single segment involvement [6, 7].

During an exam directed to distinguishing the possible origin of a hypertrophic phenotype found with echocardiography, CMR could add diagnostic clues, demonstrating a constellation of suggestive features of genetic HCM: such as anomalies in papillary muscles, right ventricle, subclinical features, and particularly tissue characterization.

Papillary muscle involvement in HCM consists in apical displacement of its insertion and the presence of multiple or bifid papillary muscles with increased mass. All these variants could favor SAM and outflow tract obstruction perturbing the normal activity of mitral valve apparatus.

In 1/3 of patients with HCM, right ventricular wall thickness and/or mass is increased, including about 10 % of patient with extreme right ventricle (RV) wall hypertrophy (>10 mm). Finally in preclinical (genotype [+]/phenotype [−]) patients with HCM, CMR may show the presence of crypts. Myocardial crypt is a deep fissuring of the muscle orthogonal to the endocardial border (often visualized also in angiography), localized predominately in the inferior septum,

although the etiology of these structural abnormalities remains uncertain.

Moreover, CMR is able to accurately define ventricular volume and function, being the gold standard for ejection fraction measurement. Frequently in patients with HCM, the ventricular volumes are reduced, and the hyperkinetic appearance of systolic contraction translates into a supernormal ejection fraction. This is true until the end stage of cardiomyopathy is reached, when the diastolic dysfunction, present from the beginning and related to myocardial thickness and rigidity, is accompanied by a reduced systolic thickening [8, 9, 10].

In 3-chamber view with cine imaging, CMR is able to elucidate the precise mechanism of outflow tract obstruction demonstrating turbulent flow generated by systolic movement of anterior mitral leaflet, chordae, and papillary muscle toward the interventricular septum [11].

Contrast-enhanced CMR with LGE sequences can detect areas of focal abnormality in approximately 50–80 % of patients. There is no specific pattern of LGE characteristic for HCM, although the distribution of LGE in HCM does not correspond to a coronary vascular territory. LGE is most often located in the most hypertrophied segment with an intramyocardial distribution (focal spot or linear deposit). Moreover, recent studies have demonstrated a significant association between the presence of LGE and ventricular tachyarrhythmias on ambulatory 24-h Holter electrocardiography. However, it is not clear whether the presence of LGE provides a strong predictive value in identifying patients with HCM at risk for sudden death, so much so the last ESC guidelines, published in 2014, do not include LGE in risk stratification algorithm [12–17].

Treatment

Treatment depends on disease expression, which can differ greatly among individuals, even within a single family. The natural history of hypertrophic cardiomyopathy includes those who remain asymptomatic and those who develop symptoms. The latter group can be further divided into those who develop outflow tract obstruction and those who do not.

Outflow tract obstruction at rest with exertional limitations is present in 25 % of all affected patients; an additional 25 % present inducible outflow tract obstruction; other groups of symptomatic patients are those with restrictive physiology and frequent tachyarrhythmias and who may experience exertional limitation because of diastolic dysfunction and those who are at risk or have already experienced ventricular arrhythmias and sudden cardiac death. At last, there is a small proportion of patients (up to 5 %) who may develop the end-stage phase of hypertrophic cardiomyopathy with left ventricular dilation and systolic impairment.

Left Ventricular Outflow Tract Obstruction

Treatment of outflow obstruction should be restricted to patients who exhibit the associated symptoms. Recognition of obstruction-related symptoms may be made challenging by both a patient's restriction in physical activity and by the presence of latent obstruction (obstruction not present at rest but only under provocative conditions such as exercise, Valsalva maneuver). First-line therapy consists in pharmacologic approach with β-blockers or disopyramide to reduce left ventricular inotropism and to prolong diastolic filling time.

Patients who cannot tolerate or who are refractory to medical therapy are candidates for surgical or catheter-based treatment of outflow obstruction. In experienced centers, both procedures are associated with low rates of complications and high successful rate. There is debate over which procedure is best, but concerns are emerging about the potential for creation of an arrhythmogenic focus with percutaneous septal ablation, as well as the increased risk of complete heart block with that procedure. The routine performance of CMR after septal reduction therapy is not recommended, but it can be of value when questions arise about LV residual function or when gradients do not resolve or recur late after the procedure.

Table 11.1 Major clinical features associated with an increased risk of sudden cardiac death in adults according to the 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy

Risk factor	Comment
Age	The effect of age on SCD has been examined in a number of studies, and two have shown a significant association, with an increased risk of SCD in younger patients
	Some risk factors appear to be more important in younger patients, most notably, NSVT severe LVH and unexplained syncope
Non-sustained ventricular tachycardia	NSVT occurs in 20–30 % of patients during ambulatory ECG monitoring and is an independent predictor of SCD
	There is no evidence that the frequency, duration, or rate of NSVT influences the risk of SCD
Maximum left ventricular wall thickness	The severity and extent of left ventricular hypertrophy measured by TTE are associated with the risk of SCD
	Several studies have shown the greatest risk of SCD in patient with a maximum wall thickness of ≥30 min, but there are few data in patients with extreme hypertrophy (≥35 mm)
Family history of sudden cardiac death at a young age	While definitions vary, a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM
Left atrial diameter	Two studies have reported a positive association between LA size and SCD. There are no data on the association between SCD and LA area and volume. Measurement of LA size is also important in assessing the risk of AF
Left ventricular outflow tract obstruction	A number of studies have reported a significant association with LVOTO and SCD. Several unanswered questions remain, including the prognostic importance of provable LVOTO and the impact of treatment (medical or invasive) on SCD
Exercise blood pressure response	Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterized by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reverse
	Various definitions for abnormal blood pressure response in patients with HCM have been reported; for the purposes of this guideline, an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mmHg from rest to peak exercise or fall of >20 mmHg from peak pressure
	Abnormal exercise blood pressure response is associated with a higher risk of SCD in patient aged ≤40 years, but its prognostic significance in patients aged >40 years is unknown

HCM hypertrophic cardiomyopathy, *LA* left atrium, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract obstruction, *NSVT* non-sustained ventricular tachycardia, *SCD* sudden cardiac death, *TTE* transthoracic echocardiography

Ventricular Arrhythmias and Sudden Cardiac Death

Ventricular arrhythmias and sudden cardiac death remain dreaded outcomes of HCM, occurring in young, otherwise healthy individuals. Well-known clinical risk factors for sudden cardiac death allow clinicians to target implantable cardioverter defibrillator therapy to those who are at the highest risk. Not all risk factors predict this outcome equally, and placement of this type of device in young patients is associated with an important lifetime risk of complications [18–22].

A personal history of cardiac arrest or sustained ventricular arrhythmia is the most powerful risk factor. Multiple risk factors in an individual strengthen the case for an implantable defibrillator, as stated by the most recent international guidelines (Table 11.1).

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Cardiac Amyloidosis

12

Alessandro Barbarossa and Erika Baiocco

12.1 Case Report

A 67-year-old man presented to the family doctor complaining of productive cough and dyspnea on exertion during ordinal physical activity. Symptoms arose about 3 weeks ago, associated with atypical chest pain (punctory, not correlated to exercise); the patient denied palpitation and fever.

Those symptoms were diagnosed by the GP as an upper respiratory tract infection and treated with i.m. antibiotic therapy (ceftriaxone 2g once daily). Despite therapy, the patient remained strongly symptomatic and his family doctor decided to program a chest X-ray that showed bi-basal pleural effusion, more evident to the right side.

The patient was referred to a cardiologist for consulting; meanwhile, he starts oral diuretic therapy (furosemide) with consequent improvement of dyspnea and pleural effusion reduction.

Medical History and Cardiovascular Risk Factors

- Smoker
- No familial history for cardiovascular disease

Allergies

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Medications

None

Vital Signs

- Temperature: 36.5 °C
- Heart rate: 70 bpm
- Blood pressure: 120/80 mmHg
- Respiratory rate: 10 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %

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Physical Examination

- *General:* fatigued, no acute distress, alert, awake, and oriented. Well developed and well nourished
- *Head, eyes, ears, nose, and throat:* normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- *Neck:* supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- *Cardiovascular:* regular rate and rhythm; S1 and S2 are normal; no murmurs, rubs, or gallops; point of maximal intensity nondisplaced and nonsustained; no hepatojugular reflux; and capillary refill less than 2 s
- *Lungs:* rales to auscultation at the bases bilaterally, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal percussion
- *Abdomen:* mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no cost vertebral angle tenderness, and no hepatosplenomegaly
- *Extremities:* no cyanosis or clubbing, with mild peripheral edema
- *Neurological:* cranial nerves II through XII intact, no focal deficit
- *Psychiatric:* normal affect, no hallucinations, normal speech, and no dysarthria
- *Skin:* intact, no rashes, no lesions, and no erythema

Which Are the Possible Causes for Dyspnea on Exertion and Atypical Chest Pain?

- Lung diseases
  - Chronic obstructive pulmonary disease (COPD)
  - Pneumonitis
  - Bronchitis
- Heart diseases
  - Heart failure (HF)
  - Tachyarrhythmias and bradyarrhythmias
- Pulmonary embolism
- Anemia
- Poor training

Symptoms arose quite recently and therefore we can exclude a poor training condition.

The patient does not refer fever, and chest X-ray didn't show pulmonary consolidations, so the hypothesis of a pneumonitis seems also unlikely.

According to the physical exam (bi-basal rales), the most probable cause is heart failure. COPD exacerbation is also unlikely (chest X-ray), but cannot be excluded because of his smoking habit.

Pulmonary embolism and anemia could not be excluded only according to physical exam.

Routine EKG at Rest (Fig. 12.1)

Conclusions: sinus rhythm, normal atrioventricular conduction, counterclockwise rotation on horizontal axis, low voltages on limb leads, and diffuse nonspecific alterations in repolarization

Routine Laboratory Tests

- *Complete blood count:* normal
- *Cholesterol (total, HDL, LDL) and TG:* normal
- *Hepatic function (GOT, GPT, γ-GGT, ALP, total bilirubin, direct and indirect bilirubin):* normal
- *Thyroid function (TSH, FT3, FT4):* normal
- *Renal function (creatinine, BUN):* normal
- *Electrolytes (Na+, K+, Ca++, Mg++, Cl−):* normal
- *Fasting blood glucose:* 78 m/dl (4.33 mmol/L)
- *Troponin I-hs: 0.16 ng/ml (n.v. < 0.055 ng/ml)*
- *BNP:* 1195 pg/ml (n.v. <100 pg/ml)
- *Inflammation index: VES 3 mm/h (n.v. < 27 mm/h), CRP 0.3 mg/dl (n.v. <0.6 ng/ml)*
- *D-dimers: 213 ng/ml (n.v. <230 ng/ml)*

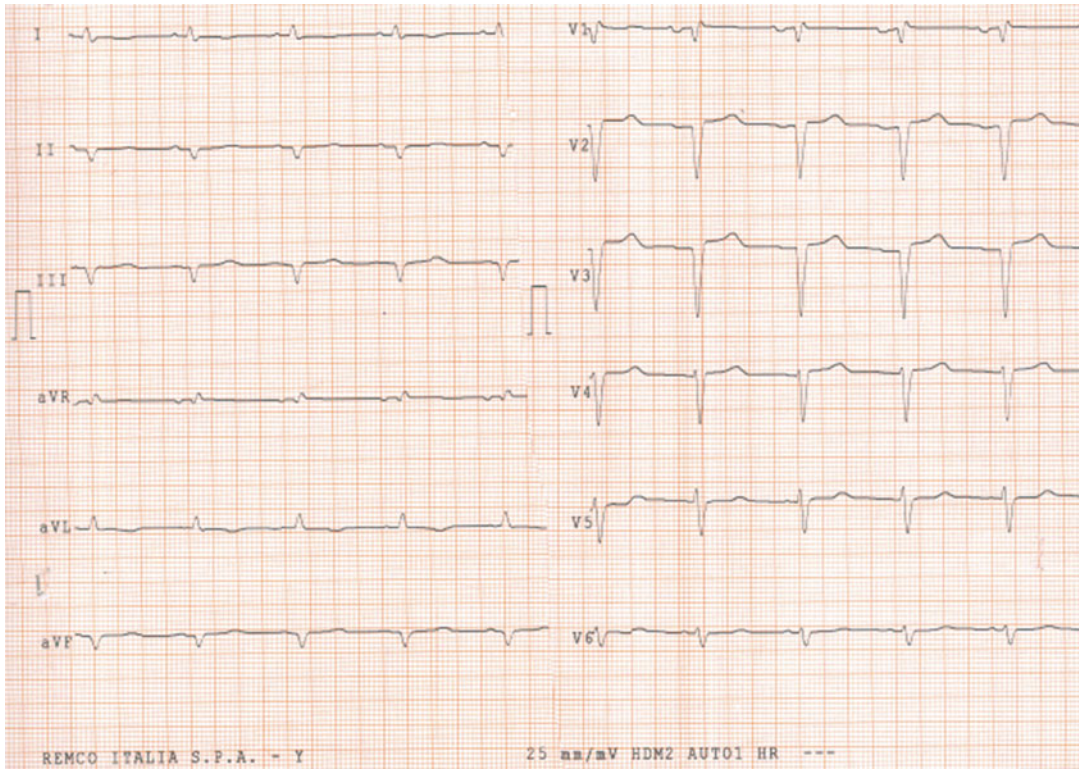

Fig. 12.1 Rest EKG performed in hospital

Pulmonary Function Tests

No alteration in pulmonary volumes and, normal Tiffeneau index, with mild reduction in DLCO.

Normal D-dimers, showed at routine laboratory tests, ruled out pulmonary embolism. According to EKG bradyarrhythmias could be excluded and normal red blood cells count excluded the presence of anemia. Finally, COPD was excluded by pulmonary function tests.

The diagnosis of heart failure is now very likely according to symptoms, physical exam, chest radiography, and laboratory tests.

Which Are the Possible Causes of Heart Failure?

- *Myocardial disease*
  - Coronary artery disease
  - Hypertension
  - Cardiomyopathy
    - Familial (hypertrophic, dilated, ARVD, restrictive, left ventricular non-compaction)
- Myocarditis (infective, immune mediated, chemotherapy, cocaine, alcohol, heavy metals)
- Endocrine/nutritional (pheochromocytoma, vitamin deficiency, hypophosphatemia, hypocalcemia)
- Pregnancy
  - Infiltration (amyloidosis, malignancy)
- *Valvular heart disease*
  - Mitral
  - Aortic
  - Tricuspid
  - Pulmonary
- *Pericardial disease*
  - Constrictive pericarditis
  - Pericardial effusion

- *Congenital heart disease*
- *Arrhythmias*
  - Tachyarrhythmias (atrial, ventricular)
  - Bradyarrhythmias (sinus node dysfunction, atrioventricular block)
- *High-output states*
  - Anemia
  - Sepsis
  - Thyrotoxicosis
  - Paget's disease
  - Arteriovenous fistula
- *Volume overload*
  - Renal failure
  - Iatrogenic (postoperative fluid infusion)

HF may be the final result of different pathological pathways. However, some possibilities can be excluded just considering medical history, physical examination, and EKG. Our patient was smoker, but did not have other risk factors for coronary artery disease (CAD); a diagnosis of ischemic cardiomyopathy was unlikely. A heart valvular disease was excluded by the physical examination. The patient had not any familiar history for genetic cardiomyopathies (ARVD, hypertrophic, non-compaction, dilated), albeit this is not an absolute exclusion criteria. The basal EKG did not show brady- or tachyarrhythmias and the patient did not complain palpitations. Finally, normal routine laboratory tests excluded anemia, thyrotoxicosis, renal failure, and sepsis.

Acute myocarditis remains a valid possibility (rapid onset of symptoms, presence of cough and dyspnea) and also pericarditis (atypical chest pain and low voltages, albeit in only limb leads, at basal EKG). In addition infiltrative cardiomyopathy cannot be excluded.

The next step was to record an echocardiogram in order to evaluate function and morphology of the left ventricle.

Echocardiography Results
(Fig. 12.2a, b)

Bi-atrial enlargement (LA diameter M-mode = 50 cm; area 4c = 26 cm^2, RA area 4c = 20 cm^2). Small size of the left ventricle (iLVEDV 44 ml/m^2), increased wall thickness (IVSDd = 1.4 cm) with granular sparkling appearance (particularly evident at the level of the inter ventricular septum) and reduced systolic function (ejection fraction with Simpson's rule 0.45). Normal size of the right ventricle, with increased free wall thickness and reduced systolic function (TAPSE 11 mm). Inter atrial septum thickening.

Mitral valve leaflets are thickened with mild regurgitation.

Tricuspid valve leaflets are also thickened with mild regurgitation and normal systolic pressure gradient (PASP = 30 mmHg).

Normal aortic and pulmonic valves.

The inferior vena cava is slightly dilated (26 mm). There is less than 50% inspiratory collapse of the IVC.

Small circumferential pericardial effusion, not hemodynamically significant.

Restrictive diastolic pattern with increased filling pressure (E/A 4, E/E' 29, E dec time 147 m/sec).

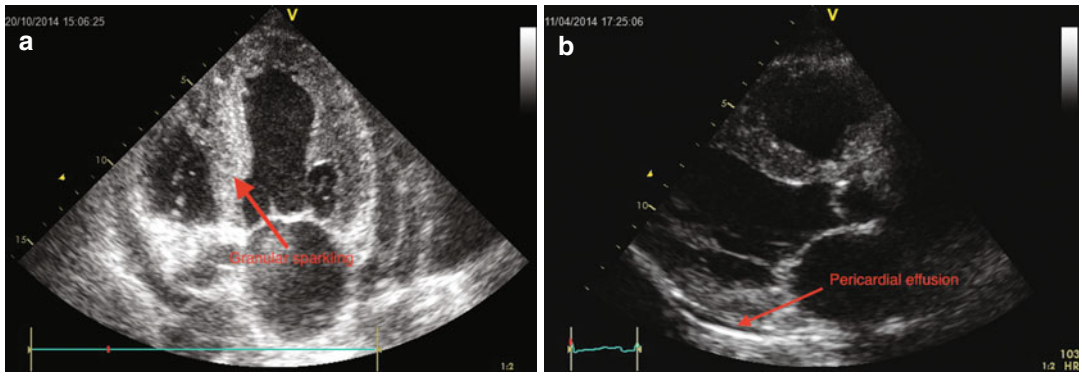

Fig. 12.2 (**a**, **b**) PLAX and apical 4-CH short axis showed left ventricular hypertrophy with "granular sparkling" appearance and pericardial effusion

> *Conclusion:* mild biventricular systolic dysfunction. Biventricular wall thicknesses with granular sparkling aspect. Bi-atrial enlargement. Severe left ventricular diastolic dysfunction. Mild pleural effusion. Not significant valve regurgitation or gradients.

The echocardiography findings were compatible with hypertrophic/hypertensive or infiltrative cardiomyopathy.

The patient had no history of hypertension and arterial pressure values were normal during physical examination, so a hypertensive cardiomyopathy was unlikely.

Distinguishing between hypertrophic and infiltrative, only by echocardiography, is an easy task. The ventricle involvement is usually concentric in the infiltrative forms and eccentric in the hypertrophic forms. The presence of dynamic obstruction of left ventricular output tract is more frequent in hypertrophic forms. A pericardial effusion and the typical pattern of granular sparkling of the myocardium are suggestive of an infiltrative form. A severe diastolic dysfunction (grade III) may be found in both diseases.

In our case the typical echocardiographic pattern (wall thickening with granular sparkling aspect and severe diastolic dysfunction) in addition to low electrocardiographic limb lead voltages makes an infiltrative cardiac disease more likely.

Cardiac RMN

In order to acquire further diagnostic elements about ventricle morphology of the ventricles, a cardiac RMN was performed (Fig. 12.3a, b).

> […] bi-ventricular parietal hypertrophy and systolic dysfunction (LVEF 41%, RVEF 47%). Bi-atrial enlargement (left > right). Mild mitral and tricuspid regurgitation. No myocardial edema. Post contrastographic diffuse subendocardial late enhancement. Moderate circumferential pericardial effusion.
> Conclusion: pattern suggestive of cardiac amyloidosis

There are three main types of cardiac amyloidosis: AL-related amyloidosis, ATTRm amyloidosis, and ATTRwt amyloidosis. According to familial history negative for cardiovascular disease, the patient's age, and epidemiology, the most likely diagnosis is AL-related amyloidosis.

The next step to confirm this hypothesis is to evaluate the presence of a high production of

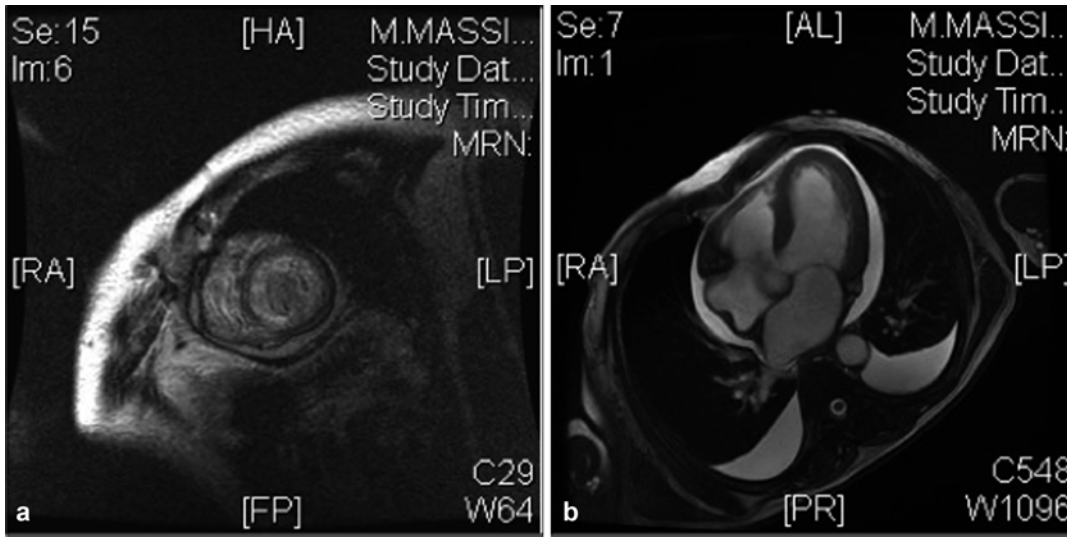

Fig. 12.3 (**a**, **b**) Magnetic resonance showed areas of delayed enhancement (DA), diagnostic for amyloidosis and pleuropericardial effusion

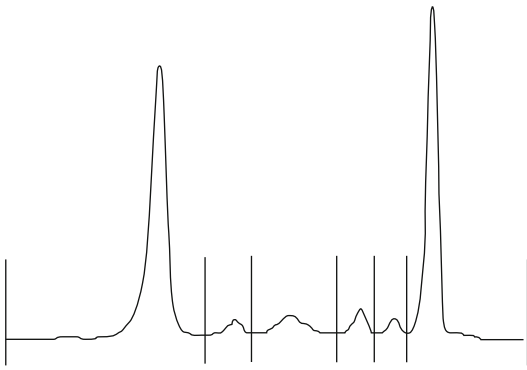

Fig. 12.4 Monoclonal proliferation at serum electrophoresis

immunoglobulin light chains. For this purpose we performed a serum electrophoresis, which showed a monoclonal peak in the gamma zone immunofixation that demonstrates an increase of light-chain quantity in blood and urine (Fig. 12.4).

Bone marrow biopsy (BOM) confirmed the diagnosis of multiple myeloma (MM), and finally, abdomen fat biopsy confirmed the diagnosis of amyloidosis.

Final Diagnosis

Cardiac-acquired monoclonal immunoglobulin light-chain (AL) amyloidosis.

The patient was treated with i.v. diuretic with consequent progressive resolution of the peripheral edema, lung congestion, and improvement of dyspnea and NYHA functional class. Because of low potassium serum level, an oral potassium-sparing diuretic was added. Other heart failure-specific drugs (that were introduced during diagnostic work up) such as renin-angiotensin-aldosterone antagonist (ACE-I and ARBs) and beta-blockers were interrupted according to scientific evidences.

Patient, after clinical stabilization, was referred to a hematologist for implementation of the amyloidosis-specific therapy.

Red Flags

Some characteristic features, founded during diagnostic work up, could help to reach the final correct diagnosis minimizing the time and use of inappropriate exams:

- Clinical history substantially negative for cardiovascular risk factors
- Cardiac physical examination negative for murmurs; presence of signs of high central venous pressure
- Low voltages in limb leads at standard EKG
- Monoclonal peak in the gamma zone at serum electrophoresis
- Typical echocardiographic appearance (concentric hypertrophy with granular sparkling pattern, mild pericardial effusion, valve and interatrial septum thickening)

12.2 Amyloidosis

Classification

According to the literature there are three most frequent type of amyloidosis [1]:

- *Acquired monoclonal immunoglobulin light-chain amyloidosis (AL):* characterized by clonal plasma cells in the bone marrow that produce the immunoglobulin light chains of the fibrillary deposits. The most common plasma dyscrasia associated with this form is multiple myeloma (MM).
- *Hereditary transthyretin-related form (ATTRm):* can be caused by >100 mutations of transthyretin, a transport protein synthesized mainly by the liver.
- *Wild-type (nonmutant) TTR-related amyloidosis (ATTRwt):* nonhereditary "senile" systemic amyloidosis, which affects mainly the hearts of elderly men caused by cardiac deposition of amyloid derived from wild-type transthyretin (with a normal amino acid constitution) [2].

Pathophysiology

Cardiac amyloidosis is a manifestation of one of several systemic diseases known as "amyloidosis." The common feature of this group of diseases is the extracellular deposition of a proteinaceous material that, when stained with Congo red, demonstrates apple-green birefringence under polarized light and that has a distinct color when stained with sulfated Alcian Blue [3].

Cardiac involvement may be the predominant feature or may casually be found during investigation of a patient presenting with another major organ involvement. Its predominance varies regarding amyloidosis type: senile systemic amyloidosis and some forms of transthyretin amyloidosis invariably affect the heart, whereas cardiac involvement ranges from absent to severe in amyloidosis derived from a light-chain precursor. Otherwise, secondary form of amyloidosis almost never affects the heart in a clinically significant manner [4].

Regardless of the underlying pathogenesis of amyloid production, cardiac amyloidosis is a myocardial disease characterized by extracellular amyloid infiltration throughout the heart. Amyloid deposits are located in the ventricles and atria, perivascularly (particularly in the small vessels), and in the valves. It may also involve the conduction system. Thus, it may result in initially diastolic dysfunction of both ventricles, followed by deterioration of systolic function and precipitating heart failure. Moreover, symptoms and signs of myocardial ischemia may occur because of the presence of vascular infiltration and conduction disturbances (such as atrioventricular blocks and bundle branch blocks) with conduction system involvement [3].

Clinical Features

Heart Failure

Patients with cardiac amyloidosis usually complain symptoms of biventricular heart failure with some differences between the three main forms.

About 50 % of patients with AL-related amyloidosis present with rapidly progressive symptoms such as dyspnea, almost always associated with evidence of elevated right-sided filling pressure and peripheral edema, and in late-stage disease, ascites is not uncommon. Also for ATTRm and ATTRwt forms, heart failure is the main clinical manifestation, albeit, differently from AL form, progression is slower but also inexorable.

Small Vessel Disease

Vascular involvement may manifest as purpura, claudication, or angina. The presence of periorbital purpura, often occurring with coughing, sneezing, or very minor trauma, suggests capillary involvement, and its presence in a patient with unexplained heart failure strongly suggests amyloidosis, almost always of the AL type. The presence of claudication (principally leg and jaw), angina, or both is suggestive of vascular amyloidosis. Typically, the involved vessels are small and intramyocardial; as a result, coronary angiography is usually normal or shows only minor abnormalities [5, 6].

Syncope

Syncope or presyncope is a common finding in patients with cardiac amyloidosis and may be due to multiple additional factors. These include postural or exertional hypotension due to excessive diuresis or autonomic neuropathy. Moreover, an exercise syncope may represent an inability to augment cardiac output; when that occurs a high mortality rate is expected in 3 months, often due to sudden cardiac death.

Documented ventricular arrhythmias are an infrequent cause of syncope, maybe because the amyloid heart reacts poorly to hypoperfusion and any severe tachyarrhythmia causing loss of consciousness is usually fatal [7].

Conduction System Disease

Despite a widespread involvement of the conduction system, high-degree atrioventricular block is an unusual feature in AL-related amyloidosis, and symptomatic sinus node dysfunction appears uncommon. In contrast a progressive conduction system disease often occurs in the ATTR amyloi-

dosis (both senile and familial), and a pacemaker implantation is often required [8].

Extracardiac Manifestation

Neurological (peripheral and autonomic neuropathy, carpal tunnel syndrome), dermatological (periorbital purpura, nail dystrophy), macroglossia (typical of AL form).

Senile cardiac amyloidosis (ATTRwt), which is different from AL and ATTRm amyloidosis, usually is not associated with other major organ involvements [3].

Diagnosis

- *Physical examination:* signs and symptoms of heart failure (rales, high jugular venous pressure, hepatomegaly); usually systolic BP is low (<100 mmHg); purpura may be present.
- *EKG:* low voltage in the limb leads is one of the most common electrocardiogram (EKG) abnormalities in AL cardiac amyloidosis (occurring in approximate 50 %), although it is less common in the other forms of cardiac amyloidosis, being reported in about 25 % of patients with familial disease (ATTRm) and in about 40 % of patients with senile cardiac amyloidosis (ATTRwt) [1, 3].
- *Echocardiography:* thickness of the atrium and ventricular walls (which may or may not be associated with increased echogenicity) as well as thickened valve leaflets and interatrial septum. Diastolic dysfunction and reduction in longitudinal systolic function precede reduction in left ventricular ejection fraction. Atrial dysfunction is frequently present and may be associated with appendage thrombus even in the absence of a history of atrial fibrillation [9–11].
- *Cardiovascular magnetic resonance:* cardiovascular magnetic resonance (CMR) imaging can provide evidence strongly suggestive of amyloid cardiomyopathy, particularly a distinctive pattern of global left ventricular late gadolinium enhancement (LGE) rarely seen in other cardiomyopathies.
- *Nuclear imaging:* scintigraphy with 99 mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) may be useful in differential diagnosis between AL and ATTR amyloidosis [12].
- *Serum electrophoresis:* the presence of a serum or urine monoclonal paraprotein in the setting of a typical echocardiogram is suggestive of AL-related amyloidosis, but it alone does not firmly establish the diagnosis. In fact, as demonstrated in some studies, older males with clinically isolated cardiac involvement and a small monoclonal gammopathy may have senile cardiac amyloid and unrelated MGUS [13].
- *Tissue biopsy:* the final diagnosis of cardiac amyloidosis requires demonstration of amyloid deposits in the heart with endomyocardial biopsy or, in patients with appropriate imaging cardiac findings, demonstration of amyloid deposits at histologic examination of other tissues, like the abdominal fat pad, rectum, or kidney.
- Abdominal fat pad aspirate staning with Congo red will result positive in more of 70 % of patients with AL-related amyloidosis, but it is subject to false positive especially in center with low expertise. Instead, bone marrow biopsy should be the test of choice to confirm the suspect of AL-related amyloidosis, because it demonstrates evidence of a plasma cell dyscrasia in >80 % of patients and shows amyloid deposits in about 60 % [14].

Prognosis and Therapy

AL-related cardiac amyloidosis is associated with a worse prognosis and more rapid progression of heart failure (mainly due to diastolic dysfunction) compared with the other forms [1], with a median survival of 6 months without specific therapy [3]. ATTRm forms, differently, have a better long-term survival [15].

Treatment

Treatment requires a twofold approach: management of cardiac-related complications due to

amyloid deposition (which is similar regardless of the specific type of amyloid) and treatment of the underlying disease to suppress new amyloid formation (which is tailored for each specific form).

Cardiac-Related Therapy

Standard drugs used for the treatment of congestive heart failure are not useful and poorly tolerated or in some cases may be dangerous in patients with amyloidosis.

Beta-blockers (BBs) and calcium channel blockers (CCBs) are deleterious because they decrease heart rate, which is the only mechanism that can maintain cardiac output in these patients with severe diastolic dysfunction; moreover, they may also aggravate autonomic dysfunction like angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARB) [16]. Moreover, these drugs may increase the risk of hypotension.

Digitalis has been shown to accumulate in cardiac amyloid deposits in in vitro studies; for this reason its use may be harmful in patients with cardiac amyloidosis [17].

Loop diuretics (e.g., furosemide), given at high dosage in patients with severe fluid retention, are the mainstay of therapy for amyloid-related symptoms, although they don't reduce mortality. When fluid retention is severe, a booster diuretic (metolazone) can be used intermittently. Furthermore, daily use of spironolactone in addition to loop diuretics could help to keep normal potassium level [18].

In case of arrhythmias, amiodarone should be considered as the first-line therapy.

Anticoagulation therapy is mandatory in patients with supraventricular arrhythmias and may be considered in patients with sinus rhythm but with severe contractile atrial dysfunction.

Pacemaker implantation may be indicated in patients with symptomatic bradycardia or conduction disorders, while the utility of implantable cardioverter defibrillators (ICDs) is still controversial because electromechanical dissociation seems to be the more frequent cause of sudden cardiac death in these patients [19].

Finally, heart transplantation could be a solution in selected young patients, with advanced amyloid cardiomyopathy, free from other comorbidities [20, 21].

Specific Therapy

- *AL-related amyloidosis:* the specific therapy aims to stop the production of abnormal light chains by the plasma cells. This can be achieved with a specific chemotherapy. Because each patient is different, the dosage and choice of drug require assessment by a hematologist in order to minimize any adverse side effects. Measuring the free light chains in the blood assesses the response to AL-related amyloidosis treatment. The levels will normalize in successful treatment, usually before there is a definite improvement in the symptoms. The initial therapy is often changed if there is no clear response over the first 2–3 cycles [18].
- *ATTRm (familial amyloidosis):* because the main source of mutant transthyretin is the liver, transplantation is currently the treatment of choice in carefully selected patients. Intensive investigation is underway to develop and test drugs that can prevent the production of amyloid in patients with the abnormal genes [18].
- *ATTRwt (senile amyloidosis):* no specific therapy currently exists.

Conclusion

Although cardiac amyloidosis is uncommon, knowledge of typical clinical and instrumental features is essential for the diagnosis in order to start the correct treatment and to avoid unnecessary, and sometimes harmful, therapies.

The distinction between the major amyloidosis forms is fundamental because specific therapies and prognosis differ greatly from one another. Moreover, early diagnosis is critical because patients with advanced disease are usually too compromised for intensive chemotherapies.

Despite recent progress in knowledge of the disease mechanism, cardiac amyloidosis is a severe disease with a poor prognosis and few therapeutic possibilities. For this reason further studies and investigation are necessary.

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Left Ventricular Non-compaction Cardiomyopathy

13

Alessandro Maolo and Simona Masiero

13.1 Case Report

A 50-year-old man referred to the family doctor for worsening dyspnea and fatigue during ordinary physical activities appearing 3 months earlier. From that time on, symptoms arise every time the patient walks a little longer than usual even at flat level.

At anamnesis, he reported two syncopes preceded by dyspnea and dizziness without any feeling of palpitation or sweating. The first one occurred while he was walking and was complicated by concussion. The second episode occurred while he was watching television. In both cases, he recovered rapidly without neurological signs.

The family doctor referred the patient to the hospital for further investigation.

Medical History and Cardiovascular Risk Factors

- Type 2 diabetes mellitus
- Hypertension
- No previous or current pathology
- No fever episode in the last 3 years

Allergies

No allergy is referred by the patient.

Social History

- He works as a photographer.
- He smokes 4–5 cigarettes per day.
- He never used illicit drugs.
- He drinks a glass of wine only in particular occasions.

Medications

Sitagliptin 50 mg + metformin 850 mg at 8:00 a.m. and 12:00 a.m., metformin 850 mg at 20:00 p.m.

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Vital Signs

- BMI: 27
- Temperature: 36.7 °C
- Heart rate: 75 bpm
- Blood pressure: 130/80 mmHg
- Respiratory rate: 16 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %

Physical Examination

- *General:* fatigued, no acute distress, alert, awake, and oriented. Well developed and well nourished
- *Head, eyes, ears, nose, throat:* normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, no conjunctival injection
- *Neck:* supple, no jugular venous distention, no lymphadenopathy, no carotid bruit
- *Cardiovascular:* regular rate and rhythm, S1 and S2 are normal, S3 present, no murmurs or rubs, point of maximal intensity nondisplaced and non-sustained, no hepatojugular reflux, capillary refill less than 2 s
- *Lungs:* rales at auscultation at the bases bilaterally, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, normal percussion
- *Abdomen:* mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, no hepatosplenomegaly
- *Extremities:* no cyanosis or clubbing, mild peripheral edema
- *Neurologic:* cranial nerve II through XII intact, no focal deficit
- *Psychiatric:* normal affect, no hallucinations, normal speech, no dysarthria
- *Skin:* intact, no rashes, no lesions, no erythema

What Are the Possible Causes for Dyspnea on Exertion and Fatigue in This Case?

The following hypotheses were considered:

- *Flu*
- *Lung diseases*
  - COPD
  - Pneumonitis
  - Bronchitis
- *Heart diseases*
  - Heart failure
  - Bradyarrhythmias
  - Tachyarrhythmias
- *Poor training*
- *Recent weight gain*

The patient denies a recent weight gain (his BMI was 27 at the last family doctor visit). The symptoms arose 3 months ago that makes a poor training unlikely considering the recent emergence of the dyspnea.

The patient doesn't refer fever, cough, or other disorders related to flu, so the hypothesis of a pneumonitis or bronchitis seems unlikely, too.

According to the physical exam (rales at the bases bilaterally and S3 present), heart failure is the most likely cause.

ECG

A routine ECG at rest was performed (Fig. 13.1): sinus rhythm, normal atrioventricular and intraventricular conduction, and no abnormalities in repolarization.

Chest X-Ray

A chest x-ray was performed too (Fig. 13.2): cardiac shadow was slightly enlarged with an increase of cardiac transverse diameter with left ventricular preponderance. A left-sided pleural effusion was seen obliterating the costophrenic recess and was associated to a bilateral hilar enlargement with widespread bronchovascular signs.

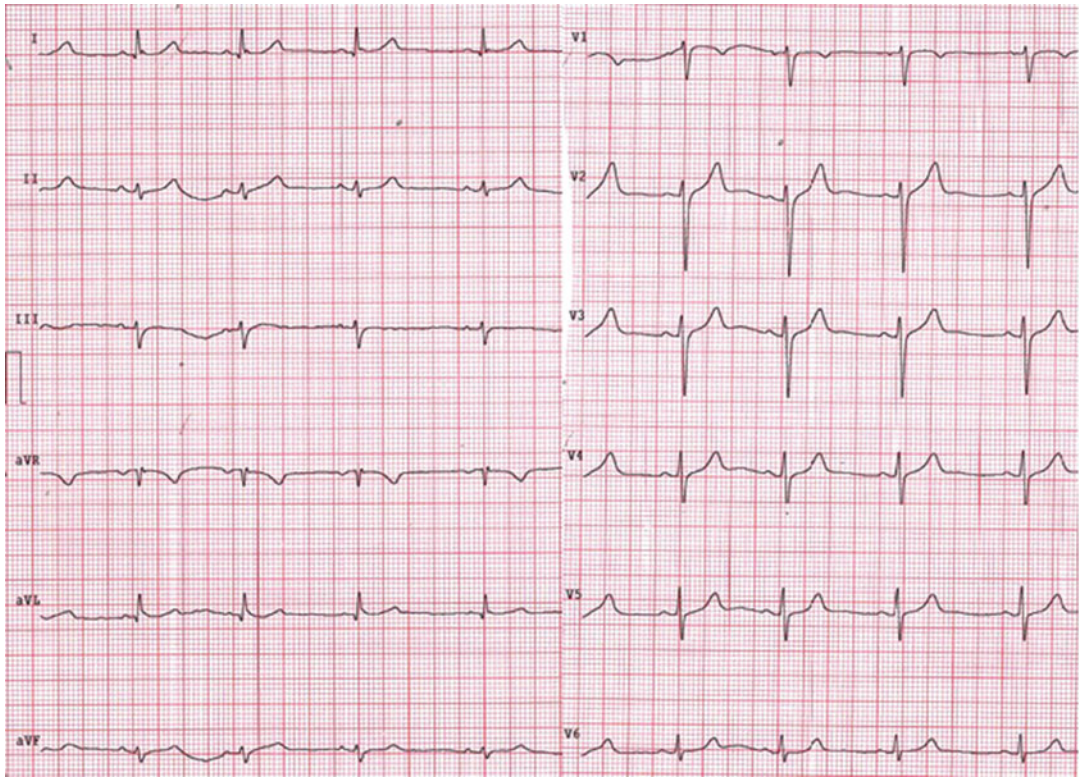

Fig. 13.1 Routine ECG. Notice the normal sinus rhythm without abnormalities in conduction or repolarization

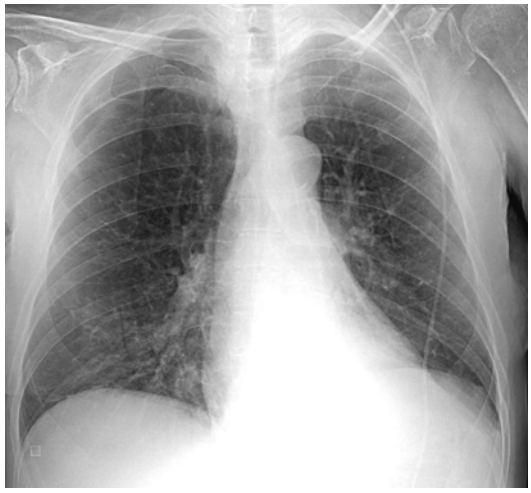

Fig. 13.2 Chest x-ray performed for the worsening dyspnea. The bronchovascular marking is evident

Routine Laboratory Tests

- *Complete blood count:* normal
- *Cholesterol (total, HDL, LDL) and TG:* normal
- *Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect):* normal
- *Thyroid function (TSH, FT3, FT4):* normal
- *Renal function (creatinine, BUN):* normal
- *Electrolytes (Na+, K+, Ca++, Mg++, Cl−):* normal
- *Fasting blood glucose:* 154 m/dl (8.56 mmol/L)
- *HbA1c:* 7.1 % (54 mmol/mol)
- *TnI-hs and CK-MB:* normal
- *BNP:* 673 pg/ml

What Are the Possible Causes of Heart Failure?

- *Myocardial disease*
  - Coronary artery disease
  - Hypertension
  - Cardiomyopathy
    - Familial (hypertrophic, dilated, ARVD, restrictive, left ventricular non-compaction)

    - Myocarditis (infective, immune-mediated, chemotherapy, cocaine, alcohol, heavy metals)
    - Endocrine/nutritional (pheochromocytoma, vitamin deficiency, hypophosphatemia, hypocalcemia)
    - Pregnancy
    - Infiltration (amyloidosis, malignancy)
- *Valvular heart disease*
  - Mitral
  - Aortic
  - Tricuspid
  - Pulmonary
- *Pericardial disease*
  - Constrictive pericarditis
  - Pericardial effusion
- *Congenital heart disease*
- *Arrhythmias*
  - Tachyarrhythmias (atrial, ventricular)
  - Bradyarrhythmias (sinus node dysfunction, atrioventricular block)
- *High output states*
  - Anemia
  - Sepsis
  - Thyrotoxicosis
  - Paget's disease
  - Arteriovenous fistula
- *Volume overload*
  - Renal failure
  - Iatrogenic (postoperative fluid infusion)

The diagnosis of heart failure is now very likely according to symptoms, physical exam, chest radiography, and laboratory tests.

Echocardiography

Echocardiography was also performed to evaluate function and morphology of cardiac valves and the left ventricle (Fig. 13.3a, b).

Aortic valve was normal and trileaflet. Normal dimensions of the left atrium (LA diameter M-mode, 3.9 cm; area 4c, 13 cm^2). The mitral valve, tricuspid valve, and pulmonic valve had normal function and morphology; the right atrium was also normal (area 4c = 13 cm^2). The right ventricle was normal in size with normal function (TAPSE 22 mm). There was a mild tricuspid regurgitation centrally directed. There was no evidence of atrial septal defects. The left ventricle was slightly dilated (indexed left end-diastolic volume 80 ml/m^2) with severe reduction of systolic function and areas of prominent trabeculae in the apex and the side wall. Ejection fraction measured with Simpson's biplane method was 30 %. The aorta was normal (aortic root dimension, 2.7 cm; ascending aorta, 3.1 cm; aortic arch, 3.1 cm; thoracic aorta, 2.8 cm; abdominal aorta, 1.8 cm). IVC was slightly dilated with an inspiratory collapse <50 % (RAP = 10 mmHg and PAPS = 35 mmHg).

Conclusions: There is severe reduction of left ventricular function. Left ventricle walls are homogeneously hypokinetic. Morphologic alterations of the apex and side wall of the left ventricle compatible with non-compaction of the myocardium.

Because of that morphologic pattern of the left ventricle, a cardiac RMN was requested (Fig. 13.4a–f). "[…] Prominent endocardic apical-subapical trabeculae, extended to the side wall and the middle of LV, compared to a compact epicardial layer (Noncompaction/compaction ratio 2.3). Those findings can be related to areas of myocardial non-compaction."

The patient was diagnosed with left ventricular non-compaction cardiomyopathy.

The patient was monitored, and an intravenous diuretic therapy was introduced with clinical benefit. Symptoms resolved and dyspnea and fatigue disappeared.

Now the Heart Failure Is Explained. But What About the Syncope? What Are the Possible Causes?

- Neurally mediated syncope (vasovagal, situational, carotid sinus syncope)
- Orthostatic hypotension (primary autonomic failure as Parkinson's disease or secondary autonomic failure as diabetes or amyloidosis, drug-induced, volume depletion)

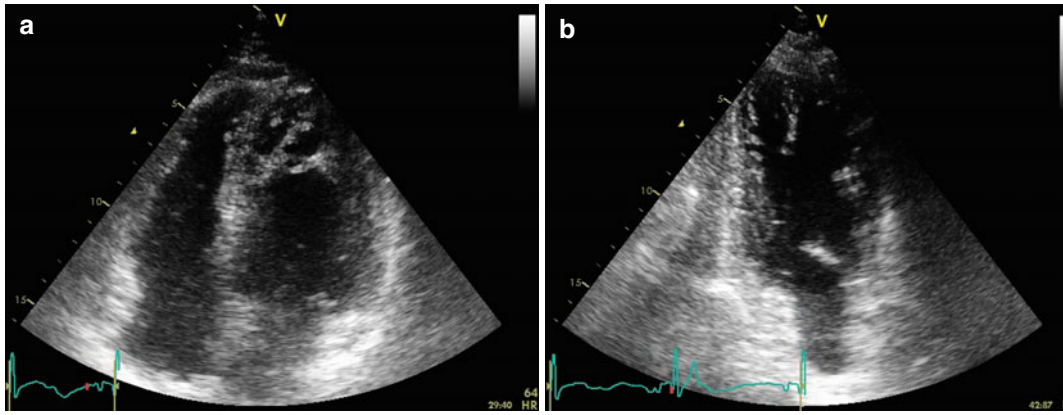

Fig. 13.3 Echocardiogram: (**a**) apical four-chamber view. The marked trabeculae of the apex can be noticed. (**b**) Apical two-chamber view. Apex trabeculae are visible also in this view

- Cardiac syncope (bradyarrhythmias, tachyarrhythmias as supraventricular or ventricular tachycardia, drug-induced, structural disease as aortic stenosis)

Episodes of hypoglycemia could be a possible cause too, but in that case, the syncope has different characteristics, and in addition, it can be excluded, thanks to the fasting glucose measured by the patient at home and the laboratory tests that indicate an elevated HbA1c.

In this case, considering the left ventricular dysfunction and the morphologic abnormalities of the myocardium, the most probable and dangerous cause of syncope could be ventricular arrhythmias.

Indeed, during hospitalization, a non-sustained ventricular tachycardia lasting 23 s was recorded at the ECG monitoring symptomatic for dizziness and profound weakness but without syncope.

Final Diagnosis

The final diagnosis was non-sustained ventricular tachycardia symptomatic of dizziness in patient with left ventricular non-compaction and heart failure.

13.2 Left Ventricular Non-compaction

Left ventricular non-compaction (LVNC) is a rare congenital cardiomyopathy characterized by a "spongy" feature of the myocardium. A thin, compacted epicardial layer under an extensive non-compacted endocardial layer can be noticed with the common cardiac image techniques. Prominent trabeculation and deep recesses that communicate with the left ventricular cavity can be visible too. The "spongy" morphologic feature is not characteristic only of the left ventricle but can also involve the right ventricle. This is why talking about "non-compaction cardiomyopathy" seems to be more correct. The non-compaction of the myocardium is a consequence of an abnormal embryonic development of the ventricular myocardium. During the eighth week of gestation, when the interventricular septum is complete, the increase of ventricular volumes is responsible of compression against the trabeculae of the ventricular walls. This lead to the growth of the compact layer and the organization of some trabeculae in the papillary muscle.

At the same time, intramyocardial vascularization develops from the coronary arteries following an epicardial to endocardial, base to apex, and septum to side wall direction [1]. For this reason, the non-compaction morphology is more common in the apex, side, and inferior walls of the left ventricle.

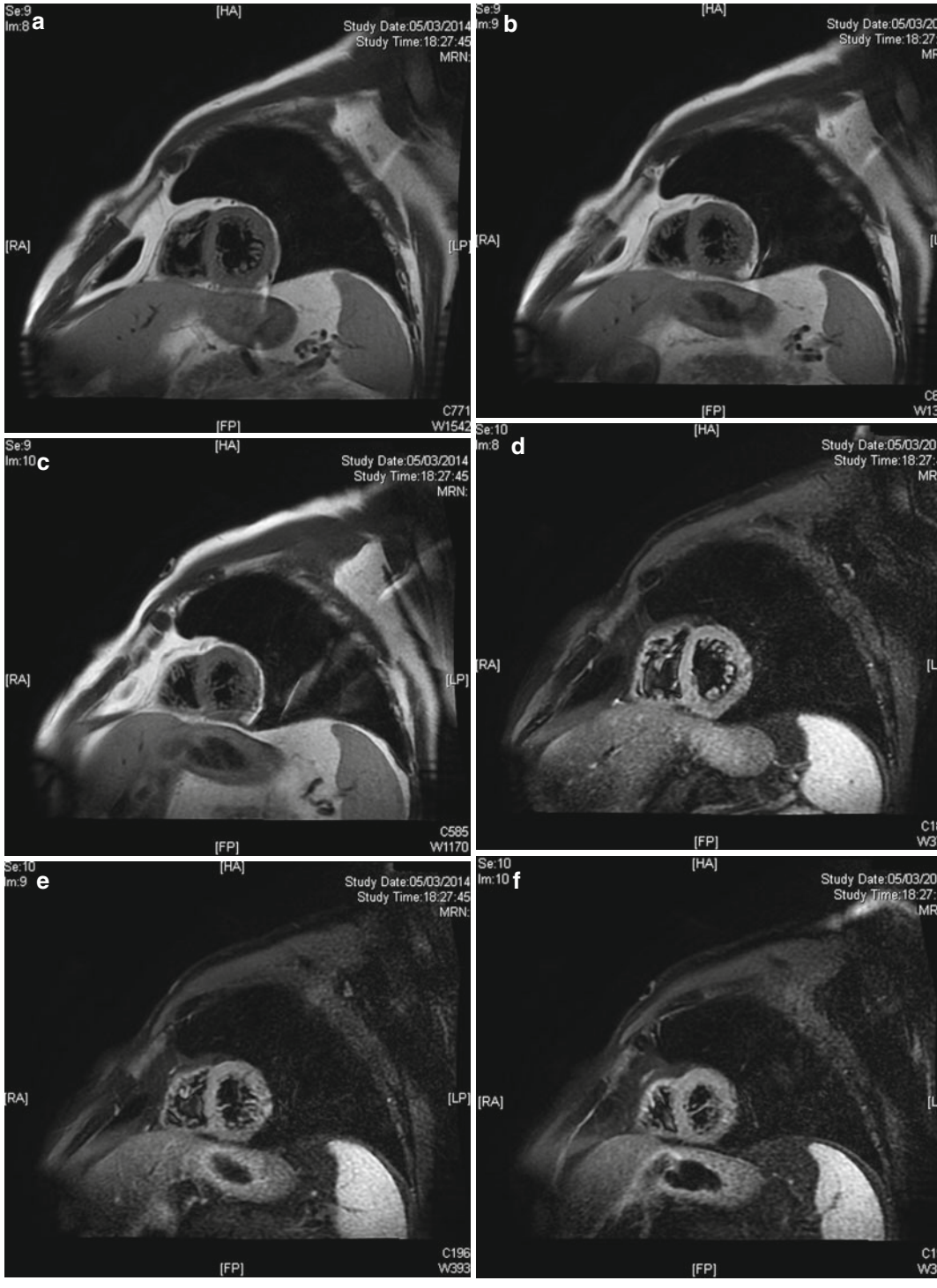

Fig. 13.4 (**a**–**f**) Cardiac RMN, short-axis view of the left ventricle in different levels (T1-weighted black blood imaging). In these images, trabecula's extension to the side wall is visible

Epidemiology

The overall prevalence of LVNC in the general population is not well known, but it seems to be ranged between 1 and 3 % [1, 2]. This percentage is probably an underestimate. The described prevalence of LVNC is 3–4 % among patients with heart failure [3, 4].

Genetics

Non-compaction cardiomyopathy is a heterogeneous disease from the genetic point of view which includes either familiar or sporadic forms [5]. Familiar forms are more frequent in the male sex, while sporadic forms are equally distributed in both sexes. The most common form of inheritance is autosomal dominant compared to either X-linked or autosomal recessive forms [6].

So far, have been reported mutation in several genes in patients with LVNC and the most frequent mutations involve genes encoding: proteins of the cytoskeleton, sarcomere, and mitochondria [7].

Tafazzin Mutations in the tafazzin gene (aka G4.5 or TAZ) lead to cardiolipin deficiency in the mitochondrial membrane and are responsible for Barth syndrome [1, 8–10], an X-linked disorder which usually causes cardiomyopathy, neutropenia, and skeletal myopathy.

Alpha-Dystrobrevin (DTNA) Alpha-dystrobrevin is a cytoskeleton protein. A mutation in the gene coding for alpha-dystrobrevin has been identified in patients with LVNC, occasionally related to congenital heart disease [8, 11].

Sarcomeric Protein Genes Mutations related to sarcomeric proteins seem to be linked to several distinct cardiomyopathies, including LVNC, with a common molecular base. The pE96K in the troponin T gene is more frequent, and it was described for the first time in a family with LVNC and with reduced ejection fraction [12]. The E101K mutation in the alpha-cardiac actin gene (ACTC) has been described in families with LVNC, septal defects, and apical hypertrophic cardiomyopathy [13].

Clinical Manifestations

Clinical manifestation of LVNC is very heterogeneous. The major clinical manifestations of LVNC are three, and they can appear simultaneously or separately: heart failure, supraventricular or ventricular arrhythmias, and thromboembolic events. In the pediatric population, heart failure is the predominant clinical manifestation, while in the adult population, there is an overlap between the three clinical manifestations as first clinical presentation without a clear predominance of one over the other [6].

Diagnosis

ECG

ECG is often abnormal in patients with LVNC, but changes of the ECG are not enough specific to allow an accurate screening of the population. The most common changes that can be seen include right or left bundle branch block, fascicular block, atrial fibrillation, ventricular tachycardia, increased left ventricular voltages, and left axial deviation. Wolff–Parkinson–White syndrome has been described in up to 18 % of pediatric patients affected by LVNC [14].

Echocardiography

Although there is no consensus on the diagnostic criteria, echocardiography still remains the main diagnostic tool. The echocardiographic criteria are illustrated in Table 13.1.

The first diagnostic criteria were published by Chin et al. in 1990. They defined for the first time the ratio between $X/Y \leq 0.5$ as fundamental for the diagnosis of LVNC where X is the distance from the epicardial surface to the base of the trabecular recess and Y is the distance from the epicardial surface to peak of trabeculation. These criteria, based on the observation of eight patients, can be applied only at the level of left ventricular apex on the subxiphoid or apical four-chamber views at end diastole [5].

Afterwards, Jenni et al. [15] in 2001 proposed the following criteria that can be applied

Table 13.1 Diagnostic criteria for LVNC

Chin et al. criteria 1990	Jenny et al. Criteria 1999	Stöllberger et al. 2002
Views: parasternal short axis and apical	Views: parasternal short axis and apical	Views: apical four chambers
Measured in end diastole	Measured in end systole	
LVNC is defined by a ratio of $X/Y \leq 0.5$ X = distance from the epicardial surface to the trough of the trabecular recess Y = distance from the epicardial surface to peak of trabeculation	A two-layer structure, with a thin compacted layer and a thick non-compacted layer measured in end systole at the parasternal short-axis views LVNC is defined by a ratio of $N/C > 2$ where N = non-compacted layer of the myocardium C = compacted layer of the myocardium Absence of coexisting cardiac structural abnormalities Numerous, excessively prominent trabeculations and deep intratrabecular recesses Recesses supplied by intraventricular blood on color Doppler	More than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in a single image plane Intertrabecular spaces perfused from the ventricular cavity, visualized on color Doppler imaging

only in patients without coexisting cardiac abnormalities:

1. A maximum ratio of non-compacted to compacted myocardium >2:1 at end systole in the parasternal short-axis view
2. Color Doppler evidence of flow within the deep intertrabecular recesses

Stöllberger et al. [16] proposed different criteria to diagnose LVNC based on the hypertrabeculation of the myocardial tissue.

1. More than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in a single image plane
2. Intertrabecular spaces perfused from the ventricular cavity, visualized on color Doppler imaging

Cardiovascular Magnetic Resonance (CMR)

The importance of CMR as a diagnostic tool for LVNC is increasing in the last few years. CMR offers a good spatial resolution of the left ventricular apex and lateral wall, and it permits better visualization of trabeculations and recesses.

CMR criteria to diagnose LVNC are slightly different from the above-described echocardiographic criteria. Petersen et al. [17] compared CMR features in seven patients with LVNC with 170 healthy volunteers, athletes, or patients with dilated or hypertrophic cardiomyopathy, hypertensive heart disease, or aortic stenosis. They found that the best distinguishing feature for LVNC was a maximum ratio in diastole of non-compacted to compacted myocardial thickness of >2.3 as assessed in three long-axis views (sensitivity 86 % and specificity 99 %). In another study, Jacquier [18] evaluated the diagnosis of LVNC based on the ventricular mass: a volume of the non-compacted tissue >20 % of the total myocardial tissue is a criterion to diagnose LVNC. Another important aspect related to CMR is the possibility to use gadolinium which permits to identify delayed enhancement areas which are expression of myocardial fibrosis. The number and the distribution of these areas seem to be related to the severity of the disease. Furthermore, it is not rare to find delayed enhancement areas far from the trabeculae, which may suggest that LVNC is a widespread cardiomyopathy involving all the myocardial tissue.

Prognosis

LVNC is associated with high rates of morbidity and mortality in children and adults. Outcomes are more closely related to the severity of the

disease at clinical presentation than to the diagnosis per se. Sudden cardiac death is relatively common among patients with LVNC, and it causes half of all deaths that occur in the adult population.

Therapy

There is no specific therapy for LVNC, even because data on treatment of LVNC are limited and there are not guidelines. Medical management varies with the clinical manifestations: heart failure, the presence or absence of arrhythmias, and perceived risk of thromboembolism.

Heart Failure

Patients with LVNC and heart failure symptoms should be treated according to the current guidelines [19]. Patients with LVNC and heart failure should receive the standard medical therapy used in heart failure with LV dysfunction that is mainly based on ACE inhibitors, beta-blockers, mineralocorticoid receptor antagonist, and diuretics.

Arrhythmias

Since patients with LVNC are at risk for atrial and ventricular arrhythmias, an annual Holter monitoring to detect asymptomatic arrhythmias is advisable. Patients with LVNC should receive ICD therapy according to standard indications for ICD therapy in patients with non-ischemic cardiomyopathy. Patients with history of sustained ventricular tachycardia or sudden cardiac arrest (SCA) should receive an implantable cardioverter–defibrillator (ICD) therapy for secondary prevention of SCA. ICD implantation for primary prevention is indicated in patients with LVNC with an LVEF $\leq$35 % and NYHA class II to III HF [20]. The efficacy of receiving an ICD for the prevention of SCA is not well proved because in patients with LVNC, the arrhythmic substrate is increased due to the dysfunction of the microvasculature and is not confined to the areas with trabeculations, but often involves all the endocardium. Therefore, the high prevalence of supraventricular arrhythmias in these patients implies a high percentage of inappropriate shocks, which can lead to increased mortality, especially if they involve an already disfunctional left ventricle [21, 22].

For this reason, only bicameral ICD should be implanted in this setting because they allow a reliable discrimination between atrial and ventricular arrhythmias. Regarding CRT-D, due to the lack of randomized studies in LVNC population, the indications for their implantation are the same as the current guidelines [20].

Prevention of Thromboembolism

Patients with LVNC with or without atrial fibrillation are at high risk for thromboembolism in the presence of impaired left ventricular function or symptomatic presentation [23]. Therefore, anticoagulation with warfarin is recommended in patients with LVNC without atrial fibrillation with LVEF <40 %. Patients with LVNC and atrial fibrillation who meet standard criteria for anticoagulation should be anticoagulated according to standard guidelines.

Clinical Course and Therapeutic Management of the Clinical Case

For the specific clinical case discussed above, the medical therapy for heart failure was administered including ramipril 5 mg a day, bisoprolol 2.5 mg a day, furosemide 25 mg 2 mg twice daily, and eplerenon 25 mg once daily.

According to the findings described above in this patient, we thought that a ventricular tachycardia was the most probable cause of the syncope and therefore the patient was at sudden death danger. A bicameral endocavitary ICD was implanted. The classical ICD was preferred because of the possibility in upgrading to CRT-D in case of a worsening of the cardiomyopathy despite an optimal medical therapy.

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Arrhythmogenic Right Ventricular Cardiomyopathy

14

Michela Brambatti and Matilda Shkoza

14.1 Case Report

A 54-year-old man with a long history of brief episodes of palpitations was referred by a spoke hospital to our cardiology department due to two episodes of hemodynamically tolerated wide complex tachycardia treated with amiodarone infusion. Two days before, the patient's complaint of palpitations occurred while he was running.

Medical History and Cardiovascular Risk Factors

- Cardiovascular risk factors: systemic arterial hypertension.
- Family history: one brother died for sudden cardiac death (SCD) at age 23.
- At age 23, episodes of exercise-induced palpitations, of variable duration (minutes up to 1 h).
- In 2002, one episode of wide complex tachycardia (left bundle branch block morphology and top axis at 200 bpm) resolved with precordial thump.
- In 2012, the patient was hospitalized in a spoke hospital for frequent non-sustained ventricular arrhythmias. An echocardiogram revealed normal left ventricle and moderate dilatation of right ventricle with hypokinesis in the mid- and apical segments. The coronary angiogram showed noncritical stenosis. He underwent cardiac magnetic resonance (MRI) that was not conclusive for arrhythmogenic right ventricular dysplasia. The patient was recommended to stop physical activity and was discharged on sotalol 80 mg t.i.d.
- Over 3 years, the patient was stable and asymptomatic and refused any further cardiologist follow-up.
- *Allergies:* none.

Medications

Sotalol 80 mg t.i.d

Vital Signs

- Temperature: 36.3 °C
- Heart rate: 60 bpm
- Arterial blood pressure: 130/70 mmHg

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- Respiratory rate: 17 breaths/min
- Oxygen saturation: 99 %

Physical Examination

- General appearance: well developed, well nourished, alert, and cooperative
- Lungs: clear to auscultation bilaterally
- Heart: regular rate and rhythm without murmurs, gallops, or rubs
- Extremities: no peripheral edema, cyanosis or pallor. Warm and well perfused
- Abdomen: Nontender, nondistended, normoactive bowel sounds throughout, no hepatosplenomegaly, and no bruits

Laboratory Tests

Tests were within normal limits (hemoglobin 14 g/dl, white blood cells 7,320/mmc, creatinine 0.88 mg/dl, potassium 4.3 mEq/l, sodium 140 mEq/l, magnesium 1.7 mg/dl).

Instrumental Examination

The patient underwent electrocardiogram (ECG) and echocardiogram to evaluate the right and left ventricle function.

Surface 12-lead ECG revealed sinus rhythm (heart rate 56 bpm), first-degree atrioventricular block, anterior fascicular block, incomplete right ventricular block, the characteristic epsilon waves in leads V1–V4, and also inverted T-waves in inferior lead and leads V2–V6, with slightly prolonged QT interval (corrected QT –QTc = 463 ms). The right bundle was very abnormal with fractionation throughout the right bundle in keeping with a cardiomyopathic process (Fig. 14.1).

Echocardiogram revealed right ventricular enlargement with hypokinesis in the mid- and apical segments and mild tricuspid regurgitation. Also, right outflow dilatation (23 mm/m^2) with normal systolic pulmonary pressure was observed. The left ventricle was mildly enlarged with an ejection fraction of 50 % without regional wall motion abnormalities.

In order to better evaluate the right ventricular size, motility, and ejection fraction, the patient underwent cardiac MRI that revealed right ventricular dilatation with wall thickening and moderate dyskinesia in the mid- and apical segments. Right ventricular ejection fraction was deeply reduced, nearly 35 %. Left ventricle was mildly dilated with normal ejection fraction (Fig. 14.2). Unfortunately, the patient refused gadolinium injection.

Clinical Course and Therapeutic Management

These imaging and clinical findings were strongly suggestive for ARVC.

According to the last AHA/ACC/ESC guidelines [1], taking into account the history of wide complex tachycardia suggestive for hemodynamically stable sustained VTs and severe right ventricle dysfunction, the patient was judged to be at moderate risk for SCD and underwent bicameral implantable cardioverter defibrillator (ICD) implant without major and minor complications. The decision to implant a bicameral ICD was based on the presence of first-degree AV block, anterior fascicular block, and incomplete right ventricular block, so the patient was judged to be at risk of developing high-degree AV block in the future. Sotalol was suspended and QTc interval became normal (440 ms). Therapy with a β-blocker was administered because of the recurrent sustained VTs. Also, a genetic test for ARVC-related mutations was performed.

On the 9th day, the patient was discharged on metoprolol tartrate 50 mg daily. Patient was advised to avoid competitive sport.

All the family members were recommended to undergo cardiologic visit, ECG and echocardiography evaluation, and eventually genetic screening once the mutation is identified in the patient.

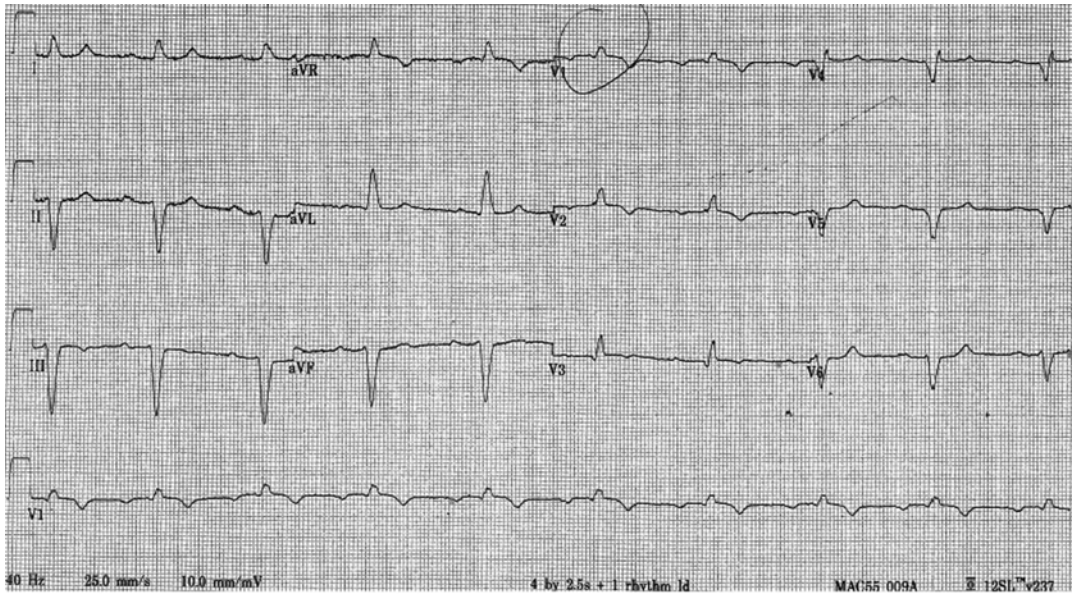

Fig. 14.1 ECG sinus rhythm (heart rate 56 bpm), first-degree atrioventricular block, anterior fascicular block, incomplete right ventricular block, characteristic epsilon waves in leads V1–V4, and also inverted T-waves in inferior lead and leads V2–V6, with prolonged QT interval (corrected QT–QTc = 463 ms). The right bundle is very abnormal with fractionation throughout the right bundle in keeping with a cardiomyopathic process

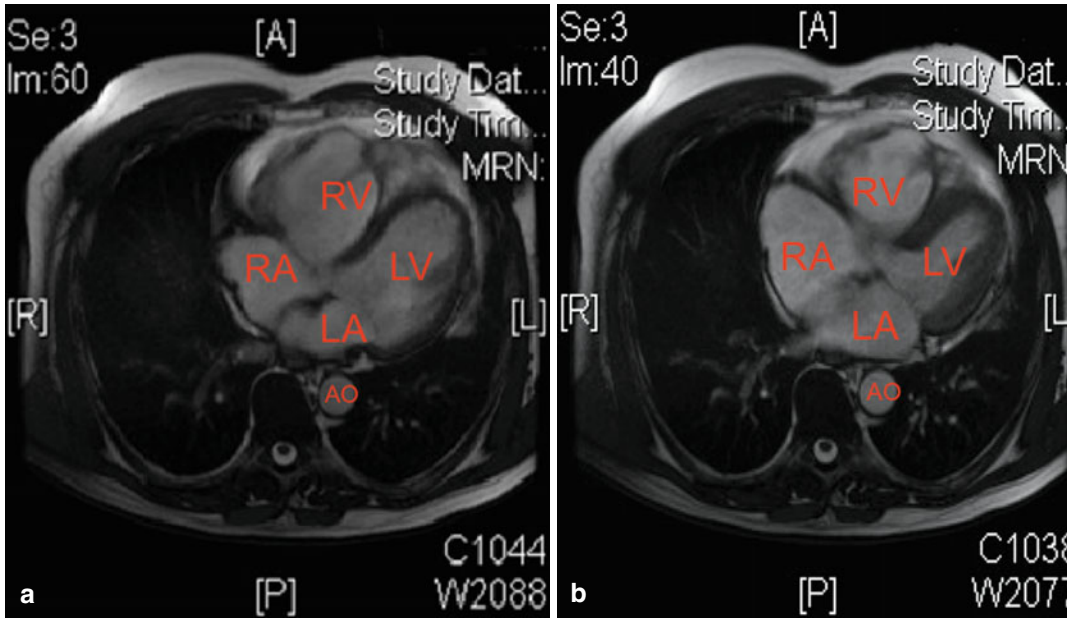

Fig. 14.2 Two axial FIESTA images (**a**, diastolic, and **b**, systolic) clearly depict a dilation of the four cardiac chambers, especially right ones. Wall of RV is prominently thinned

14.2 Arrhythmogenic Right Ventricular Cardiomyopathy

The arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia (ARVD), is a genetic disorder characterized clinically by malignant ventricular arrhythmias and an increased risk of sudden cardiac death (SCD), especially in young adults and athletes [2].

The ARVC is characterized by loss of myocytes and progressive fibroadipose replacement resulting in structural and functional changes of the right ventricle. However, considering the recent data showing a frequent involvement of the left ventricle, the ARVC is currently considered as a genetic disease of both ventricles and most properly called "arrhythmogenic cardiomyopathy" [2].

The adult prevalence in general population is about 1: 1,000–5,000 and is considered to be more common in individuals of Italian and Greek origin; however, the real prevalence in general population is likely to be underestimated [3].

Genetics

Data from genetic studies suggest that 30–50 % of cases are familial. The most common pattern of inheritance is an autosomal dominant form with incomplete penetrance and variable expressivity. The autosomal recessive inheritance form is less common and associated with cutaneous manifestations and wooly hair (Naxos disease, Carvajal syndrome).

To date, eight genes involved in the pathogenesis of CVAD have been identified; these genes encode for the desmosomal proteins [*JUP (plakoglobin), DSP (desmoplachina), Pkp2 (placofilina2), Gene (desmoglein-2), Dsc2 (desmocollina-2)*], the transforming growth factor (*TGF β3*), the transmembrane proteins (*TMEM43*), and the ryanodine receptor (*RYR2*)] [4].

Pathogenesis

The pathogenesis of ARVC is mostly related to reduced function of desmosomes which are intercellular adhesion complexes that provide mechanical connections between cardiac myocytes. In fact, it has been hypothesized that impaired cell adhesion may cause destruction and degeneration of cardiomyocytes, especially when subjected to mechanical stress (e.g., intense physical exercise) [2]. Because of the limited regeneration capacity of the myocardium, the repair process results in fibroadipose replacement which proceeds from the epicardium to endocardium. These process is completely absent at birth and likely begins during the puberty [2].

Anatomical fibrofatty replacement results in the free wall weakness and progressive ventricular dilatation with systolic dysfunction and aneurysm formation in the thinnest portions of the right ventricle, the so-called triangle of dysplasia (the apex, the inflow tract, and the outflow tract) [5]. Instead, fibrofatty replacement of the left ventricle generally involves the posterolateral wall, relatively thin, and rarely the interventricular septum [2].

Clinical Manifestations

The clinical presentation is more frequent between the second and the fourth decades. Because of genetic transmission with associated reduced penetrance, the severity of the clinical phenotype is somewhat variable.

In the natural history of ARVC, four stages are identified: (1) "concealed phase," characterized by the absence of symptoms and minor structural abnormalities (the SCD can be the first and the only manifestation of the disease); (2) "overt electrical instability," characterized by ventricular arrhythmias and morphofunctional cardiac abnormalities; (3) "right ventricular failure," with severe systolic dysfunction of the right ventricle

and initial or absent left ventricular abnormalities; and (4) "biventricular failure," with severe systolic dysfunction of both ventricles similar to a cardiomyopathy [2].

Ventricular/Supraventricular Tachyarrhythmias and Sudden Cardiac Death

VTs in patients with ARVC range from single extra beats to complex VT, symptomatic and not, and the frequency appears to be proportional to the severity of the disease. The most common VT is generally monomorphic with origin from the right ventricle and left bundle branch block morphology. The arrhythmic episodes may origin from the apex, the inflow tract, or the outflow tract; when the site of origin is the right outflow tract, a differential diagnosis with idiopathic VT is required [2].

Unfortunately, the SCD may be the first manifestation of the disease. The estimated mortality rate for SCD varies from 0.08 to 9 % per year [1].

Exercise, especially the endurance sport, is considered a precipitating factor for arrhythmias in patients with ARVC. This "trigger" effect is likely related to the increased right ventricular stimulation by catecholamine exposure; in addition, data from literature suggest that the exercise itself contributes to the right ventricle dilatation and consequently to the disease progression [2].

Supraventricular tachyarrhythmia (SVT), such as atrial fibrillation, atrial tachycardia, and atrial flutter, in association with ventricular arrhythmias, is present in up to 25 % of patients with ARVC; less commonly, SVT may be the only arrhythmia present [6].

Left Ventricular Involvement

The wider use of cardiac MRI has allowed to appreciate a more common involvement of the left ventricle in ARVC [7].

In a study of 200 patients undergoing MRI, three patterns of disease expression were identified:

- *Classic:* primarily affects the right ventricle and, only in advanced stages, the left ventricle (39 %).
- *Dominant left:* characterized by early and severe involvement of the left ventricle and relatively mild disease of the right ventricle. It is very insidious variant as fibroadipose replacement involves initially only the epicardium of the left ventricle without causing wall motion abnormalities. The use of MRI contrast medium allows the identification of nontransmural scar.
- *Biventricular:* characterized by a parallel involvement of both ventricles.

Diagnosis

The diagnosis of ARVC is complex and requires a high degree of clinical suspicion. To date, no single diagnostic test is enough sensitive and specific to confirm or rule out the disease; thus multiple parameters need to be considered.

The Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology has developed the ARVC diagnostic criteria that take into account structural, histologic, arrhythmic, and genetic features. The original version of 1994 [8] that the revised version of 2010 [9] includes major and minor criteria collected in six main categories (Table 14.1). Based on this classification, definite diagnosis of ARVC requires two major criteria or one major and two minor or four minor criteria from different categories (Table 14.1).

In the suspicion of ARVC, as a general approach, it is recommended to go through a careful personal and family medical history, a 12-lead ECG, and a transthoracic echocardiography in all patients. Additional tests should be performed according to the clinical scenario or when the results of initial tests are not conclusive. Recommended tests are as follows:

Table 14.1 Task Force Criteria [9]

2010 Task Force Criteria Definite = 2 major or 1 major + 2 minor or 4 minor from different categories Borderline = 1 major + 1 minor or 3 minor Possible = 1 major or 2 minor	
1. Global/regional dysfunction/structural alterations	
Major	By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (PLAX/BSA ≥19 mm/m^2) PSAX RVOT ≥36 mm (PSAX/BSA ≥21 mm/m^2) Fractional area change ≤33 % By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: RVEDV/BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) RV ejection fraction ≤40 % By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Minor	By 2D echo: Regional RV akinesia or dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (PLAX/BSA ≥16 to <19 mm/m^2) PSAX RVOT ≥32 to <36 mm (PSAX/BSA ≥18 to <21 mm/m^2) Fractional area change >33 to ≤40 % By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: Ratio of RVEDV to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (fem) RV EF >40 to ≤45 %
2. Tissue characterization of wall	
Major	Residual myocytes <60 % by morphometric analysis (or <50 % if estimated), w/ fibrosis replacement of RV free wall myocardium in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
Minor	Residual myocytes 60–75 % by morphometric analysis (or 50–60 % if est.) w/ fibrous replacement of the RV free wall in ≥1 sample, w/ or w/o fatty replacement of tissue on endomyocardial biopsy
3. Repolarization abnormalities	
Major	TWI (V1, V2, V3) or beyond; >14 years of age; in the absence of complete RBBB QRS ≥120 ms
Minor	TWI in V1 and V2; >14 years of age; in the absence of complete RBBB or in V4, V5, or V6 TWI in V1–V4; >14 years of age; in the presence of complete RBBB
4. Depolarization conduction abnormalities	
Major	Epsilon wave in right precordial leads (V1–V3)
Minor	Late potentials by SAECG in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on ECG: Filtered QRS duration (fQRS) ≥114 ms Duration of terminal QRS <40 μV ≥38 ms Root mean square voltage of terminal 40 ms ≤20 μV Terminal activation ≥55 ms measured from nadir of S-wave to end of QRS, including R′, in V1, V2, or V3, in the absence of complete RBBB
5. Arrhythmias	
Major	NSVT or sustained VT, LBBB morphology with superior axis
Minor	NSVT or sustained VT of RV outflow configuration, LBBB with inferior or of unknown axis >500 PVCs per 24 h on Holter monitoring
6. Family history	
Major	ARVC/D in first-degree relative who meets Task Force Criteria ARVC/D confirmed pathologically at autopsy or surgery in first-degree relative Identification of the pathogenic mutation (associated or probably associated w/ ARVC/D) in the patient under evaluation

(continued)

Table 4.1 (continued)

Minor	History of ARVC in first-degree relative in whom it is not possible to determine if the family member meets Task Force Criteria Premature SCD (<35 years of age) due to suspected ARVC/D in first-degree relative ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

RVOT right ventricular outflow tract, *PLAX* parasternal long axis, *PSAX* parasternal short axis, *BSA* body surface area, *RV* right ventricle, *RVEDV* right ventricle end-diastolic volume, *EF* ejection fraction, *TWI* T-wave inversion, *RBBB* right bundle branch block, *LBBB* left bundle branch block, *SAECG* signal-averaged electrocardiography, *NSVT* non-sustained ventricular tachycardia, *VT* ventricular tachycardia, *ARVC/D* arrhythmogenic ventricular cardiomyopathy/dysplasia, *SCD* sudden cardiac death, *PVC* premature ventricular complex

- Signal-averaged ECG (SAECG)
- 24 h ECG Holter
- Stress testing
- Cardiac MRI with gadolinium
- Right ventriculography
- Endomyocardial biopsy
- Electrophysiologic study and three-dimensional electroanatomic mapping
- Genetic testing

Electrocardiography (ECG)

In all patients with suspected diagnosis of ARVC, a 12-lead ECG is recommended. The sensitivity is suboptimal, because 40–50 % of patients have a normal ECG submission. However, reflecting the progressive nature of the disease, most patients develop characteristic ECG abnormalities years after the presentation, such as [10]:

- QRS prolongation, especially in lead V1 versus V6.
- Incomplete/complete right bundle branch block.
- Prolonged QRS terminal activation (≥55 ms measured from nadir of S-wave to end of QRS, including R′, in V1, V2, or V3, in the absence of complete RBBB).
- Epsilon waves in right precordial leads, particularly in V1 identified in 30 % of patients with ARVC. In order to detect epsilon waves and avoid ST distortion, ECG filters should be set with a low-frequency cutoff of 0.05 Hz and a high-frequency cutoff greater than 150 HZ in adults and 250 Hz in children.
- T-wave inversion in right precordial leads (V1, V2, V3) in the absence of complete right bundle branch block. This ECG feature, which can be a normal variant in children under 14 years of age, is present in 87 % of subjects with ARVC. The extension of the T-wave inversion also correlates with the degree of right ventricular dilatation and arrhythmic risk. T-wave inversion in leads V5–V6, instead, is an indirect sign of left ventricular involvement.

Late Potentials

Signal-averaged ECG abnormalities are common and have an excellent sensitivity and specificity for ARVC; however, they are not predictive of arrhythmic risk.

Late potential abnormalities are considered as minor criteria if they meet at least one of the following three conditions, without a QRS duration ≥110 ms [9]:

- Filtered QRS duration ≥114 ms
- Terminal QRS duration <40 microV and ≥38 Ms
- Root mean square voltage of terminal 40 ms ≤20 microV

Echocardiography

A transthoracic echocardiogram should be performed in all patients with the clinical suspicion

of ARVC. Echocardiography is a noninvasive method and readily available and easily allows right ventricle visualization in most patients. The echocardiographic findings frequently observed are [9]:

- Right ventricular dilation, especially the right outflow tract (RVOT)
- Reduction of right ventricular fractional area change
- Regional and global wall motion abnormalities of the right ventricle
- Morphological abnormalities of the right ventricle (trabecular derangement, hyperreflective moderator band, and aneurysms)

Left ventricular echocardiographic abnormalities are seen less frequently.

Cardiovascular Magnetic Resonance Imaging

In patients with suspected ARVC and no diagnostic results with other imaging modalities, cardiac MRI is strongly recommended. Cardiac MRI allows evaluation of right ventricle dilation, global and regional wall motion abnormalities, intramyocardial fat, focal wall thinning, and late gadolinium enhancement in fibrosis areas.

The main limitations of cardiac MRI are related to the limited experience of the centers and significant interobserver variability resulting in high rate of false positives. In addition, intramyocardial fat infiltration of the right ventricular wall should be interpreted with caution, as fat infiltration is frequently in healthy subjects, especially if elderly [2].

Right Ventriculography

Ventriculography may be useful to assess the structure and function of the right ventricle in patients with strong suspect for ARVC and nondiagnostic results with other imaging modalities. Regional right ventricle akinesia, dyskinesia, or aneurysms are generally observed [9]. However, since ventriculography is an invasive method, it is rarely used.

Electrophysiologic Testing and Electroanatomic Voltage Mapping

Electrophysiologic testing is of limited role in the diagnostic workup of patients with suspect ARVC. However, electrophysiologic testing has a role in the differential diagnosis between idiopathic outflow tract and the ARVC-related VT [11]. In fact, contrarily to VT in ARVC patients, the idiopathic outflow tract VT is not associated with ECG abnormalities, is more frequent in women, and is induced by isoprenaline infusion rather than programmed ventricular stimulation.

Electroanatomic voltage mapping is an innovative tool useful to identify and quantify areas of fibrosis by detection of low-voltage local right ventricle electrograms. Despite electroanatomic mapping increases accuracy in diagnosing, the technique is operator dependent, invasive, and costly.

Genetic Testing

The ARVC is a genetic disease and a desmosomal gene mutation identified in approximately 30–50 % of cases. However, given multiple mutations causing the disease and the variable penetrance, genetic testing should not be performed in all patients suspected for ARVC. Genetic tests are recommended for patients who meet the Task Force Criteria [9] for a definitive or borderline ARVC diagnosis and all first-degree relatives following the identification of the ARVC-causative mutation in an index case [12].

Endomyocardial Biopsy

Endomyocardial biopsy is an invasive procedure with poor sensitivity and specificity; thus, it is not recommended for the initial diagnostic workup.

When endomyocardial biopsy is performed, one major concern is related to the sampling error. The interventricular septum, which is the usual and low-risk biopsy site, is not generally useful in ARVC patients since it is not generally affected by the pathology. In addition, the istofibrofatty replacement cannot be considered a pathognomonic ARVC feature as it is also observed in healthy subjects, especially elderly. In the light of these data, in ARVC patients,

endomyocardial biopsy is a class IIb recommendation in the diagnostic workup for ARVC [13].

Differential Diagnosis for ARVC

- *Dilated cardiomyopathy*: biventricular dilated and congestive heart failure may be similar to ARVC with left ventricle involvement.
- *Uhl anomaly*: total lack of right ventricular myocardium. In ARVC, the myocardium is not completely absent but replaced by a variable degree of fibrosis.
- *Idiopathic VT*: Left bundle branch block morphology VT in a structurally healthy heart and absence of SCD familiarity.

Therapy and Prognosis

The therapeutic approach in ARVC patients is addressed to SCD prevention and relief of symptoms of arrhythmias related, as well as improvement in terms of functional capacity and survival in patients who develop heart failure. To achieve these goals, available treatment options include lifestyle changes, pharmacological therapy with β-blockers, antiarrhythmic and heart failure drugs, transcatheter ablation, ICD implantation, and cardiac transplantation.

Lifestyle Changes

Given the well-known association between endurance sports and five-time increased risk of SCD, patients with a definitive diagnosis of ARVC and asymptomatic mutation carriers should not participate in any competitive activity [14]. No absolute contraindications in practicing low-intensity physical activity are established, especially for ARVC patients treated with β-blockers.

β-Blockers and Antiarrhythmic Therapy

With the assumption that the adrenergic stimulation during exercise triggers arrhythmias, treatment with β-blockers currently represents a first-choice therapy in patients with a definitive diagnosis of ARVC. In contrast, β-blockers are not usually recommended in mutation carriers who do not express the ARVC phenotype.

Antiarrhythmic medications, in association with β-blockers or alone, may be useful to reduce ventricular arrhythmias frequency and symptoms in patients with ARVC. Although there is no evidence to suggest a specific antiarrhythmic treatment, class III drugs as amiodarone and sotalol are the drugs of choice [1]. However, any antiarrhythmic medication has demonstrated to reduce the risk of SCD; as a result, antiarrhythmic drug therapy should not be considered an equivalent alternative to ICD implantation in ARVC patients.

ICD Implantation and Arrhythmic Risk Stratification

In patients with ARVC and documented sustained ventricular fibrillation or VT (PV), ICD implantation for secondary prevention is strongly recommended. In these patients, appropriate ICD intervention occurs in about 10 % of cases per year, and the estimated survival benefit is about 25–30 % at 3 years follow-up [2].

On the contrary, due to the relatively low prevalence of the disease and lack of randomized controlled trials, the indications for ICD implantation for primary prevention are still object of intense debate among experts.

Prognostic stratification and indications for ICD implantation for primary prevention are currently based on several arrhythmic risk factors, mostly identified from retrospective studies or autopsy data, such as unexplained syncope; proband status; young age; physical activity; family history for SCD, QRS, and QT dispersion; severe right ventricular dysfunction; left ventricular involvement; and inducible VT [15]. However, not all these risk factors should be taken into account when an ARVC patient is evaluated for ICD implant.

An interesting pyramidal representation of the relationship between the arrhythmic risk and current ICD implant indications for ARVC patients was proposed by Corrado and colleagues [4]. At the apex of the pyramid, there are the high-risk patients who are most likely to benefit from an

Table 14.2 Our approach to patients with ARVC according to the arrhythmic risk

Subgroups	Risk markers	Recommendations	ICD indication
High risk (8–10 %/year)	Aborted SCD Hemodynamically unstable sustained VT	Avoid competitive sport β-blockers	Recommended
Moderate risk (1–2 %/year)	Unexplained syncope Hemodynamically stable sustained VT Non-sustained VT	Avoid competitive sport β-blockers Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Consider
Moderate risk (?%/year)	Severe dilatation and/or dysfunction of RV, LV, or both Early onset structurally severe disease (age < 35 years)	Avoid competitive sport β-blockers Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Consider
Low risk (<1 %/year)	Asymptomatic mutation carriers ARVD patients without risk factors	Reduce physical exercise Avoid competitive sport Annually FU including: ECG Cardiac imaging (ECHO vs. CMR) Holter Exercise stress testing	Not recommended

ARVD arrhythmogenic right ventricular dysplasia, *FU* follow-up, *CMR* cardiac magnetic resonance, *LV* left ventricle, *RV* right ventricle, *SCD* sudden cardiac death, *VT* ventricular tachycardia, *ICD* internal cardiac defibrillator

ICD such as those with previous heart attack, unstable hemodynamic VT, and unexplained syncope. By contrast, at the bottom, there are patients with definitive diagnosis of ARVC but without arrhythmic risk factors and patients who are mutation carriers who do not express the ARVC phenotype. For these low-risk patients, ICD implantation is not generally recommended. Patients with intermediate risk, linked to the detection of non-sustained VT or demonstration of a moderate-severe ventricular dysfunction, are represented in the middle of the pyramid. In these patients, the indication to implantation of the ICD must be evaluated taking into account both the arrhythmic profile and the risk of potential implant complications, costs, and the psychological impact, especially for the young. According to these stratification risks, our approach in patients with ARVC is described in Table 14.2.

Radiofrequency Ablation

The radiofrequency ablation is not a definitive therapy for ventricular arrhythmias and should not be considered an equivalent alternative to ICD implantation in high-risk patients for SCD. This therapeutic approach may be appropriate in selected ARVC patients who are not candidates for ICD implantation or who are ICD recipients with frequent VT episodes and ICD shocks despite antiarrhythmic therapy [1]. The ablative technique may include a multiple epicardial and endocardial mapping approach due to the multifocal nature of the disease.

Cardiac Transplantation

In rare cases, patients with ARVC who develop heart failure symptoms or refractory ventricular arrhythmias may be candidates for heart transplantation.

Conclusions

ARVC is a genetic disease of the myocardium with hereditary transmission in half of cases and associated with an increased risk of SCD. The diagnosis is complex and, if missed, can be fatal. The therapy goal is the SCD prevention. Although the benefit of the implantation of the ICD in a patient who survived to a cardiac arrest is universally recognized, the role of the ICD for primary prevention is still being debated.

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Part V

Valvular Heart Disease

Aortic Stenosis

15

Lorena Scappini, Simone Maffei,
and Alessio Menditto

15.1 Case Report

A 75-year-old man was admitted to the cardiology department from the emergency room for chest pain. He reported the occurrence of constrictive chest pain after mild exertion; this pain did not vary with breathing, with posture, or with movement and was relieved with rest until disappeared completely.

Medical History and Cardiovascular Risk Factors

- Type 2 diabetes mellitus.
- Arterial hypertension.
- Dyslipidemia.
- Stable coronary artery disease treated by percutaneous coronary intervention (PTCA) with two drug-eluting stent (DES) implantations on the proximal middle part of the left anterior descending (LAD 1–2) and on the first obtuse marginal (OM 1) (1 year ago).
- A more recent (4 months ago) acute coronary syndrome NSTEMI treated by percutaneous coronary intervention and implantation of two DES on LAD 1–2 (intrastent) and on LAD 2. A noncritical lesion on the right coronary remained.
- Peripheral artery disease (carotid plaques).
- Chronic kidney disease (fifth stage) on dialysis (11 ml/min/1.73 m^2).
- Gouty arthritis.

Allergies

No allergy is referred by the patient.

Social History

- Smoked about 15 cigarettes/day for 5 years
- Never used illegal drugs

Medications

Pantoprazole 40 mg at 8:00 a.m., clopidogrel 75 mg at 8:00 a.m., furosemide 25 mg at 8:00 a.m., repaglinide 0.5 mg at 8:00 a.m. and at 8:00 p.m., repaglinide 1 mg at 12:00 a.m., ivabradine 5 mg at 8:00 a.m. and at 8:00 p.m., doxazosin 2 mg at 8:00 a.m. and at 8:00 p.m., nitroglycerin transdermal 10 mg at 8:00 a.m.,

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aspirin 100 mg at 12:00 a.m., allopurinol 150 mg at 3:00 p.m., amlodipine 5 mg at 8:00 p.m., and ezetimibe/simvastatin 10/20 mg at 10:00 p.m

Vital Signs

- Temperature: 36 °C
- Heart rate: 53 bpm
- Blood pressure: 140/80 mmHg
- Respiratory rate: 16/min
- Oxygen saturation while breathing in ambient air: 97 %

Physical Examination

- General: alert, awake, and oriented
- Head, eyes, ears, nose, and throat: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- Neck: supple, no jugular venous distention, no lymphadenopathy, and bilateral carotid murmur
- Cardiovascular: regular rhythm, S1 normal, S2 low intensity, and aortic diamond-shaped (crescendo/decrescendo) systolic murmur 3/6 with radiation to carotid vessels
- Lungs: no rales, rhonchi, or wheezes, no egophony, no alterations in tactile fremitus, and normal percussion
- Abdomen: overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- Extremities: no cyanosis or clubbing, and no edema
- Neurologic: cranial nerves I through XII intact, and no focal deficit
- Psychiatric: normal affect, no hallucinations, and normal speech
- Skin: intact, no rashes, and no lesion

The routine laboratory tests were performed:

- Complete blood count: normal (hemoglobin 13 g/dl)
- Inflammatory markers (ESR, CRP): normal
- Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect): normal
- Impaired renal function (creatinine 6.61 mg/dl, BUN 146 mg/dl)
- Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- Fasting blood glucose: 55 mg/dl
- Myocardial necrosis markers (CK-MB and Hs-TnI): negative in two different samples

A routine rest 12-lead EKG showed sinus bradycardia (heart rate was 53 bpm) and normal atrioventricular and intraventricular conduction. Left ventricular hypertrophy was observed. ST segment depression was present in I, aVL, and V5–V6 leads (Fig. 15.1).

What Are the Possible Causes of Chest Pain in This Patient?

- Acute coronary syndrome (unstable angina)
- Valvular disease (aortic stenosis)
- Acute pericardial disease
- Chest wall pain
- Lung diseases

The characteristics of chest pain were suggestive for typical angina, the patient was apyretic, the inflammatory biomarkers were negative, there weren't clinical and instrumental signs of respiratory disease, and therefore, acute pericardial disease, chest wall pain, and lung diseases from differential diagnosis were excluded. The presence of systolic heart murmur and of ST–T downslope on rest ECG supported the hypothesis of ischemic heart disease or of aortic stenosis.

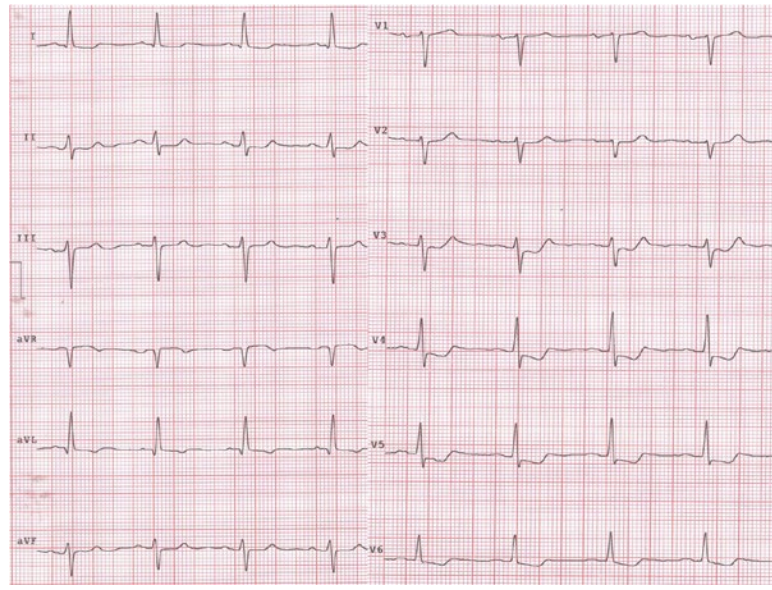

Fig. 15.1 ECG shows ST segment depression in I, aVL and V5-V6 leads

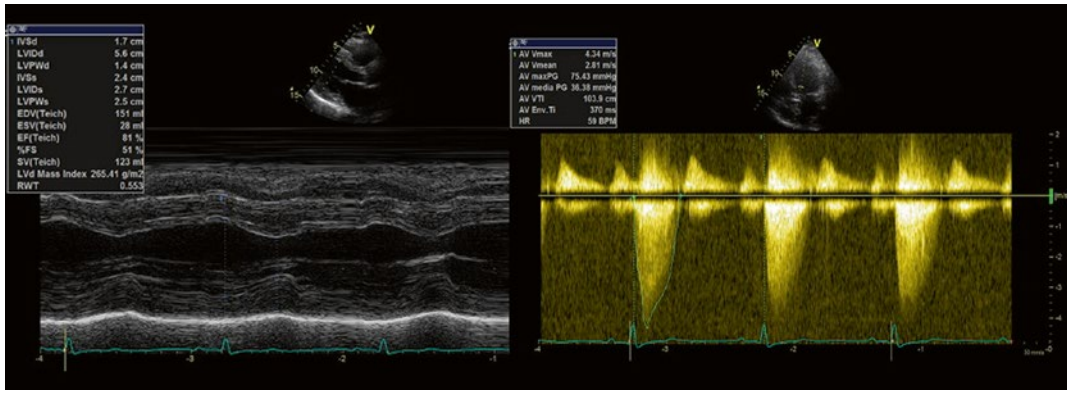

Fig. 15.2 Echocardiography. Concentric left ventricular hypertrophy (*left side*). Severe aortic valve stenosis with high trans-aortic valve gradient (*right side*)

Echocardiography

Echocardiography was performed to better evaluate the aortic area (Fig. 15.2) and showed the following results: "Concentric left ventricular hypertrophy with normal left ventricle global and regional systolic function (EF 57 %). Severe dilatation of the left atrium (index volume 66 ml/m^2). Pseudo-normal diastolic function. Normal right ventricle size and systolic function (TAPSE 17 mm). Mild dilatation of the right atrium. No pericardial effusion. Severely calcified tricuspid aortic valve with severe stenosis (peak velocity 4.3 m/s, medium gradient 36 mmHg, calculated aortic valve area 0.8 cm^2, index calculated aortic valve area 0.43 cm^2/m^2). Mild mitral regurgitation. Mild tricuspid regurgitation with high pulmonary arterial pressure (40 mmHg)."

Final Diagnosis

The final diagnosis is "severe aortic stenosis with effort angina in patient with known coronary artery disease."

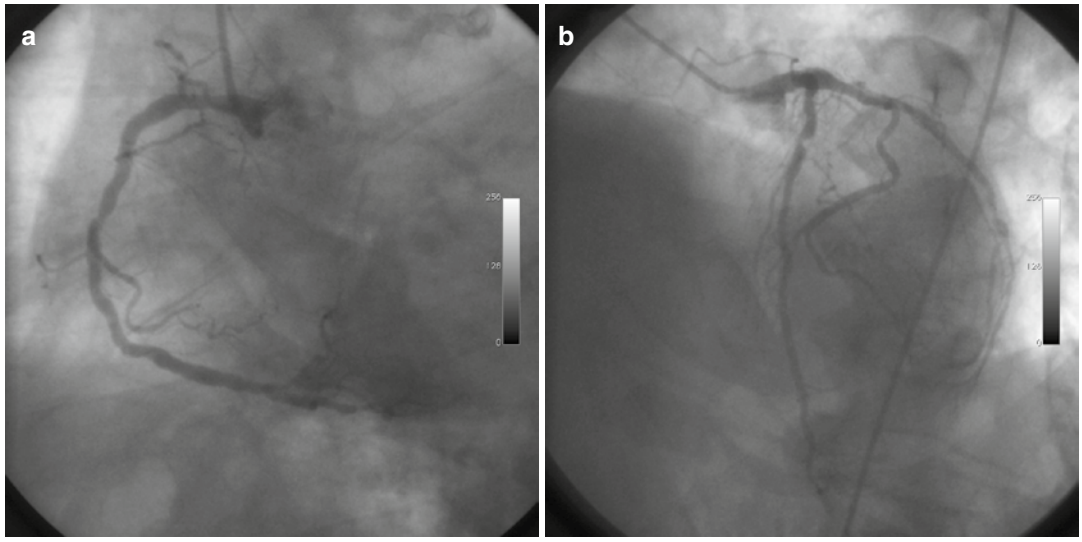

Fig. 15.3 Coronary angiography: right coronary (**a**); left coronary (**b**)

Symptomatic severe aortic stenosis has surgery correction indication; although the last PTCA was done in the previous 4 months, an invasive coronary angiography was performed because the angina symptoms show a LAD 70 % diameter stenosis (intrastent), severe stenosis of the first diagonal branch (D1) and second diagonal branch (D2), and a severe stenosis of the posterior descending artery (PDA) (Fig. 15.3a, b).

The patient was admitted to the cardio-surgery department to replace the aortic valve and for the heart to be revascularized through coronary artery bypass graft (CABG). A bioprosthetic aortic valve was implanted, and an artery graft with the left internal mammary artery to LAD and a saphenous vein graft to PDA were performed.

15.2 Aortic Stenosis

Epidemiology

Valvular aortic stenosis (AS) is the second most prevalent adult valve disease in the USA. The prevalence of AS increases with age: it occurs in 4 % of patients older than 75 years [1] and approximately in 2 % of population aged 65 years old.

Calcific aortic valve disease is the most common cause of AS among adults in the Western world [2]. Prevalence increases with age [1, 3], and severe AS, if left untreated, is fatal a few years from symptom onset [4].

Etiology

AS is a hereditary or acquired disease that causes a progressive obstruction to left ventricular outflow. Obstruction may be valvular, subvalvular, or supravalvular.

Valvular stenosis is the most common cause of aortic obstruction. Its etiology may be age related: patients younger than 20 usually have a congenital abnormality.

Patients aged 40–60 usually have a calcified bicuspid valve or a valve previously damaged by rheumatic heart disease.

The most common cause of AS in patients 70–80 years old is degenerative AS; this is an active process characterized by lipid accumulation, inflammation, and calcification of aortic valve cusps that provokes a valve degeneration [5–7].

Subvalvular AS occurs in less than 10 % of all patients with obstruction of left ventricular outflow and is frequently associated with aortic regurgitation

due to valve damage. This kind of obstruction can be due to a subvalvular ridge or diffuse tunnellike narrowing of the entire outflow tract. If severe hypertrophy of the left ventricle is present, additional dynamic outflow obstruction from systolic anterior motion of the mitral valve may occur.

Supravalvular AS is an uncommon (less than 1 % of patients with aortic stenosis) congenital abnormality, consisting of narrowing of the ascending aorta (immediately over the aortic valve) secondary to a single stenosis or a long tubular lesion of the entire ascending aorta. This type of stenosis is often associated with some congenital abnormalities like coronary dysplasia, elfin facies, mental retardation, coarctation of the aorta, hypercalcemia, peripheral pulmonary stenosis, and Williams syndrome.

Physiopathology

AS represents a continuum disease: (1) an increase in afterload, (2) a decrease in systemic and coronary blood flow from obstruction, and (3) progressive hypertrophy. These mechanisms result in the classic symptom triad of dyspnea, angina, and syncope. Left ventricular cavity size and systolic function are initially maintained; in fact, the increase in left ventricular wall thickness acts as a compensatory mechanism to normalize wall stress. So at the beginning, hypertrophy is a beneficial adaptation.

However, this phenomenon may cause a reduced coronary flow reserve and oxygen supply–demand mismatch [8]. Hypertrophic hearts are more sensitive to diffuse subendocardial ischemic injury, which may result in both systolic and diastolic dysfunctions. The latter occurs from prolonged ventricular relaxation and decreased compliance and is caused by myocardial ischemia, a thick noncompliant left ventricle, and increased afterload [9, 10].

The so-called reversible phase is characterized by an obstruction progression to a higher level that provokes a decrease of left ventricle systolic function.

If afterload excess was continued, myocyte degeneration and fibrosis would occur (irreversible left ventricular systolic dysfunction). At this point, both the high afterload and the intrinsic myocardial disease significantly increase wall stress, and a vicious cycle of deterioration in ventricular function ensues.

A "death spiral" may occur: if systemic hypotension will occur (due to either drugs or a vasovagal reaction), perfusion of the coronary arteries may decrease; this increases the myocardial oxygen supply–demand mismatch and results in myocardial ischemia. The myocardial ischemia, in turn, reduces forward cardiac output, and aortic diastolic pressure decreases, further decreasing coronary perfusion pressure. Unless immediate steps are taken to increase perfusion pressure, progressive hemodynamic deterioration and death may occur.

Clinical Manifestation

The clinical presentation of AS varies. Many patients will remain asymptomatic for decades. The diagnosis of AS is usually made in these patients on the basis of a systolic murmur on auscultation and confirmed by echocardiography.

Symptoms usually consist of one or more of the classic triad of exertional dyspnea, angina, and syncope. The cause of syncope may include ventricular arrhythmias, a sudden decrease in systemic flow caused by the obstruction, or abnormal vasodepressor reflexes caused by the high left ventricular intracavitary pressure. Albeit rare, sudden death may be the initial manifestation of aortic stenosis.

Uncommonly, patients with end-stage AS and concomitant left ventricular dysfunction present with anasarca and cardiac cachexia.

The development of symptoms is a critical point in the natural history of patients with AS. In fact, after symptom onset, the average survival is 2–3 years.

Physical Examination

The physical examination of a patient with AS reveals classic, characteristic findings that are

important for diagnosis and estimation of severity of this valvular disease.

The characteristics of the carotid upstroke are a reliable indicator of the severity of AS in most patients. There will be both parvus (small pulse) and tardus (slow upstroke) in patients with severe AS. These typical findings couldn't be present on carotid palpation in older patients with a noncompliant vasculature. When there is a thrill felt in the right carotid artery but not in the left carotid artery, the diagnosis of supravalvular AS should be suspected. This phenomenon is due to the high-velocity jet of blood directed toward the innominate artery.

A sustained bifid left ventricular impulse indicates concomitant left ventricular hypertrophy. A systolic thrill, if present, indicates the presence of severe AS (mean gradient >50 mmHg).

Accurate auscultation is an essential component of evaluating patients with AS. An absent aortic component of the second heart sound indicates severe calcification of the aortic valve. A delayed murmur apex is also present in severe AS.

A fourth heart sound is frequently audible. The turbulence across the aortic valve always produces a systolic ejection murmur. It is not necessarily the intensity but the timing of the murmur that determines the severity of AS. In patients with mild AS, the murmur is characterized by an early peak, and the duration ends before the second heart sound. As AS becomes more severe, the peak intensity of the murmur occurs in mid-to-late systole, and the murmur extends into the second heart sound. The murmur of AS must be differentiated from that of hypertrophic obstructive cardiomyopathy or mitral regurgitation due to a flail posterior leaflet. A Valsalva maneuver may be of help in this case.

So we can say that severe AS is characterized by (1) a dampened upstroke of the carotid artery, (2) a sustained bifid left ventricular impulse, (3) an absent A2, and (4) a late-peaking systolic ejection murmur.

Electrocardiography

The electrocardiography usually shows sinus rhythm with left ventricular hypertrophy and left atrial enlargement. An ST interval depression, a T wave inversion, or a left bundle block can be present.

Chest Radiography

Chest radiography may demonstrate enlargement of the ascending aorta and a left ventricular predominance. Aortic calcification is frequently seen on lateral chest radiographs (i.e., porcelain aorta). This find implies high risk for operation [11].

How to Assess Aortic Stenosis

Echocardiography

In addition to physical examination, electrocardiography, and chest radiography, various imaging modalities may be used to confirm the presence of aortic stenosis.

Transthoracic echocardiography is the gold standard modality for initial diagnosis and subsequent evaluation of aortic stenosis; with this ultrasound technology, the physician can also determine the level of obstruction (supravalvular, valvular, or subvalvular), the number of aortic cusps, and the degree of cusp fusion.

The severity of aortic stenosis cannot be determined by visualization of valve motion alone, and Doppler echocardiography must be used to further assess the severity of aortic valve disease [12].

The main hemodynamic parameters recommended for clinical evaluation of AS severity with transthoracic echocardiography are [13]:

1. AS jet velocity
2. Mean transaortic gradient
3. Valve area by continuity equation

The antegrade systolic velocity across the narrowed aortic valve, or aortic jet velocity, is measured using continuous-wave (CW) Doppler (CWD) ultrasound [14–16].

AS jet velocity is defined as the highest velocity signal obtained from any window after a careful examination. Color Doppler is also helpful to avoid recording the CWD signal of an eccentric mitral regurgitation (MR) jet.

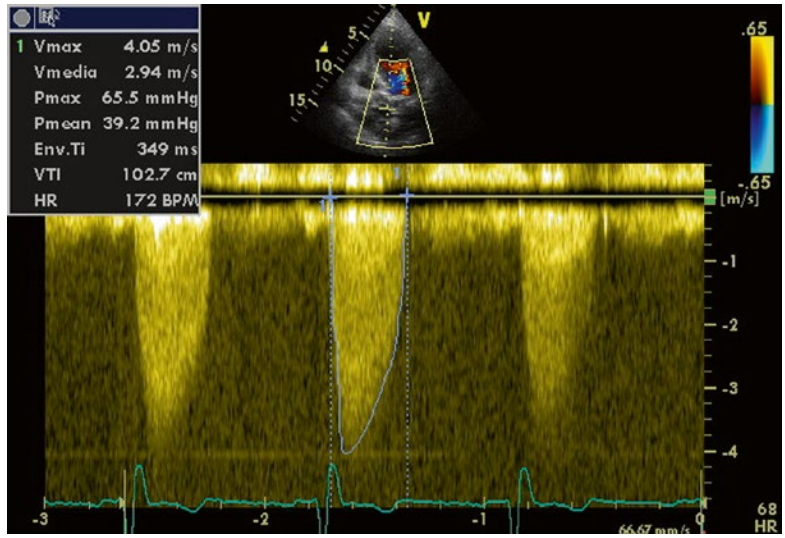

Fig. 15.4 Continuous-wave Doppler of aortic stenosis

A smooth velocity curve with a dense outer edge and clear maximum velocity should be recorded. The maximum velocity is measured at the outer edge of the dark signal. To get the velocity–time integral (VTI) for the continuity equation and the mean gradient, it is necessary to draw the outer edge of the dark "envelope" of the velocity curve (Fig. 15.4) [13].

To distinguish the level and severity of obstruction, the shape of the CW Doppler velocity is helpful; the maximum velocity occurs later in systole, and the curve is more rounded in shape with more severe obstruction [13].

To determine the fixity or the dynamism of obstruction, the shape of the CWD velocity curve also can be helpful. A characteristic late-peaking velocity curve is shown by a dynamic obstruction, with a concave upward curve in early systole (Fig. 15.5), in a patient with severe anemia.

Transaortic pressure gradient (ΔP) is calculated from velocity (v) using the Bernoulli equation as

$$\Delta P = 4v^2$$

The maximum gradient is calculated from maximum velocity

$$\Delta P_{\max} = 4v^2{}_{\max}$$

and the mean gradient is calculated by averaging the instantaneous gradients over the ejection period [13].

The aortic valve area can be calculated by Doppler echocardiography using the continuity equation.

From the parasternal long-axis view, the operator must get the left ventricular outflow tract (LVOT) diameter and convert it to the LVOT area. The LVOT velocity is obtained and traced to derive the time–velocity integral (TVI) from an apical approach with pulsed-wave Doppler.

Continuity equation

$$\text{Aortic valve area} = \frac{\left(\text{LVOT}_{\text{TVI}}\right)\times\left(\text{LVOT}_{\text{area}}\right)}{\left(\text{AV}_{\text{TVI}}\right)}$$

Significant errors in the area calculation may be caused by small errors in diameter measurement; for this reason the calculation of aortic valve area with continuity equation does require a skilled echocardiographist to ensure accurate measurement of the LVOT diameter.

When LVOT diameter is squared for calculation of cross-sectional area, it becomes the greatest potential source of error in the continuity equation [13].

To reduce the errors associated with the measurements of the LVOT, this ratio can be used:

$$\text{Velocity ratio} = \frac{V_{\text{LVOT}}}{V_{\text{AV}}}$$

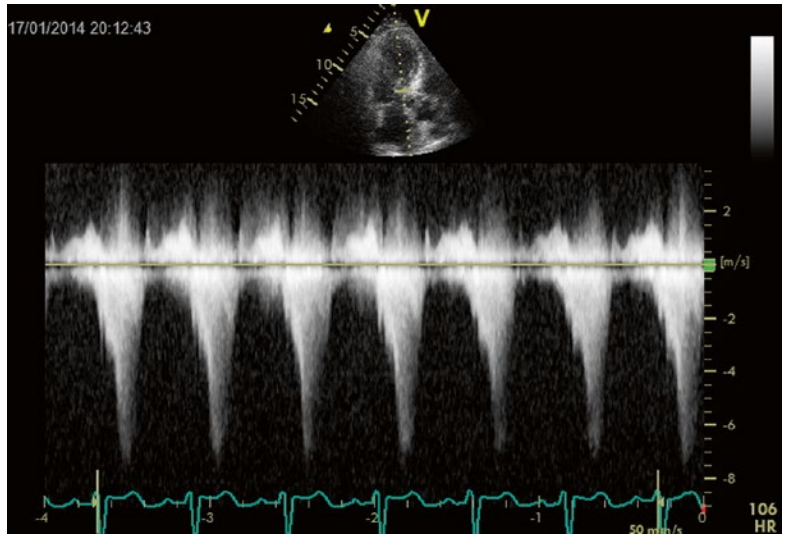

Fig. 15.5 An example of dynamic outflow obstruction. Note the different shapes of the velocity curves and the later maximum velocity with dynamic obstruction

This dimensionless velocity ratio expresses the size of the valvular effective area as a proportion of the cross-sectional area of the LVOT [13]. In the absence of valve stenosis, the velocity ratio approaches 1. If the velocity ratio is 0.25 or less, severe stenosis is present [17].

Aortic valve area planimetry may be an acceptable alternative when Doppler estimation of flow velocities is unreliable. When valve calcification causes shadows or reverberations limiting identification of the orifice, planimetry may be inaccurate.

Severe aortic stenosis can be diagnosed if a patient has these features:

- Clinical findings consistent with severe aortic stenosis
- A mean gradient greater than 40 mmHg
- AVA less than 1.0 cm^2 (<0.6 cm^2/m^2 when indexed for body surface area)

Recommendations for classification of AS severity are listed in Table 15.1.

Table 15.1 Recommendations for classification of AS severity

	Aortic sclerosis	Mild	Moderate	Severe
Aortic jet velocity (m/s)	≤2.5	2.6–2.9	3.0–4.0	>4.0
Mean gradient (mmHg)	–	<20 (<30[a])	20–40[b] (30–50[a])	>40[b] (>50[a])
AVA (cm^2)	–	>1.5	1.5–1.0	<1.0
Index AVA (cm^2/m^2)	–	>0.85	0.85–0.6	<0.6
Velocity ratio	–	>0.50	0.50–0.25	<0.25

[a]ESC guidelines
[b]AHA/ACC guidelines

Low-Flow, Low-Gradient Aortic Stenosis with Low Left Ventricular Ejection Fraction (LVEF)

Low LVEF, LF-LG severe AS is characterized by the combination of these features:

- Aortic valve effective orifice area (EOA) <1.0 cm^2 or <0.6 cm^2/m^2 when indexed for body surface area
- Low mean transvalvular gradient (i.e., <40 mmHg)
- Low LVEF (<40 %), causing an LF state [18]

The diagnostic problem in this kind of pathology is to distinguish true severe from pseudosevere aortic stenosis. In true severe AS, the LV dysfunction is a secondary or concomitant

phenomenon, while the primary culprit is deemed to be the valve disease. Instead, the main factor in pseudosevere AS is deemed to be myocardial disease, and AS severity is overestimated due to incomplete opening of the valve in relation to the LF state. Distinction between these two entities is essential: patients with true severe AS generally will benefit from aortic valve replacement (AVR), whereas those with pseudosevere AS may not benefit [18].

Dobutamine infusion is helpful in differentiating pseudosevere from true severe AS.

True severe AS is characterized by little or absent increase in effective orifice area and an increase in gradient that is congruent with the relative increase in flow; pseudosevere AS shows an increase in effective orifice area (EOA) and relatively little increase in gradient in response to increasing flow [18].

Some parameters and criteria have been proposed to identify patients with pseudosevere AS during dobutamine stress echocardiography:

- Peak stress mean gradient <30 or <40 mmHg (depending on studies)
- Peak stress EOA >1.0 or 1.2 cm^2
- An absolute increase in EOA >0.3 cm^2

The optimal cutoff values remain to be determined. The prevalence of pseudosevere AS is reported to be between 20 and 30 % [19–24].

A high plasma B-type natriuretic peptide (BNP) level (>550 pg/ml) appears to be a powerful predictor of mortality in patients with LF-LG AS regardless of treatment (medical vs. surgical) or the presence and/or absence of flow reserve [25, 38].

Low-Flow, Low-Gradient AS with Normal LVEF (Paradoxical Low-Flow Low-Gradient Aortic Stenosis)

Some authors [26] reported that a substantial proportion of patients with severe aortic stenosis (EOA <1.0 cm^2 and/or indexed EOA <0.6 cm^2/m^2) and a preserved LVEF (i.e., >50 %) might develop a restrictive physiology, resulting in low cardiac output (i.e., stroke volume index <35 ml/m^2) and lower than expected transvalvular gradients (i.e., <40 mmHg); this clinical entity was defined as *paradoxical LF-LG AS* [26, 27].

The prevalence of this entity increases with older age, female gender, and concomitant presence of systemic arterial hypertension.

Paradoxical LF-LG AS is characterized by a restrictive physiology, whereby left ventricular pump function and thus stroke volume are markedly reduced despite a preserved LVEF. Other distinctive features are:

- Marked reduction in intrinsic LV systolic function, not evidenced by the LVEF. Longitudinal shortening is reduced to a larger extent in these patients due to more advanced fibrosis in the subendocardial layer.
- More pronounced LV concentric remodeling and myocardial fibrosis both contributing to reduce the size, compliance, and filling of the LV [26, 28–30].

Several studies reported that these patients have a worse prognosis than those with moderate AS or normal flow severe AS [26].

Characteristics of low-flow low-gradient AS, paradoxical low-flow low-gradient, and pseudosevere AS are shown in Table 15.2.

Natural History

Calcific AS is a chronic disease. Patients may be asymptomatic for a long period of time [19, 22, 36, 37], and the duration of the asymptomatic phase varies a lot between individuals. Sudden cardiac death seems to be rare in the truly asymptomatic (<1 % per year), even in very severe AS, while it is a frequent cause of death in symptomatic patients. In asymptomatic patients with severe AS, reported average event-free survival at 2 years ranged from 20 % to more than 50 % [19, 22, 32, 36, 37].

There are clinical and echocardiographic predictors of symptom development and adverse

Table 15.2 Characteristics of low-flow low-gradient AS, paradoxical low-flow low-gradient, and pseudosevere AS

	EOA (cm^2)	Index EOA (cm^2/m^2)	Mean gradient (mmHg)	LVEF
Low-flow low-gradient aortic stenosis	<1.0 cm^2	<0.6 cm^2/m^2	<40 mmHg	<40 %
Paradoxical low-flow low-gradient aortic stenosis	<1.0 cm^2	<0.6 cm^2/m^2	<40 mmHg	>50 % with stroke volume index < 35 ml/m^2
Pseudosevere aortic stenosis (during dobutamine stress echocardiography)	Peak stress EOA > 1.0 or 1.2 cm^2	Absolute increase in EOA > 0.3 cm^2	Peak stress mean gradient <30 or 40 mmHg	

outcomes in asymptomatic patients: older age, presence of atherosclerotic risk factors, peak aortic jet velocity [19, 22, 36, 37], LVEF [22], rate of hemodynamic progression, increase in gradient with exercise, excessive LV hypertrophy, and abnormal tissue Doppler parameters of systolic and diastolic LV function [33, 34].

When the symptoms appear, the prognosis of severe AS is poor, with survival rates of only 15–50 % at 5 years.

Symptomatic and Asymptomatic Patients

Patients with severe aortic stenosis and symptoms should be considered for aortic valve replacement (AVR). Concomitant coronary artery bypass grafting should be performed for coronary atherosclerosis when epicardial lesions are >50 % [40], and age should not be considered a contraindication to surgery [39]. The treatment of the asymptomatic patient with severe aortic stenosis is more controversial. Surgery is reasonable to consider in asymptomatic patients when there is critical aortic stenosis:

- Gradient >60 mmHg
- Valve area <0.6 cm^2
- Expected operative mortality <1.0 %

If there is evidence of a high probability of rapid progression (Doppler peak velocity increases by >0.3 m/s per year or when the valve area decreases by >0.1 cm^2 per year), aortic valve replacement may also be considered for adults with severe asymptomatic aortic stenosis [31, 35, 40]. Treadmill testing may be appropriate for stratifying patients with asymptomatic severe aortic stenosis, but it is contraindicated in a symptomatic patient.

Indications for Intervention

Aortic Valve Replacement

Early valve replacement should be recommended in all patients with severe aortic stenosis and symptoms. As long as the mean gradient remains >40 mmHg, there is virtually no lower EF limit for surgery [22]. Paradoxical low-flow, low-gradient aortic stenosis requires special attention. In such cases, surgery should be performed only when symptoms are present and if comprehensive evaluation suggests significant valve obstruction. The management of patients with asymptomatic aortic valve stenosis still remains a topic of discussion. Recent studies do not provide convincing data to support the general recommendation of early AVR, even in patients with asymptomatic, very severe AS [22].

Balloon Valvuloplasty

In patients who will be undergoing surgery or TAVI, balloon valvuloplasty may be considered as a bridge to these types of intervention. It may also be considered in patients with symptomatic severe AS who require urgent major noncardiac surgery, in hemodynamically unstable patients who are at high risk for surgery, and as a palliative measure in selected individual cases when surgery is contraindicated and TAVI is not an option [22].

Transcatheter Aortic Valve Implantation (TAVI)

Since few years, transcatheter aortic valve implantation is the treatment of choice in patients with severe aortic valve stenosis who are not candidates for surgery. Contraindications for surgery, or risks of surgery, are defined by clinical judgment, STS score >10 %, EuroSCORE (logistic) >20 % and/or porcelain aorta, history of thoracic irradiation, severe thoracic deformity, and patent coronary bypass. TAVI should only be performed in hospitals with cardiac surgery on-site and with a "heart team" that assesses individual patient's risks [22].

It should be identified contraindications, both clinical and anatomic. Eligible patients should have a life expectancy of more than 1 year and should also be likely to gain improvement in their quality of life (see indications and contraindications below).

During TAVI, a biological valve prosthesis will be positioned within the calcific native aortic valve.

There are two types of valves used for this procedure:

Medtronic CoreValve System: this is a self-expandable nitinol stent with an inner *porcine pericardial valve* that is designed to sit into the aortic root and to anchor into the aortic annulus. The valve is available in two sizes (26 and 29 mm) and is approved only for retrograde applications [41].

Edwards SAPIEN™: this stent valve is a tubelike stainless steel balloon-expandable stent with an inner *bovine pericardial valve*; this valve is available in two sizes (23 and 26 mm) and is approved for transfemoral and transapical (TA) applications [41].

Two approaches are being mainly used for the installation of these biological valve prostheses: transfemoral (TF-TAVI) retrograde and transapical (TA-TAVI) antegrade approaches.

It is important to note that before the positioning of the prosthetic valve, a balloon aortic valvuloplasty should be performed. An angiogram is performed to confirm proper positioning of the balloon, and during a short period of rapid ventricular pacing (by percutaneous transvenous pacing wire in the right ventricle), the balloon is inflated.

The transfemoral TAVI requires good femoral access. Through a small cut in the thigh, a catheter is inserted into the body into the femoral artery (rarely the procedure requires the surgical preparation of the femoral vessel). Once inserted into the aorta, the guidewires are advanced and placed across the aortic arch and through the stenosed aortic valve. During this retrograde pathway, it is important to prevent calcium dislodgment from a diseased aortic wall.

Therefore, the valve is advanced over the guidewire into the aortic position. CoreValve auto-expands after the removal of the delivery system, whereas SAPIEN™ is expanded using the rapid inflation of the inner catheter balloon under rapid cardiac pacing (heart beat rate >180 bpm).

The *TAVI* is performed through a left anterolateral mini-thoracotomy through the fifth or the sixth intercostal space. Once the cardiac apex is identified (through the use of transthoracic echocardiography), a 3 cm incision is made over the top of the rib to avoid trauma to the neurovascular bundle. The left lung does not usually interfere with the exposure of the left ventricular apex. Therefore, a transapical sheath is placed into the left ventricle, and a stiff guidewire is placed into the ascending aorta via the sheath. The valve is advanced over the stiff wire in an anterograde manner, and it has to be ideally placed 1/3 below the base of aortic sinuses. It is extremely important to ensure accurate positioning of the valve prior to its deployment to avoid malpositioning, embolization, and significant perivalvular leak [42]. Echocardiography and fluoroscopy can be valuable aids to confirm the correct positioning of the valve.

This procedure is however not free from a series of complications, more or less serious and with different implications on outcome and quality of life (Table 15.3).

Regarding the outcome of patients undergoing TAVI, in 2013, data from a 3-year follow-up of the PARTNER trial were published.

Table 15.3 Complications of post-TAVI

Possible complications of post-TAVI
1. Stroke
1a. Early
Periprocedural hypotension Embolism of debris during valve implantation
1b. Delayed
Aggregation of platelets and fibrin on valve leaflet Incomplete endothelialization
2. Paravalvular leak
3. New-onset atrial fibrillation
4. Atrioventricular block (with subsequent implant of PMK) Edwards valve: rate of pacemaker implantation less than 10 % at 30 days CoreValve: rate of pacemaker implantation exceeding 20 % at 30 days (this could be due to the nitinol structure of this valve which exerts a high and persistent radial force on the interventricular septum, causing major changes on the atrioventricular system)
5. Other major adverse events Major ventricular tachyarrhythmia Myocardial infarction Cardiac tamponade Conversion to surgery Valve-in-valve procedure Aortic dissection/perforation

The PARTNER trial is the largest randomized trial on TAVI (a first-generation Edwards SAPIEN valve was used), and two cohorts of patients in this study were randomized: PARTNER cohort A compared treatment with TAVI versus traditional cardiac surgery in high-risk patients; PARTNER cohort B compared treatment with TAVI versus optimal medical therapy in inoperable patients.

This study demonstrated the superiority of TAVI in terms of 1-year mortality in patients who could not undergo surgery (PARTNER cohort B, inoperable patients), and non-inferiority compared traditional surgery (PARTNER cohort A, patients with high surgical risk).

At 3 years, in patients with symptomatic severe AS who were high-risk candidates for surgical aortic valve replacement, data have shown:

- No difference in all-cause mortality between TAVI and surgery (TAVI vs. SAVR, 44.2 % vs. 44.8 %; $p=0.483$) [43].
- Symptom improvement was similar in both groups and maintained for 3 years.
- At 3 years, strokes were similar in TAVI and surgery patients, despite increased periprocedural neurologic events in TAVI patients (stroke risk TAVI vs. SAVR, 7.7 vs. 4.9 % (periprocedural) → 8.2 vs. 9.3 %; $p=0.783$ (at 3 years) [43].
- TAVI hemodynamic performance was maintained with similar valve gradients and areas compared with surgery.
- Both TAVI and surgery resulted in significant LVEF improvement and LV mass regression.
- Paravalvular leak or total aortic regurgitation was associated with increased late mortality. The effect was proportional to the severity of the regurgitation, and even mild aortic regurgitation was associated with an increased rate of late death.

The authors concluded that TAVI should be considered an alternative to surgery with similar mortality and similar other major clinical outcomes; periprocedural stroke concerns after TAVI have diminished with longer-term follow-up, and periprocedural regurgitation (even mild) has emerged as a predictor of late mortality [43].

Follow-Up

The wide variability of the rate of progression of AS requires that patients be carefully educated about the importance of follow-up and reporting symptoms as soon as they develop [22]. Follow-up visits should include echocardiography with attention on hemodynamic progression, LV function and hypertrophy, and the ascending aorta.

Every 6 months asymptomatic severe AS should be reevaluated for the occurrence of symptoms, change in exercise tolerance, and change in echo parameters. Also measurement of natriuretic peptides may be considered.

Patients should be reevaluated yearly if there are mild and moderate AS with significant calcification. Intervals may be extended to 2–3 years [22] in younger patients with no significant calcification and with mild AS.

Appendix

Indications for Aortic Valve Replacement in Aortic Stenosis [22]

Class I, Level B

- AVR is indicated in patients with severe AS and any symptoms related to AS.

Class I, Level C

- AVR is indicated in asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise clearly related to AS.
- AVR is indicated in patients with severe AS undergoing CABG and surgery of the ascending aorta or another valve.
- AVR is indicated in asymptomatic patients with severe AS and systolic LV dysfunction (LVEF <50 %) not due to another cause.

Class IIa, Level B

- AVR should be considered in high-risk patients with severe symptomatic AS who are suitable for TAVI, but in whom surgery is favored by a "heart team" based on the individual risk profile and anatomic suitability.
- AVR should be considered in asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline.
- AVR should be considered in patients with moderate AS undergoing CABG and surgery of the ascending aorta or another valve.
- AVR should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal EF only after careful confirmation of severe AS.
- AVR should be considered in symptomatic patients with severe AS; low-flow, low-gradient with reduced EF; and evidence of flow reserve.
- AVR should be considered in asymptomatic patients, with normal EF and none of the abovementioned exercise test abnormalities, if the surgical risk is low, and one or more of the following findings are present:
  - Very severe AS defined by a peak transvalvular velocity >5.5 m/s
  - Severe valve calcification and a rate of peak transvalvular velocity progression ≥0.3 m/s per year

Class IIB, Level C

- AVR may be considered in symptomatic patients with severe AS low-flow, low-gradient, and LV dysfunction without flow reserve.
- AVR may be considered in asymptomatic patients with severe AS, normal EF, and none of the abovementioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings are present:
  - Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations
  - Increase of mean pressure gradient with exercise by >20 mmHg
  - Excessive LV hypertrophy in the absence of hypertension

Recommendations for the Use of Transcatheter Aortic Valve Implantation [22]

Class I, Level C

- TAVI should only be undertaken with a multidisciplinary "heart team" including cardiologists and cardiac surgeons and other specialists if necessary.
- TAVI should only be performed in hospitals with cardiac surgery on-site.

Class I, Level B

- TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a "heart team" and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities.

Class IIa, Level B

- TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favored by a "heart team" based on

the individual risk profile and anatomic suitability.

Contraindications for Transcatheter Aortic Valve Implantation [22]

Absolute contraindications: Estimated life expectancy <1 year, improvement of quality of life by TAVI unlikely because of comorbidities, inadequate annulus size (<18 mm, >29 mm), thrombus in the left ventricle, active endocarditis, plaques with mobile thrombi in the ascending aorta or aortic arch, and inadequate vascular access (vessel size, calcification, tortuosity).

Relative contraindications: Bicuspid or noncalcified valves, untreated coronary artery disease requiring revascularization, and LVEF <20 % hemodynamic instability.

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Mitral Regurgitation

16

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16.1 Case Report

A 68-year-old man is referred to his family doctor for dyspnea and fatigue for ordinary activities; symptoms arose 3 months before. At the beginning, dyspnea was mild and was present only after a moderate to intense physical activity. In the last 2 weeks, the symptoms worsened until dyspnea was evident during moderate physical activity (fast walking or after few steps of stairs) with even one episode of orthopnea at night that resolved after 30 min. No chest pain at rest or during exertion was referred; there were no syncope or dizziness and no palpitations.

Medical History and Cardiovascular Risk Factors

- Hypercholesterolemia LDL-C 145 mg/dl.
- Hypertension treated with drugs in the last 10 years.
- No previous or current pathology, but about 15 years ago, he was told to have a cardiac murmur, without further investigation.
- A mild cough without expectoration was present in the last month without fever.

Allergies

None

Social History

- Retired teacher
- Smokes 10 cigarettes per day since youth
- Never used illicit drugs
- Doesn't drink alcohol or coffee

Medications

Amlodipine 5 mg/day at 20:00

Vital Signs

- Temperature: 36.7 °C
- Heart rate: 85 bpm
- Blood pressure: 120/80 mmHg
- Respiratory rate: 16 breaths per minute

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Physical Examination

- *General:* no acute distress, alert, awake, and oriented. Well developed and well nourished
- *Head, eyes, ears, nose, and throat:* normal
- *Neck:* supple, mild jugular venous distention, no lymphadenopathy, and no carotid bruit
- *Cardiovascular:* regular rate and rhythm, S1 and S2 normal, third tone audible, blowing crescendo-decrescendo holosystolic murmur grade IV in Levine scale, and best audible at the fifth left midclavicular intercostal space and irradiated to the armpit
- *Lungs:* harsh breath sounds with rales on auscultation at the bases bilaterally, no rhonchi or wheezes, no alterations in tactile fremitus, and normal upercussion
- *Abdomen:* mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no abdominal rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- *Extremities:* no cyanosis or clubbing. Mild peripheral pitting edema at ankle
- *Neurologic:* cranial nerves II through XII intact and no focal deficit
- *Psychiatric:* normal
- *Skin:* intact, no rashes, no lesions, and no erythema

What Are the Possible Causes for Dyspnea on Exertion and Fatigue?

- Flu
- Lung diseases
  - COPD
  - Pneumonia
  - Bronchitis
- Heart diseases
  - Heart failure
  - Myocardial ischemia
  - Bradyarrhythmias
  - Tachyarrhythmias

The patient didn't refer fever and cough was mild and without expectoration. Furthermore the symptoms arose 3 months before, so the hypothesis of a pneumonitis or bronchitis seemed unlikely.

Myocardial ischemia was possible even without chest pain; dyspnea could have been an anginal equivalent.

According to the physical exam (rales at the bases bilaterally, peripheral edema, mild jugular distension, third tone, and cardiac murmur), the most probable cause seemed to be heart failure.

What Kind of Disease Is Suggested from Cardiac Physical Examination?

- Aortic stenosis
- Aortic regurgitation
- Mitral stenosis
- Mitral regurgitation

There was a left apical at the fifth left intercostal space toward the anterior axillary line. Systolic murmur was located in the mitral region and radiated to the armpit. Its quality (holosystolic, blowing) suggested a mitral regurgitation over aortic stenosis.

What Should the Family Doctor Do?

- Treat heart failure with appropriate drugs according to guidelines.
- Refer the patient to a cardiologist.
- Refer the patient to the emergency room.

The diagnosis of heart failure was done, and a myocardial ischemia should be ruled out.

The patient was referred to a cardiologist as a correct choice and also an EKG and echocardiography assessment was requested. Short-term delay should be suggested and visit undertaken within a week.

The patient was stable at rest and symptoms were stable in the last week; therefore, there was no reason for urgent access to the emergency room.

After 5 days, the patient was seen by a cardiologist which confirmed the diagnosis of MR; a routine EKG at rest (resulting normal) and echocardiography were performed.

Echocardiography (Fig. 16.1)

Normal and trileaflet aortic valve. Normal aorta. Moderate dilatation of the left atrium (LA diameter M-mode = 4.5 cm; area 4c = 26 cm^2). Eccentric hypertrophy of the left ventricle (with end diastolic diameter 60 mm). Normal systolic function (ejection fraction 60 % measured with Simpson's biplane) without focal hypokinesia or akinesia. Thickened mitral leaflet with severe prolapse of the posterior leaflet and mild prolapse of the anterior leaflet. Severe eccentric mitral regurgitation (vena contracta 7.5 mm, PISA 1.1 cm, effective regurgitant orifice area (EROA) 0.5 mm^2). Normal right atrium (area 4c = 17 cm^2). Restrictive mitral inflow pattern (grade III diastolic dysfunction). Normal tricuspid valve. Mild tricuspid regurgitation which was centrally directed with an estimated PASP = 50 mmHg. Normal pulmonic valve. Normal interatrial septum. Normal pericardium. Normal aorta. Slightly dilated inferior vena cava. Less than 50 % inspiratory collapse of the IVC.

Mitral regurgitation had major hemodynamic consequences in this patient and led to atrial enlargement due to chronic volume overload. Ventricular hypertrophy was probably the consequence of either hypertension or mitral insufficiency. These alterations led to the development of heart failure. The presence of cardiac remodeling suggested a chronic valve disease, and even if the symptoms arose 3 months before, severe insufficiency was probably present since several months or years. Myxoid degeneration of valve apparatus (Barlow disease) was the probable mechanism of valve disease. No alterations suggesting endocarditis were found. Ventricle was dilated, but the extent of dilatation wasn't sufficient to consider valve insufficiency as secondary.

Final Diagnosis

Congestive heart failure due to a severe mitral valve prolapse and regurgitation

What Should the Cardiologist Do?

- Refer the patient for cardiac surgery.
- Treat the patient for heart failure.
- Treat the patient with drugs and reevaluate after 3 months.

Cardiac surgery in primary mitral regurgitation is curative and the occurrence of symptoms is a major indication for surgery. The presence of increased PASP is a further indication for surgery. Medical therapy may alleviate symptoms, but

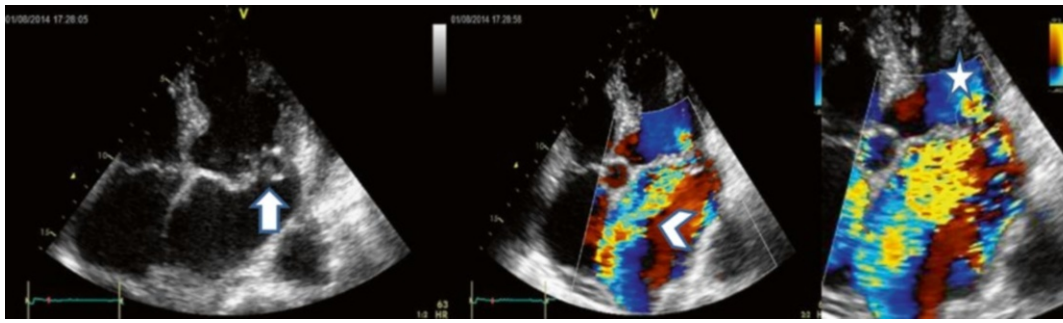

Fig. 16.1 Echocardiography, four-chamber view. From left to right: two-dimensional imaging shows thickened mitral leaflet with posterior leaflet prolapse (*arrow*). Color Doppler shows severe eccentric mitral regurgitation swirling toward interatrial septum and reaching the pulmonary veins (Coandă effect, *arrow point*). Nyquist limit is shifted downward to detect proximal isovelocity surface area (PISA) >1 cm (*star*)

reduction of valve regurgitation is unlikely (which is possible in secondary MR). Hence evaluation for cardiac surgery, including coronary angiography for the detection of asymptomatic coronary artery disease, is the right choice. Concurrent medical therapy for heart failure, including diuretics, beta-blockers, and ACE inhibitors or ARBs, is important until cardiac surgery is undertaken.

16.2 Mitral Regurgitation

Definition and Classification

Mitral regurgitation (MR) is characterized by a systolic blood flow reversal from the left ventricle (LV) to the left atrium (LA). MR can be classified based on etiology and mechanisms. The etiology of MR is generally stratified as ischemic that occurs in up to 40 % of patients affected by myocardial infarction [1] and nonischemic. Mechanisms of MR are stratified as functional (mitral valve is structurally normal and MR is due to valve deformation caused by ventricular remodeling) or as organic (intrinsic valve lesions). A further classification of MR, according to Carpentier, is by observation of leaflet movement: type I (normal valve movement such as annular dilatation, perforation), type II (excessive movement), and type III (restrictive movement: IIIa, diastolic restriction such as rheumatic disease; IIIb, systolic restriction as in functional MR) (Table 16.1).

Etiology

The mitral valve apparatus is made of the leaflets, the annulus, the chordae, the papillary muscles, and the left ventricular wall [2]. When one of these portions of the apparatus becomes abnormal, MR may develop. Also left ventricle dilatation or papillary muscle displacement can provoke the dysfunction of the mitral valve apparatus.

As seen above, the etiology of MR can be stratified into nonischemic and ischemic.

Nonischemic etiologies include:

(a) Degenerative MR includes myxomatous degeneration of the mitral valve with resultant mitral valve prolapse with or without ruptured chordae, mitral valve leaflet sclerosis or calcification, and mitral annulus calcification.
(b) Rheumatic MR is usually due to commissure fusion in chronic type, while in pure active rheumatic MR, annulus dilatation and anterior leaflet prolapse from chordal elongation are described [3].

MR etiology is predominantly degenerative in developed countries and rheumatic in developing countries:

(c) Infective endocarditis (5 % of severe MR) that causes MR mainly through tissue destruction.
(d) Congenital lesions (isolated cleft mitral valve or associated with persistent atrioventricular canal, corrected transposition with or without Ebstein's abnormality of the left atrioventricular valve).
(e) Iatrogenic (radiation/drugs).
(f) Cardiac tumors.
(g) Other causes (connective tissue diseases, systemic lupus erythematosus, antiphospholipid antibody syndrome, cardiac trauma, hypertrophic cardiomyopathy or sarcoidosis,

Table 16.1 Severity of mitral regurgitation in adults

	Mild	Moderate	Severe
LV and LA size	Normal size LV	–	LV and LA enlarged
Vena contracta	<3	3–6.9	>7
PISAr (Nyquist limit of 40 cm/s)	<0.4 cm		>1 cm
Regurgitant volume	<30 ml/bpm	30–59 ml/bpm	>60 ml/bpm
Regurgitant fraction	<30 %	30–49 %	>50 %
Regurgitant orifice area	<0.20 cm^2	0.20–0.39 cm^2	>0.40 cm^2

eosinophilic syndromes, endocardial fibroelastosis, carcinoid tumors).

Ischemic etiologies include papillary muscle (PPM) displacement, leaflet tethering, and annular dilatation. Functionally the leaflets present a restricted systolic motion due to tethering forces that displace the coaptation surface toward the left ventricle (LV) apex [4].

According to the classification of the mechanisms of MR, it is possible to distinguish two types of pathologies: functional MR and organic MR. While the former includes all forms of MR that are not secondary to alterations of the valve per se, the latter is due to primary mitral valve disease (fusion of commissures, annulus dilatation, leaflet prolapse, chordal elongation, retractile fibrosis, etc.).

Even if etiology and mechanism are not synonymous (a single etiology may generate MR by different mechanisms), the mechanism of ischemic and functional MR is similar; in fact mitral leaflets are intrinsically normal, but their coaptation is incomplete [5] because of annular and left ventricular dilatation due to ischemia, previous myocardial infarction and scarring, aneurysm formation, cardiomyopathy, or myocarditis.

Pathophysiology

Anatomic malcoaptation of mitral leaflets during systole results in a regurgitant orifice (ERO), which under the influence of the pressure gradient between the LV and LA allows abnormal regurgitant flow into the LA. The systolic pressure gradient between the LV and LA begins when mitral valve closes (S1) and persists after aortic valve closure (S2) up to mitral opening [6]. Thus, regurgitant flow is typically holosystolic. The regurgitant flow throughout systole is the regurgitant volume (RVol) accumulated in the LA, which reenters the LV during the next diastole, causing a volume overload of LA and LV.

Determinants of this volume overload are the area of ERO [7], the regurgitant gradient, and duration of regurgitation. In both organic MR [8] and functional MR [9], ERO increases when afterload increase and decreases with afterload reduction or improved contractility. Its change is independent of rate [8]. The consequences of volume overload of the LA and LV are different depending on the fact that regurgitation is acute or chronic. In acute severe MR, the left ventricle responds to the sudden volume overload with increased sarcomere stretch and augmented left ventricular stroke volume (Frank-Starling mechanism). The larger volume increases left ventricular diastolic pressure, which in turn increases left atrial pressure. However, left atrial compliance is normal in the acute state and the large regurgitant volume markedly increases left atrial pressure. This phenomenon causes pulmonary congestion, edema, and dyspnea. Otherwise, chronic MR progresses slowly, so the LA has enough time to remodel and accommodate the RVol with a near normal LA pressure. As a result, clinical tolerance may be excellent [10]. In these patients, the Frank-Starling mechanism continues to augment total stroke volume. The left atrium dilates, thus increasing its compliance. The blood that reflows from a dilated left ventricle to a dilated atrium provokes only a small rise of filling pressures, with minimal symptoms of pulmonary congestion (chronic compensated stage).

LV dysfunction (chronic decompensated stage) is a frequent complication of severe MR that occurs if the disease is not treated properly during the reversible phase [11, 12]. It is associated with myocardial structural damage as interstitial fibrosis and reduction in myofiber content that provokes decrease in myofiber contractility [13] and increase in left ventricular filling pressures and finally pulmonary congestion. A downward cycle is now activated: increased ventricular pressure further dilates the left ventricle, increasing systolic wall stress and afterload, which in turn reduces ventricular systolic function. The time during which patients progress from compensated to decompensated MR depends on some variables as the severity of the regurgitation, afterload, and ventricular contractility.

In ischemic/functional MR, blood regurgitation is provoked by tethering and tenting of the leaflets and loss of coaptation surface [14, 15] due to localized LV deformation with apical and

posterior displacement of the papillary muscles. The RVol in ischemic MR is usually less than in organic MR [16], and LV dilatation and LA dilatation are in excess to the degree of MR [7], due to the presence of a dilatated, poor performant heart.

Clinical Manifestations

Chronic MR is a slow process that allows a gradual LA enlargement and a consequent increase in LA compliance that permits to maintain a normal or near normal LA pressure. For this reason, patients may remain asymptomatic for years despite severe MR. However, once symptoms arise, fatigue and generalized weakness predominate early. As left ventricular function deteriorates, exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea become more prominent. Frank pulmonary edema or hemoptysis may also develop and is usually triggered by atrial fibrillation or increase in the degree of MR. Sudden death as the initial presentation of MR is possible [17].

Diagnosis

Symptoms

Clinical manifestations of mitral regurgitation (MR) are related to the severity of regurgitation, the rate of progression, and the associated cardiopathy.

Acute MR due to chordal rupture (flail), endocarditis, or trauma leads to an increase in left atrial pressure due to a volume overload in a noncompliant left atrium. Pulmonary edema or cardiogenic shock may be the presenting symptoms owing to elevated filling pressures and low cardiac output. The dramatic increase of pulmonary pressure may also cause right heart failure.

Chronic MR leads to a progressive left atrial enlargement without elevated left atrial pressure. Patients usually remain asymptomatic for years unless there is left ventricular (LV) failure. Dyspnea and fatigue gradually worsening over the years are the most frequent symptoms.

Physical Examination

MR is usually diagnosed by auscultation. S1 may be diminished due to the failure in the closure of the mitral valve. A soft systolic murmur, best heard at the apex and radiated to the axilla, is the most frequent finding, but its timing and intensity depend on severity and mechanisms of MR. The murmur has little variations with respiration and becomes louder when the preload (i.e., raising legs) or afterload (i.e., squatting) increases. Sometimes the systolic murmur isn't audible even in the presence of moderate or severe MR (silent MR), especially in ischemic MR, owing to a low pressure gradient between the left ventricle and atrium (low systemic blood pressure with elevated LA pressure). A systolic click may suggest a valve prolapse, while a thrill or S3 suggests a severe regurgitation.

Electrocardiogram

Electrocardiogram usually shows left atrial enlargement (notched P wave >0.12 s in DII). Left ventricular enlargement is less frequent [17] and right ventricular hypertrophy rare. Fibrillation is a common arrhythmia in these patients due to atrial enlargement and increased shear stress. Q wave or ST-T abnormalities may be found in ischemic MR.

Echocardiography

Transthoracic echocardiography (TTE) is a sensitive technique in initial evaluation and longitudinal assessment of mitral valve disease. TTE allows to detect the presence of regurgitation and hemodynamic consequences. A careful evaluation of mitral structures with the determination of mechanisms and etiology is required. Assessment of left ventricular and atrial size and function is mandatory as it provides information about the mechanism and helps in defining a correct surgical timing.

Transesophageal echocardiography (TOE) is useful when TTE quality is suboptimal or when a more accurate definition of valvular lesions is required like in reparative surgery. TOE plays also a role in intraoperative assessment.

Three-dimensional echocardiography is an emerging technique in assessing MR mechanisms

and etiologies providing more accurate evaluation on leaflet motions and multiple images similar to surgeon view.

Primary Mitral Regurgitation

Primary MR is due to intrinsic valvular disease with a large spectrum of possible valve lesions. Progressive thickening of the valve with fusion of commissures and doming of the anterior leaflet may suggest a rheumatic disease, with vegetations or abscess points at endocarditis. When the etiology is chordal or papillary rupture, a flail leaflet may be observed.

Degenerative MR is the most common cause of surgical repair and ranges from billowing to complete prolapse or floppy valve (>5 mm diastolic excursion in left atrium). The presence of redundant and thickened leaflets may suggest myxoid infiltration by Barlow's disease. Mitral calcifications are a frequent finding in older patients and may be a limitation to surgical repair when too extended.

Functional Mitral Regurgitation

Functional MR is related to alterations in LV geometry due to ischemic or dilated cardiomyopathy with distortion in normal spatial relationship between mitral valve apparatus. The disproportion between closing forces (LV contractility, annular contraction, papillary muscle synchrony) and tethering forces (LV and annular dilatation with displacement of papillary muscles) leads to incomplete coaptation and MR. The regurgitant flow during systole usually varies with an early systolic peak and a progressive decrease.

Ischemic MR may result from a restricted systolic motion of the leaflet leading to inadequate apposition particularly in posterior infarction (asymmetric pattern). A mitral incompetence due to a deficit in coaptation of both leaflets (symmetric pattern) may be found in more complex infarction or dilated cardiomyopathy [4].

The LV is usually spherical with multiple regional dysfunctions. Tenting distance should be measured as the distance between annulus plane and coaptation point, while the tenting area is the area enclosed between annulus plane and leaflets.

Grading Severity

Based on the 2014 ESC Guidelines [18] for the Management of Patients With Valvular Heart Disease, the easiest approach is the measurement of the narrowest part of the jet on Doppler color flow (vena contracta) [19]. More accurate echocardiographic evaluations may be obtained by calculation of regurgitant volume, regurgitation fraction, and effective regurgitant orifice area (EROA) based on the evaluation of the convergence signal during color flow imaging [20]. EROA should be calculated by dividing the flow rate through the regurgitant orifice (product of the area of the hemisphere and aliasing velocity) by the peak velocity of the jet:

$$\mathrm{EROA} = \left(2\prod r^2 * \mathrm{Va}\right) / \mathrm{PkVreg}$$

where $2\prod r$ = surface area of hemisphere, Va = aliasing velocity, and PkVreg = peak V of regurgitant jet.

The presence of systolic flow reversal in the pulmonary vein is a significant marker of severity but may not be present in the absence of sinus rhythm [21]. Left atrial and ventricular enlargements are also typical findings and often reflect the "history" of the disease.

Sometimes in ischemic MR, the regurgitant flow may be trivial at rest and worsens under exercise due to papillary muscle dysfunction related to the hypokinesis of left ventricular walls.

Cardiac Catheterization

Cardiac catheterization for the evaluation of intracardiac pressures or left ventricular angiography is not recommended in routine evaluation of MR. Coronary angiography should be performed when coronary disease is suspected on the basis of symptoms or the presence of reduced LV systolic function and risk factors [18].

Right heart catheterization may demonstrate the presence of significant "v" wave due to the regurgitant blood volume in the left atrium.

Treatment

Severe MR imposes a significant overload to LV leading to progressive hypertrophy and dilatation.

Acute MR carries a poor prognosis and in most cases requires surgery after hemodynamic stabilization. Chronic severe MR, even if asymptomatic, reduces the patient's prognosis to 5 years [18]. The management of MR largely depends on pathophysiology, severity, and the presence of indications to surgery. Two mitral surgery techniques are available: valve repair and valve replacement. Recently a percutaneous edge-to-edge procedure has been proposed with good clinical results [22] and may be performed in inoperable patients who meet the echocardiographic criteria.

Primary Mitral Regurgitation

Acute MR due to papillary or chordal rupture is an emergency and often requires surgical treatment after medical stabilization with an intra-aortic balloon pump and inotropes or vasodilators. According to the most recent guidelines on valvular disease, mitral valve repair should be preferred when feasible [18]. In chronic MR, surgical treatment is indicated in symptomatic patients with no contraindications for surgery. Indications for surgery as suggested by the guidelines are reported in Table 16.2.

Mitral Valve Repair

Valve repair should be the preferred surgical treatment in primary MR when feasible. Current techniques include the use of artificial chord replacement and ring annuloplasty with excellent outcomes in experienced centers [23]. The major benefits in valvular repair are the preservation of subvalvular apparatus and the absence of prosthetic valves. Preoperative echocardiography is needed to correctly evaluate the anatomy of the regurgitant valve and to choose the appropriate surgical approach. TOE is also recommended intraoperatively to enhance surgery outcomes.

The durability of mitral repair is a potential limitation. In experienced centers with appropriate patient's screening, the rate of freedom from reoperation is similar to valve replacement. Extensive calcifications, prolapse of more than one-third of the leaflet, or complete muscle rupture usually suggests replacement over repair.

Table 16.2 Indications for mitral valve surgery in primary MR according to the 2012 ESC guidelines

Class I – evidence or agreement that mitral valve surgery is indicated
Patients with severe MR undergoing CABG and LVEF >30 %
Class IIa – weight of evidence favors mitral surgery
Patients with moderate MR undergoing CABG
Patients with severe MR, LVEF <30 %, and the need for revascularization with evidence of myocardial viability
Class IIb – weight of evidence less well established
Symptomatic severe MR with LVEF >30 % despite medical treatment, low comorbidity, and no need for revascularization

LVESD left ventricular end systolic diameter, *LVEF* left ventricular ejection fraction

Mitral Valve Replacement

Mitral valve replacement requires the use of a prosthetic valve. The choice between mechanical or bioprosthetic valves and issues about prosthetic valves will be best developed in Chap. 17. According to ESC guidelines [18], a bioprosthetic valve must be preferred in patients with contraindication to warfarin or >65 years. Chordal preservation should be preferred if possible (i.e., subvalvular scarring or calcification) due to the negative impact of left ventricular function.

Medical Therapy

Management of acute MR with hemodynamic instability should be pointed on reduction of filling pressures and reduction of the regurgitant blood volume. Sodium nitroprusside should be used to reduce afterload and regurgitant fraction as intra-aortic balloon pump (IABP). IABP and inotropes may be added in case of hypotension or shock. There's no evidence about the use of vasodilators in chronic MR.

Functional Mitral Regurgitation

In functional or secondary MR, mitral valve apparatus is normal and the regurgitant volume results from a disproportion between closing and tethering forces. The ischemic etiology carries a poor prognosis. Severe tricuspidal regurgitation is often associated, and right ventricular dysfunction may be a predictor of worse outcome [24].

Medical Therapy

In functional MR with heart failure, the role of medical therapy must be emphasized. Optimal medical therapy, according to guidelines [18], including ACE inhibitor/ARB, beta-blocker, and aldosterone antagonist, is the first step in these patients with a benefit in improving cardiac function and overall survival. Some data suggest a possible role of medical therapy in reducing the degree of functional MR [25]. Diuretics and/or nitrates may be added to reduce volume overload and treat symptoms.

Mitral Valve Repair

The role of mitral surgery remains controversial as it carries a higher operative mortality than primary MR and worse long-term prognosis. When indicated (Table 16.3), the preferred technique should be mitral annuloplasty with an undersized ring that ensures low surgical risk but a high recurrence of MR.

Table 16.3 Indications for mitral valve surgery in functional MR according to the 2012 ESC guidelines

Class I – evidence or agreement that mitral valve surgery is indicated
Acute severe MR
Severe MR in symptomatic patients with LVESD <55 mm and LVEF >30 %
Asymptomatic patients with LV dysfunction (LVESD >45 mm and/or LVEF <60 %)
Class IIa – weight of evidence favors mitral surgery
Asymptomatic severe MR with preserved LV function and new onset of atrial fibrillation or pulmonary hypertension (defined as systolic pulmonary pressure at rest >50 mmHg)
Asymptomatic severe MR with preserved LV function with high likelihood of surgical repair and low surgical risk and/or flail leaflet
Severe MR with LV dysfunction (LVEF <30 % or LVESD >55 mm) with high likelihood of surgical repair and low comorbidity
Class IIb – weight of evidence less well established
Severe MR in patients with severe LV dysfunction (LVEF <30 % or LVESD >55 mm) with low likelihood of surgical repair and low comorbidity

CABG coronary artery bypass grafting, *LVEF* left ventricular ejection fraction

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is a pacing modality that provides synchronized biventricular stimulation to improve cardiac function (discussed in Chap. 10). CRT may also reduce the degree of MR and left ventricular volumes by reducing papillary dyssynchrony and increasing closing forces [26]. Ischemic MR seems to have a worse response to CRT, so a careful evaluation is needed in this population. Benefits gained by CRT disappear with therapy discontinuation [27].

Percutaneous Mitral Repair

A percutaneous edge-to-edge mitral valve repair has been recently proposed in patients with functional MR already judged inoperable by a "Heart Team" and who fulfill echocardiographic criteria (IIb, level of evidence C).

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Prosthetic Valve Dysfunctions

17

Alessia Urbinati, Marco Marchesini, and Ilaria Mazzanti

17.1 Case Report

A 73-year-old man was admitted to the hospital with dyspnea and fatigue. Past medical history revealed a previous inferior myocardial infarction complicated by rupture of the posteromedial papillary muscle resulting in severe mitral regurgitation and cardiogenic shock. The patient was successfully treated with a mechanical bileaflet mitral valve replacement (St. Jude 25) and concomitant coronary artery bypass grafting. Since the surgery, the patient was regularly on warfarin.

Vital Signs

Heart rate: 68 bpm
Blood pressure: 115/70 mmHg
Respiratory rate: 12 breaths per minute
Oxygen saturation: 98 %

Physical Examination

Physical examination revealed an extra sound (S3) and a holosystolic murmur at the apex radiating toward the left axilla. There were crackles in both lungs and ankles are swelling. The liver was palpable 1 cm below the right lower costal margin, in the midclavicular line; the spleen tip was not palpable below the left costal margin neither were the lymph nodes. The patient showed mildly icteric sclerae.

Cardiovascular Risk Factors

- Hypertension
- High blood cholesterol
- Chronic kidney disease

EKG on Admission

Sinus rhythm, normal atrioventricular and intraventricular conduction, no alterations in repolarization.

Laboratory Exams on Admission

Complete blood cell count revealed a hemoglobin level of 6.7 g/dL (mean corpuscular volume, 86.9 fL; mean corpuscular hemoglobin, 25.8 pg),

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a hematocrit of 22.6 %, white blood cell count of 7.98×10^9/L, and platelets of 386×10^9/L. Serum iron, total iron-binding capacity, and ferritin level were 71 ug/dL, 247 ug/dL, and 35 ug/dL, respectively. Basic metabolic panels were 137 mmol/L for sodium, 3.9 mmol/L for potassium, 104 mmol/L for chloride, and 2.36 mg/dL for creatinine (previous value of 1.6 mg/dl). Serum bilirubin was 1.57 mg/dL (direct bilirubin, 0.31 mg/dL). Aspartate aminotransferase was 95 IU/L and alanine aminotransferase was 24 IU/L. Lactate dehydrogenase (LDH) level was 2006 U/L, and the haptoglobin level was 1 mg/dL. The hematological features were suggestive of hemolytic anemia that may occur in patients with prosthetic valve.

Transthoracic Echocardiography

While the exam was performed, the patient experienced an episode of paroxysmal atrial flutter (ventricular rate approximately 150 bpm).

Normal left ventricular volume, wall thickness, and mass, with normal ejection fraction (about 60 %). Normal motion of the moving parts of the mitral prosthesis. No leaflet calcifications or abnormal echo density attached to the valve. Apparently normal valve sewing ring integrity and motion. No occluder movement. Mild mitral regurgitation. Mild aortic regurgitation. Moderate tricuspid regurgitation. Severe pulmonary hypertension (75 mmHg).

Chest X-Ray

Widened vascular pedicle width. Perihilar haze, septal lines, and accentuated interstitium. Bilateral pleural effusion.

The patient, after a red blood cell transfusion, showed a hemoglobin level of 11 g/dl. However, there was just a mild improvement in the dyspnea.

A transesophageal echocardiogram was then performed for a better evaluation of the prosthetic valve.

Transesophageal Echocardiography

Dehiscence of the prosthetic valve. Severe mitral regurgitation. Two physiologic jets due to lavage volume (Fig. 17.1) and a perivalvular leakage due to dehiscence of the prosthesis (Fig. 17.2). Severe pulmonary hypertension. Normal left ventricular volume and normal ejection fraction.

Final Diagnosis

Acute heart failure caused by severe mitral regurgitation due to dehiscence of the prosthetic valve. Hemolytic anemia due to the mechanical disruption of red blood cells.

The patient has been recommended to undergo further surgery, but he refused and asked to be discharged. After 3 weeks, he experienced the same symptoms and was admitted again at the hospital. Since the early clinical decompensation, the patient agreed with the previous plan. He underwent a successful mechanical valve replacement.

The patient was keen to switch from warfarin to one of the new oral anticoagulants (NOACs). Unfortunately, while NOACs were proved to be more effective and safer than vitamin K antagonist in prevention of stroke in patient with non-valvular atrial fibrillation, they failed in the setting of valvular atrial fibrillation especially in patients with mechanical prosthetic valves and severe mitral stenosis. Warfarin is, at the present

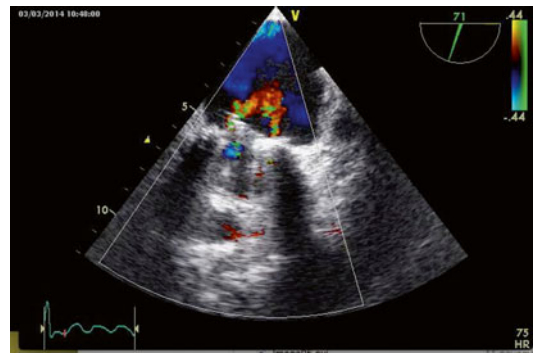

Fig. 17.1 Transesophageal echocardiography showing two physiologic jets due to lavage volume

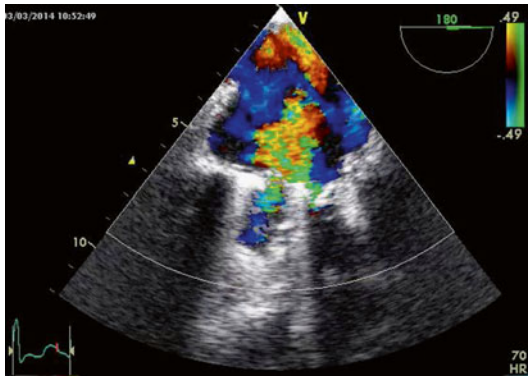

Fig. 17.2 Transesophageal echocardiography showing the perivalvular leakage due to dehiscence of the prosthesis

time the only available anticoagulant for patients with prosthetic valvular atrial fibrillation. Since that, no switch was possible for the patient.

17.2 Prosthetic Valve Dysfunctions

Prosthetic valve dysfunctions may be due to regurgitations or obstructions. Sometimes, in case of high velocity flow rate, it is possible to encounter hemolytic anemia due to the mechanical disruption of red blood cells. It ranges from a mild level to a critical hemolysis requiring blood transfusions. This happens mainly in perivalvular regurgitations, but also in normal or accelerated anterograde flow in a mechanical valve.

There are several types of *regurgitations* that must be differentiated. The most important classification is between pathologic and physiologic regurgitations [1–5].

Mechanical Prosthetic Valves

In mechanical prosthetic valves, color Doppler is the mainstay in identifying, localizing, and grading the severity of regurgitation. The knowledge of the specific model and type of the prosthetic valve we are facing is mandatory. At the same time, it's important to keep in mind that regurgitation of a prosthetic valve can be physiologic. There are two different types of physiologic regurgitations: The first is the closure volume, that is, the volume of blood pulled back by the closure of the occluders and is confined just after the valve closure; the second is the lavage volume that consists in the blood flow that passes between the occluders and the prosthetic ring throughout the closing state of the valve and is functional to the correct washing of the valve elements. A caged ball valve realizes small and variable jets along the whole circumference of the ball. A tilting disk valve presents jets, one at each side of the occluder; in the bileaflet valve, we can see three regurgitant jets: one central and two near the hinges; making a distinction from perivalvular leakages could be very difficult [4].

Pathologic intra-valvular regurgitation could be secondary to the blockage of an occluder in opening position due to thrombosis, vegetation, or pannus, that is, a fibrous overgrowth of the endocardial tissue over the valve elements. When facing a perivalvular or suspected perivalvular regurgitation, we are called to distinguish a lavage volume passing near the hinges of the occluders from an anomalous regurgitation due to an initial prosthetic valve detachment. Pathologic perivalvular regurgitations are bigger than physiologic ones and show an extensive aliasing. Grading criteria are the same of regurgitation in native valves although the eccentricity and the valve masking phenomenon could make a purely quantitative approach misleading [6].

Biologic Prosthetic Valve

Regarding biologic prosthetic valve, physiologic regurgitation rarely occurs 2 years before the implant, but when present has a central origin, a short length, and low velocities without aliasing. It is important to bear in mind that biologic stentless valves could present physiologic central regurgitation also just after the implant. Pathologic regurgitations of different origin, direction, and nature, either intra- or perivalvular, can occur due to calcific degeneration and

endocarditis that could damage a biologic valve even more frequently than a native one.

Prosthetic valve detachment is the most dramatic complication that should be monitored after the recognition of a true perivalvular regurgitation. It is commonly due to an infective endocarditis, frequently with an early onset within 1 year from the implant and related to the implant itself. The infective process disrupts the sewing ring directly generating a perivalvular regurgitation or creating a periprosthetic aneurysm that could be silent until its emptying, when a loss of tissue occurs and the valve anchorage is lost. Beside regurgitation that could range from moderate to severe leading to heart failure manifestations, we can see the rocking movement of the valve that is a sign of a more extensive detachment with a more urgent indication to surgery. The most dreadful consequence is prosthetic valve embolization.

On the opposite side, we can face prosthetic valve *obstruction* generating valve stenosis of different severity [3]. In this setting, knowing the exact type (mechanical, single disk, bileaflet or biologic, stented/stentless, etc.), model, and dimension of the valve is of paramount importance because the normal values reported by the manufacturers differ in relation to these factors. Moreover, it is essential, at every follow-up, to know the early post-implant gradient values in order to avoid an incorrect diagnosis of prosthetic valve dysfunction. In mechanical valves, the obstruction could be suspected in the presence of a gradient higher than expected for the specific prosthesis. Sometimes the cause is evident such as the presence of a voluminous mass (thrombus or vegetation) occupying space and then reducing the effective orifice area or blocking an occluder in close position; sometimes the cause consists of a small pathologic process that interferes with the hinges that is not directly visible with 2D echocardiography. In those cases, we must look for an anomalous or incomplete opening of the occluders, although it is often difficult to see without the use of fluoroscopy.

In biologic prosthesis, the main clue of suspicion is the presence of increased thickness (>3 mm) and extensive calcification, beginning at the commissures and at the base of the leaflets, reducing the excursion movement.

A different scenario is the patient-prosthesis mismatch, more frequently viewed with aortic stented bioprosthesis, where the increased afterload of the left ventricle is due to a normal functioning valve that is however undersized in relation to the patient's body surface area [7]. This situation occurs mainly in patient with a small native aortic annulus in which it is possible to lodge only a small prosthesis. The clinical scenario consists of a patient with a valvular stenosis that is not solved [8–12].

For patients with prosthetic valves, regardless of the type or model, most recent international guidelines and experts' consensus recommend a visit, a chest X-ray, a 2D echocardiography within 4 weeks from the implant in order to obtain a picture in a moment in which the valve is thought to work at best, and be able to register any modifications from this optimal condition. Then the follow-up consists of an annual cardiology visit, with adjunctive controls with echocardiography in case of symptoms variations or new cardiac murmur discovery [2, 8]. If any dysfunction is detected, a 2D echocardiography should be performed every 3 or 6 months in relation to the severity of the valve dysfunction. On the other side, to perform an echocardiogram every 12 months, as a routine in a patient with stable clinical conditions, is not recommended [13–20].

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Part VI

Rhythm Disorders: Tachyarrhytmias

Wide QRS Complex Tachycardias

18

Alessandro Barbarossa, Daniele Contadini, and Marco Flori

18.1 Case Report

A 72-year-old man was presented to the ER for an episode of palpitations, fatigue, and dyspnea lasting more than 6 h.

Medical History and Cardiovascular Risk Factors

- Arterial hypertension.
- Hypercholesterolemia (LDL 98 mg/dl on drug therapy).
- Stage 3 chronic kidney disease (GFR 40 ml/min).
- Previous inferior myocardial infarction (STEMI) 9 years ago with consequent coronary artery bypass graft (CABG) surgery: sequential venous graft (VG) between ascending aorta and right coronary artery (RC) and first left marginal artery (LMA1) and VG between ascending aorta and left anterior descending artery (LAD).
- Unstable angina (UA) 3 years ago. The patient was subjected to coronary arteriography that documented a total occlusion of the sequential VG to RC and LMA 1 and a stenosis of 95 % of the VG between aorta and LAD. For this reason, another CABG surgery consisting of left internal mammary artery (LIMA) to LAD was performed.
- Benign prostatic hypertrophy.

Allergies

None

Social History

- He never smoked.
- He never used illicit drugs.
- He has a sedentary lifestyle.

Home medications: pantoprazole 20 mg at 8:00 AM, ramipril 2.5 mg at 8:00 AM and 2.5 mg at 8:00 PM, metoprolol 50 mg at 8:00 AM and 50 mg at 8:00 PM, aspirin 100 mg at 12:00 AM, furosemide 50 mg at 8:00 AM and 25 mg at 4:00 PM, simvastatin 40 mg at 10:00 PM, tamsulosin 0.4 mg at 10:00 PM

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Vital Signs at ER Entrance

- Temperature: 36.7 °C
- Heart rate: 120 bpm
- Blood pressure: 105/70 mmHg
- Respiratory rate: 16 breaths/min
- Oxygen saturation while breathing in ambient air: 91 %

Physical Examination

- General: fatigued, sweaty, alert, awake, and oriented
- Head, eye, ear, nose, and throat: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclerae anicteric, no conjunctival injection
- Neck: supple, no jugular venous distention, no lymphadenopathy, no carotid bruit
- Cardiovascular: regular rhythm, tachycardia rate, S1 and S2 are normal, holosystolic murmur III/VI on Levine scale at the apex and at the anterior axillary area
- Lungs: rales only at the pulmonary bases. No rhonchi or wheezes, no egophony, no alterations in tactile fremitus, normal percussion in remaining areas
- Abdomen: flat, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, no hepatosplenomegaly
- Extremities: no cyanosis or clubbing, mild edema at both ankles
- Neurologic: cranial nerves I through XII intact, no focal deficit
- Psychiatric: normal affect, no hallucinations and normal speech
- Skin: intact, sweaty, no rushes, no lesion

Routine Laboratory Tests

- Complete blood count: normal (hemoglobin 12.9 g/dl)
- Inflammatory markers: ESR 46 mm/h, CRP 1.3 mg/dl
- Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect): normal
- Renal function: creatinine 1.71 mg/dl, BUN 25.2 mg/dl
- Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- Thyroid function (TSH, fT3, fT4): normal
- Fasting blood glucose: 131 mg/dl
- HbA1C: 7.0 % (53 mmol/mol)
- Hs-TnT: 12 pg/ml (highest value)

ECG

A standard 12-lead ECG, at rest, was performed. The ECG (Fig. 18.1) showed a wide QRS tachycardia. Heart rate was 120 bpm (RR 500 ms). QRS axis was about −160°. QRS duration was 200 ms. The QRS morphology was right bundle branch block type (Rr' in lead V1). P waves were not clearly visible. ST segment was not assessable.

What are the possible types of wide QRS complex tachycardia?

- Ventricular tachycardia (VT)
- Supraventricular tachycardia with aberrant AV conduction
  - Atrial fibrillation
  - Atrial flutter
  - Focal atrial tachycardia
  - Atrioventricular reciprocating tachycardia (ortho- or antidromic)
  - Atrioventricular nodal reciprocating tachycardia
- Pre-excited tachycardia (with anterograde conduction on the accessory pathway)
  - Atrial fibrillation
  - Atrial flutter
  - Focal atrial tachycardia

The presence of a regular rhythm excludes the hypothesis of atrial fibrillation and atrial flutter/tachycardia with variable AV conduction.

In the present ECG, there are not any visible P waves (or F wave); the P wave could be inside the terminal part of the ventricular complex or inside the T wave. So, a clear atrioventricular dissociation (suggestive for VT) is not demonstrable.

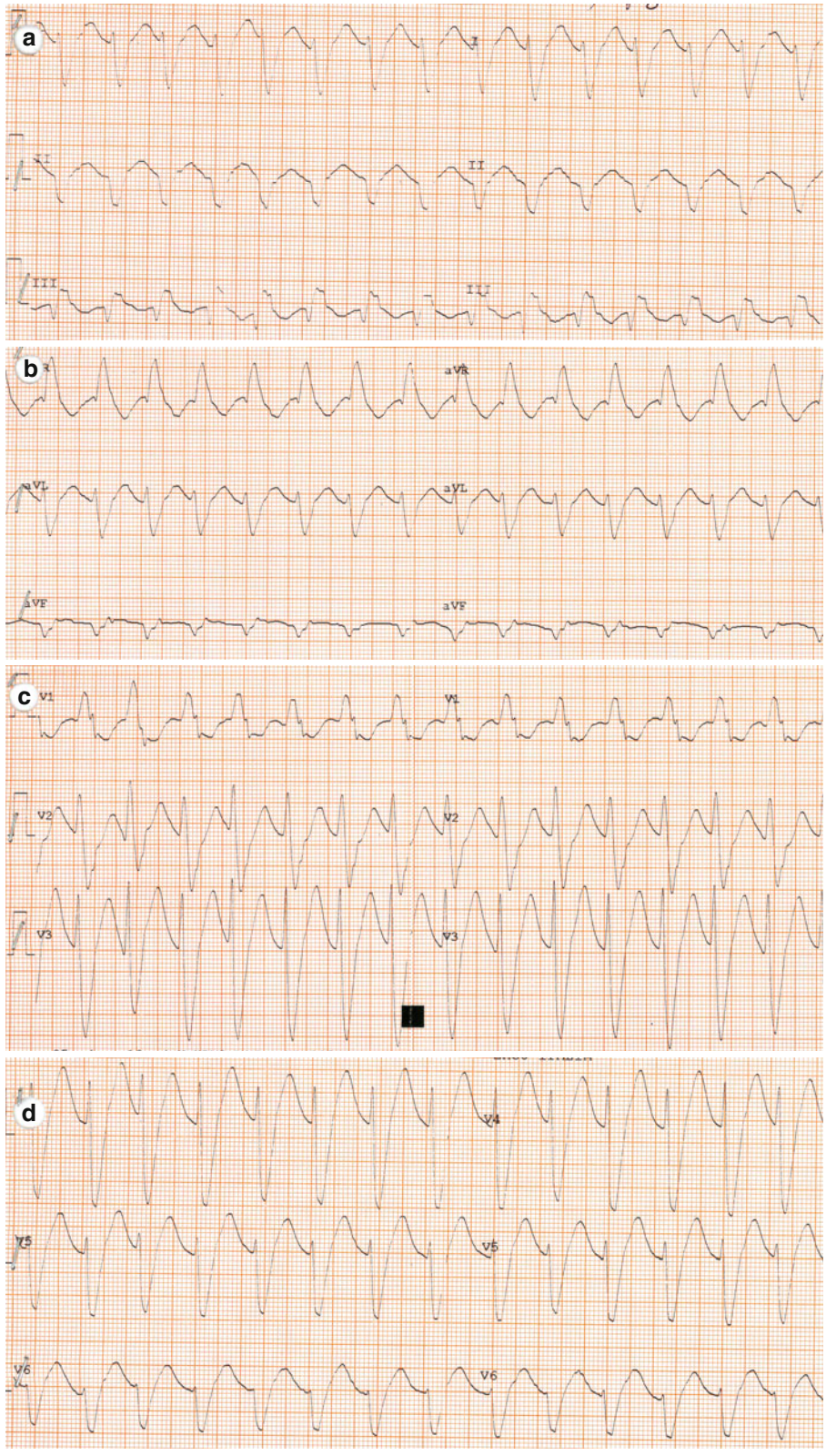

Fig. 18.1 (**a**–**d**) Rest ECG showing a wide complex tachycardia

Moreover, the heart rate (120 bpm) is too slow for a 2:1 atrial flutter. Even if P wave is not visible, hypothesis of a sinus tachycardia is unlikely because there were not physiological reasons for having an elevated rest heart rate.

There are not fusion or capture beats (diagnostic for VT).

There was hemodynamic stability, and therefore we performed carotid sinus massage that did not modify the tachycardia cycle. The QRS complexes in the precordial leads were not concordant: V1 positive and negative from V2 to V6 (concordance is high suggestive of ectopic ventricular beats, if negative specifically for VT). We measured the distance from the onset of QRS to the nadir of S wave in a precordial lead (we chose V2), and it is about 120 ms (when this interval is more or equal to 100 ms, you should consider VT). Finally, our ECG analysis ends with QRS morphological criteria: we are in front of a RBBB-type wide QRS tachycardia. In V1 the QRS complex morphology is Rr' and in V6 rS. This morphological pattern is suggestive for VT. The QRS axis at −160° and the QRS duration of 200 ms are other adjuvant criteria for VT.

Owing these criteria, we postulated the diagnosis of ventricular tachycardia.

The patient, after sedation with midazolam 5 mg IV, was successfully treated with electric cardioversion (DC shock 200 J) with an immediate return to sinus rhythm (Fig. 18.2).

At sinus rhythm, the QRS complex had a complete different morphology. The signs of the previous inferior MI were visible.

Admission to the Arrhythmology Department

The patient was then admitted to our cardiology and arrhythmology department to seek the cause of arrhythmia.

Electrolytec imbalance, hyper- or hypothyroidism, and coronary acute syndrome were excluded.

ECG: sinus rhythm, normal AV conduction, QRS axis +30°, Q wave in inferior leads as a previous inferior myocardial infarction, normal repolarization.

At echocardiography: mild dilatation of the left atrium. Moderate dilatation of the left ventricle (iEDV 92 ml/m^2). Severe left ventricular systolic dysfunction (EF 40 %). Akinetic and thinned inferior wall of the left ventricle. Normal dimensions of the right ventricular dimension and systolic function (TAPSE 19 mm). II grade diastolic dysfunction. Moderate mitral regurgitation. Mild tricuspid regurgitation with normal pulmonary arterial pressure. No pericardial effusion.

There were not any clues attributable to accessory AV pathways or to channelopathies (e.g., Brugada syndrome or long and short QT syndrome). Also, cardiomyopathies like hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, or non-compacted myocardium were excluded. Finally, the presence of an inferior wall necrosis was confirmed.

Because of the low EF unknown in previous controls, we repeated a coronary arteriography that showed occlusion of VG between RC and LMA1, occlusion of VG between aorta artery and LAD, and a good flow on LIMA to LAD.

Amiodarone therapy was started (400 mg/die for the 1st week then 200 mg/die) to prevent recurrences. During hospitalization at ECG monitor, a lot of premature ventricular beats (PVBs), couple of PVBs, non-sustained VT (nsVT), and another VT (which required cardioversion with DC shock) were recorded. All these ventricular arrhythmias had the same QRS morphology of the first VT episode.

An invasive electrophysiological study (EPS) was performed and documented:

> […] easy induction by programmed ventricular pacing of a ventricular tachycardia coming from the inferior wall of left ventricle. A catheter ablation of the site of origin of ventricular tachycardia was performed successfully with no more induction of arrhythmia after programmed ventricular pacing of the area. […]

The final diagnosis was "ventricular tachycardia starting from the inferior wall of the left ventricle due to macro-reentrant circuits secondary to a myocardial scar."

VT did not return during hospitalization.

One month after discharge, we performed a 7-day-long ECG-Holter monitoring that did not document any VT recurrence.

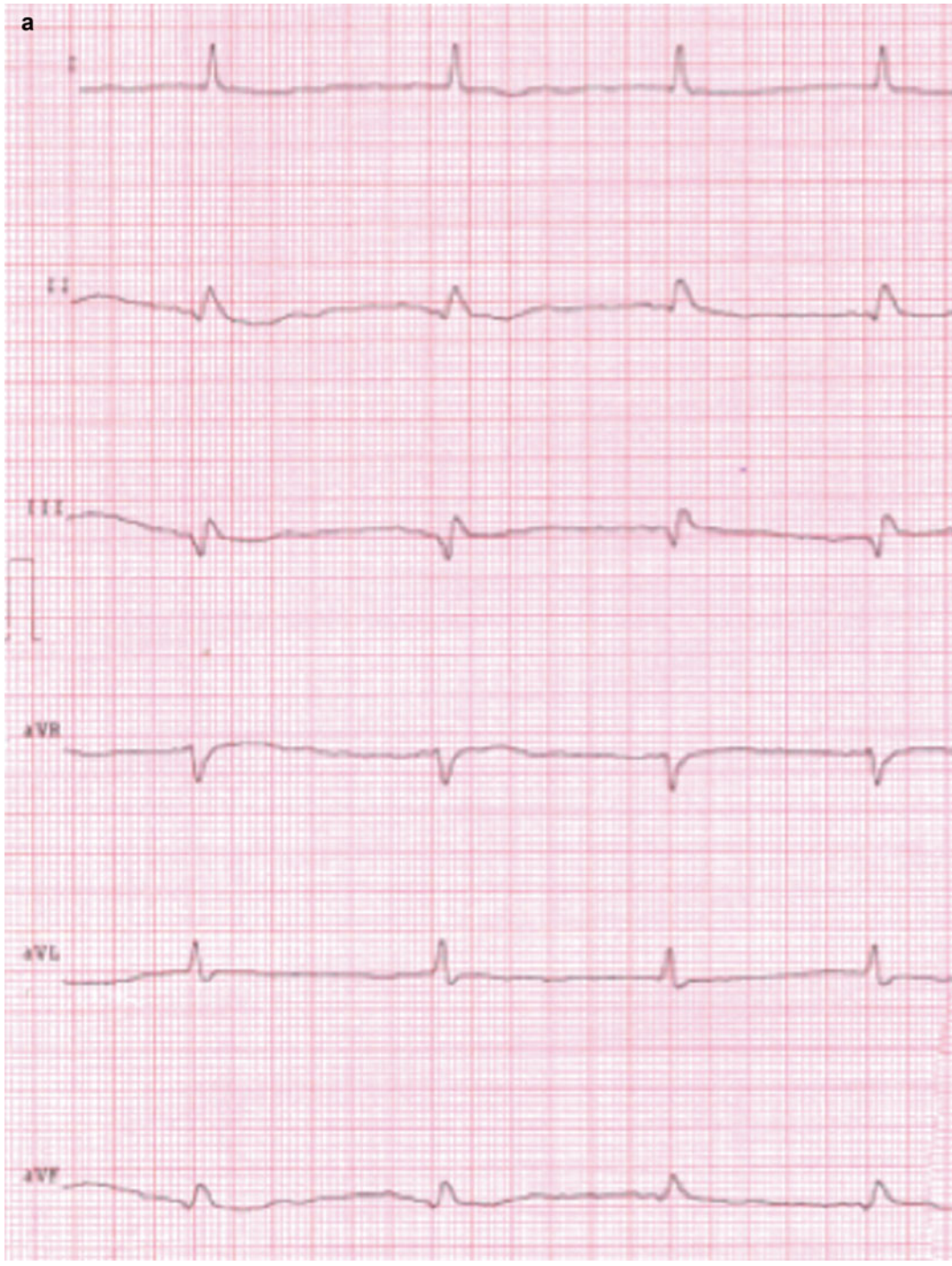

Fig. 18.2 (**a**, **b**) ECG performed after electrical cardioversion

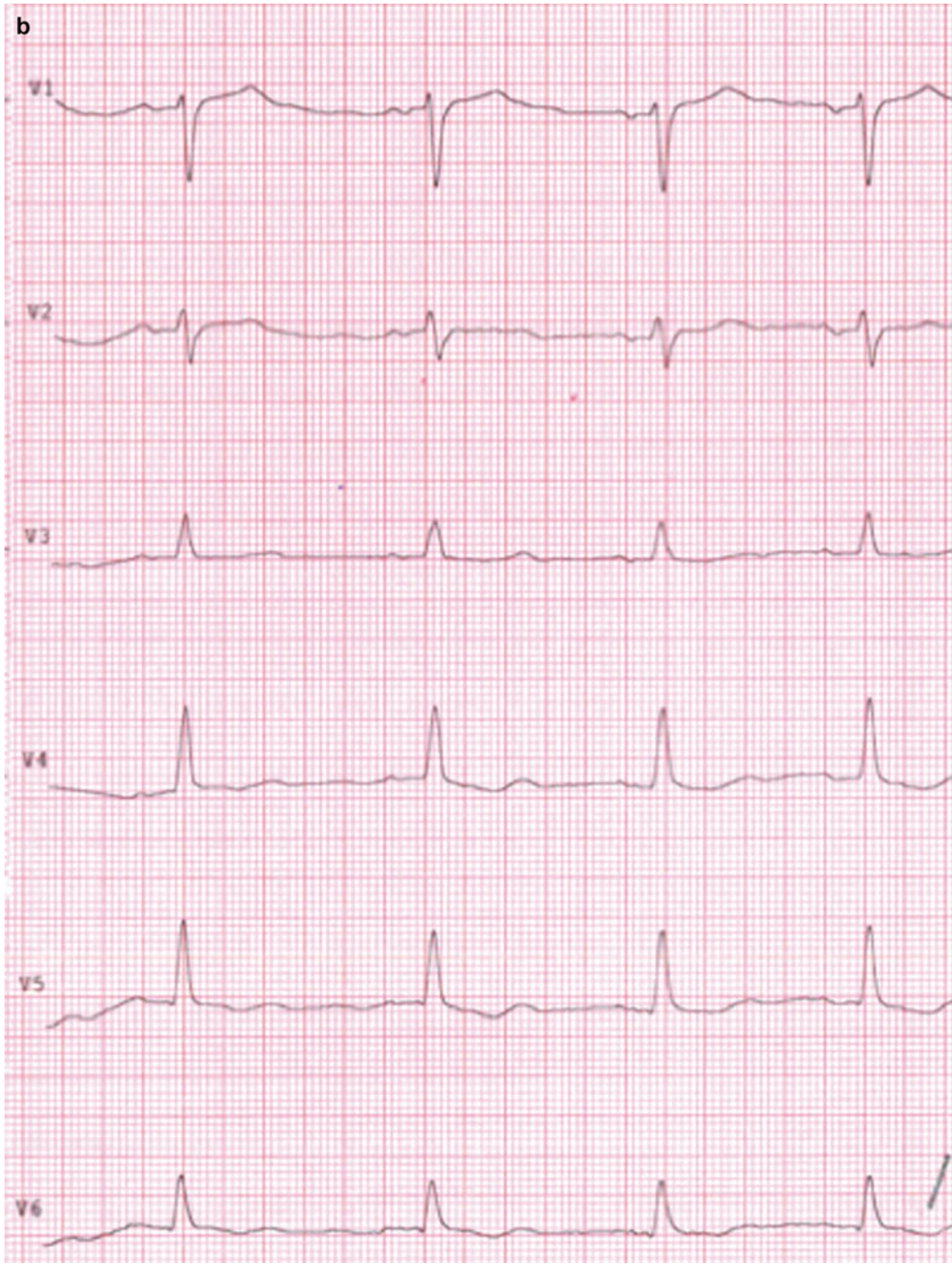

Fig. 18.2 (continued)

18.2 Ventricular Tachycardia

Definition

VT is a tachycardia that rises from the ventricles and lasts at least 3 beats. Non-sustained VT (nsVT) is a VT that lasts less than 30 s; contrarily, a VT that lasts longer than 30 s is called sustained ventricular tachycardia (sVT).

Epidemiology and Etiology

VTs are associated with a structural heart disease, but can occur also in its absence. Ischemic heart disease is the most common cause of VT. During the acute phase of ischemia, a polymorphic VT or a ventricular fibrillation (VF) is the principal cause of sudden cardiac death (SCD).

Monomorphic VT is usually a consequence of a myocardial scar zone that became a reentrant substrate in patients with structural heart disease. The scars can derive from an old myocardial infarction but also from nonischemic cardiomyopathies, including idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM), infiltrative heart disease (e.g., amyloidosis), and arrhythmogenic right ventricular dysplasia (ARVD).

Moreover, some genetic syndromes (channelopathies) are mainly associated with polymorphic ventricular arrhythmias: Brugada syndrome, long and short QT syndromes, and catecholaminergic polymorphic ventricular tachycardia (see specific chapters).

Finally, a VT that occurs in the absence of structural heart disease and genetic conditions is referred to as idiopathic VT. This form of VTs usually originates from the right ventricular outflow tract (RVOT) and is associated with good prognosis [1].

ECG Diagnostic Criteria

In the presence of a tachyarrhythmia with wide QRS, a possible diagnosis of ventricular tachycardia (VT) has to be taken into account. The mainstay of differential diagnosis is the ECG itself, but there are other elements that may help the diagnosis.

ECG in Wide QRS Tachycardias

Wide QRS complex tachycardias are one of the most challenging questions of ECG. A regular wide QRS complex tachycardia may represent one of the following rhythms:

- Aberrant atrioventricular conduction of supraventricular tachycardia (SVT)
- Ventricular tachycardia (VT)
- Preexisting right (RBBB) or left (LBBB) bundle branch block with SVT
- Anterograde conduction over the bypass tract of atrioventricular connection in patients with Wolff-Parkinson-White (WPW) syndrome

Irregular wide QRS complex tachycardia may represent one of the following rhythms:

- Atrial fibrillation with aberrant ventricular conduction
- Atrial fibrillation with ventricular pre-excitation
- Torsade de pointes
- Polymorphic VT

Differentiating ventricular tachycardia from other rhythms is of ut most importance for prognosis and therapeutic management. The following elements have been suggested for helping the differential diagnosis [2].

ECG During Sinus Rhythm

The presence of conduction defect during sinus rhythm in a previous or subsequent ECG and the comparison with the QRS complex during tachycardia may guide the diagnosis. Furthermore, the presence of PVCs with the same morphology of tachycardia may orientate to VT. If the onset of tachycardia is recorded, the initiation by a premature P wave suggests SVT, whereas initiation by PVC may be either SVT or VT. If the wide QRS tachycardia starts with shorter PR interval between last sinus P and first wide QRS complex, VT should be suspected.

Atrioventricular Dissociation During Tachycardia

AV dissociation, when present, is diagnostic for VT. Detection of P waves may be challenging. Notches and irregularities repeated cyclically may be the only indication of underlying P waves. AV dissociation also may be seen in junctional tachycardias with retrograde second-degree block, but this condition is rare [3]. Conversely a 1:1 AV correspondence is possible even during VT as 1:1 retrograde conduction may be present.

Precordial Concordance

When in all the six standard precordial leads the QRS complexes have the same polarity (all positive or all negative), that so-called concordance suggests VT diagnosis. Exceptions may occur: a negative concordance has a higher specificity; a positive concordance may be also observed in WPW during conduction through a left lateral pathway.

Captures and Fusions

During tachycardia a sinus beat may be conducted to the ventricle, resulting in a normal (capture) or a hybrid narrower (fusion) QRS complex. This finding is a strong evidence of VT. Exceptionally, fusion beats may be present during aberrant supraventricular tachycardia when in presence of BBB a contralateral PVC (i.e., PVC from the right ventricle during RBBB) results in pseudonormalization of the QRS complex.

Morphology of QRS Complex

The abovementioned findings are a strong evidence of VT but available only in a small number of cases. Most of the times, there are no clues for the diagnosis other than the QRS itself. Hence, QRS morphology analysis is of ut most importance. During aberrant conduction, the ventricle is activated through the left or right bundle, and VT is suspected when QRS complexes do not resemble typical LBBB or RBBB. The first portion of the QRS complex is called intrinsicoid deflection or R wave peak time and represents the conduction through the His bundle. Since aberrant conducted impulses follow the His pathway, the intrinsicoid deflection remains narrow or less wide during aberrance (about <0.04 s) but enlarges during VT. Exception may occur depending on the underlying heart disease (MI scar, ventricular remodeling, or drug treatment) and origin of arrhythmias (the closer the arrhythmia is to His bundle, the narrower the intrinsicoid deflection is). Wide QRS tachycardias have been classically divided in RBBB morphology depending on the polarity of the main QRS deflection in lead V_1 (positive deflection is RBBB and negative deflection is LBBB). Table 18.1 shows the morphology criteria for VT diagnosis, based on intracardiac studies [4, 5].

Diagnostic Elements Other than ECG

In diagnosis of wide-complex tachycardias, there are few elements other than ECG that may help the diagnosis. AV dissociation may be diagnosed during tachycardia with echocardiography: pulse Doppler of mitral inflow shows dissociation between A wave and QRS complexes. Clinically AV dissociation is suggested by first-tone intensity variability as clinical sign, but this finding has poor sensitivity.

Table 18.1 ECG findings indicating VT in wide complex tachycardia

	Lead V1	Lead V6
LBBB morphology	R wave >30 ms, onset of QRS to nadir of S wave >60 ms	Any Q wave
RBBB morphology	Monophasic R or biphasic qR, QR, RS	rS, QR, qr

Response to vagal maneuvers and adenosine may help the diagnosis. The arrhythmia interruption or variation in AV ratio with unmasking of underlying P or flutter waves favors VT.

What May Be Misleading

Age should not be considered. Older patients have higher probability to have both VT and SVT.

Heart rate should not be used for absolute diagnosis, but at a regular frequency of 150 bpm, atrial flutter with 2:1 VA conduction should be suspected. In this setting, vagal maneuvers or adenosine may unmask flutter waves through transient AV block.

Although the QRS tends to be wider during VT than during SVT, width itself should not be used as a diagnostic element.

Last, the hemodynamic tolerance of VT and SVT relies on several factors and is of most clinical importance but is not useful for differential diagnosis.

What If the Diagnosis Remains Unclear?

Despite accurate ECG analysis, differentiation between VT and SVT is not always clear. The patient should be treated as VT when the diagnosis remains unclear.

Clinical Presentation

Clinical symptoms and signs of VT presentation may have a wide variability. VT can be classified as hemodynamically stable and unstable. The patient with a hemodynamically stable VT can be totally asymptomatic or contrariwise show symptoms such as palpitations, dyspnea, chest pain, fatigue, dizziness, pre-syncope, and syncope. The hemodynamically unstable VT is characterized by systolic hypotension and all the signs of organ hypoperfusion up to pulseless VT and cardiogenic shock. Another important complication of high-rate VT is its degeneration into ventricular fibrillation, a condition that without a rapid treatment can cause patient's death.

Management of VT

Acute Management

The first step in the management of VTs is to assess the hemodynamic stability of the patient:

Unstable patient: hemodynamic compromise may occur with any VT, regardless of the etiology. Furthermore, patients who initially appear stable may deteriorate rapidly.

Unstable patients but still responsive and with an arterial pulse should undergo emergent synchronized cardioversion (100–200 j in monophasic shock or 50–100 j in biphasic shock) with uptitration of energy as needed [6]. If the QRS complex and T wave cannot be distinguished accurately, a synchronized shock could not be possible. Such patients should be treated with immediate defibrillation (unsynchronized shock using 360 J in monophasic shock or 200 J in biphasic shock).

Use of intravenous sedatives may be appropriate but must be balanced against the risks of further hemodynamic deterioration.

Patients who become unresponsive or pulseless should be managed according to ACLS resuscitation algorithms, with immediate high-energy defibrillation [7].

Stable patients: in hemodynamically stable patients, additional time can be given for the differential diagnosis between VT and SVT, and therapy may be targeted to the specific arrhythmia substrates.

Ventricular Tachycardia or Uncertain Diagnosis (Should Be Treated as a VT) [7]

- Elective electrical cardioversion:
  - Synchronized cardioversion (100–200 j in monophasic shock or 50–100 j in biphasic shock) with uptitration of energy as needed.
- Pharmacological cardioversion [7]:
  - Procainamide (10–15 mg/kg): proved to be superior to lidocaine (1.5 mg/kg) for termination of hemodynamically stable monomorphic VT. It can be administered at a rate of 20–50 mg/min until the arrhythmia is

suppressed. It should be avoided in patients with long QT or heart failure or low EF.
- Sotalol (100 mg IV over 5 min): also more effective than lidocaine in patients with sustained monomorphic VT. It should be avoided in patients with long QT.
- Amiodarone (150 mg IV over 10 min up to 1.2 g/24 h) is useful in recurrent monomorphic or refractory VTs.
- Lidocaine (1–1.5 mg/kg IV bolus): should be considered the second-line antiarrhythmic therapy for monomorphic VT and only in ischemic setting.

Supraventricular Tachycardia

Management is similar to an SVT with a normal QRS duration.

In SVT due to a reentrant circuit:

- Vagal maneuvers may be considered such as carotid sinus pressure (if no carotid bruits are present) or Valsalva maneuver as the initial intervention.
- Adenosine (6 mg IV over 1–2 s): highly effective in terminating many SVTs (e.g., AVNRT, AVRT), and for others (e.g., AF, atrial flutter), adenosine may facilitate the diagnosis by slowing the ventricular response to allow clearer assessment of atrial activity. If the initial dose is ineffective, a 12 mg dose may be given and repeated once if necessary. Adenosine has a very short half-life (less than 10 s), reducing the risk of an untoward reaction.
- Calcium channel blockers or beta-blockers: intravenous verapamil (2.5–5 mg IV) or beta-blockers (e.g., metoprolol 5–10 mg IV) may be given if the SVT persists after adenosine administration. These medications can terminate AVNRT as well as some atrial tachycardias. If the specific SVT diagnosis remains unknown, these drugs may slow the ventricular response and facilitate diagnosis. Finally, calcium channel blockers and beta-blockers should not be used in AVRT.
- Cardioversion is rarely necessary in patients with a stable SVT. However, if AVNRT or AVRT persist after the above interventions, synchronized cardioversion is usually effective in restoring sinus rhythm.

In atrial fibrillation, atrial flutter, or atrial tachycardia, a strategy of rate or rhythm control may be chosen according to clinical indications.

Chronic Management

Ventricular Tachycardia

In patients who survived a sudden cardiac arrest/VT, the first step is to exclude possible transient reversible causes. In the presence of sign of acute myocardial ischemia, myocardial revascularization (PTCA, CABG) may be performed. Myocardial revascularization may be sufficient in patients surviving VF in association with myocardial ischemia (normal ejection fraction and no history of MI). Instead, sustained monomorphic VT with prior MI is unlikely to be affected by revascularization [8]. Electrolyte abnormalities should be also excluded as the cause of the arrhythmias.

In sudden cardiac arrest/VT without removable cause, randomize controlled trials showed ICD superiority compared with antiarrhythmic drug therapy in prevention of sudden death [8].

2012 AHA/ACC/HRS guidelines recommended:

- ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. (Class I, Level of Evidence: A)
- ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. (Class I, Level of Evidence: B)
- ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. (Class IIa, Level of Evidence: C)
- ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). (Class III, Level of Evidence: B)

Antiarrhythmic drug therapy may be considered as the second choice in patients who cannot receive ICD therapy or in patients with recurrent VT/VF associated with ICD shocks [9].

Supraventricular Tachycardia

WCTs due to SVT should be treated as SVT with narrow QRS complex (see Chap. 19).

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Supraventricular Reentrant Tachycardias

19

Daniele Contadini and Alessio Menditto

19.1 Case Report

A 61-year-old man presented to the emergency room for an episode of malaise characterized by palpitations, sweating, dizziness, and chest pain that lasted for more than an hour.

Medical History and Cardiovascular Risk Factors

- Type 2 diabetes mellitus
- Arterial hypertension
- Dyslipidemia
- Overweight
- Post-traumatic subdural hematoma which required neurosurgical drainage about 1 year ago

Allergies

No allergy is referred by the patient.

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Social History

The patient does regular physical activity, smoked about 30 cigarettes/day until 7 years ago, and never used illicit drugs.

Medications

Pantoprazole at 8:00 AM, telmisartan/hydrochlorothiazide 80/12.5 mg at 8:00 AM, aspirin 100 mg at 12:00 AM, metformin 500 mg at 12:00 AM and at 8:00 PM, and atorvastatin 20 mg at 10:00 PM

Vital Signs

- Temperature: 35.4 °C
- Heart rate: 200 beats per minute
- Blood pressure: 115/80 mmHg
- Respiratory rate: 18/min
- Oxygen saturation while breathing in ambient air: 98 %

Physical Examination

- General: fatigued, sweaty, alert, awake, and oriented
- Head, eye, ear, nose, and throat: normocephalic, atraumatic, mucous membranes moist,

A. Capucci (ed.), *Clinical Cases in Cardiology: A Guide to Learning and Practice*,
DOI 10.1007/978-3-319-19926-9_19

extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- Neck: supple, no jugular venous distention, no lymphadenopathy, no carotid bruit
- Cardiovascular: regular rhythm, tachycardia rate, S1 and S2 normal, and no murmurs
- Lungs: no rales, rhonchi, or wheezes, no egophony, no alterations in tactile fremitus, and normal percussion
- Abdomen: overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitch or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- Extremities: no cyanosis or clubbing and no edema
- Neurologic: cranial nerves I through XII intact and no focal deficit
- Psychiatric: normal affect, no hallucinations, and normal speech
- Skin: intact, sweaty, and no rushes, and no lesion

Routine Laboratory Tests

- Complete blood count: normal (hemoglobin 13 g/dl)
- Inflammatory markers (ESR, CRP): normal
- Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect): normal
- Renal function (creatinine, BUN): normal
- Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- Thyroid function (TSH, fT3, fT4): normal
- Fasting blood glucose: 93 mg/dl
- HbA1C: 7.0 % (53 mmol/mol)
- Hs-TnT: 120 pg/ml (highest value)

Routine 12-Lead ECG at Rest (Fig. 19.1)

The ECG showed a narrow QRS complex tachycardia. Heart rate was 200 beats per minute (RR 300 ms). The QRS axis is about + 20°. P waves were not clearly visible. ST segment depression was present in I, II, aVF, and V3–V6 leads. ST segment elevation was present in aVR and V1 leads.

What Are the Possible Types of Supraventricular Arrhythmias?

- Sinus tachycardia
- Reentrant supraventricular tachycardias
  - Atrioventricular reciprocating tachycardia
  - Atrioventricular nodal reciprocating tachycardia
- Focal atrial tachycardia
- Atrial flutter
- Atrial fibrillation

The presence of a regular rhythm excludes the hypothesis of atrial fibrillation. There isn't a clearly visible P wave, probably because it is inside the terminal part of the ventricular complexes. The atrioventricular ratio is 1:1. Heart rate (200 bpm) is too low for a 1:1 atrial flutter, so this hypothesis is unlikely. Even if the morphology of the P wave is not assessable, we can exclude the hypothesis of a sinus tachycardia because there were no physiological causes for having high heart rate at rest. RP interval was shorter than PR and longer than 70 ms. The most likely diagnoses left are therefore atrioventricular reciprocating tachycardia, atrioventricular nodal reciprocating tachycardia, and atrial tachycardia.

Vagal maneuver response may allow to distinguish between the different forms of supraventricular tachycardias. Atrial tachycardia generally is conducted with a transitory high-grade atrioventricular block. Reentrant supraventricular tachycardias end suddenly. In this case, the sinus carotid massage caused a sudden tachycardia interruption (Fig. 19.2).

Therefore, the diagnosis was reentrant supraventricular tachycardia. The high heart rate (about 200 bpm) was more suggestive for an

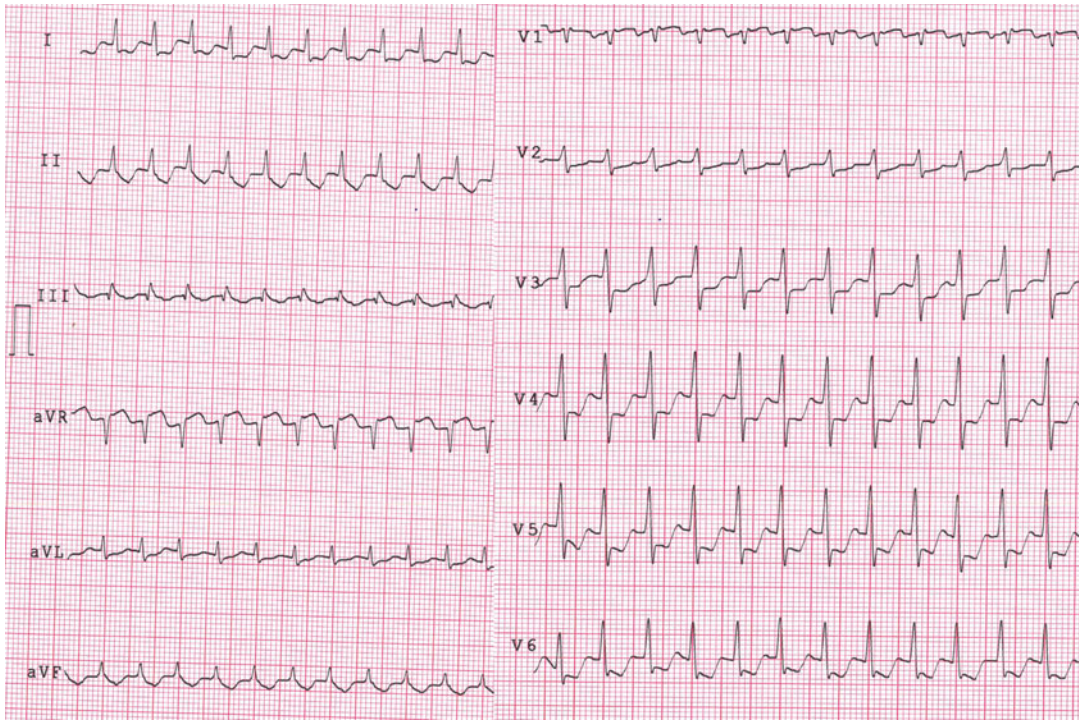

Fig. 19.1 ECG shows a narrow QRS tachycardia

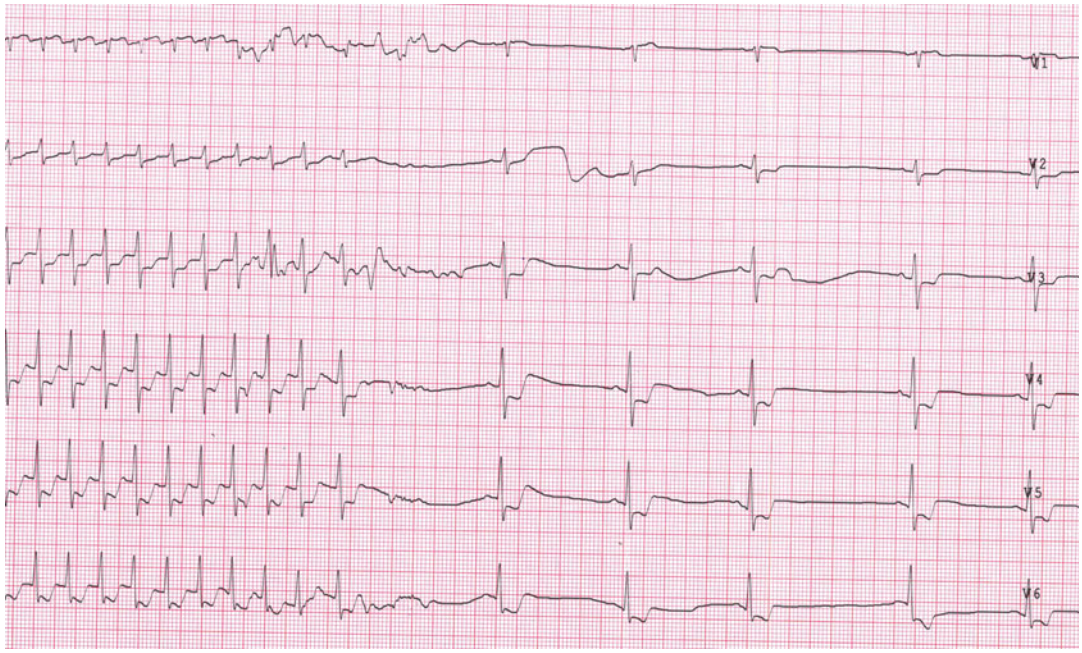

Fig. 19.2 Tachycardia termination during sinus carotid massage

atrioventricular reciprocating tachycardia, but this is not a definite clue.

The patient was admitted to the cardiology department to perform an invasive electrophysiological investigation with subsequent catheter ablation of the tachycardia.

Invasive Electrophysiological Investigation (Fig. 19.3)

> […] eccentric type ventriculo-atrial retrograde conduction. Early retrograde conduction in left posterolateral region (CS 5–6). Induction by programmed atrial pacing of an orthodromic atrioventricular reciprocating tachycardia (concealed accessory pathway). During tachycardia a catheter ablation of the posterolateral accessory pathway with termination of tachycardia was performed. […]

The final diagnosis was *atrioventricular reciprocating tachycardia from posterolateral concealed accessory pathway.*

What Is the Meaning of ST Segment Depression During Supraventricular Paroxysmal Tachycardia? Can It Be a Sign of Atherosclerotic Coronary Disease?

This patient had a high cardiovascular risk profile (type 2 diabetes mellitus, arterial hypertension, dyslipidemia, overweight, past smoking status), and he was symptomatic for chest pain during tachycardia. Echocardiography and a treadmill test were performed.

Echo: Normal atrial size. Normal left ventricle size and systolic function (EF 60 %). Normal right ventricle size and systolic function (TAPSE 19 mm). Normal diastolic function. Mild mitral regurgitation. Mild tricuspid regurgitation with normal pulmonary arterial pressure. No pericardial effusion.

The exercise test was interrupted at the end of Bruce's protocol 5th stage. The patient reached

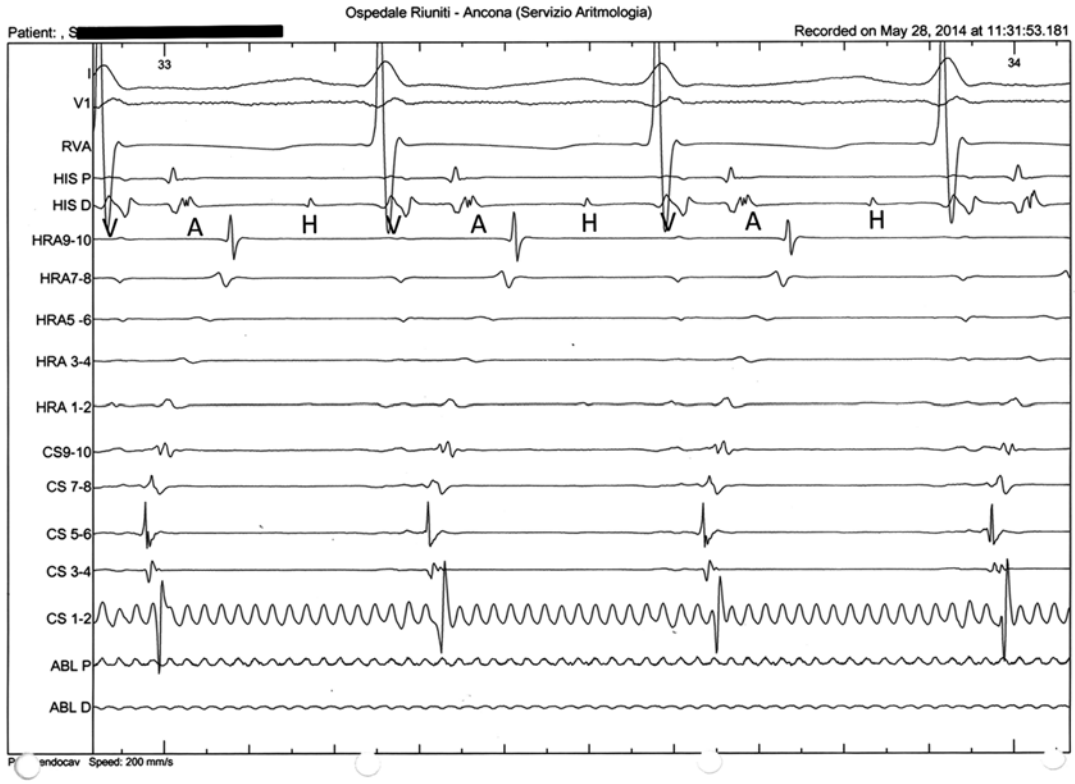

Fig. 19.3 Electrophysiological study. Endocavity ECG during tachycardia. *A* atrium, *H* His, *V* ventricle

the peak exercise with a heart rate of 154 bpm (96 % of theoretical maximum heart rate) and a systolic blood pressure of 170 mmHg (double product: 26,180). Heart rate and blood pressure showed a normal behavior. There were no symptoms of ischemic ECG changes.

We conclude for nonischemic ST alteration. The abnormal repolarization may be the consequence of a distinct pattern of retrograde atrial activation through accessory pathway. This phenomenon (ST depression >2 mm) is more frequent in AV reentrant tachycardia than in AV nodal reentrant tachycardia. Indeed, in orthodromic AV tachycardia, atrial retrograde activation, as assessed by intracardiac electrograms, occurs during the ST segment on the surface ECG. In contrast, in AV nodal reentrant tachycardia, the retrograde atrial activation is most frequently simultaneous with the QRS complex and therefore does not interfere with repolarization [1–4].

19.2 Atrioventricular Nodal Reentrant Tachycardia (AVNRT)

Definition and Epidemiology

Atrioventricular nodal reentrant tachycardia is the most common form of regular paroxysmal supraventricular tachycardia. Although it was classically described more often in the young and women, it can be detected at any age and sex. The overall prevalence of atrioventricular nodal reentrant tachycardia is 2–3 cases per 1000 persons. Atrioventricular nodal reentrant tachycardia is not usually associated with structural heart disease [5–7].

Physiopathology and Classification

The reentrant circuit is confined not only in the compact AV node, but the perinodal atrial tissue has an important role too. Atrioventricular nodal reentrant tachycardia is related to the presence of two functionally and anatomically distinct AV nodal pathways (dual AV nodal pathways). The fast pathway, which conducts more rapidly (PR interval 100–150 ms and AH <220 ms) and has a long refractory period, appears to be located near the apex of Koch's triangle. The slow pathway, which conducts more slowly (PR interval >220 ms) and has a short refractory period, extends inferoposterior to the compact AV node tissue and extends along the septal margin of the tricuspid annulus at the level of the coronary sinus. The fast pathway constitutes the normal, physiological, AV conduction axis [6].

AVNRT has been categorized into typical or atypical. This categorization is based on the retrograde limb of the circuit: if it is the fast pathway, it is defined typical; if it is the slow pathway, it is atypical. Typical atrioventricular nodal reentrant tachycardia is the more common type (90 %) and involves the slow pathway for antegrade conduction and the fast pathway for retrograde conduction (slow-fast variant). Atypical atrioventricular nodal reentrant tachycardia is less common (10 %) and includes fast-slow and slow-slow variants [6].

An atrial premature complex that is blocked in the fast pathway and is conducted through the slow pathway generally initiates typical AVNRT. If the fast pathway has recovered excitability, the impulse can conduct retrogradely over the fast pathway, resulting in an atrial echo. If the impulse reenters into the slow pathway, typical AVNRT may be initiated. Seldom it is initiated by a ventricular premature complex (Fig. 19.4).

Atypical AVNRT (fast-slow variant) initiates with a ventricular premature complex that is blocked in the fast pathway. The impulse then conducts to the atrium via the slow pathway and returns to the ventricle via the fast pathway. Seldom an atrial premature complex initiates tachycardia (Fig. 19.5).

In AVNRT, neither the atrium nor the ventricle has a critical role in the reentrant circuit [6].

Clinical Presentation and Diagnosis

AVNRT usually has a sudden onset and termination, without a warm-up period. Its symptoms

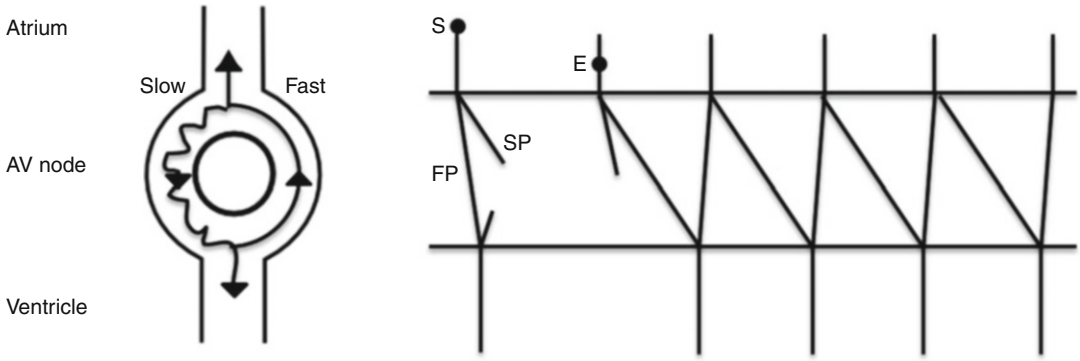

Fig. 19.4 Typical AVNRT (slow-fast) mechanism. *FP* fast pathway, *SP* slow pathway, *S* sinus beat, *E* extrasystoles

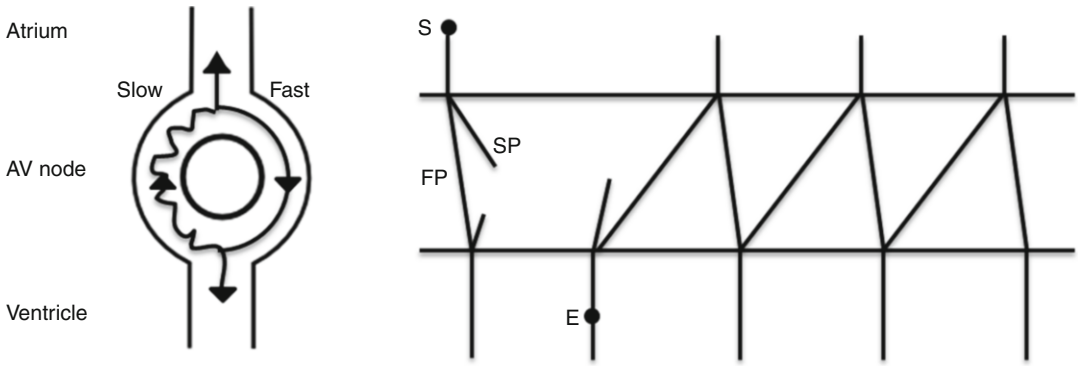

Fig. 19.5 Atypical AVNRT (fast-slow) mechanism. *FP* fast pathway, *SP* slow pathway, *S* sinus beat, *E* extrasystoles

include palpitations, neck pulsations, dizziness, and in some cases chest pain or dyspnea. Tachycardia can last a few minutes or hours, and the termination can be spontaneous or not. Sometimes precipitating factors (drugs, physical and psychological stress, menstruation, anemia, hyperthyroidism, etc.) can be found [5–7].

A 12-lead ECG is fundamental for the diagnosis. ECG, during AVNRT, shows in most cases a regular narrow QRS complex tachycardia; sometimes the QRS complex can be wide with the typical bundle branch block morphology (LBBB or RBBB). Rate of tachycardia is more often between 140 and 250 per minute. The AV relationship is practically in all cases 1:1. Atrial activation is concentric type because the retroconducted stimulus comes from the AV node, so the retroconducted P wave is narrow and negative in inferior leads. In typical AVNRT, the impulse conducts to the atrium via the fast pathway so the atrium and ventricle are activated simultaneously during tachycardia; the retrograde P wave is either hidden within the QRS or embedded in the terminal portion of the QRS, resulting in RP<PR (usually RP is less or equal to 70 ms) with pseudo-r waves in lead V1 and pseudo-s waves in inferior leads. Comparison with the QRS in sinus rhythm can help in identifying pseudo-r and pseudo-s waves. In atypical AVNRT, the conduction to the atrium is through the slow pathway; the atrium is activated late relative to the ventricle, so the retroconducted P wave is away from the previous QRS and it is near the following QRS (RP>PR) [6].

Invasive electrophysiological investigation (EPS) allows to detect the presence of dual AV nodal pathways, to induce and identify AVNRT (typical or atypical), and to perform catheter ablation of tachycardia. Dual pathway can be demonstrated with delivery of a premature atrial

complex that results in a "jump" in AH conduction curve (defined as an increase >50 ms in AH interval with a 10 ms increase in atrial extrastimulus prematurity). This "jump" is due to antegrade block in the fast pathway with the conduction through the slow pathway. The electrophysiological characteristic of AVNRT is the concentric retrograde activation of the atrium, with a short ventriculoatrial (VA) interval or with a "A on V" (simultaneous activation of the atrium and ventricle) in typical AVNRT or with a long VA time in atypical (fast-slow) AVNRT [6].

Differential Diagnosis

Surface ECG can make differential diagnosis between AVNRT and the other narrow QRS complex tachycardia during tachycardia, by the induction and termination of tachycardia and by the response to vagal maneuvers [5].

ECG features to assess are shown in Fig. 19.6.

The response to vagal maneuvers or to adenosine can help to distinguish between the different types of supraventricular tachycardia. Gradual slowing then reacceleration of rate is typical of sinus tachycardia or focal atrial tachycardia. Sudden termination is typical of AVNRT and AVRT. Persisting tachycardia with transient high grade of AV block is typical of atrial flutter or atrial tachycardia [5].

Termination of tachycardia is due to block in slow pathway in AVNRT and in AV node in AVRT. Thus, typical AVNRT ends with a retroconducted P wave, atypical AVNRT ends with a QRS complex, and orthodromic AVRT ends with a retroconducted by accessory pathway P wave [5, 6].

Treatment

Acute treatment: patients with hemodynamic compromise should be electrically cardioverted without delay. Usually, AVNRT does not cause significant hemodynamic compromise. Vagal maneuvers (Valsalva maneuver, dive reflex, carotid sinus massage) can be used to terminate the tachycardia. These maneuvers increase the vagal tone resulting in slow pathway conduction blockage. If vagal maneuvers are ineffective, medications known to prolong refractoriness of the slow pathway of the AVNRT circuit can be used. These agents include adenosine, calcium channel blocker (verapamil or diltiazem), and beta-blockers (metoprolol, atenolol, propranolol, esmolol). Intravenous administration of these drugs should be performed with continuous ECG monitoring. These agents are very effective in terminating the AVNRT [5, 6].

Long-term treatment: in patients with recurrent sustained episodes of AVNRT, we have two strategies of long-term treatment, catheter ablation and oral drug therapy. For oral therapy, the first choice includes AV nodal blocking agents like nondihydropyridine calcium channel blockers (verapamil, diltiazem) or beta-blockers. The use of other antiarrhythmic agents like class IC (flecainide, propafenone) or class III (sotalol, amiodarone) is not common for treating AVNRT

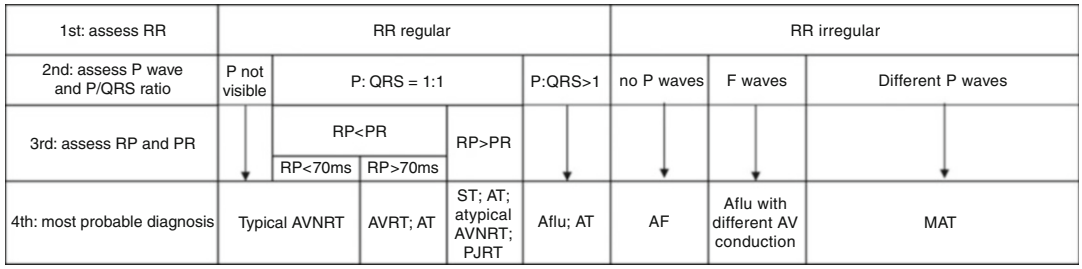

Fig. 19.6 ECG features to assess. *AVNRT* atrioventricular node reentrant tachycardia, *AVRT* atrioventricular reentrant tachycardia, *AT* atrial tachycardia, *ST* sinus tachycardia, *PJRT* permanent junctional reciprocating tachycardia, *Aflu* atrial flutter, *AF* atrial fibrillation, *MAT* multifocal atrial tachycardia

today; these are used only when the AV nodal blocking agents have failed to prevent recurrence of tachycardia and patient refuses catheter ablation. Radiofrequency catheter ablation is the non-pharmacologic treatment option. Success rates for this technique are approximately 90 %. The major procedural risk is the AV complete block. The ablation of slow pathway, rather than the ablation of the fast pathway, reduces the risk of AV complete block (1 % vs 8 %) and results in the absence of hemodynamic consequences of marked prolongation of PR interval that derives from fast pathway ablation. Therefore, slow pathway ablation represents the first choice today [5].

Prognosis

Atrioventricular nodal reentrant tachycardia has a good prognosis, and it is not usually associated with structural heart disease. In some patient, AVNRT coexists with atrial fibrillation, and recent reports suggest that it may serve as a trigger for atrial fibrillation and its eliminations can help to treat atrial fibrillation [6].

19.3 Ventricular Preexcitation and Atrioventricular Reentrant Tachycardia (AVRT)

Definition and Epidemiology

Ventricular preexcitation is a congenital alteration of the normal conduction of the electrical impulse in the heart. In this pathology, an accessory pathway is present through which the electrical impulse can activate an area of the myocardium more rapidly bypassing the normal conduction system. In 1930, Louis Wolff, John Parkinson, and Paul Dudley White described a series of young patients who experienced paroxysms of tachycardia and had characteristic abnormalities on electrocardiography (ECG) of ventricular preexcitation. When ventricular preexcitation is associated to symptoms and signs of tachycardias, it is defined as Wolff-Parkinson-White (WPW) syndrome. The expression WPW pattern defines the ventricular preexcitation in the absence of tachycardias' symptoms and signs [5, 7].

The prevalence in the general population is about 1–3 per 1000 people. Men have an higher incidence of ventricular preexcitation than women (M/F = 2.2:1), and there is a higher incidence of multiple accessory pathways in men, too. Some cases of WPW are inherited. Parents who have accessory pathways may pass them onto their children. The incidence of preexcitation in first-degree relatives could be as high as 5.5 per 1000 people. In a recent clinical study, a mutation to the gene that codifies for PRKAG2 (γ-2 regulatory subunit of AMP-activated protein kinase) was identified to be responsible for a syndrome associated with ventricular preexcitation and early onset of atrial fibrillation and conduction disease. About 7–20 % of patients with WPW also have congenital defects within the heart [5–7].

Accessory Pathways' Anatomy

The anatomical substrate of ventricular preexcitation is an accessory pathway. There are four different types of them. The most common accessory pathway is the bundle of Kent (more of 96 % of cases). This is an atrioventricular bypass: the electrical impulse from the atria directly reaches the ventricles. The bundle of Kent is made of common myocardial cells. They are "sodium-dependent cells," and for this reason, they have a faster conduction of the electrical impulse than the specialized cells of the heart conduction system that are "calcium dependent." The electrical conduction through the bundle of Kent is often frequency-independent and occurs with an "all-or-nothing" mode (non-decremental conduction). It means that an electrical impulse can be conducted through the accessory pathway or blocked, and when conducted, it isn't slowed down. The bundle of Kent can conduct the electrical impulse in different ways: both directions (anterograde and retrograde, about 68 % of cases), only in retrograde direction (from ventricles to atria, about 21 % of cases), or only in anterograde direction (from atria

to ventricles, about 11 % of cases). In addition to the bundle of Kent, there are three other types of accessory pathways grouped under the name of "fibers of Mahaim": atriofascicular tract (from atria to one of the bundle branches, sometimes also called Brechenmacher tract), nodoventricular tract (from AV node to one of the bundle branches or to ventricles), and fasciculoventricular tract (from the bundle of His or one of the bundle branches). Finally, there are some rare cases where multiple accessory pathways can be found [8, 9].

Ventricular Preexcitation's ECG Pattern

The WPW ECG pattern with full preexcitation contains the following elements:

1. Short PR: a PR interval equal or less than 0.12 s, with a normal P wave. When the electrical activation from the atria reaches the ventricles through the bundle of Kent (by a faster pathway), as a consequence, the PR interval reduces its length.
2. Wide QRS complex: abnormally wide QRS complex with a duration of 0.11 s or more. The QRS complex represents a fusion's beat made of two wavefronts: one from the normal pathway and the other from the accessory. Each of them depolarizes a portion of the ventricular mass.
3. Delta wave: the presence of initial slurring of the QRS complex. This is the most important finding in WPW pattern. Delta wave is in the initial part of the QRS complex and is visible as a very slow initial deflection. The duration of the delta wave varies between 0.02 and 0.07 s. Theoretically, the delta wave should be present in all leads, but it may become isoelectric and be easily overlooked in the leads with the lead axis, which is nearly perpendicular to the initial QRS forces. The end of delta wave joins to the QRS complex (sometimes a little notch can be found between the end of the delta wave and the QRS complex). The entity of the preexcitation depends on the difference of the times of conduction of the accessory and normal pathways. Indeed, a larger preexcitation will be the consequence of a rapid conduction through the accessory pathways. This fact depends on the anatomical position of the accessory pathway: one, near to the sinus-atrial node thus achievable rapidly from the electrical impulse, will show a large preexcitation; another, far from the sinus-atrial node thus achievable slowly from the electrical impulse, will show a little preexcitation.
4. Alterations of repolarization: secondary ST segment and T-wave changes. The altered sequence of ventricular activation in patients with the WPW pattern results in secondary repolarization abnormalities. Most commonly, the direction of the ST segment displacement and the T-wave polarity is opposite to the direction of the delta wave and the major deflection of the QRS complex. In some cases, any abnormalities are seen. The alteration of repolarization can persist after disappearance of preexcitation, too. This is the phenomenon of the "heart electrical memory." They completely regress within several weeks after ablation of the accessory pathway [8, 9] (Fig. 19.7).

Classification

Ventricular preexcitation can be classified by the direction (anterograde, retrograde, or both) of the accessory pathways and by the presence or absence of signs of WPW on the ECG:

- Manifest preexcitation: the basal ECG shows the WPW pattern. The direction of the conduction through the accessory pathways must be necessarily anterograde, but can be possibly retrograde conduction too.
- Not manifest preexcitation: the basal ECG doesn't show the WPW pattern. The direction of the conduction through the accessory pathways must be necessarily anterograde, but can be possibly retrograde conduction too.
- Concealed preexcitation: the basal ECG doesn't show the WPW pattern. The direction of the conduction through the accessory pathways must be only retrograde [8, 9].

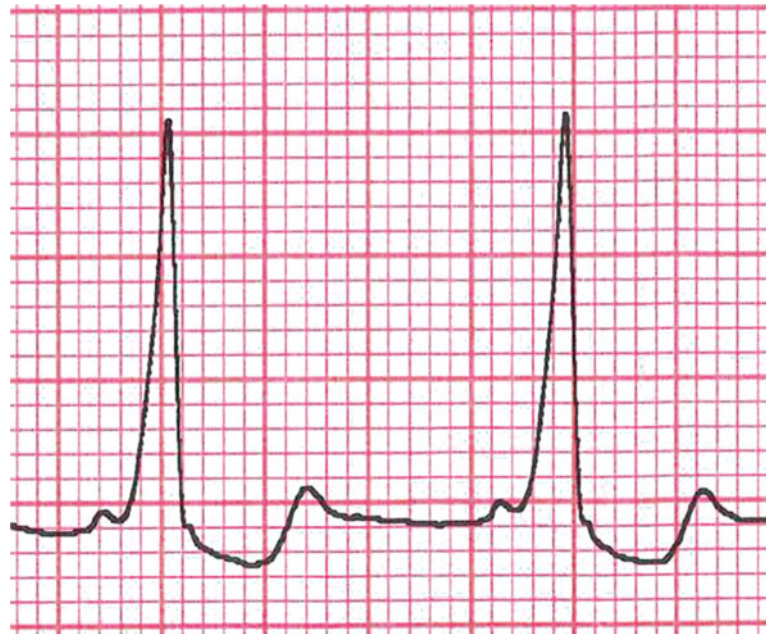

Fig. 19.7 ECG WPW pattern. Short PR interval, delta wave, wide QRS complex, ST-T alteration

Localization of Accessory Pathway Using ECG

Sometimes with the standard 12-lead ECG, it is possible to identify the position of the accessory pathway on the patient's heart. An almost correct localization can be reached only when delta wave is visible on the ECG. A perfect localization can be made only with EPS. The possible localization of accessory pathway and their characteristics on the ECG is listed in Table 19.1 (Fig. 19.8a, b).

Physiopathology of Arrhythmias

Paroxysmal tachycardias are the most important clinical manifestations in patients with WPW syndrome. They were recorded in about 47 % of patients with the WPW pattern. The possible arrhythmias in the patient with an accessory pathway are:

- Orthodromic atrioventricular reentrant tachycardia: the tachycardia is based on an electrical loop made up of the atrium, AV node, His-Purkinje system, and ventricular myocardium in the anterograde direction, returning to the atrium via accessory pathway in the retrograde direction. In this arrhythmia, the delta wave is not visible during the tachycardia, and the duration of QRS complex is normal (narrow). The average heart rate is 140–250 beats/min. Tachycardia is often initiated by premature atrial or ventricular complexes. Diagnostic criteria on the ECG are (1) not sinus P wave (negative in DI), (2) PR longer than RP, (3) P wave after the QRS complex (at least after 0.07 s), (4) occasional occurrence of electrical alternation of different voltages of QRS complex, and (5) P/QRS ratio always 1:1; an AV block during tachycardia rules out the AV reentrant one (Fig. 19.9).
- Antidromic atrioventricular reentrant tachycardia: the tachycardia is based on an electrical loop made up of the atrium, accessory pathway, and ventricular myocardium in the anterograde direction, returning to the atrium via the His-Purkinje system and AV node. In this arrhythmia, the QRS complex is fully preexcited and completely made of delta wave. The duration of the QRS complex is increased (wide complex tachycardia). Tachycardia is often initiated by premature

Table 19.1 Main accessory pathway ECG features

	Delta wave's axis	QRS's axis	Delta wave in V1	Delta wave in V6	Transition on precordial leads
Lateral left	+90° to +150°	+90° to +150°	+	±	V1
Posterolateral	−150° to −90°	−150° to −90°	+	+	V1
Lateral right	−30° to +45°	+45° to −45°	−	+	V3–V4
Anteroseptal	+30° to +90°	0° to +90°	−	+	V3–V4
Posteroseptal left	−30° to −90°	−30° to −90°	+	+	V1
Posteroseptal right	−30° to −90°	−30° to −90°	−	+	V2

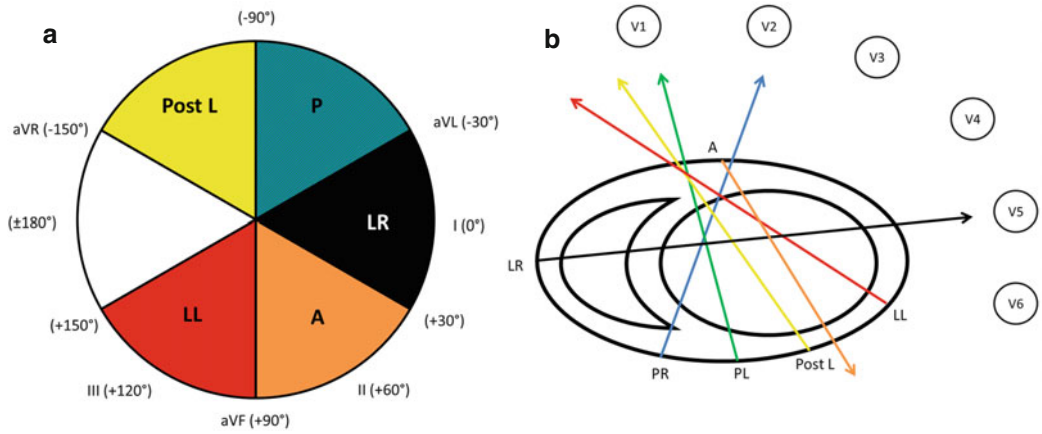

Fig. 19.8 Accessory pathway axis. Peripheral leads (**a**) and precordial leads (**b**). *LL* lateral left, *PostL* posterolateral, *P* posteroseptal, *PL* posteroseptal left, *PR* posteroseptal right, *LR* lateral right, *A* anteroseptal

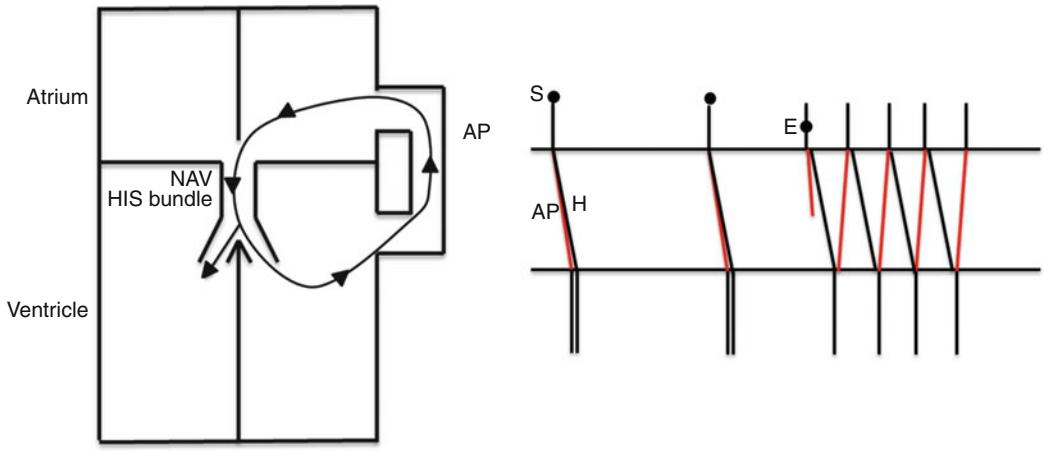

Fig. 19.9 Orthodromic AVRT mechanism. *NAV* atrioventricular node, *AP* accessory pathway, *S* sinus beat, *E* extrasystoles, *H* His bundle

atrial or ventricular complexes. Diagnostic criteria on the ECG are (1) wide QRS regular tachycardia; (2) QRS morphology identical to that of the fully preexcited complex; (3) not sinus P wave, when visible; and (4) P/QRS ratio always 1:1; an AV block during tachycardia rules out the AV reentrant one (Fig. 19.10).

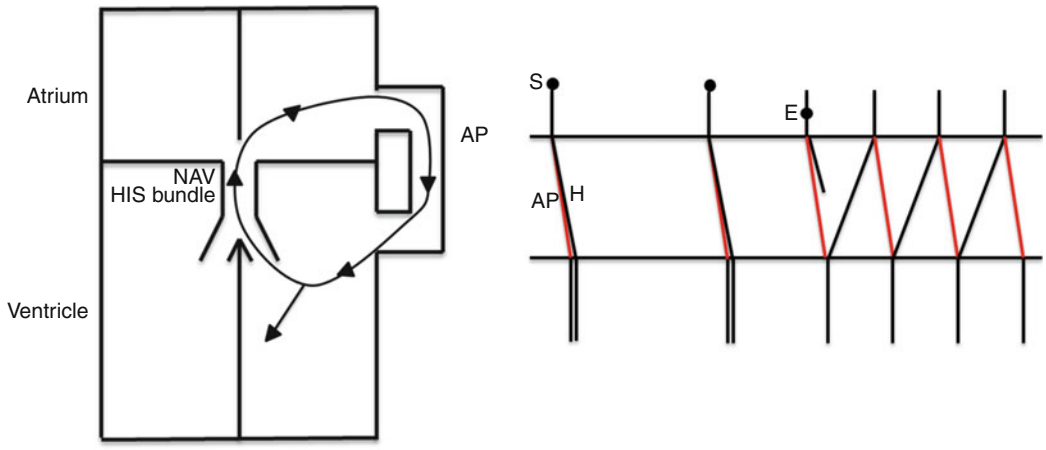

Fig. 19.10 Antidromic AVRT mechanism. *NAV* atrioventricular node, *AP* accessory pathway, *S* sinus beat, *E* extrasystoles, *H* His bundle

- Preexcited atrial fibrillation/atrial flutter: atrial fibrillation and flutter are less common than AV reentrant tachycardia in the WPW syndrome. Atrial impulses during atrial fibrillation and atrial flutter are conducted to the ventricles through the accessory pathway. The result is a wide complex tachycardia with irregular RR in the case of atrial fibrillation and regular in the case of atrial flutter. This tachycardia may be as rapid as 220–360 beats/min. This high rate is possible in the presence of a short, effective refractory period of the accessory bundle. Because of the rapid ventricular response during atrial fibrillation, patients with the WPW syndrome may develop ventricular fibrillation that results in sudden death. In the case of atrial flutter, the AV conduction ratio may be 2:1 or 1:1 (Fig. 19.11).
- Permanent junctional reciprocating tachycardia (Coumel type): the tachycardia is based on an electrical loop made up of the atrium, AV node, His-Purkinje system, and ventricular myocardium in the anterograde direction, returning to the atrium via accessory pathway in the retrograde direction. In this case, the accessory pathway has retrograde decremental conduction properties. The accessory pathway is located near to the His bundle (para-Hisian). It is usually a long-lasting tachycardia [5, 6, 8, 9].

Clinical Presentation

Patients with WPW can remain completely asymptomatic, and the preexcitation can be discovered with an ECG made for other reason. Usually, patients become symptomatic when paroxysmal arrhythmias occur. In this case, common symptoms are palpitations, fatigue, lightheadedness, chest discomfort, dyspnea, presyncope, or syncope.

Arrhythmic episodes usually have sudden onset and termination. The episode may have different duration, from few minutes to several hours. It is important to investigate all the symptoms, number of episodes, duration, frequency, mode of onset, and possible triggers [5, 7, 10].

Diagnosis and Differential Diagnosis

The diagnosis can be suggested in the presence of symptoms of the paroxysmal arrhythmias referred by the patient (previously discussed). The 12-element ECG is crucial for the diagnosis. Indeed, in case of preexcitation, the ECG shows the typical features: short PR, wide QRS complex, delta wave, and alterations of repolarization. In the case of strong clinical suspect, an EPS is recommended in order to identify the accessory pathway and/or to evocate possible arrhyth-

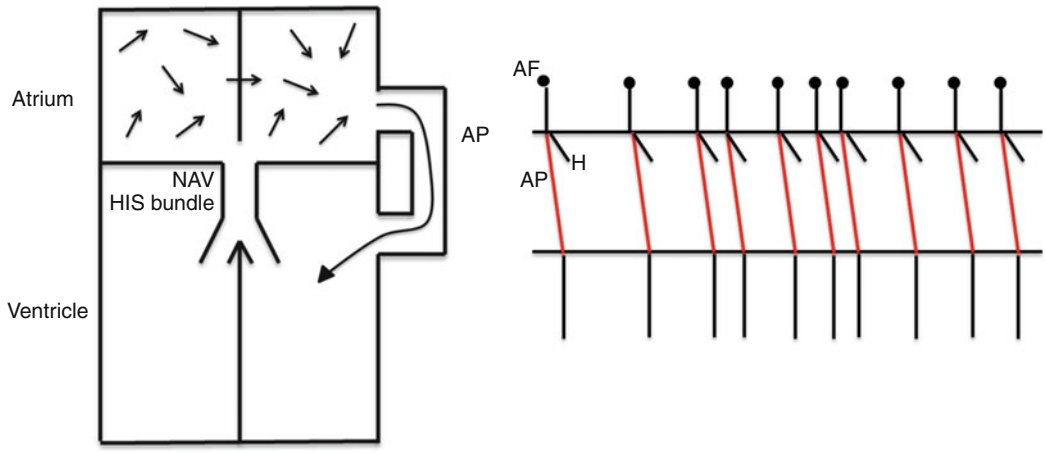

Fig. 19.11 Preexcited atrial fibrillation mechanism. *NAV* atrioventricular node, *AP* accessory pathway, *AF* atrial fibrillation, *H* His bundle

mias. Invasive EPS allows overstimulating the atria to identify if there is another way (in addition to the AV node) for the electrical impulse to reach the ventricles and overstimulating the ventricles to identify if there is another way to reach the atria. In addition, studying the first activated and the last activated area is possible to localize exactly the position of the accessory pathway. In some cases, it is possible to induce tachycardia, too [5–7, 10].

The differential diagnosis has already been discussed in the AVNRT paragraph.

Treatment

Acute treatment: if the patient, during the arrhythmia, is hemodynamically unstable, an immediate electrical cardioversion is mandatory. In the case of a regular narrow QRS complex tachycardia, in a hemodynamically stable patient, it is important to do vagal maneuvers (Valsalva, carotid sinus massage, and facial immersion) to terminate the arrhythmia. If these fail, IV antiarrhythmic drugs should be administered. Adenosine or nondihydropyridine calcium channel antagonists are the drugs of choice (the first one should be avoided in patients with severe bronchial asthma). Second-choice drugs are IV calcium channel blockers or beta-blockers. An ECG should be recorded during the maneuvers for the termination of the tachycardia. In fact a P wave at the end of the tachycardia is suggestive for AVRT or AVNRT. Continuation of tachycardia with AV block rules out AVRT. In case all the maneuvers for the termination of the tachycardia are not effective, electrical cardioversion should be considered. In patients with a regular wide QRS complex tachycardia, if a differential diagnosis of ventricular tachycardia (VT) is unclear, the arrhythmia should be treated as VT. In case of preexcited tachycardias, AV nodal blocking agents should be used cautiously. It is preferable to treat preexcited AF with IV ibutilide, flecainide, or procainamide.

Chronic treatment: in patients with WPW syndrome, the first-line therapy is catheter ablation of the accessory pathway. This approach is recommended in patients with preexcitation and symptomatic arrhythmias, mostly in the case of preexcited tachycardias or when the arrhythmic episodes are frequent or poorly tolerated. In these patients, when catheter ablation is not possible, a prophylactic antiarrhythmic therapy should be considered. The advised drugs are flecainide or propafenone or sotalol or amiodarone. AV-blockers (nondihydropyridine calcium channel antagonists or beta-blockers) should not be used as single therapy in patients with preexcited tachycardia (especially AF) because there is concrete risk to favor the conduction through the accessory pathway. In case of rare episodes of AVRT without preexcitation or in asymptomatic

patients with preexcitation, catheter ablation should be considered. In such cases, patient's choice should be taken into consideration. In this case, a pharmacological – pill in the pocket – therapy (taking an antiarrhythmic drug only at the onset of a tachycardia episode) could be made with verapamil, diltiazem, or beta-blocker. Sometimes none therapy could be another strategy, too [5, 6, 10].

Prognosis

The risk of sudden cardiac death due to the presence of accessory pathway has been estimated to range from 0.15 to 0.39 % over 3–10 years follow-up. If the risk of sudden cardiac death after accessory pathway ablation is the same or less is debated yet [5, 10].

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Atrial Fibrillation and Related Disorders

20

Jenny Ricciotti and Alessio Menditto

20.1 Case Report

A 51-year-old man was admitted to the emergency room for exertional dyspnea, orthopnea, and edemas at lower limbs. He reported a constrictive chest pain at rest lasting almost 2 h. He denied any recent episodes of fever or infection diseases.

There is negative anamnesis for previous diseases. Cardiovascular risk factors were absent.

Allergies

No allergy was referred.

Social History

The patient worked in a bakery, never smoked, and did not use illicit drugs.

Medications

No home medications

Vital Signs

- Temperature: 36.4 °C
- Heart rate: irregular, about 130 beats per minutes
- Blood pressure: 120/95 mmHg
- Respiratory rate: 24/min
- Oxygen saturation while breathing in ambient air: 93 %

Physical Examination

- General: alert, awake, and oriented
- Head, eye, ear, nose, and throat: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- Neck: supple, jugular venous distention, and no lymphadenopathy
- Cardiovascular: irregular rhythm, about 130 beats per minutes, and no murmurs
- Lungs: bilateral rales at medium-basal lung fields, no rhonchi or wheezes, no egophony,

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no alterations in tactile fremitus, and normal upon percussion
- Abdomen: no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant on percussion, soft, non-distended/nontender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- Extremities: no cyanosis or clubbing, with lower limb edema
- Neurologic: cranial nerves I through XII intact, no focal deficit
- Psychiatric: normal affect, no hallucinations, and normal speech
- Skin: intact, no rashes, and no lesion

Routine Laboratory Tests

- Complete blood count: normal (hemoglobin 14.8 g/dl)
- Inflammatory markers (ESR, CRP): normal
- Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect): normal
- Renal function: normal (creatinine 1.2 mg/dl)
- Electrolytes (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- Elevated myocardial necrosis markers (Hs-TnI 4.21 ng/ml, CK-MB 21.7 ng/ml)
- Elevated BNP (872 pg/ml)
- Normocapnic hypoxemia at arterial blood gas analysis (pH 7.38, PaO_2 63 mmHg, PCO_2 31 mmHg, HCO_3^- 18 mEq/l)

Routine 12-Lead ECG at Rest (Fig. 20.1)

ECG showed atrial fibrillation (AF) with high ventricular rate (130 beats per minute). There were diffuse and nonspecific repolarization alterations.

Chest X-Ray (Fig. 20.2)

A standard chest X-ray demonstrated the presence of bilateral lung interstitial edema and heart enlargement.

The patient was admitted to the cardiology department with the initial diagnosis of heart failure in patient with AF at high ventricular rate.

He was treated with a diuretic (furosemide) and rate-control agents (digoxin and metoprolol) with an improvement of symptoms after 24 h.

Echocardiography was recorded and showed the following findings: "normal-sized left ventricle (60 ml/m^2) with severe depression of global systolic function (EF less than 20 %) due to diffuse hypokinesia. Severe dilatation of the left atrium (index volume 40 ml/m^2). High filling pressure. Normal right ventricle size with reduced systolic function (TAPSE 12 mm). Moderate dilatation of the right atrium. No pericardial effusion. No gradients. Mild to moderate mitral regurgitation. Moderate to severe tricuspid regurgitation with high pulmonary arterial pressure (40 mmHg)" (Fig. 20.3).

What Are the Possible Causes of This Severe Depression of Left Ventricular Systolic Function?

Possible alternatives:

- Ischemic heart disease
- Idiopathic dilated cardiomyopathy
- Myocarditis
- Tachycardiomyopathy

An invasive coronary angiography was performed in order to exclude a coronary disease (chest pain, elevated myocardial necrosis markers) but didn't show any coronary lesion (Fig. 20.4a, b).

The patient had heart failure and therefore an electrical cardioversion was indicated.

Because AF was not datable, a transesophageal echocardiography (TEE) was done to exclude atrial thrombi before going to electrical cardioversion. TEE didn't show atrial thrombi and a successful electrical cardioversion was performed. The sinus rhythm was restored after a single synchronized biphasic shock at 150 J. Amiodarone was there introduced for rhythm control together with warfarin to prevent thromboembolic events (Fig. 20.5).

An acute myocarditis was also later excluded by magnetic resonance imaging.

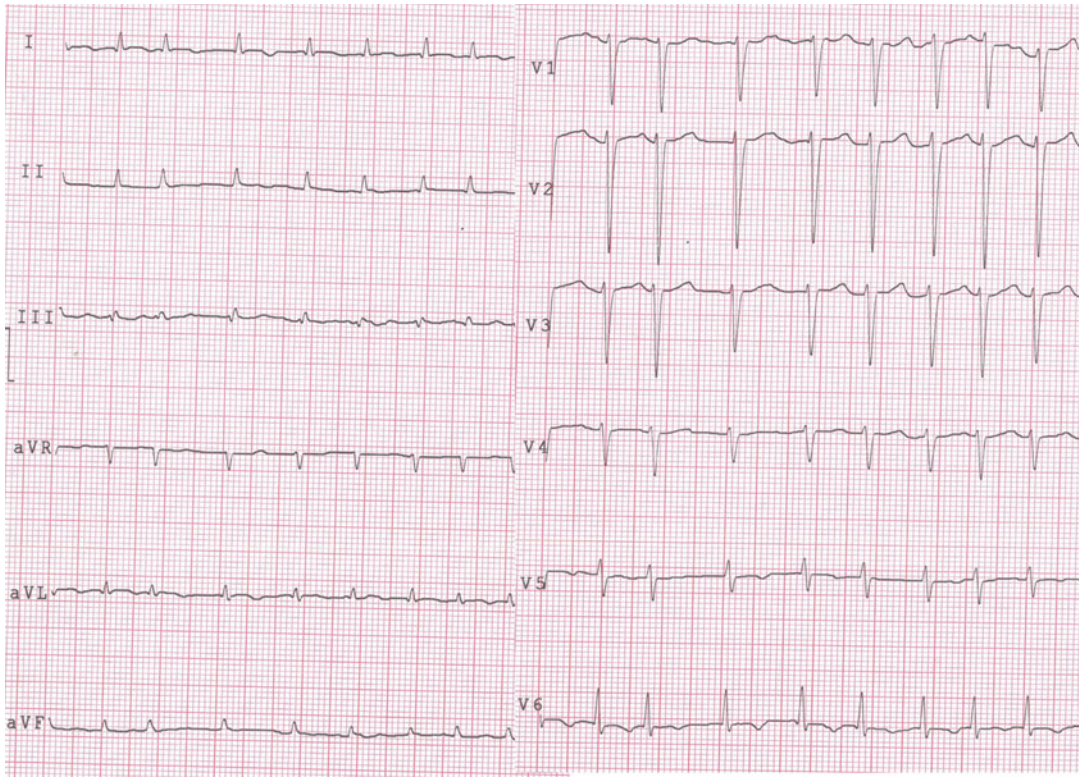

Fig. 20.1 ECG shows atrial fibrillation with high ventricular rate

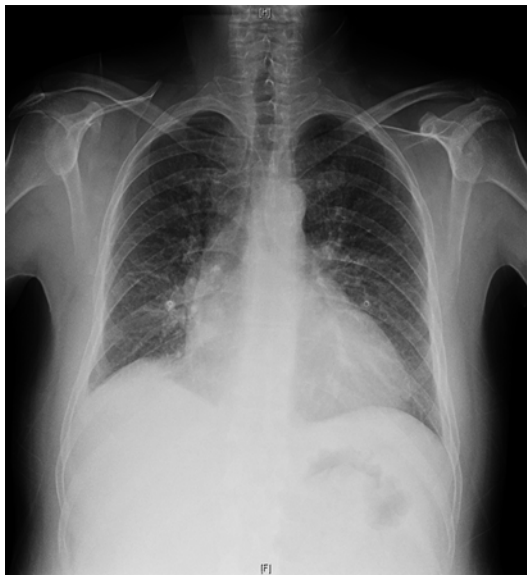

Fig. 20.2 Chest X-ray

The final diagnosis was "severe biventricular systolic dysfunction secondary to tachycardiomyopathy (high-rate AF)." The patient was dismissed after 3 days in good clinical state with the following medical therapy: amiodarone 200 mg at 8.00 a.m., losartan 25 mg at 8.00 a.m., furosemide 50 mg at 8.00 a.m. and at 6.00 p.m., warfarin at 4.00 p.m. (variable dose to maintain INR from 2.0 to 3.0), eplerenone 25 mg at 6.00 p.m., and metoprolol 50 mg at 8.00 a.m. and at 8.00 a.m.

After 1 month, another echocardiogram was recorded. It showed a great biventricular systolic function improvement (EF 57 %; TAPSE 17 mm) and a reduction of mitral and tricuspid regurgitation (now mild). Also pulmonary arterial pressure returned to normal. ECG confirmed sinus rhythm maintenance (Fig. 20.6a, b).

The full systolic function recovery consequent of a stable sinus rhythm confirmed the previous diagnosis of tachycardiomyopathy. Warfarin was stopped after 1 month from cardioversion because patient had not any stroke risk factor (CHA_2DS_2-VASc = 0).

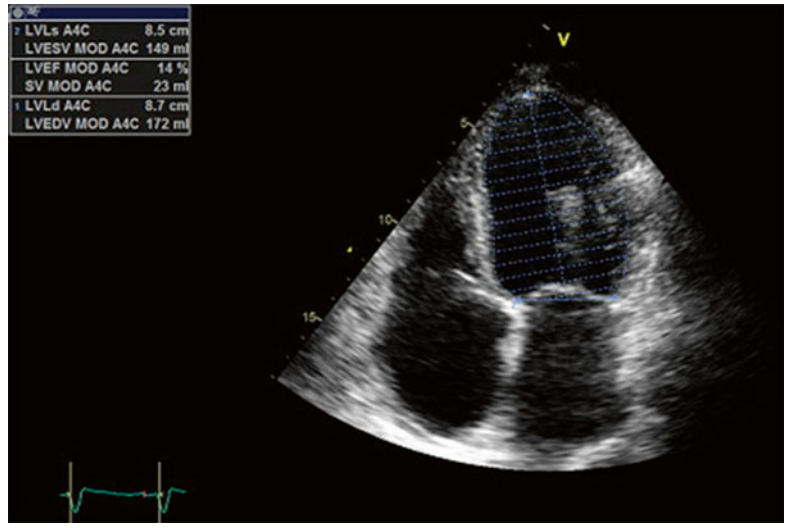

Fig. 20.3 Echocardiography. Severe depression of left ventricular global systolic function. *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction

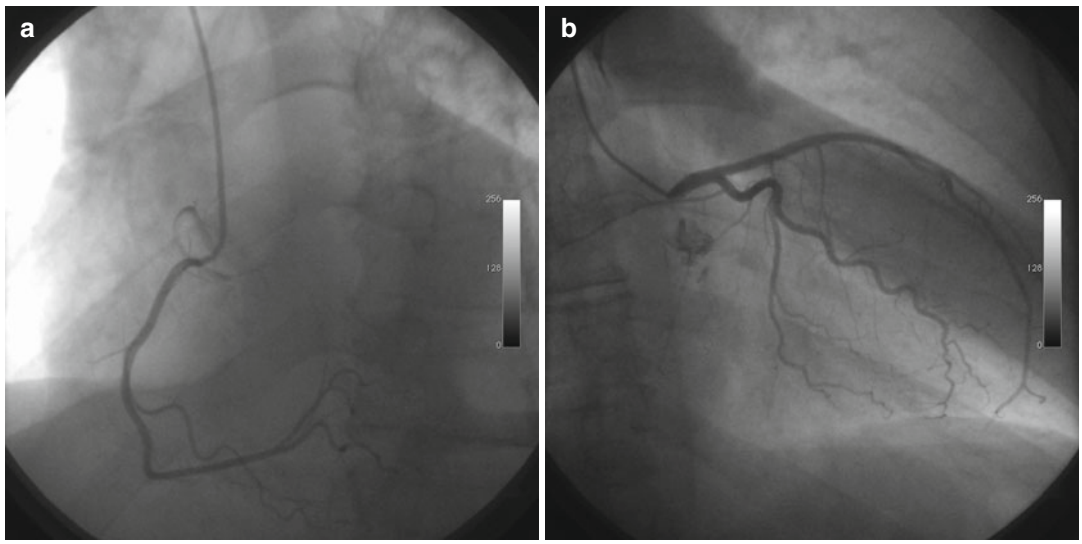

Fig. 20.4 Coronary angiography. Right coronary angiography (**a**) and left coronary angiography (**b**)

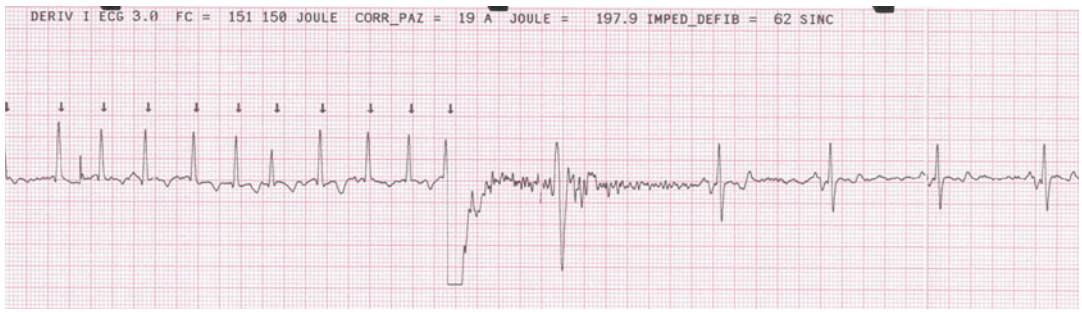

Fig. 20.5 Electrical cardioversion. Synchronized biphasic shock at 150 J restores sinus rhythm

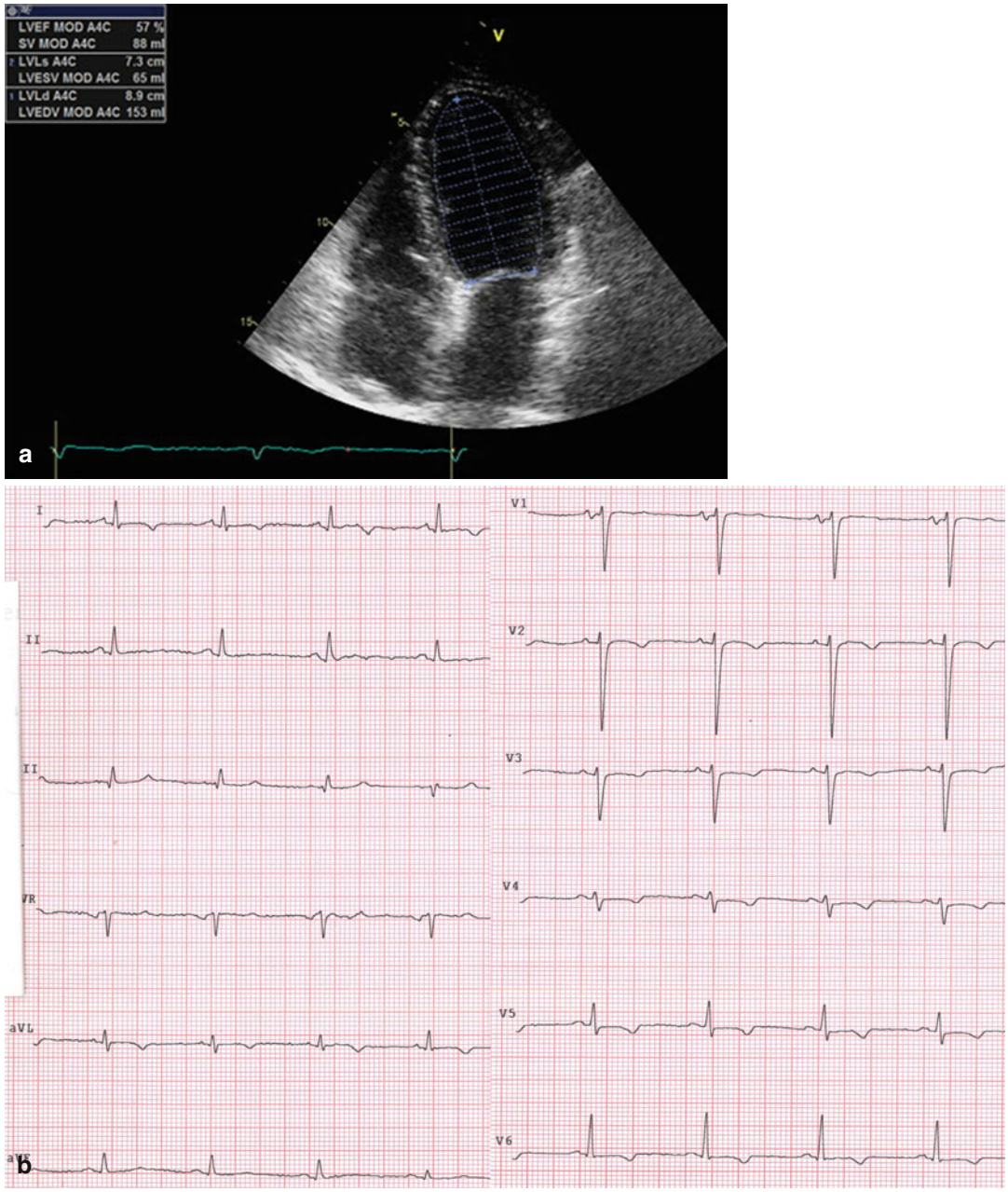

Fig. 20.6 Echocardiography. Normal left ventricular global systolic function (**a**). ECG with sinus rhythm (**b**)

20.2 Atrial Fibrillation (AF)

Definition and Epidemiology

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by chaotic and irregular atrial electrical activity. It's the most common sustained arrhythmia in clinical practice and is the leading cause of hospitalization for arrhythmias.

The prevalence of AF in the general population is about 1–2 % and increased with age; 70 % of patients with atrial fibrillation are more than 65 years old [1, 2].

More than six million in Europe have this form of arrhythmia, and its prevalence is expected to double over the next 50 years with the aging population.

Classification

AF is classified according to the modality of presentation, its duration and the possibility of restoration of sinus rhythm into:

1. *First diagnosed AF*, in patients presenting with the arrhythmia for the first time
2. *Paroxysmal AF*, in general, self-terminating within 48 h, but with a maximum duration up to 1 week
3. *Persistent AF*, when an episode of AF lasts more than 7 days or requires cardioversion to restore sinus rhythm
4. *Long-standing persistent AF* if AF lasts more than a year when an attempt is made to restore the rhythm
5. *Permanent AF* if it is chronic and no more attempts to restore normal heart rhythm will be made [3]

Clinical Presentation and Diagnostic Evaluation

The most common symptoms in patients with AF are palpitations (54 %), which are more common in paroxysmal forms, and dyspnea (44 %), which is prevalent in permanent type. Other common symptoms are easy fatigability and asthenia (14 %), chest pain (10 %), and dizziness and syncope (10 %) [4, 5].

AF may be also asymptomatic and consequently silent; the frequency of silent FA varies depending on the method used for recording, reaching up to 51–74 % if considering the memories of pacemakers and ICD [6, 7].

The high prevalence of asymptomatic AF has implications on the need to start the oral anticoagulant therapy; various trials showed that only episodes of AF long enough (>5–24 h) are associated with an increased risk of thromboembolism [8, 9].

The European Heart Rhythm Association had proposed a new classification for assessing symptoms during AF (EHRA score) [10, 11]: class I, related to no symptoms; class II mild symptom, with no impairment of normal daily activities; class III, severe symptoms that affected normal daily activity; and class IV, disabling symptoms with disruption of normal daily activity.

The diagnosis of AF requires an ECG performed during the arrhythmia. ECG provides information not only on heart rhythm but also on the presence of ventricular hypertrophy, ventricular pre-excitation, bundle branch block, myocardial necrosis, and concomitant arrhythmias.

Transthoracic echocardiography (TTE) is extremely useful for assessing the existence of an underlying heart disease; it helps to define the presence of a valvular disease and its severity to evaluate chamber dimension and left ventricular systolic and diastolic function and estimate pulmonary pressure.

Transesophageal echocardiography (TEE) is used to assess the presence of e.g., left atrial appendage thrombi before cardioversion of non-datable AF.

Chest X-ray is useful in particular in cases of AF associated to symptoms of heart failure for the evaluation of the state of pulmonary circulation. It can reveal the presence of concomitant AF-associated pulmonary diseases (e.g., COPD).

Laboratory tests to be performed are tests for thyroid hormones (TSH, FT4), serum electrolytes, blood counts, and renal and hepatic functions that help in choosing antiarrhythmic and anticoagulant drugs.

ECG monitoring system as ambulatory ECG Holter or external loop recorder may be used in case of palpitations suspicious for paroxysmal AF but without previous electrocardiographic documentation of arrhythmia and for the diagnosis of asymptomatic episodes of AF.

Performing other imaging studies should be evaluated case by case.

Treatment

In AF treatment, we have to consider two aspects: (1) prevention of thromboembolism and (2) treatment of the arrhythmia.

Antithrombotic Therapy

Patients, during prolonged (more than 48 h) AF episode, have to do anticoagulant therapy to reduce cardio embolic stroke risk. Indication to lifelong oral anticoagulant therapy in patients with previous AF episodes (regardless of current rhythm) is based on a stroke risk score (CHA_2DS_2-VASc score). CHA_2DS_2-VASc score [congestive heart failure (1 point), hypertension (1 point), age more than 75 (2 points), diabetes (1 point), previous stroke or TIA (2 points), vascular disease (1 point), age more than 65 (1 point), sex category female (1 point)] greater than or equal to 1 identifies patients at risk of stroke who have indication to do lifelong oral anticoagulant therapy. The stroke rate in AF patients increases progressively from 1.3 %/year (CHA_2DS_2-VASc = 1) to 15.2 %/year (CHA_2DS_2-VASc = 9). HAS-BLED score [hypertension (1 point), abnormal renal and liver functions (1 point each), previous stroke (1 point), bleeding (1 point), labile INRs (1 point), elderly more than 65 years (1 point), drug or alcohol abuse (1 point each)] is used to assess the bleeding risk but not to contraindicate the oral anticoagulant therapy. When HAS-BLED score is greater than or equal to three, the bleeding risk is high and a close follow-up of anticoagulated patients is necessary.

The oral anticoagulant therapy can be practiced with vitamin K antagonist (warfarin) dosing to obtain INR values from 2.0 to 3.0 or with the new oral anticoagulants (NOAC) (dabigatran, a direct factor II inhibitor; apixaban; rivaroxaban; and edoxaban, a direct factor X inhibitor). NOAC are fixed-dose drugs (twice daily for dabigatran and apixaban, once daily for rivaroxaban and edoxaban) that do not require periodical coagulation assessment; neither the dose has to be varied in response to changes in laboratory coagulation parameter (INR or aPTT). NOAC are not indicated in patients with severe renal impairment (creatinine clearance, assessed by Cockcroft-Gault formula, less than 30 ml/min) and in valvular AF (prosthetic valves and rheumatic valvular disease, in particular mitral stenosis).

In patients with important contraindications to lifelong anticoagulant therapy, it is possible to perform the occlusion of the left atrial appendage (surgical or percutaneous). This is a non-pharmacological method to reduce stroke risk. The rationale of this technique is that the left atrial appendage is the main (but not the only) site of thrombi formation.

Treatment of Arrhythmia

Acute Therapy: In unstable patient, an immediate electrical cardioversion is mandatory. A stable patient with a rapid ventricular response needs an acute therapy to control the ventricular rate (beta-blockers, non-dihydropyridine calcium-channel antagonist, digoxin, or a combination of them). In case of slow ventricular rate AF, a therapy with atropine or temporary pacemaker may be useful in symptomatic patient.

If AF is of recent onset (less than 48 h), it is possible to try to restore sinus rhythm by electrical or pharmacological cardioversion. Electrical cardioversion consists of a synchronized electrical shock delivery in sedated patients, and it is more effective than pharmacological cardioversion. For pharmacological cardioversion, the choice is between class IC antiarrhythmic drugs (flecainide or propafenone for patients without structural heart disease and amiodarone for patient with structural heart disease). Class IC antiarrhythmic drugs can be administered intravenously or with oral high dose ("pill-in-the-pocket" approach), and their efficacy length is about 2–4 h. Pharmacological cardioversion does not require sedation of patient.

If AF onset is prolonged upto 48 h, the cardioversion can be made only after a TEE that excludes left atrium or left atrium appendage thrombi or after at least 3 weeks of correct anticoagulation (INR 2.0–3.0 or constant intake of NOAC). If TEE reveals thrombi, cardioversion is not indicated and a new TEE has to be recorded after at least 3 weeks of correct anticoagulation before cardioversion to assess if thrombi are still present. In this case, long-term oral anticoagulant

therapy is indicated regardless of CHA_2DS_2-VASc score and a rate-control strategy is recommended.

In patients with AF more than 48 h, 4 weeks of anticoagulation therapy is indicated after cardioversion independently from CHA_2DS_2-VASc score.

Long-Term Therapy: there are two strategies for long-term management of AF, rhythm control and rate control.

Rhythm-control strategy is based on preventing AF recurrence and maintaining sinus rhythm by the administration of antiarrhythmic drugs. There are different antiarrhythmic drugs used to try to maintain sinus rhythm (flecainide, propafenone, sotalol, dronedarone, amiodarone). Class IC antiarrhythmic drugs (flecainide and propafenone) can be safely used to maintain sinus rhythm in patient without structural heart disease. Amiodarone is better than other antiarrhythmic drugs to maintain sinus rhythm (the number of patients needed to be treated is three for amiodarone, four for flecainide, five for propafenone, and eight for sotalol), but it is generally used in patients with AF recurrences despite other drug therapies because it has several side effects (thyroid dysfunctions, vision problems, liver disease, lung disorder, etc.). Dronedarone is less effective than amiodarone, but it can be used in patients experiencing amiodarone toxicity or side effects.

The presence and type of structural heart disease are important for choosing among different antiarrhythmic drugs (Fig. 20.7).

In patients without structural heart disease and recurrent symptomatic episode of paroxysmal or persistent AF despite rhythm-control therapy, catheter ablation (usually pulmonary vein isolation) is an alternative strategy to maintain sinus rhythm or to reduce recurrences. Pulmonary vein isolation can be made by radiofrequency or by cryo ablation. Radiofrequency ablation technique is based on the production of several lesion lines to separate electrically the left atrium from the pulmonary veins. In cryo ablation technique, the pulmonary vein isolation is obtained by a circular continuous lesion made by a cryo-balloon positioned in the pulmonary vein ostia. The effectiveness of AF ablation to prevent recurrence after single procedure is about 60–75 % for paroxysmal AF and about 45–60 % for persistent AF in the first year. Multiple procedures increase the effectiveness to about 10 %.

The rate-control strategy is based on getting a "normal" heart rate during AF to reduce patient's symptoms. Drugs used for rate control (beta-blockers, non-dihydropyridine calcium-channel antagonist, digoxin, amiodarone, or a combination of them) act by reducing the atrioventricular node conduction and consequently the ventricular rate. The choice between different drugs has to be made considering patient's associated diseases: in patients with heart failure, the first choice is beta-blockers, followed by digoxin; in patients with asthma or COPD, non-dihydropyridine calcium-channel antagonist and digoxin are preferred over beta-blockers.

The rest ventricular frequency target is less than or equal to 110 beats per minutes (lenient rate control). A more intensive rate control (rest heart rate ≤80/min and heart rate during moderate exercise ≤110/min) is necessary when patient

	Minimal or no heart disease	Structural heart disease				
		HT		CAD	HF	
		No LVH	LVH		Stable (NYHAI-II)	NYHA III-IV or unstable NYHA II
First choice	F, P, D, S	F, P, D, S	D	S, D	D	A
Second choice	A	A	A	A	A	

Fig. 20.7 Antiarrhythmic drugs for rhythm control. *HT* hypertension, *CAD* coronary artery disease, *HF* heart failure, *F* flecainide, *P* propafenone, *D* dronedarone, *S* sotalol, *A* amiodarone

remains symptomatic or if tachycardiomyopathy occurs despite lenient rate control. If the rate control has failed, despite maximum tolerated medical therapy, the "ablate and pace" (radiofrequency ablation of atrioventricular node and pacemaker implant) is a non-pharmacological strategy to obtain rate control.

There are no differences in terms of mortality, quality of life, and stroke rate between rhythm- and rate-control strategies; the choice depends on symptoms, structural heart disease, patient's age, number of previous episodes, and comorbidity [3].

20.3 Atrial Fibrillation and Related Disorders

AF is correlated with an increased risk of mortality, ischemic events, and heart failure.

In the Framingham Heart Study, AF resulted in an increased risk of mortality of 1.5-fold in men and 1.9-fold in women, independently from the presence of concomitant cardiovascular disease [12]. Moreover, AF has a significant impact on the quality of life, with a lower score of 16–30 % of all the parameters commonly examined. The deterioration of the quality of life in AF patients is similar or even more pronounced than in patients with myocardial infarction or heart failure and patients undergoing coronary angioplasty [13].

AF and Heart Failure

AF and heart failure are two conditions that often coexist. About a third of AF patients have a history of congestive heart failure, and 10 to 30 % of patients with heart failure have a history of AF. The prevalence of AF in heart failure increases with the progression of the NYHA functional class (from 4 % in class I to 50 % in class IV).

These two conditions (AF and heart failure) share the same risk factors, and the presence of one predisposes to the development of the other: the loss of atrial contribution to ventricular filling, the high heart rate, the irregularity of cardiac cycles, and the reduced duration of diastole during AF lead to a reduction in cardiac output; in the other side, the increased filling pressures in heart failure favor wall stress and atrial dilatation and fibrosis; the increase in adrenergic tone and neurohumoral activation typical of chronic heart failure determines changes in the electrical substrate, which are responsible for AF onset.

Therefore the coexistence of AF and heart failure leads to increased mortality and quality of life.

AF and Stroke

Stroke is the most important complication in patients with AF. It is estimated that up to 25 % of strokes in the elderly are a result of AF, which increases its risk fivefold [14].

Cardioembolic strokes due to AF are the result of emboli originating from the left atrium and the left auricle; they are often very large, with a higher risk of disability [15] and an increased poststroke mortality than other types of strokes; moreover AF is an independent risk factor for stroke severity and recurrence [16].

Therefore proper stratification and prevention of thromboembolic risk are a very important part in the management of AF patients. Actually ESC AF guidelines recommend to use the $CHADS_2$ score and more recently the CHA_2DS_2-VASc score that consider various major and minor clinical risk factor predictors of stroke for evaluating the indication for anticoagulation treatment (see "Antithrombotic Therapy").

Several randomized clinical trials and meta-analyses have shown that oral anticoagulation therapy is highly effective in the primary and secondary prevention of stroke in patients with AF; anticoagulation therapy reduced the relative risk of stroke by 64 %, corresponding to an absolute annual risk reduction in all strokes (2.7 %) [17].

AF and Tachycardiomyopathy

Tachycardiomyopathy or tachycardia-induced cardiomyopathy (TIC) is defined as a condition of systolic and/or diastolic dysfunction secondary to chronic or frequent recurrent tachyarrhythmias. It is characterized by ventricular dilatation

and signs and symptoms of heart failure, completely or partially reversible after normalization of heart rate and/or heart rhythm abnormality.

TIC may result from various types of chronic or frequent paroxysmal supraventricular and ventricular tachyarrhythmias, even if the most frequent etiology is AF.

The incidence of TIC is not exactly known but it can occur at any age. In selected studies of patients with AF, based on retrospective series, it was reported that 25 to 50 % of patients with left ventricular dysfunction and AF can have some degree of TIC [18].

The time needed to the onset of ventricular dysfunction and its extent vary from subject to subject; many variables must be considered as the type of arrhythmia, its rate and duration, the age of the patient, drugs, the presence of pre existing heart disease, or other comorbidities [19].

The diagnosis of TIC is often made retrospectively, after the recovery of ventricular function once the normalization of cardiac rhythm and/or heart rate is obtained.

Diagnostic tests include an EKG that may show the responsible arrhythmia. Chest X-ray can reveal a dilated cardiac silhouette and interstitial edema in the pulmonary circulation. Echocardiogram shows dilatation of the left and right ventricles with systolic and/or diastolic dysfunction and signs of elevated filling pressure; mitral insufficiency secondary to valvular annulus dilatation is often present.

Other causes of hypokinetic dilated cardiomyopathy must be excluded, as idiopathic, ischemic, and post-myocarditis types. TIC can occur also in patients with underlying heart disease and worsen the preexistent systolic function.

The treatment of TIC aims to control heart rate and/or normalization of the rhythm. This can be achieved through non-pharmacological and pharmacological approaches.

In patients with AF, the initial approach is the control of the heart rate, which can be achieved with drugs that affect the AV node slowing the ventricular response (beta-blockers, digitalis, calcium-channel blockers).

Subsequently restoration of sinus rhythm can be achieved with DC cardioversion or antiarrhythmic drugs. The return to sinus rhythm improves cardiac output, ejection fraction, and ventricular volumes and also restores AV synchrony and the atrial contribution to ventricular filling.

In general, the choice of pharmacological therapy depends on the type of the arrhythmia.

Class IC antiarrhythmic drugs should be used with caution in these patients because of their negative inotropic effect. Beta-blockers and class III antiarrhythmic drugs (amiodarone, sotalol) are the drugs of choice in patients with atrial fibrillation, ventricular tachycardia, and frequent PVCs.

However when the medical treatment is not effective, a non-pharmacological approach must be considered; these include catheter radiofrequency ablation by electrical isolation near the ostia of the pulmonary veins and ablate and pace strategy with radiofrequency ablation of the AV node with pacemaker implantation.

The recovery of contractile function may be complete, partial, or totally absent. This can result from the prolonged duration of the arrhythmia, which causes irreversible histopathological alterations, and from the concomitant presence of an underlying heart disease. The time required for recovery of left ventricular function is very variable; in experimental animal models, the range is about 2 weeks after the end of the cardiac stimulation; in clinical studies, the time necessary for the improvement of ventricular function can range from 1 month up to a maximum of 6–8 months.

AF and Acute Coronary Syndromes

AF is common in patients with ischemic heart disease, and it's a frequent complication in acute coronary syndrome (ACS), with a reported incidence of new-onset AF in patients hospitalized for ACS varying from to 2 to 23 % [20].

The prevalence of AF in the setting of ACS reduced in the last years, as a consequence of the increasing use of revascularization strategies (PCI in the acute phase).

Several risk factors are associated with incidence of AF in ACS patients, including advanced

age, infarct size and severity (ST-segment elevation myocardial infarction), higher Killip class and left ventricular dysfunction, female gender, and poorer renal function [21].

In the management of patients with AF during ACS first of all in case of severe hemodynamic instability, if an adequate rate control can't be obtained with pharmacological therapy, urgent DCC is indicated. In the choice of antiarrhythmic drugs, patient underlying comorbidities must be considered; current guidelines recommend the use of amiodarone, sotalol, and dronedarone in the presence of ischemic heart disease; class I antiarrhythmic drugs are contraindicated during acute ischemia.

In AF patients undergoing revascularization (PCI) during ACS with stent implant, triple therapy (warfarin, aspirin, and clopidogrel) must be administered in the initial period (3–6 months) and subsequently replaced by warfarin plus clopidogrel up to 12 months; after that, warfarin can be continued alone. For patients at high bleeding risk, bare metal stents instead of drug-eluting stents must be considered to reduce the duration of antiplatelet therapy [3].

In patients with ACS complicated with AF, an increase in hospital and long-term mortality and an increased risk of ischemic stroke were observed; in the large multinational GRACE registry, a decline in short-term mortality over the study period in AF patients (between 2000 and 2007), as a reflex of improvements in ACS therapy, was reported.

AF and Troponin Elevation

In patients presenting with AF and high heart rate, mild elevation of troponin is frequent, also in the absence of other signs and symptoms of ischemic heart disease.

Potential mechanisms of troponin elevation in AF patients, other than coronary syndromes, are related to supply-demand mismatch secondary to increased heart rate, with shorter diastolic filling time, that can lead to a reduction in coronary flow and possible subendocardial ischemia. Increased left ventricular wall strain and myocardial stretch have also been postulated as responsible of troponin and BNP release during increased heart rates [22, 23].

Some trials reported that troponin elevation may help in the risk stratification in patients with AF. In the biomarker substudies of two recent and larger AF trials, RE-LY (*r*andomized *e*valuation of *l*ong-term anticoagulant therap*y*) and ARISTOTLE (*a*pixaban for *r*eduction *i*n *st*roke and *o*ther *t*hromboembo*l*ic *e*vents in atrial fibrillation), including a total of 21,081 patients, elevated troponin levels were associated with an increased risk of stroke or systemic embolism and of cardiovascular death, independently from other clinical characteristics [24, 25].

AF and Cognitive Dysfunction

It has suggested that AF may be a risk factor for the development of cognitive impairment.

In the prospective, population-based Rotterdam Scan Study [26], dementia and Alzheimer's disease were correlated with the presence of AF in the elderly, and a subsequent substudy [27] revealed an association between "silent" brain infarcts with the risk of dementia and decline in cognitive function in older patients. Other possible causes are concomitant heart failure and microcirculatory dysfunction, secondary to hypertension.

In a recent review [28], the incidence of cognitive impairment and/or dementia in patients with and without AF was compared. It was observed that patients with AF had a greater risk of cognitive impairment and a 2.3-fold (95 % CI 1.4–3.7) increased risk of dementia, compared with patients in sinus rhythm.

AF and Pericarditis

A great number of studies have reported that inflammation has an important role in AF etiology. AF is observed between 2 and 3 days after cardiac surgery; this time coincides with the peak of inflammatory proteins (C-reactive protein, IL-6). In acute pericarditis, the inflammation of

pericardial sack can induce AF. In this case, AF is secondary to inflammation and generally resolves after the acute phase [29].

A different mechanism is responsible for the onset of AF in constrictive pericarditis. Altered filling pressure for a long time leads to remodeling of heart chamber and atrial dilatation. This atrial dilatation increases the possibility of AF onset; about one-third of patients with constrictive pericarditis develop AF [30].

AF and Vagal Tone

Vagally mediated AF is not a clinical entity, with paroxysmal episodes that occur generally in healthy young males at night when there is an increase in vagal tone. An increase in vagal tone can induce AF by shortening the atrial refractory period; this can facilitate premature beats and reentry. This type of AF is more frequent in endurance sports athletes [31]. An AF onset during the night does not imply a vagal AF [32].

AF and Chronic Obstructive Pulmonary Diseases (COPD)

COPD are associated with a high incidence of atrial fibrillation and atrial flutter, with a 10–15 % of AF patients having COPD; pulmonary diseases and sleep-disordered breathing are emerging risk factors for the development of AF. Patients in which the two conditions coexist have a worse prognosis with higher mortality.

The presence of hypoxia and hypercapnia with respiratory acidosis in chronic lung diseases is responsible for autonomic system alterations and increase in intrathoracic pressures; these hemodynamic modifications may induce repolarization abnormality, atrial stretch, and structural remodeling leading to AF.

Reduced lung function and pulmonary hypertension are independent risk factors for AF in patients with COPD exacerbation [33].

Drugs used to treat bronchospasm, as theophyllines and β adrenergic agonists, may trigger AF and the control of heart rate may be difficult in this setting. In case of AF during an acute respiratory decompensation, treatment of underlying pulmonary disease is the primary target, as restoration of sinus rhythm may be ineffective until respiratory failure is corrected.

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Atrial Flutter

21

Erika Baiocco and Azzurra Fabbrizioli

21.1 Case Report

A 66-year-old man presented to the family doctor complaining of abrupt onset of palpitation, initially associated with mild dizziness, occurred a few days ago (probably 3 days) while he was working. He had a recent episode of acute bronchitis treated with empirical antibiotic therapy (amoxicillin) with slow resolution. During physical examination, the physician detected a rhythmic tachycardia pulse. The patient was at rest and was not agitated. By suspecting the presence of an arrhythmia, the doctor referred the patient to the emergency room for further assessment.

Medical History and Cardiovascular Risk Factors

- Arterial hypertension
- Dyslipidemia
- Overweight
- Hiatal hernia
- No previous cardiovascular events

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Allergies

No allergy is referred by the patient.

Social History

- He works as a bank employee.
- He never smoked.
- He never used illegal drugs.
- He occasionally drinks one glass of wine and a couple of beers a week.

Medications

Valsartan 160 mg/day

Vital Signs

- Temperature: 36.5 °C
- Heart rate: 150 bpm
- Blood pressure: 100/80 mmHg
- Respiratory rate: 22 breaths per minute
- Oxygen saturation while breathing ambient air: 98 %

Physical Examination

- *General:* awake, oriented, and cooperative

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- *Head, eyes, ears, nose, and throat:* normocephalic, atraumatic, mucous membranes moist, pupils equally round and reactive to light and accommodation bilaterally, normal sclera and conjunctiva, and normal tympanic membranes and external auditory canal
- *Neck:* movable without resistance, no jugular venous distention, no lymphadenopathy, and no carotid bruit. No thyroid enlargement
- *Cardiovascular:* regular rhythm tachycardia; S1 and S2 normal in intensity; no murmurs, rubs, or gallops; point of maximal intensity non-displaced and non-sustained; no hepatojugular reflux; and capillary refill less than 2 s
- *Lungs:* no rales on auscultation in the lung bases bilaterally, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal upon percussion
- *Abdomen:* mild overweight, no pulsatile masses, normal bowel sounds in all areas, no high-pitched or tinkling sounds, resonant on percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, and no hepatomegaly or splenomegaly
- *Extremities:* no cyanosis, clubbing, or edema
- *Neurologic:* cranial nerves II–XII intact and no focal deficit
- *Psychiatric:* normal affect, no hallucinations, normal speech, and no dysarthria
- *Skin: normal in appearance, texture, and temperature*

Routine EKG at Rest (Fig. 21.1)

Conclusions: regular tachycardia, heart rate 150 bpm, incomplete right bundle branch block (100 ms), QRS axis +10°, apparent atrial rhythm at a rate of 300 bpm and 2:1 AV conduction, ST stretch segment from V4 to V6 with flat T waves, and normal corrected QT segment duration

The cardiologist was called to analyze the arrhythmia.

The presence of narrow QRS (100 ms) complex indicates supraventricular tachycardia.

Differential Diagnosis for Narrow QRS Complex Tachycardia

(see Chap. 19)

- Sinus tachycardia
- Reentrant supraventricular tachycardias
  - Atrioventricular reciprocating tachycardia
  - Atrioventricular nodal reciprocating tachycardia
- Focal atrial tachycardia
- Atrial flutter
- Atrial fibrillation

The regular RR interval excludes atrial fibrillation. The presence of an organized atrial rhythm at a rate of 300 bpm, with no isoelectric segment between the typical "sawtooth" waves, best seen in inferior leads, suggests the diagnosis of typical atrial flutter.

The two-to-one conduction makes difficult to recognize the atrial waves superimposed on the QRS complex or T waves, but the cardiologist performed vagal maneuvers (carotid massage) to reveal atrial waves increasing AV block (Fig. 21.2).

The presence of AV block and the ineffectiveness of carotid massage to terminate the tachycardia exclude the hypothesis of supraventricular reentrant tachycardia. The atrial tachycardia may be excluded because of higher atrial rate and the absence of isoelectric baseline between regular atrial activations.

At the end, the cardiologist concluded a diagnosis of typical atrial flutter.

Routine Laboratory Tests

- *Complete blood count:* normal (Hgb 14.6 g/ dl)
- *Cholesterol (total, HDL, LDL) and TG:* normal
- *Hepatic function (GOT, GPT, γ-GT, ALP, total bilirubin, direct and indirect):* normal

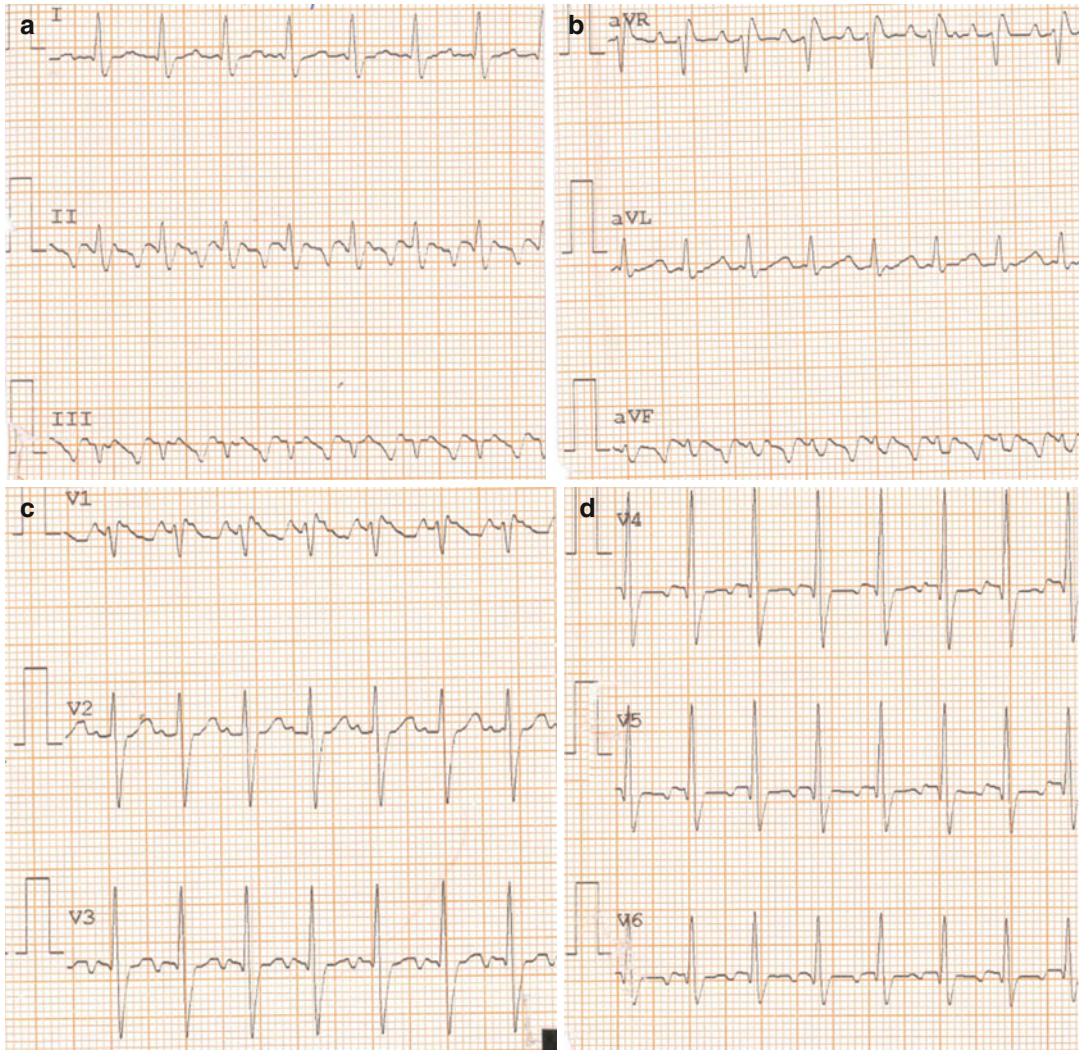

Fig. 21.1 Clockwise-type typical atrial flutter with 2:1 ventricular response

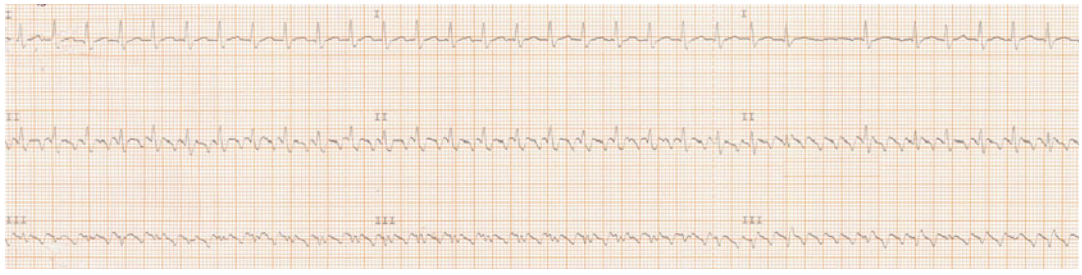

Fig. 21.2 ECG strip of leads I, II, and III shows carotid sinus massage with progressive increase in atrioventricular block

- *Thyroid function (TSH, FT3, FT4):* normal
- *Renal function (creatinine, BUN):* normal
- *Electrolytes (Na+, K+, Ca++, Mg++, Cl−):* normal
- *Fasting blood glucose:* 90 mg/dl
- *HbA1c:* 5.0 %
- *TnI-hs and CK-MB: 0.25 ng/ml* (normal <0.055 ng/ml)
- *BNP:* 127 pg/ml (normal 1–100 pg/ml)

The routine laboratory did not show any reversible proarrhythmic trigger such as electrolyte imbalance, anemia, and thyroid dysfunction. The troponin I-hs value was slightly increased due to the tachyarrhythmia. The high myocardial rate may cause an imbalance between myocardial oxygen supply and demand by enhancing myocardial oxygen requirements and reduces the diastolic coronary filling time. Also the BNP value was slightly increased as a result of initial atrial increased filling pressure.

Chest X-Ray

Both lung fields and costophrenic angles are clear. The mediastinum is within normal limits. Cardiac size and shape are normal.

In agreement with patient's symptoms and physical examination, chest X-ray did not show radiographic signs of pulmonary stasis.

Echocardiography Performed to Assess Cardiac Function and the Presence of Structural Heart Disease

Normal trileaflet aortic valve and normal aorta dimension (aortic root dimension = 2.7 cm; ascending aorta = 3.1 cm; aortic arch = 3.1 cm; thoracic aorta = 2.8 cm; abdominal aorta = 1.8 cm). Mild enlarged left atrium (LA diameter M-mode 41 mm; LA indexed volume 36 ml/m^2). Normal right atrium. No atrial septal defect. Mild left ventricular hypertrophy with normal systolic function (mass indexed volume 70 ml/m^2; EF 0.65) in the absence of regional wall motion abnormalities. Normal right ventricle size with normal function. Mild mitral and tricuspid regurgitation with normal pulmonary arterial pressure (PAPs = 30 mmHg). No pericardial effusion. Slightly dilated inferior vena cava (24 mm) with >50 % respiratory collapse. Monophasic diastolic flow pattern with initial increase of estimated filling pressure.

Conclusions: hypertensive cardiomyopathy (HCM). The absence of any signs of ventricular dysfunction excludes a tachycardiomyopathy.

The patient was a young active person and he had never had heart rhythm problems before; in fact this episode of arrhythmia was the first in his life. Furthermore it could be triggered by bronchitis.

For these reasons, and in consideration of the presence of only mild left atrium enlargement, the cardiologist chose a rhythm-control strategy. The patient was electrically cardioverted. Catheter ablation is indicated for recurrent, symptomatic, or drug-refractory arrhythmia and therefore was not performed in this case.

The exact duration of atrial flutter was unknown and lasted longer than 48 h. The patient had a CHA2DS2-VASc score of 2, suggesting a considerable risk of stroke.

Many risks and complications of cardioversion are associated with thromboembolic events, so effective anticoagulation for at least 3 weeks is mandatory for AFL of >48 h or AFL of unknown duration, unless the patient was hemodynamically unstable (LGAF).

At this point, the cardiologist proposed to perform a transesophageal echocardiography (TEE) as an alternative to 3 weeks of adequate pre-cardioversion anticoagulation.

In the meantime, a good control of ventricular rate was achieved by administrating a calcium-channel blocker (verapamil).

Transesophageal echocardiography was performed.

Conclusion: TEE excluded the presence of thrombus in the left atrium or left atrial appendage.

The patient was fully informed about the risk of cardioversion procedure.

He was sedated with a light anesthetic (midazolam). Two electrode paddles were placed on his chest: the anterior patch was placed under the

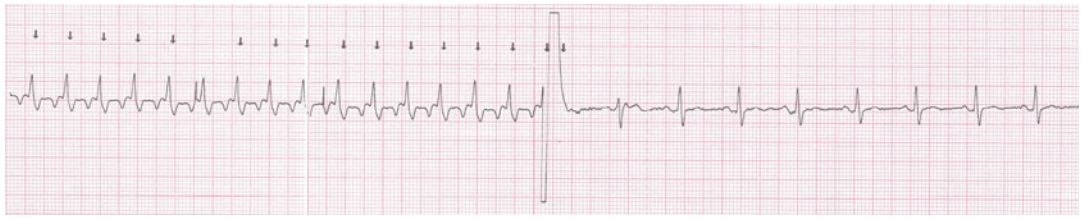

Fig. 21.3 Electrical cardioversion. The atrial flutter is converted to sinus rhythm after one synchronized biphasic electrical shock at 50 J

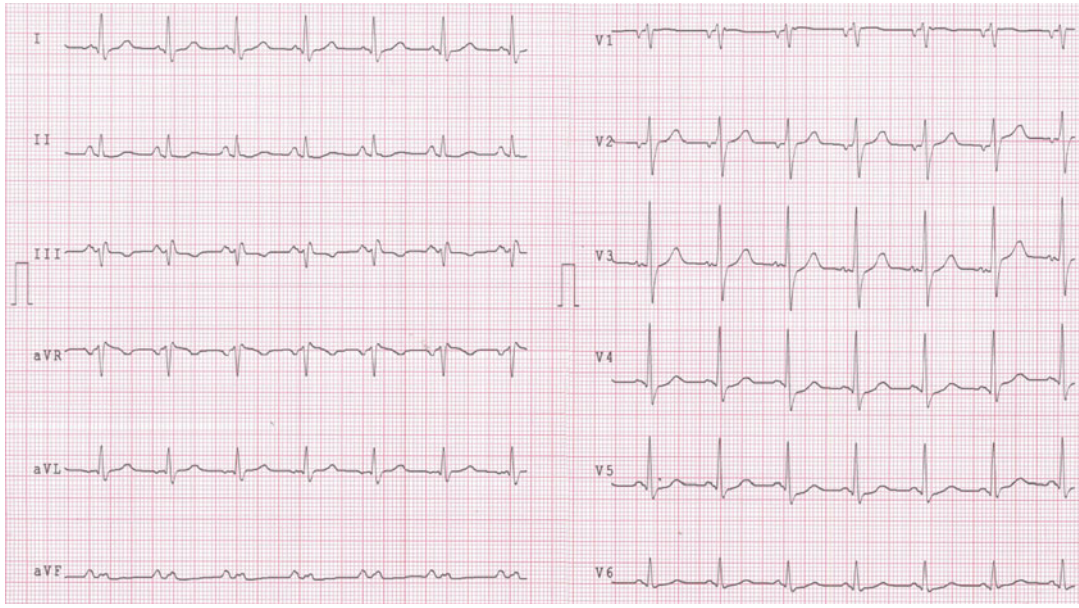

Fig. 21.4 Sinus rhythm, 85 bpm, normal atrio and inter- ventricular conduction, normal ripolarization

right clavicle and the apical patch was placed at the apex (anterior-apical paddle position). Electrical cardioversion was performed during a close oxygen level, blood pressure, and heart rhythm monitoring. Atrial flutter was successfully converted to sinus rhythm after one synchronized biphasic electrical shock at 50 J, without complications (Figs. 21.3 and 21.4).

21.2 Atrial Flutter

Atrial flutter (AFL) management includes antithrombotic and antiarrhythmic therapy, correction of possible underlying causes, and treatment of associated comorbidities. The patient had a considerable risk of thromboembolism (CHADS2VASc = 2) and a low risk of bleeding (HAS-BLED = 1). In this case, oral anticoagulant (OAC) therapy is indicated not only for 4 weeks after cardioversion (atrial stunning-related risk), but it should continue lifelong irrespective of an apparent maintenance of sinus rhythm. The cardiologist explained pros and cons of the OAC therapy and following the patient's preferences prescribed a new oral anticoagulant (NOAC).

Catheter ablation and chronic prophylactic antiarrhythmic therapy were not recommended because it was the patient's first episode of AFL and his AFL was probably due to a respiratory trigger (bronchitis). It was also well tolerated.

Catheter ablation is indicated in case of poorly tolerated or recurrent symptomatic AFL.

Hypertension is a risk factor for atrial flutter and its related complications. The patient referred optimal blood pressure control with systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg; the antihypertensive therapy was not changed.

Definition

The atrial flutter is a common supraventricular arrhythmia caused by an intra-atrial macro-reentrant circuit. It is characterized by a rapid and organized atrial depolarization at a rate between 250 and 350 bpm and a different degree of AV nodal blocking [1].

Epidemiology

The Marshfield Epidemiological Study Area (MESA) shows an incidence of atrial flutter of 88/100,000 person-years with 200,000 new cases [2]. Overall, atrial flutter represents approximately 10 % of supraventricular tachycardia, and it is much less common than atrial fibrillation [3]. However atrial flutter occurs in approximately 25–35 % of patients with atrial fibrillation. The incidence is greater in men than in women and increased markedly with age [4].

In 60 % of cases, atrial flutter occurs with a specific precipitating event such as thyroid dysfunction, respiratory infections, pulmonary embolism, or recent major surgery, while in remaining cases, atrial flutter is usually associated with chronic comorbid conditions such as heart failure, valve abnormalities (especially mitral valve), congenital defects, hypertension, chronic lung disease, alcoholism, or use of stimulants such as cocaine, amphetamines, diet pills, and even caffeine. More rarely (only 1.7 % of cases), atrial flutter can occur in the absence of structural heart disease, like *idiopathic* form (lone atrial flutter) [4]. The possibility of a genetic predisposition is unclear.

Physiopathology

AFLs comprise a heterogeneous group of atrial arrhythmias produced by abnormalities of impulse conduction that are underpinned by macro-reentrant circuits. The mechanism of reentry consists of a repetitive excitation of a specific myocardial region (excitable gap) with consequent conduction of the electrical impulse across a defined circuit, around a fixed obstacle. The macro-reentry circuit is supported by conditions of slowed conduction constrained by barriers that may be anatomical, functional, or both. The development of a unidirectional conduction block starts the arrhythmias, and it is usually a consequence of an acceleration of the heart rate or block of a premature impulse, while for its maintenance, a slow conduction is required [4].

Different types of macro-reentrant are possible.

Atrial flutter and atrial fibrillation may be present in the same person. A common trigger is recognized such as repetitive premature impulse originating from pulmonary veins or from both atria. Furthermore the AF originating from the left atrium may invade the right atrium following macro-reentrant circuit triggering AFL. In addition atrial remodeling consequently to AFL may promote the onset of AF [5].

Atrial Flutter Classification

The classification of atrial flutter proposed by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology is based on both anatomical features and electrophysiological mechanisms, determined at the time of electrophysiological testing [6]. Atrial flutter is categorized into typical or atypical.

Typical Atrial Flutter

Typical atrial flutter is subdivided into two subtypes:

- *Counterclockwise atrial flutter* is the most common type of AFL (90 %). The reentrant circuit is located in the right atrium, whose fundamental component is the isthmus, a posteroseptal part of slow conduction bounded by the inferior vena cava, Eustachian ridge, coronary sinus, and the tricuspid valve annulus. The impulse activation rotates in a counterclockwise direction through the atrial septum, by the superior vena cava, and then inferiorly down the right atrial free wall, through the isthmus to reenter the atrial septum.
- *Clockwise atrial flutter* is less prevalent (10 %). It is supported by the identical reentrant circuit to those in counterclockwise atrial flutter but with a clockwise direction of rotation around the tricuspid annulus.

Atypical Atrial Flutter

The reentrant circuit is not cavo tricuspid isthmus dependent, and it can be located either in the right or left atrium. The circuit curves around a scar or surgical incision, especially after surgical repair of congenital heart defect, atrial patch implantation or radiofrequency, and cryotherapy catheter ablation.

The most common forms of right atrial atypical flutter can show a macro-reentry circuit located in the right atrial free wall or around the superior vena cava (upper loop atrial flutter) [7–9].

Left AFLs are usually associated with hypertension, mitral valve disease, LA dilation, and cardiac failure. The circuits may be located around the mitral valve annulus, around the region of scar, and the ostia of the pulmonary veins [10].

The following are the classification of atrial flutter based on specific atrial circuits proposed by Scheinman et al. [11]:

- *Right cavo tricuspid isthmus-dependent atrial flutter*
  - Counterclockwise or typical atrial flutter
  - Clockwise or reverse typical atrial flutter
  - Double-wave reentry
- *Right non-cavo tricuspid isthmus-dependent atrial flutter*
  - Scar-related atrial flutter
  - Upper loop reentry
  - Critical flutter circuits
- *Left atrial flutter*
  - Mitral valve annulus atrial flutter
  - Scar-related atrial flutter
  - Left membranous circuits

Surface ECG Atrial Flutter Characteristics

AFL is characterized by a rapid regular atrial rhythm at the rate of 250–350 bpm [1]. Atrial rate lower than 250 bpm is generally caused by antiarrhythmic drugs (IA and IC sodium channel blocking) that slow down macro-reentrant circuit and may cause one-to-one conduction of AFL. Also patients with markedly enlarged atria, which increases duration of flutter circuit, have a slower atrial rate. Digitalis may increase atrial rate and induce AF. Commonly the ventricular response in the absence of treatment is due to the functional atrioventricular (AV) block; the most common is 2:1 but may be 4:1, 3:1, or 3:2 or second-degree AV block. A third-degree AV block is possible for impaired AV conduction or drug treatment, and it is visible on surface ECG for the presence of flutter waves without constant relation to the regular QRS complexes [1, 5].

ECG and Atrial Flutter Circuit Location

- *Typical counterclockwise atrial flutter* electrocardiographically shows a characteristic "sawtooth" pattern in leads II, III, and aVF,

with a dominant negative flutter wave characterized by a sharp steep ascent followed by a gradual descent. Lead V1 shows positive flutter wave, with an isoelectric component between the oscillations. The positive deflection progressively becomes inverted across the precordium, and the flutter wave is completely negative in V6. This type of AFL is characterized by a rate of 250–350 bpm [4, 12–14].

- *Typical clockwise atrial flutter* shows symmetrical flutter waves in the inferior leads, with the same ascent and descent segments without isoelectric line between oscillations. Lead V1 is characterized by negative deflections, and the flutter waves show a gradually transition across the precordium to an upright deflection in V6 [4, 9, 14, 15].

Some people may present both typical AFLs with either counterclockwise or clockwise right atrial macro-reentrant circuit.

Atypical atrial flutter shows a more variable surface ECG appearance depending on macro-reentry anatomical location, direction of rotation, and the presence of more loop circuits, sometimes mimicking a focal atrial tachycardia. In the inferior leads, the morphology of flutter waves is not typically "sawtooth" and usually the isoelectric line is present. The surface ECG findings are often similar for different underlying substrates, making the localization within the LA based on the ECG difficult. The flutter wave usually shows a prominent positive deflection in lead V1 and uncommonly is flat or isoelectric. The flutter waves in leads II, III, and aVF may be upright but are frequently of low amplitude. LA AFL may sometimes mimic a focal atrial tachycardia [14].

Clinical Presentation

Patients with atrial flutter can be asymptomatic, but more commonly, they present with palpitations, shortness of breath, dizziness, and fatigue. Patients with underlying heart or lung disease may complain also of syncope and chest pain. The hemodynamic stability depends on ventricular response. Patients with AFL are usually more symptomatic than those with just AF because the heart rate is more rapid during AFL and because AF is usually associated with increased AV nodal penetration and slower ventricular responses. Atrial flutter with one to one AV conduction may be life-threatening. Rapid ventricular rate may be caused by antiarrhythmic treatment (IA and IC) that slows the atrial rate or precipitated by increased sympathetic stimulation such as during exercise or induced by anesthesia. Another high-risk condition is present in patient with accessory AV pathways capable of rapid conduction and excessive ventricular rate. Moreover, in patients with impaired cardiac function, the hemodynamic instability may be due to loss of regular atrial rate and diastolic atrial contribution even if the ventricular rate is not excessively rapid.

Sometimes thromboembolism with transient ischemic attack or stroke can be the first manifestation of arrhythmia. Polyuria is another typical symptom; it is caused by the release of atrial natriuretic peptide in response to increased atrial pressure during atrial contraction against a closed AV valve, and that indicates a sustained arrhythmia [4].

Atrial flutter typically has a sudden onset. As atrial fibrillation, this arrhythmia can be clinically distinguished into [4]:

- *Paroxysmal form:* when it is transient and ends spontaneously
- *Persistent form:* when AFL is present and either lasts longer than 7 days or requires termination by cardioversion (either with drugs or by direct current cardioversion)
- *Permanent form:* when the presence of the arrhythmia is accepted by the patient and the physician and the rhythm-control strategy is, by definition, not carried out
- *Long-standing persistent AFL form:* when AFL is present for at least ≥1 year when it is decided to pursue a rhythm-control strategy

Diagnosis

The surface EKG usually allows to diagnose AFL; it is essential to obtain documentation of the arrhythmia for the choice of treatment. When the ventricular response is one to one or two to one, EKG analysis may be difficult, because flutter waves are superimposed on the QRS complex and T waves. In these cases, vagal maneuvers or intravenous adenosine administration can be used to unmask atrial activity. When arrhythmia is only suspected, it is necessary to perform Holter ECG monitoring (24 h to 7 days) or to implant a loop recorder to establish the diagnosis and to choose the strategies of treatment. Sometimes, the surface EKG is limited to define anatomical localization of macro-reentrant circuits, so the endocardial mapping can be used to identify precise anatomical circuit.

Differential Diagnosis

See Chap. 19.

Complications

Thromboembolic Events

AFL presents an increased risk for the development of thromboembolic events. In non-anticoagulated patients, the incidence of atrial echo-dense material or clots increases with atrial flutter duration longer than or equal to 48 h, and the risk of embolism was 2.2 % [16]. This is due to the high atrial rate that determines the paralyses of either the RA or LA with consequent blood stasis and development of thrombus. Clots are more frequently observed in the appendage where the blood velocity is lower.

Risk factors related to these complications are similar to those described for atrial fibrillation, and the CHADS2VASc score remains the simplest scheme of stroke risk stratification [15]. Furthermore AF and AFL often coexist in the same patient (20–30 %), so the same management of antithrombotic therapy is recommended (see Chapter 20 – AF and related disorders).

Tachycardiomyopathy

AFL with persistent high ventricular rate (120–130 bpm), if untreated, may induce reversible ventricular dysfunction (ventricular tachycardiomyopathy) [4].

Treatments

The treatment of atrial flutter should be directed to relief symptoms, prevention of complications, achieving control of ventricular rate, conversion to sinus rhythm, and maintenance of sinus rhythm.

Acute Therapy

Acute management of patients with atrial flutter depends on clinical presentation. The main goals are to reduce symptoms and to prevent AFL-related complications. It includes the management of antithrombotic therapy, achieving control of ventricular rate through the administration of AV nodal-blocking agent, conversion to sinus rhythm through electrical or chemical cardioversion, or atrial overdrive pacing.

If the patient is hemodynamically compromised or complains of significant symptoms (chest pain, congestive heart failure), like often occurred in case of one-to-one AV conduction, urgent rate control or DC cardioversion is required.

There are four options possible for the acute treatment of AFL:

- Emergent synchronized external DC cardioversion (CV), performed under anesthesia, is the treatment of choice because of very high likelihood of success (terminates AFL in >90 % of episodes) and safety (class I with level of evidence C). DC cardioversion is very effective because of rapid homogeneous depolarization of the entire atrium. The necessary energy to revert AFL to sinus rhythm is less than 50 J using monophasic shocks and with less energy using biphasic shocks [4, 17]. Unsuccessful conversion is usually associated with prolonged period of the tachycardia, and a higher CV energy is necessary that may compromise left ventricular function or

increase left atrial size. One option is pretreating patient with an antiarrhythmic agent (ibutilide is the most effective) and then the lower CV energy may be sufficient.

- Atrial overdrive pacing by transesophageal route or with atrial electrodes should be considered as an option for conversion to sinus rhythm, mainly in patients with implantable devices and after cardiac surgery, because these patients frequently have epicardial atrial pacing wires. It does not require anesthesia. Nevertheless, high-frequency atrial pacing can induce sustained atrial fibrillation. Pretreatment with antiarrhythmic agents may reduce the risk of inducing AF with atrial overdrive [4]. This method has a success rate of about 80 %. Overdrive atrial pacing is preferred in patients who have a history of sick sinus syndrome with risk for significant bradycardia after conversion.
- Chemical cardioversion is another method to terminate AFL without the need for anesthesia. The effect is not instantaneous but the success is recorded within 1 h after start of drug infusion. The drug necessary to pharmacological CV should prolong the refractory period within the tachycardia circuit, inhibiting continuation of the circulating wave front. Class III agents, such as amiodarone and ibutilide, are typically used because they prolong refractoriness and may terminate the arrhythmia because the circulating wave front encounters tissue that is refractory. Intravenous amiodarone has longer latency period. Ibutilide is more effective (70 % of success) and rapid (about 30 min), but it may produce torsades de pointes arrhythmias in 2–5 % of cases, and ECG monitoring for at least 6 h is necessary. But ibutilide should not be used in patients with structural cardiac diseases, prolonged QT interval, or underlying sinus node disease [5].
- The administration of drugs to slow AV nodal conduction and ventricular response (rate control) is another pharmacological strategy. It should be achieved with class II, III, and IV drugs [4, 5]; also if in AFL, the rate control may be more particularly difficult to achieve than in AF. Intravenous diltiazem (IV) is rapid acting (about 30 min), and it is highly effective in slowing ventricular rate response but may provoke hypotension (10 %) especially in patients with significant left ventricular dysfunction. Verapamil is just effective as diltiazem for rate control but with higher incidence of symptomatic hypotension in particular in patients with left ventricular dysfunction. The beta-blockers are effective as class IV drugs, but they should be avoided in patients at risk for reactive airway disease exacerbation. Digoxin and amiodarone are favored for rate control in patients with significant congestive heart failure since other drugs (classes II and IV) may worsen cardiac decompensation.

However, these are not a permanent solution and the arrhythmia may come back.

If the patient is hemodynamically stable and atrial flutter presents higher grades of AV block, conversion to sinus rhythm should be deferred, especially with arrhythmia of more than 48 h in duration, because in these cases, anticoagulant therapy is a priority. When a patient is adequately anticoagulated, the DC cardioversion is the first choice (class I with level of evidence B).

Prevention of Recurrence and Chronic Therapy

Chronic pharmacological treatments in patient with AFL include:

- For pharmacological prevention of recurrence, class IA drugs such as quinidine and class III drugs are used because they can prevent atrial premature beats, reduce the excitable gap, and increase atrial refractoriness. Class IC drugs alone are usually ineffective and dangerous and should be combined with AV nodal-blocking agents [5].

When currently available antiarrhythmic drugs for the prevention of AFL are not efficient and poorly tolerated (in particular IC or sotalol), dronedarone can be used that decreases the risk of arrhythmic recurrence [18].

In 60 % of patients, AFL is triggered by exacerbation of pulmonary disease, postoperative

cardiac or pulmonary surgery, or during acute myocardial infarction. In this clinical condition, the use of chronic therapy is not required [5].

The preferred therapies of poorly tolerated (also first episode) and recurrent or persistent atrial flutter is radiofrequency and cryotherapy catheter ablation (class I with level of evidence B) [4]. The typical flutter can be mapped with multipolar catheter (e.g., halo) located in the anterolateral area of RA that allows to record the direction of the cavo tricuspid isthmus macro-reentrant circuit and to distinguish between typical clockwise and counterclockwise AFL circuits. Diagnosis by this endocavity electrophysiological study is simple and usually more complex techniques such as NavX are not necessary. Radiofrequency ablation of CTI-dependent AFL involves creating a linear lesion from the inferior vena cava (IVC) to the tricuspid ring to eliminate the critical isthmus in the macro-reentrant circuit. Successful ablation interrupts macro-reentrant circuit and it is demonstrated by bidirectional conduction block. For diagnosis of atypical atrial flutter, typical flutter in RA is necessary to exclude and to identify the location of macro-reentrant circuit. This is not possible with conventional electrophysiological study, and it is necessary to use CARTO or NavX techniques. The CARTO technique records an electroanatomic map of the RA and LA in sinus rhythm showing scar area. This system uses a magnetic field generated around the patient's chest which allows to identify the specific tip position of the electrophysiological catheter in the RA or LA showing three-dimensional anatomical reconstruction of the heart chambers (anatomical virtual map). At the same time, the system records the electric signal from each point using color code (electric map). Then the two maps are integrated. Moreover the activation and propagation map recorded with a color scale identifies the macro-reentrant circuit, the direction, and the point with slower conduction target for ablation. The NavX technique uses an electric current between two surface electrodes that generates a voltage gradient between the two electrodes. This voltage gradient is recorded by a standard electrophysiological catheter located in the heart chambers. Usually, in NavX technique, three surface electrodes that form a Cartesian reference system (X-Y-Z) are used. The myocardial virtual anatomical map is created by moving the electrophysiological catheter in the heart chamber and recording the precise point of the electrophysiological catheter's electrodes rather than the surface electrodes, thanks to the recorded voltage gradient. The system analyzes the voltage of each myocardial point and identifies the sequence of activation compared with the reference electrodes recording more points of the same camera (electric map of voltage and activation). The sequence of activation time is shown with color map and is integrated with the scar areas recorded with voltage map. The macro-reentrant circuit identified by these techniques can be interrupted by linear RF lesion. For pharmacological prevention of recurrence, class IA drugs such as quinidine and class III drugs are used because they can prevent atrial premature beats, reduce the excitable gap, and increase atrial refractoriness. Class IC drugs alone are usually ineffective and dangerous and should be combined with AV nodal-blocking agents [5].

Long-term anticoagulation is advised for patients with persistent or paroxysmal atrial flutter, whereas after successful catheter ablation, anticoagulation can be stopped 4–6 weeks later if sinus rhythm is still present.

For several reasons, follow-up is very important for patients with AFL. The risk profile can change as well as the indication for anticoagulation, for example, when a new diagnosis of diabetes or hypertension will be done or when a renal dysfunction occurred. Because of the potential side effects and proarrhythmic risk related to chronic antiarrhythmic therapy, patients that receive these drugs should be monitored through 12-lead ECG, laboratory tests, and echocardiogram at regular intervals [15].

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Part VII

Rhythm Disorders: Bradyarrhytmias

Sinoatrial Exit Block

22

Andrea Romandini and Lorena Scappini

22.1 Case Report

A 77-year-old man was referred to the cardiology department from the emergency room of our hospital due to dyspnea, asthenia, and dizziness which arose a few hours before. The patient also reported that he had taken up to 2 days before treatment levofloxacin for bronchopneumonia. ECG revealed the presence of mild bradycardia (58 bpm) with type II sinoatrial block (Fig. 22.1); it was also observed that biphasic T waves in some leads (V4, V5, V6) and negative T waves in III and aVF were present. Urgent laboratory blood test showed a high level of serum creatinine (2.3 mg/dl) and hyperkalemia (7 mEq/l). All other blood tests were normal, including the values of troponin I and CK-MB. The patient was treated according to the protocol for hyperkalemia with infusion of $NaHCO_3$, hydration with glucose and insulin 10 IU, and administration of furosemide IV. Echocardiography demonstrated upper limits of normality for LVM (left ventriccle dimension) index with slightly reduced ejection fraction and mild mitral regurgitation. All echocardiographic findings were already present in a previuos echocardiogram performed elsewhere. No abnormalities were observed in other heart valves, not even on the right ventricle.

The patient was then transferred to our arrhythmology and cardiology clinic for further evaluation and treatment.

Medical History and Cardiovascular Risk Factors

1. Cardiovascular risk factors: hypertension, dyslipidemia, overweight body, and family history of cardiovascular disease
2. In 2011 the patient had a non-ST-elevation myocardial infarction treated with PCI + stenting of the first segment of the left anterior descending coronary. The angiography did not reveal significant stenoses of other

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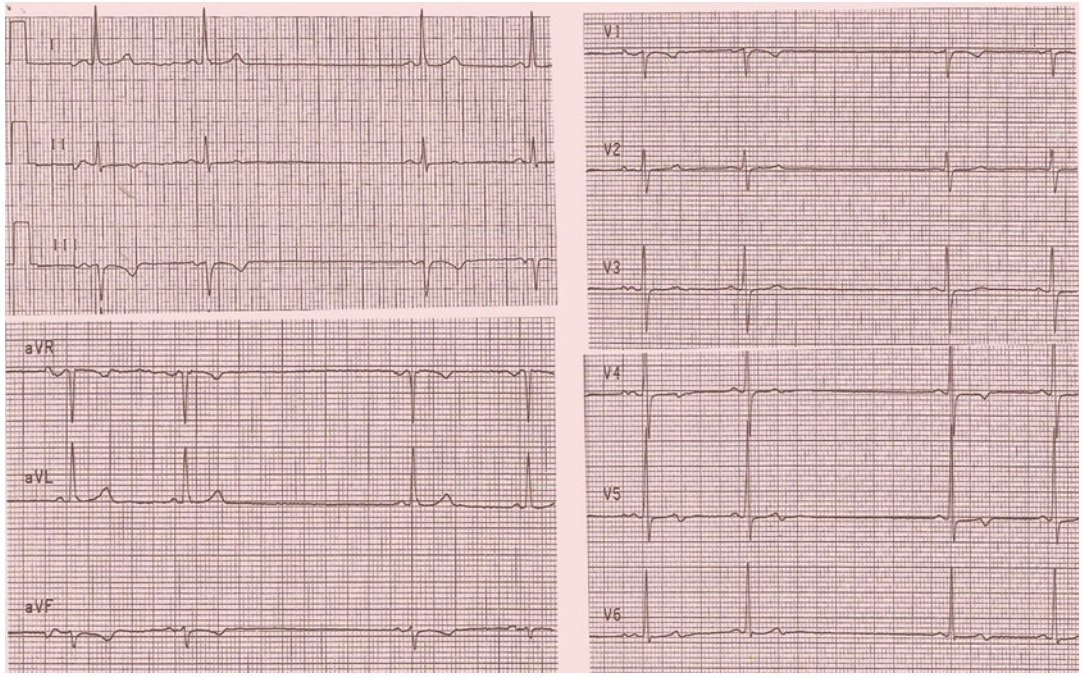

Fig. 22.1 The figure shows the patient's ECG when he arrived at the emergency room: it was characterized by type II sinoatrial block; biphasic T waves were present in V4, V5, and V6, and negative T waves in III and aVF

coronaries. Since then, the patient underwent annual cardiology visit with EKG and echocardiography, the last of which dated back about 1 month before he entered the emergency room. No abnormalities were found during that visit. The echocardiogram reported the same alterations listed above. Moreover, he denied angina, dyspnea, or syncope before that day.

Medications

ASA 1 cp, ramipril 2.5 mg 1 cp bid, potassium canrenoate 100 mg 1 cp, bisoprolol 2.5 mg 1 cp, atorvastatin 80 mg 1 cp, pantoprazole 20 mg 1 cp, tamsulosin chlorhydrate 1 cp, and allopurinol 1 cp

Vital Signs

Temperature 36.5 °C, heart rate 35 bpm, arterial blood pressure 95/55 mmHg, respiratory rate 20 breaths/min, and oxygen saturation 98 %

Physical Examination

General appearance: alert and cooperative and slightly dyspneic

Lungs: clear to percussion and minimal rales on pulmonary bases

Cardiovascular system: normal S1 and S2. Murmur 2/6 at the apex. Bradycardic rhythm. No peripheral edema, cyanosis, or pallor. Warm and well-perfused extremities

Abdomen: positive bowel sounds. Soft and nondistended. No guarding or rebound. No masses

Routine Laboratory Test

Potassium 6.1 mEq/l, sodium 136 mEq/l, and creatinine 2 mg/dl. Normal in other blood tests

Instrumental Examination

A complete echocardiogram was performed and showed upper limits of normality for LVM index

(LV diastolic volume/BSA 75 ml/m^2) with a slightly reduced ejection fraction (EF 48 %) due to hypokinesia of interventricular septum and apical segments of the anterolateral wall. Normal dimensions and function of right cardiac chambers, a mild mitral regurgitation, a calcification of the aortic valve without regurgitation nor stenosis, a slightly enlarged tubular ascending aorta (38 mm), and a mild tricuspid regurgitation with 32 mmHg pulmonary artery systolic pressure were already shown by the echocardiogram that the patient underwent 1 month before.

A chest radiograph was done and disclosed normal cardiac and pulmonary findings.

Clinical Course and Therapeutic Management

These findings altogether were suggestive of symptomatic sinoatrial block. All possible removable causes of sinoatrial block were checked: a strict control of kalemia was performed, and the patient continued to be treated by hydration with glucose and insulin 10 IU and administration of furosemide and Kayexalate. Moreover, administration of bisoprolol, ramipril, and potassium canrenoate was interrupted. A continuous telemetric monitoring was placed and showed a restoration of sinus rhythm when the level of potassium reached values of 5.5 mEq/l. The protocol for hyperkalemia was continued until the values of potassium in the blood were normal. The patient became asymptomatic dyspnea, asthenia, and dizziness. During the hospitalization he underwent an ECG stress test that showed a normal chronotropic competence and no ischemia signs. On the 5th day, he was discharged with a diagnosis of "symptomatic sinoatrial block secondary to iatrogenic acute renal failure and hyperkalemia in patient with ischemic cardiomyopathy." Since the ECG was unchanged from the previous, myocardial enzymes were normal, and there was no evidence of ischemia at the ECG stress test, it was then decided to not perform a coronarography. Before the discharge, a *patch-type* long-term external Holter recorder was applied to the patient.

A follow-up visit was performed 1 month later. The patient was completely asymptomatic. Physical examination was normal. The ECG showed a sinus rhythm (heart rate of 62 bpm). Holter monitoring did not record any arrhythmia. Laboratory blood tests were normal, including the values of potassium (4 mEq/l) and creatinine (1.4 mg/dl). Blood pressure level was 145/95 mmHg, so it was decided to resume administration of ramipril 2.5 mg ½ cp bid. It was also recommended to perform periodic checks of renal function and echocardiographic follow-up of the tubular ascending aortic dimensions.

22.2 Electrocardiographic Diagnosis of Sinoatrial Exit Block

The major electrocardiographic expressions of sinus node dysfunction (SND) are the presence of abnormal sinus bradycardia or the occurrence of "sinus pause."

The term "sinus pause" is usually used to describe the occurrence on ECG of a sudden pause in the underlying sinus rhythm: one or more sinus beats fail to appear at the expected time and a pause occurs (long P-P interval). After the pause, the resumption of the basic sinus rhythm can be slower for some cycles (temporary rate suppression); some rescue rhythms (escape beats or rhythm) may also appear from ectopic subsidiary supraventricular sites (perisinus, atrial, or junctional).

The occurrence of a sinus pause can be due to the failure of a sinoatrial (SA) node to initiate (sinus arrest) or to conduct the impulse (sinus exit block). Some authors don't distinguish the sinus pause from the sinus arrest, restricting the latter in case of prolonged sinus inactivity, even if no precise definition exists [1]. For practice purposes in this text, we refer to sinus pause in its broadest sense.

Electrocardiographically the sinus impulse is only recorded once it has left the sinus node and activated the atrium, thereby resulting in the P wave. The presence of delay or block in conduction at the SA junction can be detected

by calculation of certain rhythmic sequences involving the pause and the P-P intervals [2].

In *sinus arrest* there is a failure of impulse formation within the sinus node, disappointing the timing of SA node discharge. In this case the underlying rhythm would not resume on time after the pause; the long cycle has no mathematical relation with the basic P-P interval but is random in duration, often interrupted by escape beats or rhythm.

In *sinus exit block,* an electrical impulse is initiated by the SA node but not conducted to the atria because it is blocked within the SA node or the sinoatrial junction. The dropped beats may occur sporadically or in regularly recurring patterns as fixed block. In the presence of a regular basic sinus rhythm, SA block can almost always be distinguished from sinus arrest because the sinus block generating pause is mathematically related to the baseline P-P interval (see later in the text).

Sinoatrial exit block can be divided into three types (first, second, and third degrees), analogous to those occurring at the atrioventricular (AV) node. Being characterized by a prolongation of the sinoatrial conduction time (SACT), the first SA exit block cannot be recognized on the surface ECG.

The second-degree exit block is further classified into type I (SA block with Wenckebach conduction) and type II (SA Mobitz II). *Type I block* is characterized by the decremental progressive lengthening of the conduction between the sinus node and the atria, until a sinus impulse is not conducted to the atria. The classical criteria for the diagnosis of SA Wenckebach conduction are: (1) The P-P interval following the dropped SA impulse is larger than the interval preceding it. This phenomenon is common to all Wenckebach forms, even in the most atypical, and it is due to the fact that the lengthening of SA conduction is present at the beginning of the sequence (the second beat in typical series) [3]. (2) The P-P interval including a blocked SA impulse is shorter than double (or multiple in case of more than one consecutively dropped beat) the distance of the P-P interval preceding it. (3) There is a progressive diminution of the P-P intervals until the pause. The pause generated in a Wenckebach series is twice the sinus cycle minus the sum of the increments of conduction delay at each cycle. However, the P-P interval doesn't accurately reflect the sinus interval, as it has been modified by varying SA conduction times.

For this reason, the duration of presumed sinus cycle may be calculated on the basis of Wenckebach principle periodicity, by dividing the total duration of the period by the number of visible cycles + 1 (sinus impulses which are conducted after a long pause will probably have SA intervals of similar length, i.e., they are corresponding impulses. The isoconduction interval between these corresponding impulses will be the same at both sinus and atrial levels) [2].

Type II SA block shows a failed conduction of a sinus impulse without previous prolongation of SCAT. For this reason the pattern of type II block is characterized by the following: (1) a P-P interval following the dropped SA impulse is not significantly larger than the interval preceding it (this is the most important criterion for diagnosis) [3], (2) the P-P interval including a blocked SA impulse is an exact multiple of the P to P cycle length, and (3) the P-P intervals until the pause are constant.

In the presence of concomitant sinus arrhythmia causing beat to beat variations, it could be impossible to distinguish between sinus arrest and SA exit block because of the presence of the variable and unpredictable long intervals without mathematical relation to short P-P intervals (which are not constant). In this case the ECG panel may be categorized as a *pathological or chaotic sinus arrhythmia* usually associated with sinus bradycardia and representing another sign of underlying sinus node dysfunction [4].

Sinoatrial 2:1 block is a pattern that may be suspected in the presence of severe sinus bradycardia on ECG (usually <40 bpm). This pattern of SA exit block resembles a severe sinus bradycardia but may be distinguishable from it because in SA 2:1 block, the acceleration and deceleration of the sinus rhythm do not occur progressively. For diagnostic purposes, it is useful to have a more prolonged ECG recording to follow the onset/termination of the bradycardia or the

observation of a sudden heart rate doubling during atropine test.

High-degree type II sinoatrial block – occasionally more than one sinus impulse in succession fails to reach the atrium, and two or three successive P waves are dropped, giving a 3:1 or 4:1 exit block and a long pause. The diagnosis is possible only in the presence of pause exactly multiple of an underlying regular sinus cycle. Usually it is difficult because this long pause is interrupted by the intervention of escaped beats/rhythm.

The third-degree (or complete) SA exit block is a term used to describe a complete absence of P waves because no SA node impulse is conducted to the atria. ECG shows an escape rhythm from a lower pacemaker site after a sinus pause, and so it is not distinguishable from a sinus arrest.

The occurrence of a sinus pause (or a long P-P interval) on ECG may result also from mechanisms that should be differentiated: marked sinus arrhythmia, sinus suppression after ectopic premature (often atrial) impulses even blocked or conducted, overdrive suppression after ectopic tachycardia, and single reciprocating "echo" P waves.

Respiratory sinus arrhythmia can be easily recognized because the cyclic lengthening of P-P interval is usually gradual and phasic; on the other hand, non-respiratory sinus arrhythmia presents variable and unpredictable long P-P intervals with different durations and no mathematical relationship with short P-P intervals.

Clinical Presentation: The Sick Sinus Syndrome

SA exit block may be chronic but often occurs as intermittent episodes, so patients may have normal sinus rhythm for several days or weeks between episodes. Furthermore, patients with SA block usually have additional rhythm disturbance because this arrhythmia is included in a broader clinical scenario, the so-called sinus node dysfunction or sick sinus syndrome.

Sick sinus syndrome (SSS) is a term used to describe the clinical manifestations associated with a collection of cardiac rhythm disturbances marked by sinus node inability (sinus node dysfunction) to generate an atrial rate matching the body's physiologic requirements [5]. When SND is associated with symptoms or prolonged asystole, it is referred as SSS. Sick sinus syndrome is not a disease with a single etiology and pathogenesis.

Abnormalities encompassed in this syndrome include various bradyarrhythmias such as sinus bradycardia, sinus arrest with or without escape rhythm, or sinus exit block, associated or not with supraventricular tachyarrhythmias.

When complicating supraventricular arrhythmias are present, the condition is termed "the syndrome of alternating bradycardia and tachycardia" or simply the "bradycardia-tachycardia syndrome" (BTS) [6]. This syndrome is more common in older patients with advanced sick sinus syndrome. The most common tachyarrhythmias are atrial fibrillation and atrial flutter [7, 8]. It is argued that different electrophysiological mechanisms may be responsible for BTS: bradycardia associated with SND may favor reentrant beats and related tachycardias, while many evidences suggest that atrial fibrillation and atrial flutter can lead to atrial remodeling and subsequent SND [9, 10].

Clinically, SSS may produce a variety of ECG manifestations consisting in inappropriate sinus bradycardia, SA exit block or sinus arrest, prolonged sinus arrest with failing ectopic pacemaker, persistent atrial or atrioventricular escape rhythm, episodes of alternating supraventricular tachyarrhythmias with bradyarrhythmias, and long pause following cardioversion of atrial tachyarrhythmia.

Chronotropic incompetence (CI) is another manifestation of SSS. It is defined as a failure to achieve 85 % of the maximum predicted heart rate during exercise testing.

Prevalence of Sinus Node Dysfunction and SSS

Bradycardia is frequently seen in healthy individuals, especially in trained subjects, with a waking hour rate usually >40 bpm [11]. In highly trained athletes, a slower heart rate (30–35 bpm)

may be seen, so that only profound sinus bradycardia and/or marked sinus arrhythmia (heart rate less than 30 bpm and/or pauses ≥3 s during wake hours) needs to be distinguished from sinus node disease [12].

Heart rate between 30 and 35 bpm, asymptomatic sinus pauses lasting between 2 and 3 s, escape junctional beats or rhythms (with functional AV dissociation), and first- and second-degree atrioventricular nodal block are normal variants during sleep [11].

Even if asystole longer than 3 s and heart rate <20 bpm are usually secondary to SND [13], this condition per se is not sufficient to define a clinical disorder like SSS (a pause of at least ≥6 s is necessary to cause symptoms) [14, 15].

The exact incidence of SND is unknown. It may develop at any age, but it is primarily diseased in the elderly with the average age of occurrence being about 68 years [16, 17]. In young patients it is often related to underlying heart disease or previous cardiac surgery. The natural history of SND may be highly variable, although it tends to be progressive. SSS approximately affects 1 in 600 cardiac patients older than 65 years [18] and for this reason is more prevalent in countries with longer life expectancies. Currently, in Europe, SSS represents the second leading cause of permanent pacemaker implantation after AV block [19–24].

Sign and Symptoms

All symptoms would be uncommon in the early disease course. They are related to low cardiac output that occurs with brady- and/or tachyarrhythmias, causing acute end-organ hypoperfusion or worsening preexisting organ failure (heart failure, angina pectoris, or cerebral vascular accident). The extent of bradycardia or length of pause that results in symptoms however varies among individuals because stroke volume, peripheral resistance, and local vascular patency also contribute to the extent of regional blood flow at any heart rate.

Cerebral hypoperfusion is the most common manifestation often causing abrupt symptoms like near fainting or syncopal episodes. However, many patients may have mild and nonspecific symptoms for months or years like dizziness, light-headedness, confusion, exertional fatigue, dyspnea, weakness, nocturnal wakefulness, and vague digestive disturbance. Patients with BTS may have also palpitations or peripheral thromboembolic accidents related to atrial flutter or atrial fibrillation episodes.

Causes of SSS

Sometimes SND is associated with abnormalities intrinsic to the sinus node that include degenerative age-related fibrosis (idiopathic SSS), ischemia-induced fibrosis (e.g., coronary artery disease, arteritis), infiltrative disease process (amyloidosis, sarcoidosis, connective tissue disease, hemochromatosis, tumors), remodeling of the SA node associated with heart failure or atrial fibrillation, primary ion channel dysfunction (familiar or congenital form), and surgical injury.

Moreover, many extrinsic factors, usually transient and reversible, can alter SA node function, mimicking the SSS (or exacerbating an underlying subclinical intrinsic SA node dysfunction): autonomic dysfunction of vagal reflex (vasovagal, situational, carotid sinus hypersensitivity), increased vagal tone (training, sleep, anesthesia, and surgical interventions), metabolic disturbances (electrolyte abnormalities like hypo-/hyperkalemia, hypocalcemia, hypothermia, hypoxia, hypothyroidism), obstructive sleep apnea, drugs (beta-blockers, calcium channel blockers, digoxin, antipsychotic agents, membrane-active antiarrhythmics like class I and preferentially IA and IC, amiodarone, sympatholytic medication, morphine), increased intracranial pressure, and temporal lobe seizure.

Clinical Diagnosis: Diagnostic Workup

The cornerstone for the diagnosis of SSS is the correlation of end-organ perfusion symptoms with the occurrence of bradyarrhythmias, with or without tachycardia. The presence of the sinus node dysfunction should always trigger a proper workup to rule out reversible extrinsic causes before the definitive diagnosis of SSS is made. For this purpose, a full review of systemic conditions and medications used is necessary as these conditions could be potential reversible causes of SSS.

Since manifestations of SSS may be erratic especially in the early stages, the resting ECG could not reveal abnormal heart rhythm. Furthermore, symptoms are often nonspecific (e.g., dizziness, fatigue, weakness, or heart failure) and in common with other disorders occurring with progressive aging.

Depending on the severity of symptoms and the overall clinical risk stratification, this can be done by in-hospital telemetry or by outpatient cardiac monitoring devices.

The true challenge in SSS is to capture a recording of the cardiac rhythm during symptoms, so that the type of device that has to be chosen depends on the frequency of symptoms. Ambulatory Holter monitoring that allows recording for 24–48 h may be sufficient for patients with almost daily symptoms. In other patients with intermittent symptoms, longer monitoring is often necessary. Recently, several new external long-term devices have been developed:

- *Patch-type* long-term external Holter recorders using comfortable adhesive patches that enable a continuous single-lead monitoring up to 14 days.
- *Event recorders* (post-event/symptom) are small portable devices applied to the patient's skin and manually activated whenever symptoms are experienced. These devices usually provide one-lead electrocardiographic recording for 30–90 s (with up to 6–10 min of memory storage capacity) that needs to be transmitted transtelephonically or via mail to a central monitoring site (healthcare provider) for validation and analysis. Recently, a new generation of event recorder "smartphone-based" device has been launched for this purpose (AliveCor). However, this type of monitoring has several limitations because it's useless in patients with syncope or short arrhythmias and has no pre-event data.
- *External loop recorders* (looping memory system or continuous loop recorder) are devices connected continuously to the patient by means of skin ECG electrodes and equipped with a memory loop. The device has a built-in looping memory in which the ECG signal is steadily stored, with the oldest ECG samples being overwritten by the newest (typically 10–20 min in duration). When activated (patient activated or by auto-trigger algorithm), data are stored for a programmable fixed amount of time before and after the activation. Recently, a new generation of wearable garment-inserted ECG system has been developed (Nuubo system).
- *Mobile cardiac outpatient telemetry (MCOT) systems* are devices made up of an external loop recorder with a portable receiver that allows wireless transmission of ECG data (non-real time or in real time) to a remote operating center or to a dedicated website via the mobile telephone line or Internet. Typical duration use is 1–4 weeks. However, nowadays appropriate use guidelines for this type of ECG monitor have not yet been developed.

Implantable loop recorders (ILR) are leadless subcutaneously implanted arrhythmia monitoring devices requiring a minor invasive procedure through a small skin incision of about 2 cm in the left precordial region. A single-lead ECG signal is recorded through two electrodes within the device. The memory loop is activated by the patient through an external activator or even automatically (auto-trigger algorithm). ILR can be used by patients for a long period of time (up to 3 years with the newest devices) until a diagnosis is reached or the battery runs down. This type of monitoring is considered when all other investigation results are inconclusive.

Other tests to identify the presence of SND may include the exercise testing and intracardiac electrophysiologic tests.

Exercise testing may confirm the diagnosis of chronotropic incompetence but is not useful for detecting the arrhythmias that occur in SSS.

Electrophysiological study (EPS) may be sometimes helpful in patients with highly suspected SSS and no symptom-rhythm correlation demonstration after prolonged cardiac monitoring. It is no longer routinely recommended for diagnosis because of its poor sensitivity and specificity (about 50 %) [25]. The two most

common EPS tests for sinus node function measure are:

1. The sinus node recovery time (SNRT), i.e., the time taken for the sinus rhythm to resume after 30 s or 1 min of overdrive atrial pacing. This interval is measured in the high lateral right atrium from the last paced beat to the first spontaneous sinus beat. This test is based on the assumption that automaticity suppressed by overdrive recovers less rapidly when the SA node is dysfunctional, so the longer the sinus node takes to recover, the more abnormal sinus node function is evident. Its poor diagnostic yield may be due to the fact that sinus recovery time is a more complex event and many factors besides automaticity are involved. A delay of longer than 1500 ms is abnormal. The corrected value (CSNRT) can be determined by subtracting the intrinsic sinus cycle length from the SNRT value: values longer than 550 ms suggest sinus node dysfunction.
2. The other EPS test for sinus node function measure is the sinoatrial conduction time (SACT) used for detecting delayed conduction between the sinus node and surrounding atrial tissue. This technique involves resetting the sinus node by an eight-beat period of atrial pacing at rates just above sinus *(Narula protocol):* the difference between the post-pacing pause and the sinus cycle length would equal to the SACT. SACT values greater than 120 ms are considered abnormal.

Our approach to the diagnosis of SSS is summarized as follows:

A. Perform a comprehensive history and physical examination.
B. Carefully review for systemic conditions and medications used as potential remediable causes for apparent SSS.
C. Obtain a resting ECG and if nondiagnostic proceed with in-hospital telemetry or ambulatory ECG monitoring to identify episode of bradycardia and eventually correlated symptoms. The type of monitoring depends on the severity and frequency of symptoms and the overall clinical risk stratification.
D. In a symptomatic patient in whom ECG events compatible with SSS fail to correlate with symptoms, consider implantable loop recorder or additional laboratory testing (exercise stress testing, electrophysiological study, carotid sinus massage, tilt test).

Treatment

Nowadays there are no medications that reliably increase the heart rate in patients with bradyarrhythmias. Cardiac pacing therapy through an artificial pacemaker is the only choice.

As discussed above, early identification of a potential reversible cause is the first step of treatment. Discontinuation or dose reduction of nonessential concomitant drugs affecting sinus node function is recommended to see whether normal sinus function returns. All other medical conditions which may precipitate the SSS should be treated.

If bradyarrhythmia persists, indications for cardiac pacing therapy should be evaluated. The cause-effect correlation between symptoms and bradyarrhythmias is an essential critical step when positive effects of pacemaker placement are evaluated. Indeed, there is no evidence that cardiac pacing prolongs survival in patients with SND [26–28]. The primary goals of pacemaker placement are symptom relief and improved quality of life.

However, in clinical practice some patients affected by sinus node disease may not have a clear symptom-ECG correlation because of the slow and erratic course of syndrome and frequent comorbidities. In such circumstances, in the absence of other symptoms clearly attributable to SND, the mechanism of intermittent clinical significant events like syncope remains uncertain as other competitive causes (e.g., autonomic dysfunction) may play an important role. From a practical perspective, when a competitive diagnosis can be ruled out (after head-up tilt testing, carotid sinus massage, and eventually an EPS excluding a very prolonged csnrt, i.e.,

Table 22.1 The following table is a summary of the main recommendations in the European Society of Cardiology guidelines on cardiac pacing (ESC guidelines on cardiac pacing 2013)

Recommendations	Class	Level
Pacing is indicated when symptoms can clearly be attributed to persistent bradycardia or to documented (intermittent) sinus arrest or sinoatrial block	I	B
Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive	IIb	C
Pacing is not indicated in patients with bradycardia which is asymptomatic or due to reversible causes	III	C
Dual-chamber pacing mode with preservation of spontaneous AV conduction is indicated for reducing the risk of AF and stroke, avoiding PM syndrome and improving quality of life	I	A (vs. VVI) B (vs. AAI)

>800 ms), cardiac pacing may be reasonable in patients with syncope and intrinsic node disease with documentation of significant asymptomatic pauses (>6 s).

Table 22.1 lists the latest practice recommendations with level of evidence from the European Society of Cardiology task force on cardiac pacing (2013) in patients with sinus node disease [25].

In SSS dual-chamber pacing mode with preservation of spontaneous AV conduction (AV delay management algorithm) is the first choice. A recent study [29] suggests that dual-chamber pacing mode, compared to AAI and VVI pacing mode, confers a modest reduction in AF and stroke (but not in hospitalization and death) and reduces the risk of PM syndrome (compared to VVI pacing mode) which is associated with a reduction in quality of life. Furthermore, patients with sick sinus syndrome have also a slightly increased risk of developing atrioventricular block (0.6–1.9 %/year) [29–32]. This result supports the advantages of dual-chamber over single-chamber pacing mode in this condition.

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Atrioventricular Blocks

23

Andrea Romandini and Marco Morelli

23.1 Case Report

A 69-year-old man was referred to our cardiology department from the ER because of the 4-day appearance of asthenia and dyspnea (NYHA III), associated with sporadic precordial pains. At the entrance, ECG revealed a total third-degree atrioventricular block with a ventricular escape rhythm of 35 bpm. There was atrioventricular dissociation with atrial rate faster than the ventricular one and left bundle branch block (LBBB) QRS type.

Medical History and Cardiovascular Risk Factors

- Risks factors: arterial hypertension, cigarette smoking, dyslipidemia, and impaired glucose tolerance.
- 1992: aortic valve replacement with a mechanical prosthesis Starr-Edwards n.27.
- 1996: transient ischemic attack (TIA).
- 2009: admitted to cardiology department due to fainting. In that circumstance, an electrophysiological study showed a second-degree atrioventricular block induction located above the His bundle; therefore, it was considered benign.
- 2010: access to the emergency room for a paroxysmal tachycardia associated with asthenia. At ECG frequent ventricular premature beats were recorded, and the patient was addressed to take amiodarone therapy.

Allergies

None

Medications

VKA, ARB, ASA 100 mg od, amiodarone 200 mg od, and furosemide 25 mg od

Vital Signs

Temperature, 36.5 °C; heart rate, 35 bpm; arterial blood pressure, 115/70 mmHg; respiratory rate, 16 breaths/min; and oxygen saturation, 99 %

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Physical Examination

- General appearance: well developed, well nourished, alert, and cooperative
- Lungs: clear to auscultation and percussion without rales, rhonchi, wheezing, or diminished breath sounds
- Cardiovascular: Normal S1 and S2. No S3, S4, or murmurs. Regular bradycardic rhythm. No peripheral edema, cyanosis, or pallor. Warm and well-perfused extremities
- Abdomen: Positive bowel sounds. Soft, nondistended. No guarding or rebound. No masses

Routine Laboratory Tests

Tests were substantially normal (hemoglobin 13.6 g/dl, white blood cells 7840/mmc, creatinine 1.05 mg/dl, potassium 4.6 mEq/l, sodium 140 mEq/l, magnesium 1.6 mg/dl). Creatine kinase-MB and troponin I were within normal limits, while brain natriuretic peptide (BNP) was slightly increased (499 pg/ml).

Instrumental Examination

ECG (Fig. 23.1a, b) shows a third-degree atrioventricular block with slow ventricular escape rhythm (35 bpm); There is a clear atrioventricular dissociation with atrial rate faster than the ventricular. QRS has a left bundle branch block (LBBB) pattern.

Echocardiogram showed normal dimensions and function of cardiac chambers (ejection fraction 55–60 %), aortic valve prosthesis normally functioning, mild mitral regurgitation, and mild tricuspid regurgitation with a normal pulmonary artery systolic pressure.

Clinical Course and Therapeutic Management

A continuous electrocardiographic monitoring was placed, and we started isoproterenol infusion that increased HR up to 44 bpm (0.02 mcg/kg/min). After a complete diagnostic workup aimed to

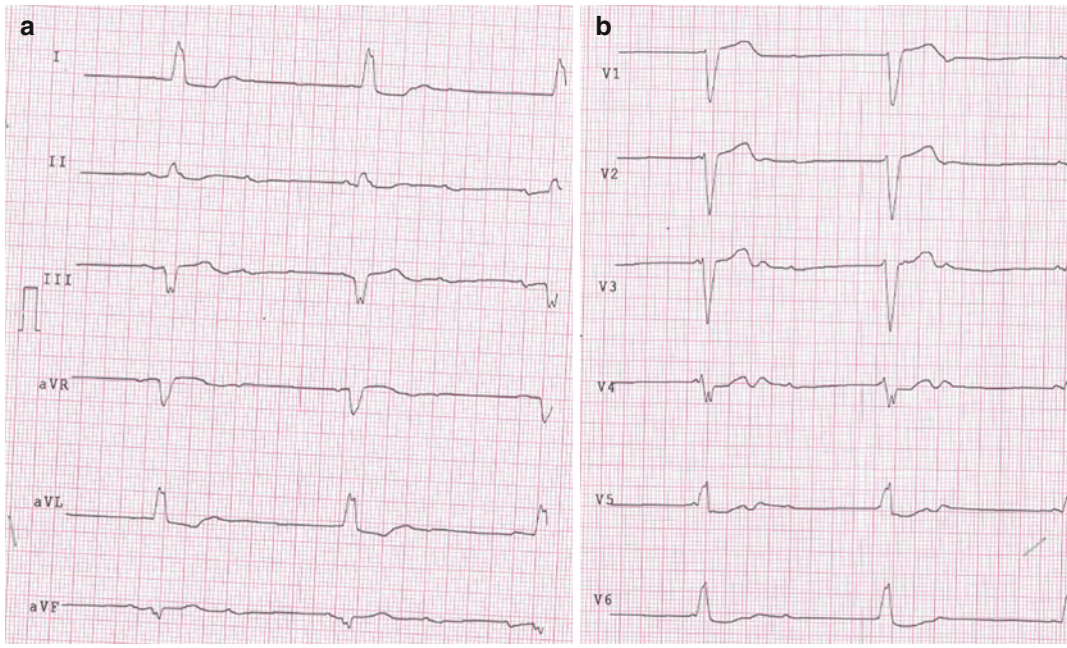

Fig. 23.1 (**a, b**) A third-degree atrioventricular block with slow ventricular escape rhythm (35 bpm) is shown. Atrioventricular dissociation with atrial rate faster than the ventricular rate is clearly visible. QRS has a left bundle branch block (LBBB) pattern

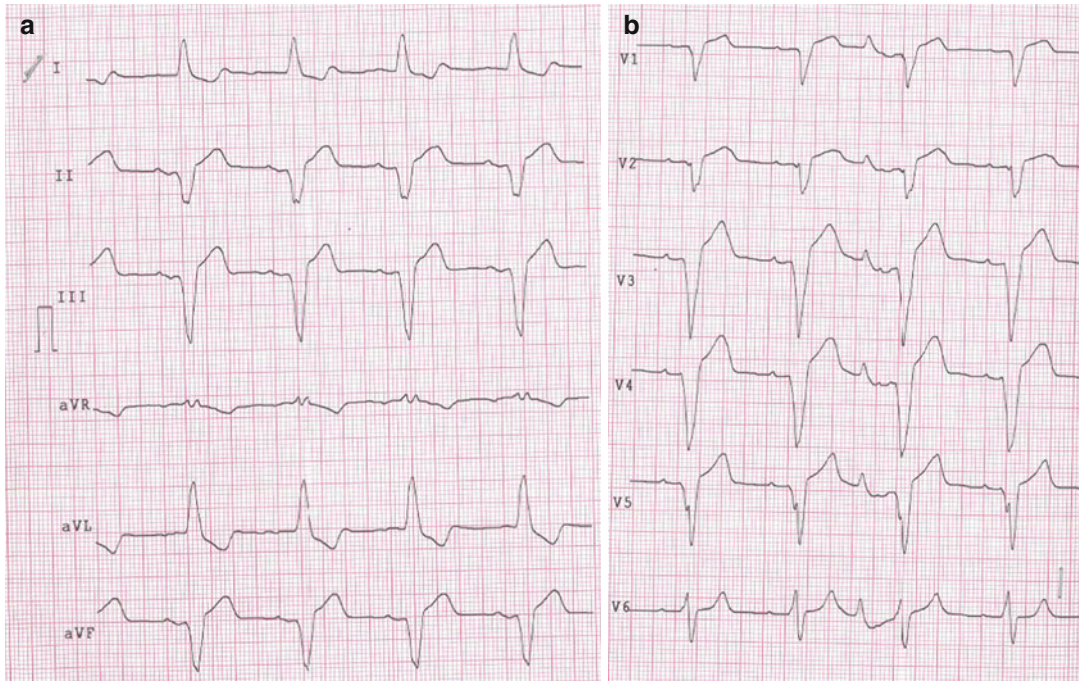

Fig. 23.2 (**a**) Atrial flutter with third-degree atrioventricular block and junctional escape rhythm. (**b**) The same patient after cardioversion: sinus rhythm with AV dissociation is shown

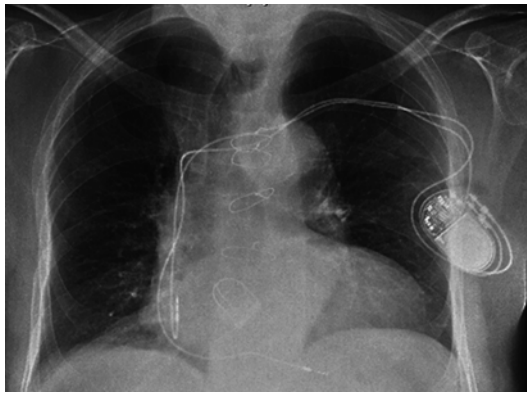

Fig. 23.3 Chest X-ray showing normal cardiac and pulmonary dimensions, correct positioning of the pacemaker leads, and no complications related to the surgery procedure

exclude secondary reversible causes for AV block, a dual-chamber pacemaker was implanted the day after hospital admission. After implantation ECG showed sinusal P waves followed by paced QRS complexes (Fig. 23.2a, b). The chest X-ray showed the following things: the normal cardiac and pulmonary dimensions, and a correct positioning of the pacemaker leads, and no complications related to the surgery procedure.

On the 3rd day, the patient was discharged.

A follow-up visit was performed 1 month later. The patient was completely asymptomatic. Physical examination was normal. ECG showed regular rhythm with paced QRS following sinusal P waves (VDD mode). PMK was interrogated and did not show any malfunction.

23.2 Atrioventricular Blocks

An AV block is present when the atrial impulse is conducted with delay or is not conducted at all to the ventricle. The block can occur within the AV node, His bundle, or bundle branches. In the first-degree heart block, conduction time is prolonged but all impulses are conducted. Second-degree heart block is characterized by occasional or repetitive sudden block of conduction of an impulse. In third-degree AV block, no impulses are conducted from atria to ventricles. The term *advanced heart block* indicates blockage of two

or more consecutive impulses. Retrograde conduction can occur in the presence of anterograde AV block [1, 2].

First-Degree AV Block

During first-degree AV block, every atrial impulse conducts to the ventricles and a regular ventricular rate is present. The prolonged PR interval exceeds 200 ms in adults. The conduction delay can be located within the AV node (A–H interval prolonged), in the His–Purkinje system (H–V interval prolonged), or both. If the QRS complex has a normal width, the AV delay most likely resides within the AV node and rarely within the His bundle. On the contrary, if the QRS has a bundle branch block pattern, the conduction delay may be within the AV node or His–Purkinje system as well. Enhancement of vagal tone by carotid massage can cause first-degree AV nodal block to progress to type I second-degree AV block [2].

Second-Degree AV Block

In second-degree AV block, the nonconducted P wave can be intermittent and the preceding PR interval duration may be fixed or prolonged. In this type of block, the P–QRS relationship is not random. Mobitz type I (Luciani–Wenckebach) is characterized by progressive PR prolongation until a nonconducted P wave. In contrast, in Mobitz type II, the PR interval remains constant before a P wave is blocked [3, 4].

During Mobitz type I block, the conduction time delay is longer in the second beat of the Wenckebach group; meanwhile, prolonged conduction time decreases progressively in the subsequent beats. The consequence is that the interval between the successive beats progressively decreases, although the conduction time increases. The RR interval produced by the block is shorter than the double of the RR interval that precedes the block impulse (the shortest interval). The R–R interval that follows the nonconducted beat (the first beat of the new Wenckebach group) is longer than the cycle preceding the blocked impulse [5].

Type II AV block is often a precursor of syncope and complete AV block, because it is more likely to be sub-Hisian. Type I AV block with a normal QRS complex generally does not progress to more advanced forms of AV conduction disturbances. In elderly people, type I AV block may be associated with a clinical course similar to that seen in type II.

In the acute coronary syndromes (ACS), type I AV block generally develops with inferior infarction, is transient, and does not require temporary pacing [4].

Type II AV block occurs usually in the setting of an anterior myocardial infarction, can require temporary or permanent pacing, and is associated with a high mortality rate.

A high-degree AV block can occur also in patients with acute inferior myocardial infarction (MI) and is associated with an extended myocardial damage and a higher mortality rate than those without AV block. All types of AV blocks in the setting of an acute MI can be reversible within 14–21 days.

In type I AV block with a normal QRS duration, the conduction delay is likely to be at the AV node level proximal to the His bundle. A type I intra-Hisian block is uncommon. Type II AV block, particularly in association with a bundle branch block, may be localized within or below the His–Purkinje system. Type I AV block in a patient with a bundle branch block can be caused by a block in the AV node or in the His–Purkinje system as well [2].

Type 2:1 AV block can be due to type I or type II AV block.

Abrupt transient alterations in autonomic tone can also cause sudden block of one or more P waves without altering the PR interval of the conducted P wave before or after the block. Such condition is a typical normal finding at night during sleep. Thus, apparent type II AV block would be produced at the AV node. Increased vagal tone, producing an AV block, usually lengthens the P–P interval at the same time [4].

Vagal stimulation generally increases and vagolytic agents decrease the extent of type I AV

block. Atropine can minimally improve conduction in the AV node and markedly faster sinus rate, which may result in higher AV block degree. Counterwise, carotid sinus massage generally improves and atropine worsens AV conduction in patients with a conduction block within or below the His bundle.

Similarly, exercise or isoproterenol by increasing the sinus rate and improving AV conduction may resolve the supra-Hisian block and impair sub-Hisian one [2].

First-degree and type I second-degree AV block can occur in normal healthy children; a Wenckebach AV block can be also normal in well-trained athletes, probably related to a higher vagal tone at rest.

Third-Degree AV Block

In the total AV block, no atrial activity is conducted to the ventricles; the atria and ventricles are controlled by independent pacemakers (atrioventricular dissociation) [4]. The atrial pacemaker can be sinus or ectopic (tachycardia, flutter, or fibrillation) (Fig. 23.4).

Complete AV block may arise at AV node level (usually congenital), within the bundle of His, or distally below the His (usually acquired).

The ventricular focus that arise below the region of the block. Sites of ventricular pacemaker activity that are in or closer to the His bundle are more stable and can produce a faster escape rate than those located distally in the ventricular conduction system. The ventricular escape rate in acquired total heart block is less than 40 beats/min but can be faster in congenital complete AV block [5].

Blocks proximal to the His bundle generally exhibit normal QRS complexes and rates of 40–60 beats/min.

In patients with AV nodal block, atropine usually speeds both atrial and ventricular rates. Exercise can reduce the extent of AV nodal block.

An acquired complete AV block is more often distal to the bundle of His because of trifascicular conduction disturbance. The QRS complex is abnormal (wide QRS complex), and the ventricular rate is less than 40 beats/min. A hereditary form caused by degeneration of the His bundle and bundle branches has been linked to the *SCN5A* gene [2].

Paroxysmal AV block can be caused by a too strong response of the AV node to vagotonic reflexes. Surgery, electrolyte disturbances, myoendocarditis, tumors, Chagas disease, rheumatoid nodules, calcific aortic stenosis, myxedema, polymyositis, infiltrative processes (e.g., amyloidosis, sarcoidosis, scleroderma), and many other common and unusual conditions can produce AV block.

In children, the most common cause of AV block is congenital. Children are most often asymptomatic, but in some cases symptoms develop and pacemaker implantation becomes necessary. Mortality from congenital AV block is highest in the neonatal period, decreases during childhood and adolescence, and increases slowly later. Syncope can occur in patients with congenital heart block at any age. It is difficult to predict the prognosis. A persistent heart rate at rest of 50 beats/min or less correlates with the incidence of syncope in children with congenital complete AV block [2].

> The association of a long PR plus a right bundle branch block and left anterior hemiblock is called bifascicular block.

General Management

First- or second-degree AV blocks are usually asymptomatic. Sometimes clinical manifestations of first- and second-degree AV block consist of palpitations or subjective feelings of the heart's "missing a beat." Persistent 2:1 AV block can produce symptoms of chronic bradycardia. Complete AV block can be accompanied by signs and symptoms of reduced cardiac output, syncope or presyncope, angina, or palpitations from ventricular tachyarrhythmias [2].

Death in patients with untreated atrioventricular (AV) block is due not only to heart failure

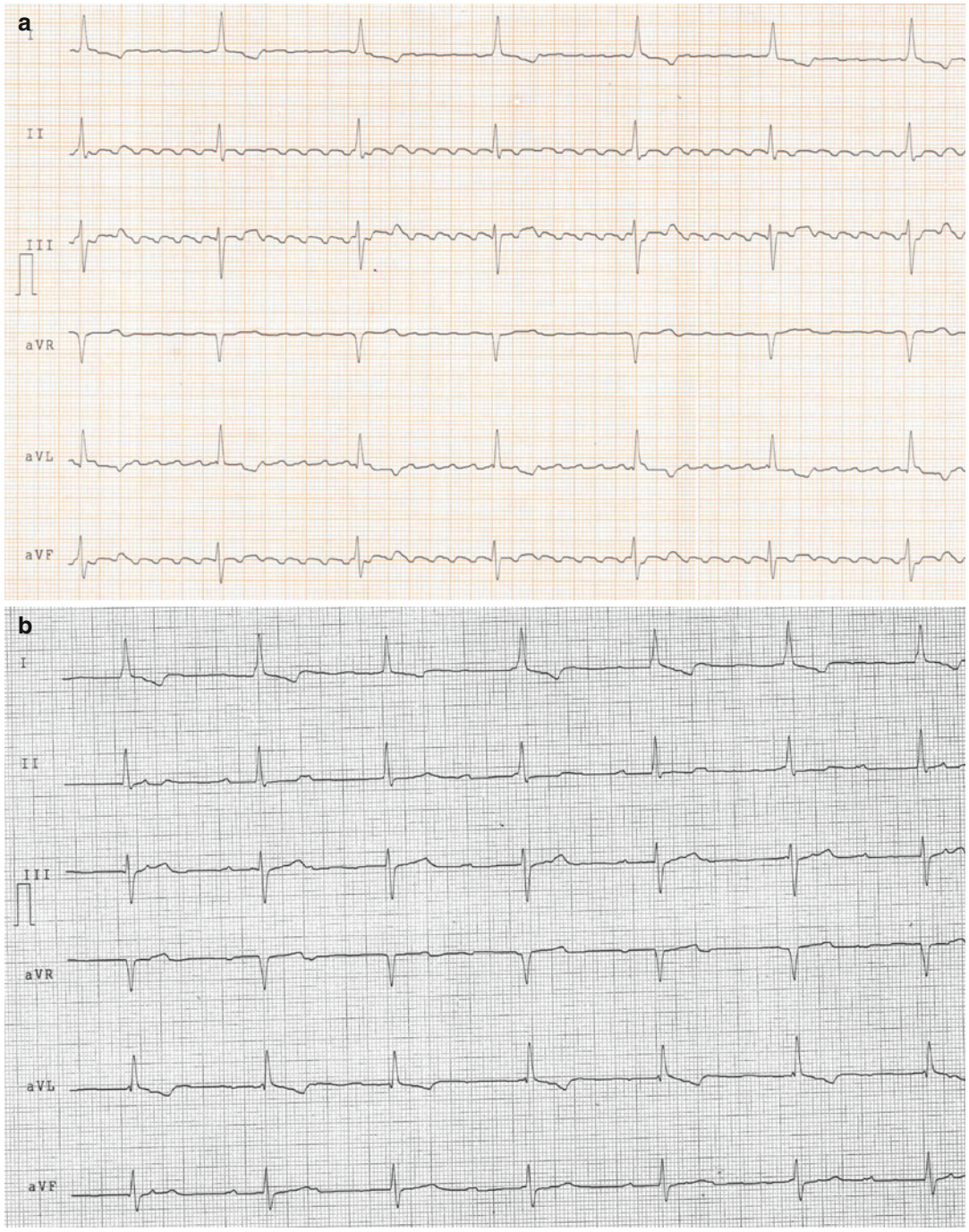

Fig. 23.4 The ventricular rate arise below the region of the block. The atrial pacemaker can be (**a**) ectopic (tachycardia, flutter, or fibrillation) or (**b**) sinus

(HF) secondary to low cardiac output but mainly to sudden cardiac death caused by prolonged asystole or bradycardia-triggered ventricular tachyarrhythmia [3].

During early in-hospital phase, when conduction blocks are likely to be evanescent, vagolytic agents (such as atropine) are useful for patients who have AV nodal disturbances, whereas cate-

cholamines (such as isoproterenol) can be used transiently to treat patients who have heart block at any site. Isoproterenol should be used with extreme caution in patients who have acute myocardial infarction. The use of transcutaneous or temporary transvenous pacing is preferable [2].

For symptomatic AV block or high-grade AV block (e.g., infra-Hisian, type II AV block, third-degree heart block not caused by congenital AV block), permanent pacemaker is the treatment of choice.

23.3 Guidelines

Diagnosis

Early identification of a potentially reversible cause (drug effects, acute myocardial infarction, intoxication, electrolyte disorders) is the first step toward treatment.

As long as the stroke volume increases in order to compensate for the decrease in heart rate, patients with bradycardia can remain completely asymptomatic. First-degree AV block and type I second-degree AV block with marked PR prolongation (≥0.3 s) can lead to symptoms, because atrial contraction occurs very early in diastole overlapping with early diastolic filling and diastolic mitral regurgitation may occur between the end of atrial filling and the onset of ventricular contraction.

While the permanent forms of AV blocks are caused by an intrinsic disease of the AV conduction system, the etiology of intermittent block can be difficult to determine. The diagnosis of intermittent AV block is often only presumed but not documented by ECG [6].

AV block can be asymptomatic in young, healthy individuals or during sleep, but patients with sustained or frequent bradyarrhythmia are often symptomatic (e.g., easy fatigability, reduced exercise capacity, symptoms of HF, irritability, lassitude, and inability to concentrate). Dizziness, presyncope, and syncope, due to a sudden decrease in cerebral blood flow, are common symptoms with intermittent severe forms of AV block.

The diagnosis of AV block is usually made from standard ECG when persistent. Prolonged electrocardiogram monitoring strategy [standard 24 h Holter ECG or implantable loop recorder (ILR)] may be needed to diagnose an intermittent AV block (Table 23.1). When an AV block is suspected but not documented, provocative testing or an electrophysiological study (EPS) may also be needed (Table 23.2). Since there is no defined heart rate below which treatment is indicated, correlation between symptoms and bradyarrhythmia is essential to give the indication for permanent cardiac pacing.

Tilt table testing and carotid sinus massage are indicated when reflex syncope is suspected in the setting of an atypical presentation. Exercise testing is indicated in patients who experience syncope during or shortly after exertion.

Table 23.1 Prolonged electrocardiogram monitoring strategy (standard 24 h Holter ECG or implantable loop recorder) may be needed to diagnose an intermittent AV block

Prolonged electrocardiogram monitoring strategy	Provocative test strategy
Holter	Carotid sinus massage
External loop recorder	Tilt table test
Remote at-home telemetry	Electrophysiological study
Implantable loop recorder	Exercise test

Table 23.2 When an AV block is suspected but not documented, provocative testing or an electrophysiological study (EPS) may also be needed

Frequency of symptoms	Suggested ECG monitoring technique
Daily	24 h Holter, in-hospital telemetric monitoring
Every 2–3 days	48–72 h Holter, in-hospital telemetric monitoring
Every week	7–day Holter or external loop recorder
Every month	14–30-day external loop recorder
Less than once per month	Implantable loop recorder

Indications for Pacing in Patients with Persistent Acquired Atrioventricular Block

- Pacing is not indicated in patients with AV block which is due to reversible causes (class I, level C).
- Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS (class IIa, level C).
- Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptom (class I, level C).

In patients with third- or second-degree type 2 AV block, pacing prevents recurrence of syncope and improves survival in adults [3].

Intermittent AV Block

Persistent AV block clearly indicates an intrinsic conduction system disease. On the other hand, the meaning of intermittent block is less clear, resulting from variable contributions of intrinsic and extrinsic mechanisms.

Intermittent/paroxysmal AV block that occurs in patients with underlying heart disease and/or BBB is usually considered as a manifestation of intrinsic disease of the AV conduction system. The diagnosis of intrinsic AV block is supported by an infra-Hisian block documented at the EPS and, if the block onset is located after atrial or ventricular premature beats, during increased heart rate (tachy-dependent AV block) or decreased heart rate (brady-dependent AV block).

During the intermittent block, the cardiac rhythm may become dependent on ectopic, unreliable, pacemaker sites that often have slow rates (25–40 bpm). Syncope can occur due to long delay before ectopic pacemaker sites take over, leading to inadequate cerebral perfusion. In patients with syncope and documented third- or second-degree AV block due to intrinsic disease of the AV conduction system, there is general consensus that pacing prevents recurrence of syncope and may improve survival regardless of documented symptom – ECG correlation [1].

Other types of intermittent AV block include vagal (extrinsic) and idiopathic forms.

In the setting of reflex syncope when ECG–symptom correlation is established, there is evidence that dual-chamber pacing can at least partially prevent recurrences, reducing the syncope burden in patients ≥40 years [6].

In patients with a clinical diagnosis of reflex syncope and asymptomatic pause >6 s, there is weak evidence that cardiac pacing may be effective for the reduction of syncopal recurrences.

In patients with reflex syncope, cardiac pacing should be the last choice in selected patients (e.g., elderly; history of recurrent syncope and frequent injuries, probably due to lack of prodromal symptoms).

As a general rule, for intermittent bradycardia, pacing may be required only for short periods of time; therefore, permanent ventricular stimulation should be avoided through proper device setting.

Indications for Pacing in Intermittent Documented AV Block

Intermittent/paroxysmal AV block (including AF with slow ventricular conduction)

- Pacing is indicated in patients with intermittent/paroxysmal intrinsic third- or second-degree AV block (I; C).

Reflex asystolic syncope

- Pacing should be considered in patients >40 years with recurrent, unpredictable, reflex syncopes and documented symptomatic pause/s due to sinus arrest or AV block or the combination of the two (IIa; B).

Asymptomatic pauses (AV block)
- Pacing should be considered in patients with history of syncope and documentation of asymptomatic pauses >6 s due to sinus arrest, sinus-atrial block, or AV block (IIa; C).
- Pacing is not indicated in reversible causes of AB block (III).

Suspected AV Block in Patient with Syncope and Baseline Bundle Branch Block (BBB)

Electrophysiological study (EPS) should measure the His–ventricular (HV) interval at baseline and during stress by incremental atrial pacing. The progression rate to AV block at 4 years was ≤4 % in patients with HV interval <70 ms, 12 % in those with HV interval of 70–100 ms, and 24 % in those with HV interval >100 ms. The development of intra- or infra-His block at incremental atrial pacing is highly predictive of impending AV block but is rarely observed [3].

In patients with unexplained syncope and bifascicular block, EPS is highly sensitive in identifying patients with intermittent or impending high-degree AV block, though a negative electrophysiological investigation cannot rule out intermittent/paroxysmal AV block as the cause of syncope. Indeed, in patients with negative electrophysiological studies, intermittent or stable AV block was still documented by ILR in about 50 % of cases [3].

The alternating bundle branch block is defined as block in all three fascicles detected on successive ECGs: right bundle branch block (RBBB) and left bundle branch block (LBBB) or RBBB with associated left anterior fascicular block on one ECG and associated left posterior fascicular block on another ECG]. These patients progress quickly toward complete AV block. Therefore, a PM is usually implanted as soon as possible, even in the absence of a history of syncope [3].

Only half of patients with unexplained syncope, basal bundle branch block, and nondiagnostic investigations had a documented AV block during ILR observation. Decision to implant a PM in this setting is determined by an individual risk–benefit evaluation. There are some subgroups of patients who could benefit from this strategy: old patients with unpredictable (no or very short prodromes) and recurrent syncope that expose them to high risk of traumatic injury.

Obviously, for asymptomatic patient with BBB, permanent PM implantation is not indicated.

Indication for Cardiac Pacing in Patients with BBB

- *BBB, unexplained syncope, and abnormal EPS:* Pacing is indicated in patients with syncope, BBB, and positive EPS defined as interval of ≥70 ms, or second- or third-degree His–Purkinje block demonstrated during incremental atrial pacing or with pharmacological stress (I; B).
- *Alternating BBB:* Pacing is indicated in patients with alternating BBB with or without symptoms (I; C).
- *BBB, unexplained syncope, and nondiagnostic investigations:* Pacing may be considered in selected patients with unexplained syncope and BBB [old patients with unpredictable (no or very short prodromes) and recurrent syncope that expose them to high risk of traumatic injury] (IIb; B).
- *Asymptomatic BBB:* Pacing is not indicated for BBB in asymptomatic patients (III).

Choice of Pacing Mode

Dual-chamber pacing is superior over ventricular pacing as regards symptom improvement, while there is evidence of non-superiority about survival and morbidity (hospitalization, HF). On the other hand, bicameral pacing increases complication risk and costs [3].

Acquired AV block: In patients with sinus rhythm, dual-chamber PM should be preferred over single-chamber ventricular pacing for avoiding PM syndrome and improving quality of life [IIa; A].

CRT should be considered if clinical symptoms of HF (NYHA II–III), a wide QRS complex (>120 ms with appearance left BBB like), and a severely reduced LVEF (<35 %) are present [3].

It is advisable that mode-switch algorithm be activated; episodes of AF during follow-up should be assessed (to anticoagulant therapy).

In patient with AF associated with AV block, rate-responsive pacing is associated with better exercise performance, improved daily activities, decreased dyspnea, reduced chest pain and palpitations, and improved quality of life, compared with fixed-rate pacing [3].

Permanent AF and AV block: Ventricular pacing with rate-response function is recommended (I; C).

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Part VIII

Channelopathies

Brugada Syndrome

24

Alessandro Barbarossa and Giulia Pongetti

24.1 Case Report

A 35-year-old man was referred to the emergency room (ER) for acute syncope, at rest, during a febrile state. Its onset was sudden and without any prodromic symptom or convulsion. There was a rapid recovery of consciousness without any neurological impairment and loss of urine. The patient was admitted to our hospital for further investigations.

Medical History and Cardiovascular Risk Factors

- Smoker
- No personal history for cardiovascular disease. Previous routine ECGs recorded for professional sport level resulted normal.
- Positive familiar history for sudden cardiac death (SCD): One 40-year-old cousin suddenly died during sleep.
- The patient had a previous (5 years ago) syncopal episode also at rest, without prodromes, that was not deeply evaluated.

Allergies

None

Medications

None

Vital Signs

- Temperature: 39 °C
- Heart rate: 105 bpm
- Blood pressure: 120/80 mmHg
- Respiratory rate: 18 bpm
- Oxygen saturation while breathing ambient air: 98 %
- Glasgow coma scale (GCS): 15

Physical Examination

- *General*: No acute distress, alert, awake, and well oriented. Normally developed and nourished
- *Head*, *eyes*, *ears*, *nose*, and *throat*: Normocephalic, atraumatic, mucous membranes moist,

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extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- *Neck*: Supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- *Cardiovascular*: Regular rate and rhythm; S1 and S2 are normal; no murmurs, rubs, or gallops; point of maximal intensity non-displaced and non-sustained; no hepatojugular reflux; and capillary refill less than 2 s
- *Lungs*: No rales, rhonchus, or wheezes; no egophony; no alterations in tactile fremitus; and normal percussion
- *Abdomen*: Mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- *Extremities*: No cyanosis or clubbing and mild peripheral edema
- *Neurological*: Cranial nerve II through XII intact and no focal deficit
- *Psychiatric*: Normal affect, no hallucinations, normal speech, and no dysarthria
- *Skin*: Intact, warm, no rashes, and no lesions

What Are the Possible Causes of Syncope? [1]

1. Cardiac syncope: arrhythmias (brady- or tachycardia) and structural heart disease
2. Reflex (neurally mediated): vasovagal, situational, carotid sinus syncope
3. Syncope due to orthostatic hypotension: primary and secondary autonomic failure, drug induced, and volume depletion
4. Neurogenic syncope

Reflex syncope seems unlikely because there were no triggering situations (like emotion, gastrointestinal stimulation, or postprandial situation) and the patient was at rest and did not complain of any prodromic symptom (like dizziness, headache, sweating, pallor, and nausea). Syncope due to orthostatic hypotension seems also unlikely because he was sitting when the episode occurred; moreover, he was not taking any drug therapy.

A neurogenic cause of the loss of consciousness (like epilepsy) could be a possible hypothesis if we consider the young age and the sudden onset, but the absence of other signs (tongue bite, tonic-clonic seizures, typical aura, urinary incontinence, rapid recover without neurological impairment) made it less likely.

According to these clinical features, cardiac syncope was the most likely diagnosis. ECG and echocardiogram were performed during hospitalization together with routine laboratory tests.

ECG (Fig. 24.1)

Sinus rhythm, heart rate 95 bpm, normal atrioventricular conduction (PQ 150 ms), cardiac electrical axis +60°, and coved-type ST-segment elevation about 4 mm, followed by a negative T wave in V1 and an ST-segment elevation with a saddleback appearance in V2 with a biphasic T wave. QTc 450 ms

Echocardiography

Normal dimension of both atria (LA diameter M-mode = 30 mm, LA area 4 c = 16 cm^2, RA area 4 c = 12 cm^2). Normal size and wall thickness of the left ventricle (iLVEDV 61 ml/m^2) which shows a preserved systolic function (ejection fraction with Simpson's method 0.61). Normal size and global function of the right ventricle (TAPSE 24 mm)

Normal morphology of the cardiac valves; mild tricuspid regurgitation and normal systolic pressure gradient (PASP = 20 mmHg)

The inferior vena cava has a normal size (16 mm) and physiological collapsing during inspiration.

Absence of pericardial effusion

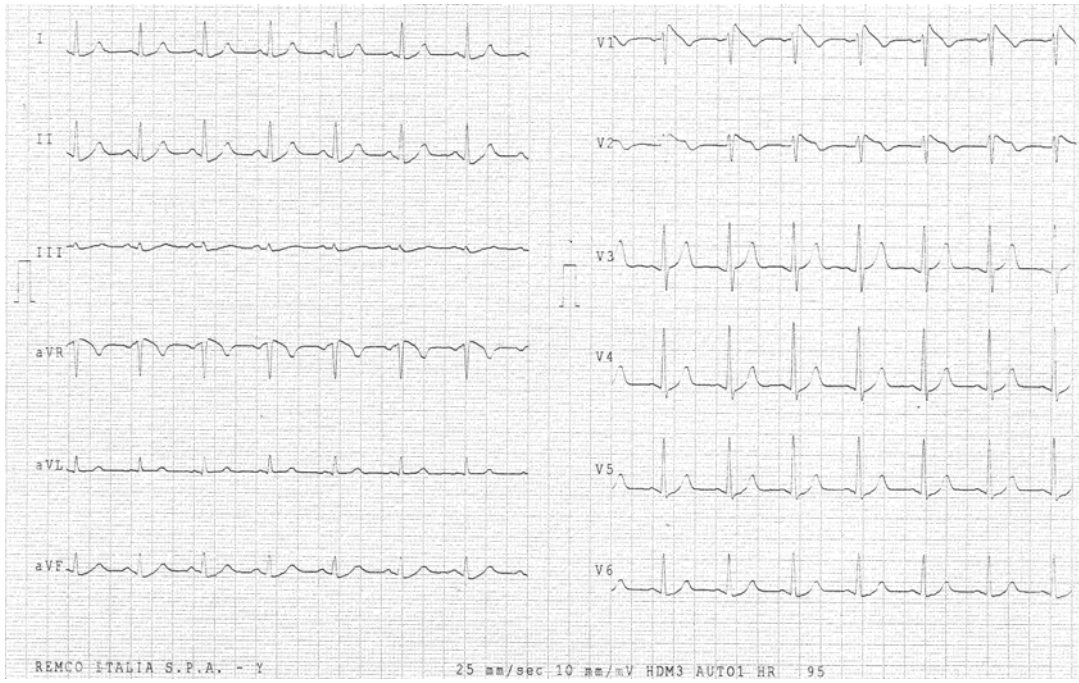

Fig. 24.1 ECG performed at hospital admission

Normal diastolic pattern without increased filling pressure (E/A 0.8, E/E' 3.7, E dec time 193 m/s).

Conclusion There are normal echocardiography findings for a 35-year-old man.

Routine Laboratory Tests

- *Complete blood count*: mild leukocytosis (13.3 × 10^3/mmc)
- *Cholesterol* (*total*, *HDL*, *LDL*) *and TG*: normal
- *Hepatic function* (*GOT*, *GPT*, *γ-GT*, *ALP*, *total bilirubin*, *direct and indirect*): normal
- *Thyroid function* (*TSH*, *FT3*, *FT4*): normal
- *Renal function* (*creatinine*, *BUN*): normal
- *Electrolytes* (Na^+, K^+, Ca^{++}, Mg^{++}, Cl^-): normal
- *Fasting blood glucose*: 94 m/dl (5.22 mmol/l)
- *Troponin I-hs*: 0.006 ng/ml (n.v <0.055 ng/ml)
- *Inflammation index*: VES 30 mm/h (n.v <27 mm/h) and CRP 0.9 mg/dl (n.v <0.6 ng/ml)

What Are the Possible Causes of Cardiac Syncope?

Arrhythmia

- Bradycardia
  - Sinus node dysfunction (including bradycardia/tachycardia syndrome)
  - Atrioventricular conduction system disease (AV blocks)
  - Implanted device malfunction
- Tachycardia
  - Supraventricular arrhythmias
  - Ventricular arrhythmias (idiopathic, secondary to structural heart disease or to channelopathies)
- Drug-induced bradycardia and tachyarrhythmias

Structural Disease

- Cardiac
  - Cardiac valvular disease
  - Acute myocardial infarction/ischemia
  - Idiopathic dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Arrhythmogenic right ventricular dysplasia (ARVD)
  - Cardiac masses
  - Pericardial disease/tamponade
  - Congenital anomalies of coronary arteries
  - Prosthetic valves dysfunction
- Others
  - Pulmonary embolism
  - Acute aortic dissection
  - Pulmonary hypertension

A precise and careful medical history is the key to achieve a correct etiologic diagnosis of syncope. Thanks to this we have already removed some possible causes of syncope (orthostatic hypotension, reflex, and neurological syncope) and epilepsy (we executed an electroencephalography which did not show any abnormality). So we focused on the most likely cardiac causes.

The patient did not show any metabolic disorder at the laboratory tests or physical signs of intoxication. He did not assume any drug as possible cause of arrhythmias.

Physical exam together with ECG and echocardiography did exclude a structural heart disease together with pulmonary embolism and acute aortic dissection.

A possible arrhythmic origin seemed to us to be the most likely cause of this syncope. During hospitalization, the patient never showed bradycardia or paroxystic atrioventricular block of different grades. At ECG, the repolarization pattern did show a typical Brugada type 1 pattern with a coved ST-segment elevation ≥2 mm and a negative T wave in V1. The febrile state during which the ECG has been recorded could have unmasked the Brugada pattern, because the previous ECGs have been described to be normal. It is well known that the typical Brugada pattern may vary according to body temperature, autonomic tone, and also drug intake. This ECG pattern is described to be associated with risks of ventricular tachyarrhythmias (torsades de pointes or ventricular fibrillation mainly), as possible cause of syncope or sudden cardiac death.

Final diagnosis Brugada syndrome (syncope in young man with Brugada type 1 pattern at the ECG)

An electrophysiological study was specifically not indicated in this particular situation because the patient was "symptomatic" for unexplained syncope and there was a familiar example of sudden death at young age.

Therefore, we implanted a subcutaneous cardioverter defibrillator (S-ICD) in primary prevention. We chose a subcutaneous device instead of an intravenous one because sudden death in Brugada syndrome is due to polymorphic ventricular tachycardia (e.g., torsades de pointes) or ventricular fibrillation (VF) that did not required anti-tachycardial pacing (ATP) but only defibrillation. Moreover, our patient was young and did not require cardiac pacing. Finally, the subcutaneous device implantation is less invasive (device lead is extrathoracic), and an eventual explant (e.g., for infection) is easier compared to an intravenous device.

Quinidine has been reported as a possible pharmacological aid, but the existing data are not so numerically sufficient to be considered a life-saving therapy.

24.2 Brugada Syndrome

Definition

Brugada syndrome is an autosomal dominant genetic disorder, first described in 1992, with variable expression characterized by typical patterns on the surface electrocardiogram (ECG) and an increased risk of ventricular tachyarrhythmias and sudden cardiac death [2, 3].

Pattern Versus Syndrome

Brugada pattern (BrP) and Brugada syndrome (BrS) differ each other for the presence or absence of symptoms:

Brugada pattern: patients with typical ECG features who are asymptomatic and have no other clinical criteria
Brugada syndrome: patients with typical ECG features who have experienced sudden cardiac arrest (SCA), sustained ventricular tachyarrhythmia, or unexplained syncope

ECG Patterns

Initial classification considered three main ECG patterns [4], but in the last consensus, this classification was changed unifying types 2 and 3 into a unique pattern (Fig. 24.2) [5]:

Type 1 (classic Brugada type 1 ECG): ST-segment elevation (≥2 mm) descends with an upward convexity to an inverted T wave in at least one right precordial chest lead (V1–V2). This is referred to as the "coved type."
Type 2 (combined from the original designation of type 2 and 3 patterns): ST segment has a "saddleback" ST–T wave configuration, in which the elevated ST segment descends toward the baseline and then rises again to an upright or biphasic T wave.

Moving the right precordial chest leads (V1–V2) up to the second or third intercostal space may increase the sensitivity of detecting these abnormalities [6]. This may be crucial because those with a type 1 Brugada pattern only in high chest leads seem to have a similar rate of cardiac events during >1 year of follow-up as those with type 1 Brugada ECG in standard position [7]. With that single ECG recording, it is likely to diagnose a Brugada type 1 without referring to a drug challenge (see below) in a high percentage of patients.

Epidemiology

Prevalence of type 1 Brugada ECG pattern ranges from 0.012 to 1.0 % in different population registries [8–10]. A meta-analysis reports an event rate of 10 % at 2.5 years in patients with type 1 ECG pattern [11].

Pathogenesis

A variety of factors may contribute to the clinical manifestations of Brugada syndrome including cardiac sodium channel (SCN) gene mutation, right ventricular abnormalities, autonomic tone, and fever.

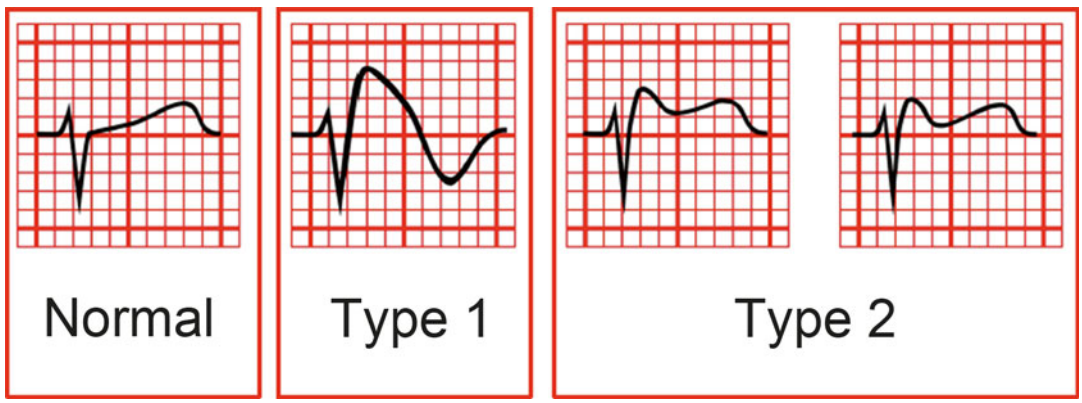

Fig. 24.2 Current electrocardiographic classification of Brugada pattern

Genetic Brugada syndrome demonstrates autosomal dominant inheritance with variable expression of mutation in the cardiac sodium channel genes (mainly SCN5A) [12]. The ST-segment elevation and T wave inversions seen in the right precordial leads seem to be due to a different length of the action potentials in the epicardial compared to the endocardial cells of the right ventricle [3, 13].

Arrhythmias The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction blocks. Due to the abbreviation of phase two, these cells have a much shorter refractory period and recovery of excitability compared to the surrounding cells. This combination (short refractory periods and localized conduction blocks) provides the substrate for localized reentry (phase 2 reentry) between epicardium and endocardium as arrhythmia substrate [14].

Structural abnormalities Historically, Brugada syndrome is not associated with structural heart disease. However, new evidence suggests the presence of microscopic area of fibrosis in the right ventricular output tract (RVOT). Nevertheless, further investigations in this filed are necessary.

Fever Data from a retrospective review of patients with Brugada syndrome suggest that fever is a main trigger for ECG changes and also possibly cardiac arrest [15].

Autonomic tone An imbalance between sympathetic and parasympathetic activation seems to be also present in the Brugada syndrome, as suggested by frequent nocturnal occurrence of the tachyarrhythmias (torsades de pointes) and ST elevation occurrence during the recovery phase of exercise tests (vagal rebound) [16, 17].

Clinical Features

Patients with a Brugada pattern may remain asymptomatic and the typical pattern may be a casual finding. Usually the first clinical manifestations of the syndrome are sudden cardiac arrest or syncope (due to a tachyarrhythmia). Palpitations are rare and usually are caused by an episode of atrial fibrillation that is common in Brugada syndrome [18].

Sudden cardiac arrest (SCA) and syncope One-third of patients have SCA or syncope as the first manifestation of Brugada syndrome. Usually these manifestations are more common during the night and during sleep but not during physical exercise [19].

Atrial fibrillation Patients with Brugada have an increased incidence of atrial fibrillation (10–20 %). Its presence has been associated also with an increased risk of ventricular fibrillation (VF) [20].

Nocturnal agonal respiration As abovementioned, ventricular arrhythmias are frequent during sleep; the clinical manifestation of these arrhythmias may be nocturnal agonal respiration associated with a gasping breath.

Diagnosis and Risk Stratification

Drug Challenge

In patients with type 2 Brugada pattern, a type 1 pattern may be unmasked by sodium channel blocker drugs (e.g., flecainide, procainamide, ajmaline). The importance of unmasking the type 1 Brugada ECG pattern relates to its relevance in confirming the diagnosis of Brugada syndrome, particularly in patients without symptoms [4]. The test may be useful in patients with type 2 pattern, asymptomatic, and with familiar history for SCD.

- Flecainide: 2 mg/kg over 10 min intravenously
- Procainamide: 10 mg/kg over 10 min intravenously
- Ajmaline: 1 mg/kg over 10 min intravenously

Electrophysiological Study (EPS)

EPS is not indicated in patients with Brugada patterns and high risks features (previous SCA or syncope and positive familiar history). EPS in asymptomatic patients with type 1 pattern remains

an area of investigation and debate in which there is discordant evidence [21, 22]. Despite this, 2005 guidelines recommended EPS test in asymptomatic patients with type 1 pattern [4]. A recent study founded a short refractory period recovery (<200 ms) as an adjunctive parameter to possibly indicate an ICD implantation [21].

Genetic Testing [12]

- Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing can be useful particularly for the patients in which there is a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiogram (resting 12-lead ECGs and/or provocative drug challenge testing).
- Genetic testing is not indicated in the setting of an isolated type 2 Brugada ECG pattern.

Prognostic Factors

The major risk factor for patients with the Brugada ECG pattern is a history of ventricular tachyarrhythmias leading to SCA or syncope; these patients should be considered at high risk [4, 22].

Atrial fibrillation, positive familiar history for SCD, and male gender are less powerful predictors of future events.

Treatment

To date, the only proven effective therapeutic strategy for the prevention of SCD in BrS patients is the implantable cardioverter defibrillator (ICD), and this therapy is principally guided by the clinical history.

Recommendation [23] are as follows:

- Class I: ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who are survivors of a cardiac arrest and/or have documented spontaneous sustained ventricular tachycardia (VT) with or without syncope.
- Class IIa: ICD implantation can be useful in patients with a spontaneous diagnostic type 1 ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
- Class IIb: ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during programmed electrical stimulation (inducible patients).
- Class III: ICD implantation is not indicated in asymptomatic patients with a drug-induced type 1 ECG and on the basis of a family history of SCD alone.

Pharmacological therapy plays a marginal role in Brugada syndrome; quinidine has been shown to prevent induction of VF and suppress spontaneous ventricular arrhythmias in a clinical setting. However, quinidine is recommended only as [23]:

- Class IIa: patients with ICD and multiple shocks
- Class IIa: patients with contraindication to ICD

Conclusions

Brugada syndrome is one possible cause of SCD in the young population with an incidence that is probably underestimated. ECG is fundamental for diagnosis; however, it is important to remember that the typical pattern may not always be founded in all the consecutive ECGs in the same subject, because it can vary in relation to different environmental conditions. About risk stratification, medical history plays a central role because history of syncope or SCA is so far the only major risk criteria.

ICD implantation is the only effective therapy for these patients at the moment. S-ICD could be chosen because of the external lead in a relative young patient not needing ATP therapy or cardiac pacing.

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Long QT Syndrome

25

Maria Vittoria Matassini and Alessandro Maolo

25.1 Case Report

A 33-year-old woman was referred to our cardiology department after an aborted sudden cardiac death.

Few days before cardiologic visit, an accidental diagnosis of long QT interval was done. The cardiologist noticed a QT interval of 560 ms with a cardiac rate of 58 bpm. Therefore, a 24-h ECG Holter recording was booked. On the day of the recording, the patient collapsed while standing at the red traffic light. She had a spontaneous recovery of consciousness in a few seconds with no memory left.

The patient was then transferred to the ER at the nearest hospital. She fully recovered without neurological sequelae, and the ECG showed sinus rhythm with a prolonged QT interval (580 ms, 55 bpm). Routine blood tests including electrolytes were all within the normal ranges.

The 24-h Holter ECG recording revealed during syncope an episode of polymorphic ventricular tachycardia that was very likely to be a torsade de pointes with later spontaneous sinus rhythm restoration, despite the presence of many artifacts (Fig. 25.1).

The patient was then transferred to our arrhythmology and cardiology clinic for further evaluation and treatment.

Medical History and Cardiovascular Risk Factors

- No cardiovascular risks factor.
- No family history of sudden cardiac death or other structural heart diseases.
- No history of syncope.
- 2009: the patient underwent cardiologic visit for nocturnal episodes of palpitations with sudden awakening from sleep and sweating. ECG showed a long QT interval (QTc 560 ms).

Allergies

Dust, cat hair, pollen

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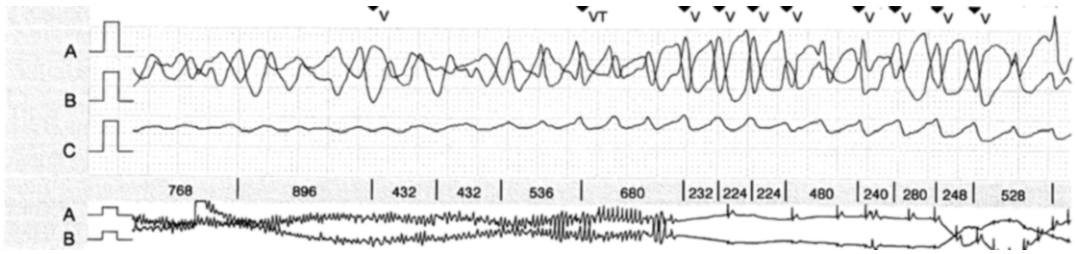


Fig. 25.1 Holter ECG recording showing a torsade de pointes. The smaller trace below shows the spontaneous sinus rhythm recovering

Medications

None

Vital Signs

- Temperature: 36 °C
- Heart rate: 55 bpm
- Arterial blood pressure: 100/60 mmHg
- Respiratory rate: 18 breaths/min
- Oxygen saturation: 100 %

Physical Examination

- *General*: no fatigue, no acute distress; alert, awake, and oriented. Well developed and well nourished
- *Neck*: supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- *Cardiovascular*: regular rate and rhythm, S1 and S2 normal, no murmurs, rubs or gallops, point of maximal intensity non-displaced and non-sustained, no hepatojugular reflux, and capillary refill less than 2 s
- *Lungs*: no rales, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal percussion
- *Abdomen*: no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- *Extremities*: no cyanosis or clubbing and no peripheral edema

Routine Laboratory Tests Performed

- *Complete blood count*: normal
- *Cholesterol* (*total*, *HDL*, *LDL*) *and TG*: normal
- *Hepatic function* (*GOT*, *GPT*, *γ-GT*, *ALP*, *total bilirubin*, *direct, and indirect*): normal
- *Thyroid function* (*TSH*, *FT3*, *FT4*): normal
- *Renal function* (*creatinine*, *BUN*): normal
- *Serum electrolytes*: potassium 4.4 mEq/l, sodium 138 mEq/l, and magnesium 1.8 mg/dl

Instrumental Examination

The recorded ECG (Fig. 25.2a, b) revealed sinus rhythm with 58 bpm heart rate, normal atrioventricular and intraventricular conduction, and normal ventricular repolarization with a corrected QT interval 600 ms long.

A complete echocardiographic examination was performed and showed normal dimensions and function of cardiac chambers, a mild prolapse of the posterior mitral leaflet with trace of mitral regurgitation, and a mild tricuspid regurgitation with normal pulmonary artery systolic pressure.

No reversible cause of QT interval prolongation was found.

All the family members underwent ECG evaluation, and either the father or brother

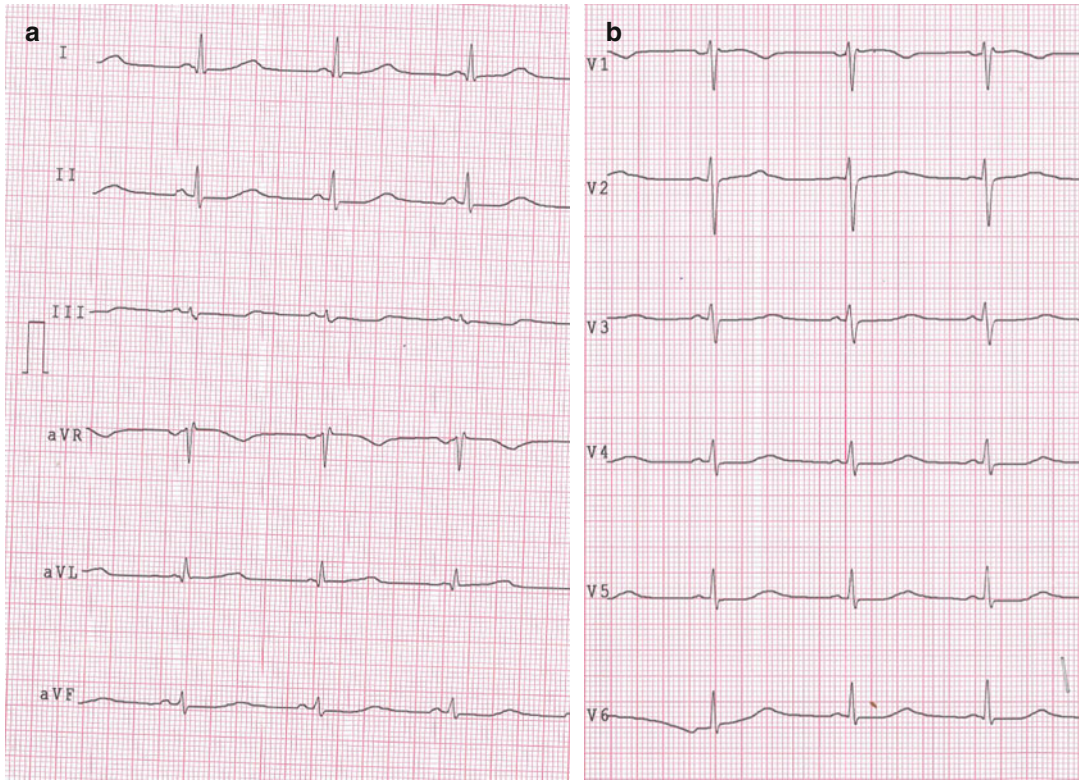


Fig. 25.2 (**a**, **b**) Standard rest 12-lead ECG showing a prolonged QT interval (600 ms)

showed a prolonged QT interval. They both were not taking any medications which could alter the QT interval, and laboratory findings did not show electrolyte abnormalities.

Final Diagnosis

These findings altogether were suggestive for hereditary long QT syndrome. Genetic assessments were therefore performed and it is still underway.

25.2 Long QT Syndrome

Epidemiology

Hereditary long QT syndrome (LQTS) is a congenital disorder characterized by a prolongation of the QT interval detectable on the standard 12-lead ECG with or without T wave [1]. These abnormalities of ventricular repolarization can be present in other family members of the affected subject.

The natural history of LQTS is characterized by the development of life-threatening ventricular arrhythmias such as torsade de pointes (TdP). This arrhythmia can be self-limiting and asymptomatic or they can manifest with syncope or sudden cardiac death (SCD) [2].

The prevalence of this genetic disorder is estimated to be at least 1:5,000 subjects. Considering that the affected subject can be asymptomatic and there are cases of sudden cardiac death with no defined etiology, the real prevalence of LQTS may be considerably higher [1, 2].

Moreover, 10–40 % of affected patients present a nondiagnostic QT interval at rest because of an intermittent nature of the ECG abnormalities or a borderline QT value that make the diagnosis challenging [3].

Long QT syndrome more often manifests before puberty in males and after puberty in females, and the probability of a cardiac event depends on the degree of QT prolongation.

Among untreated symptomatic patients, mortality is high, with 20 % of deaths in the first year after the first cardiac event and approximately 50 % within 10 years [2].

Pathophysiology

Since the discovery of the first LQTS-responsible genes in 1990s, a lot more genes have been related to the syndrome and more than 500 mutations are described nowadays, resulting in 10 different phenotypes (LQTS 1–10).

In about 75 % of patients, mutations involve three main causative genes:

- KCNQ1-encoded Kv7.1 channel subunit (IKs potassium channel alpha subunit; LQT1)
- KCNH2-encoded Kv11.1 subunit or hERG (IKr potassium channel alpha subunit; LQT2)
- SCN5A-encoded Nav1.5 (INa sodium channel alpha subunit, LQT3)

Nearly 70 % of all LQTS are secondary to loss-of-function mutations involving IKs (30–35 %) or IKr (25–40 %) potassium channels, while approximately 5 % result in a gain-of-function mutation involving sodium channel. Less frequently, patients with congenital LQTS present mutation involving:

- Ankyrin-B gene: a cytoskeletal membrane adapter which acts as an anchoring protein that binds proteins involved in cardiac electrophysiology and cellular calcium homeostasis (LQT4)
- The auxiliary subunits to KCNQ1 (mink; LQT5) or KCNH2 (MiRP1, LQT6)
- KCNJ2-encoded Kir2.1 potassium channel with consequent reduction in Kir2.1 current (LQTS7), known as Andersen-Tawil syndrome (ATS), with the phenotype dominated by skeletal abnormalities
- CACNA1C-encoded L-type calcium channel subunit with increase in Cav1.2 current and associated with syndactyly in both hands and feet, phenotype known as Timothy syndrome (LQT8)
- Cavelolin-3 gene, with increase in late sodium current (LQT9)
- SCN4B gene, with increase in late sodium current (LQT10)

In addition, 15–20 % of affected patients present a negative genetic assessment.

The majority of LQTS is inherited as an autosomal dominant trait: the Romano-Ward syndrome affects 1 per 5,000 persons. Sporadic (or de novo) alterations occur 5–10 % of the time. The autosomal recessive form of LQTS, also known as Jervell and Lange-Nielsen syndrome, was firstly described in 1957. It probably affects less than 1 per million people and results from complete loss of Kv7.1 channel function, which precipitates sensorineural deafness in addition to LQT1 or LQT5 mutation [2, 4].

Genotype-Phenotype Correlation

The three main genotypes (LQT1, LQT2, and LQT3) present distinctive clinical phenotypes with important implications in diagnosis, treatment, and long-term clinical course. Indeed, the recognition of gene-specific features can be used to choose the most suitable therapy and to give the correct recommendations to probands and their family. The gene-specific phenotypes include different triggers of ventricular arrhythmias, different ages of symptom onset, and specific ECG morphologies [2, 4].

Patients with LQT1 and less part of LQT2 patients usually present the greater risk of cardiac events after triggers associated with adrenergic stimulation [5]. Life-threatening arrhythmias have been shown to occur under specific circumstances: while diving and swimming for LQT1 patients or acoustic stimuli (such as alarm clock ringing) or sudden awakening for LQT2 patients [4, 6–8].

On the other hand, LQT3 is characterized by the higher risk of events at rest or during sleep.

Patients with LQT3 have fewer events during exercise or stress because they significantly shorten their QTc at high frequencies and therefore they become less susceptible to catecholamine-induced arrhythmias [9]. These

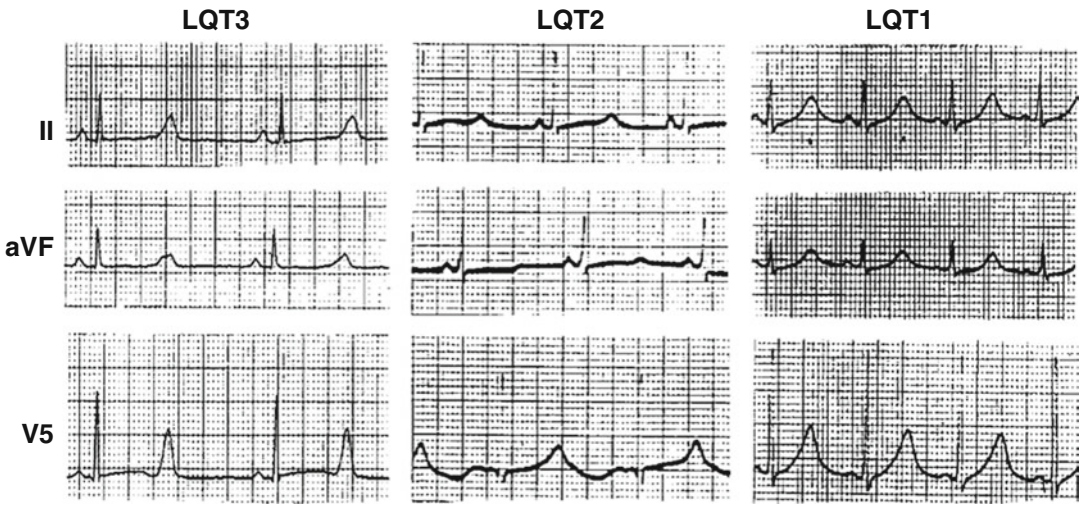


Fig. 25.3 Distinctive ECG patterns of the three main LQTS genotypes. (With permission from Prof. Arthur Moss with the consens of the original publisher (Circulation))

Table 25.1 Characteristics of different genotypes of LQTS

Genotype	Higher risk of events	ECG	QT shortening during exercise	Age of first presentation
LQT1	Diving/swimming	T waves broad-based with high amplitude	No; may lengthen	Lower
LQT2	Alarm clock	Low-amplitude ST-T in the limb leads, biphasic in the precordial leads	Variable	
LQT3	Rest/sleeping	Narrow T waves, late-onset peak or biphasic, long isoelectric ST-T segment	Yes	

findings have consistent clinical implications and explain why these patients have less or no benefit at all from beta-blocker therapy.

Age of first manifestations varies from one genotype to another. In fact, generally, the age of first events is lower in LQT1 than in LQT2 and LQT3 [4].

Some differences can be noticed on the standard 12-lead ECG too. Each one of the three major genotypes (LQT1 to LQT3) seems to have a distinctive T-wave repolarization pattern on the ECG, as shown in Fig. 25.3.

- LQT1: T waves are broad-based with a high amplitude.
- LQT2: ST-T segment has a low amplitude in the limb leads and a biphasic pattern in the precordial leads.
- LQT3: T waves are narrow, with late-onset peak or biphasic and preceded by a long isoelectric ST-T segment [1, 2, 4].

Moreover, every genotype has a different response to exercise. LQT1 patients fail to appropriately shorten their QT interval during exercise and QTc may further lengthen. This effect is due to IKs that in normal subjects is responsible for the abbreviation of the action potential at higher heart rates. On the contrary, patients with LQT3 show shortening of QT interval during exercise. In LQT2, QTc duration behavior is variable [4].

Finally, LQT1 patients have a peculiar response to epinephrine. Epinephrine infusion has an excellent performance in the detection of LQTS1 because it provokes a significant and stable prolongation of the QTc in these patients [10, 12].

Table 25.1 shows the characteristics of different genotypes of LQTS.

Clinical Presentation

The long QT syndrome's main manifestations are electrocardiographic anomalies, syncope, cardiac arrest, and sudden cardiac death.

Table 25.2 Scoring system to evaluate the probability of LQTS

ECG findings	QTc ≥480 ms	3
	QTc = 460–470 ms	2
	QTc = 450 ms (in males)	1
	Torsade de pointes	2
	T wave alternans	1
	Notched T waves (three leads)	1
	Rest heart rate below the second percentile for age	0.5
Clinical history	Syncope with stress	2
	Syncope without stress	1
	Congenital deafness	0.5
Family history	Family members with LQTS (score ≥4)	1
	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

The ECG anomalies are very different and they depend in part on the type of QT syndrome. The main alteration is the prolongation of the QT interval, but is not always present at rest. In a certain percentage of patients, the QT interval can even be normal (10 % in LQT3 and 37 % in LQT1) [12]. In these cases, the QT interval's prolongation can be evident during exercise test or infusion of epinephrine [4, 9–11]. Furthermore, repolarization can have strange aspects. For example, notches on the T wave are typical of LQT2.

Syncope, cardiac arrest, and sudden death are the result of ventricular arrhythmias due to the arrhythmogenic condition strictly linked to the genetic and electrical disorders of the disease. These arrhythmias are most of all torsade de pointes VT that become clinically manifest depending on their duration. Sudden death occurs when the arrhythmia is not self-limiting and degenerates into ventricular fibrillation.

Diagnosis

In many cases, the diagnosis of LQTS can easily be done with a standard 12-lead ECG at rest, measuring the QT interval and correcting it with Bazett's formula ($QTc = QT\ (ms)/\sqrt{RR(s)}$). However, there are hidden cases of LQTS in which the QT interval can be normal or borderline at rest (about 20–25 %) [12–16].

Some useful tests have been proposed to unmask the concealed forms of LQTS, and ongoing clinical trials are evaluating and validating them. These tests are:

- Exercise test: patients with LQT1 mutation seem to have a more marked QT prolongation during exercise (burst and gradual exercise showed the same results), while those with LQT2 mutation have an exceeding hysteresis of the QT interval (difference between QT interval measured during exercise and 2 min in the recovery phase at similar heart rates) [17–19].
- Changing position: sudden changes from supine to standing position can provoke a prolongation of the QT interval mostly in LQT1 and LQT2 patients. This can be explained by the complex mechanism involving sympathetic and vagal systems and their recruitment of I_{Ks} and I_{Kr} currents for an adequate inotropy and chronotropy response [17, 18, 20, 21].
- Epinephrine test: epinephrine infusion showed excellent results in unmasking concealed forms of LQTS, but the clinical trials available by now have few patients, and this test cannot be used as a routine exam so far.

According to the latest consensus paper, the presence of a pathogenic mutation in LQTS genes per se can be a diagnostic criterion [22].

A scoring system was created to evaluate the probability of LQTS when QT interval is normal or the genetic mutation is not unequivocal [23]. This scoring system is still used and is shown in Table 25.2.

That's why according to the latest HRS/EHRA/HPRS consensus document, diagnosis of LQTS can be surely done if:

- There is an LQTS risk score of ≥3.5 (excluding secondary causes of QT prolongation).
- There is a pathogenic mutation in LQTS genes.
- There is a QTc ≥500 ms in repeated ECG (excluding secondary causes of QT prolongation).
- Moreover, LQTS can be diagnosed if there is a QTc ≤499 ms and >480 ms in repeated

ECG (excluding secondary causes of QT prolongation).

Management

Before deciding the appropriate therapy for a patient affected by LQTS, it is important to make a careful risk stratification. Even if in some cases identifying high-risk patients could be easy (i.e., some specific genetic mutation such as those found in Jervell and Lange-Nielsen syndrome or in Timothy syndrome [see below]), more frequently risk stratification becomes a hard matter, and a wrong conclusion about the arrhythmic risk could be made.

According to the latest consensus document [22] could be considered as high-risk patients with:

- Jervell and Lange-Nielsen syndrome (1.6–6:1,000,000): particular variant of LQTS associated with severe and bilateral sensorineural deafness, caused in 90 % of the cases by mutations in KCNQ1 (the remaining 10 % is related to KCNE1 mutations) [24, 25]
- Timothy syndrome (20 cases worldwide): rare congenital defect (autosomal dominant) caused by mutations of CACNA1C (gene encoding the $Ca_v1.2$ α subunit) and characterized by physical malformation (syndactyly), neurological and developmental defects (autism), and QT prolongation with high arrhythmic risk (frequent early childhood sudden death) [26, 27]
- Documented mutations of LQT1 affecting in particular the cytoplasmic loops and those responsible for dominant-negative ion current effects
- QTc >500 ms (in particular if affected by two unequivocally variants by genetic testing) and very high risk if >600 ms
- Syncope or cardiac arrest before age 7 and very high risk if it occurs in the first year of life
- Recurrence of arrhythmic events during optimal medical therapy

After adequate risk stratifications, the management of patients with LQTS includes:

- Lifestyle changes: in particular avoidance of hard physical exercise (especially swimming) in LQT1 subjects, exposure of sudden loud noises (i.e., alarm clock or phone ringing) in LQT2 subjects, and any drug prolonging QT interval in all LQTvS patients. Prompt correction of electrolyte impairment is important too.
- Beta-blockers: are the first-line therapy, and they are indicated with full dosing for age and weight in all LQTS patients (regardless of QT prolongation) in the absence of contraindication such as asthma. Nadolol and sustained-release propranolol should be preferred considering their long-acting activity and their demonstrated better efficacy compared to metoprolol [28].
- Implantable cardioverter defibrillator (ICD): is recommended in secondary prevention (patients who survived cardiac arrest) and in primary prevention only for patient at very high risk for arrhythmia (see above). It could be considered in patients that experience recurrent syncope while receiving beta-blocker therapy. It is not indicated in asymptomatic patients with LQTS (excluding those at very high risk) especially if not receiving beta-blockers.
- Left cardiac sympathetic denervation (LCSD): is a surgical procedure aimed at the dissection of the main sympathetic trunk in the upper thoracic region. The procedure is done usually through a left supraclavicular incision and seems to be effective in preventing the recurrence of arrhythmic events in high-risk subjects [29]. In particular, LCSD is recommended for patients refusing ICD therapy or having contraindications to it and in those patients experiencing recurrence of syncope or arrhythmias during beta-blocker therapy, when these drugs are not tolerated, contraindicated, or refused by the patient.

Other channel-specific therapies such as mexiletine, flecainide, and ranolazine (all sodium channel blockers) have been used in high-risk patients with recurrent events despite optimal dosed beta-blockers, ICD, and LCSD. Their effectiveness is encouraging, but they are still not considered as a routine therapy.

25.3 Clinical Course and Therapeutic Management of the Clinical Case

For the specific clinical case discussed above, we finally decided implanting one-chamber endocavitary ICD. This choice was due to torsade de pointes occurrence unrelated to secondary reasons. Furthermore, the classical ICD was preferred to S-ICD because we thought that the anti-tachycardia and anti-bradycardia pacing could have been useful in this patient.

Nadolol 40 mg once daily was also administered as starting dose. When employing a beta-blocker, the choice is usually between two drugs: nadolol and sustained-release propranolol. As explained above, these two drugs were demonstrated to be superior to metoprolol in preventing arrhythmic events in patients with LQTS. Nadolol 40 mg once a day is the starting dose, but the dosage could be increased up to 160 mg/day.

A follow-up visit was performed 3 months later. The patients were completely asymptomatic. The physical examination was normal. At the ICD interrogation, any arrhythmia was recorded.

25.4 Short QT Syndrome

Short QT syndrome (SQTS) is a relatively new disease and one of the rarest channelopathies. The first hypothesis of a possible correlation between an idiopathic short QT interval and sudden cardiac death dates back to 2000, when Gussak, P. Brugada, and J. Brugada described the finding of a persistent short QT interval in an entire family, including a 17-year-old girl having frequent episodes of atrial fibrillation requiring electrical cardioversion. Moreover, they described the clinical case of a 37-year-old man with history of malignant ventricular arrhythmias and a short QT interval on the ECG who died suddenly at home [30].

Genotypes-Phenotypes

The SQTS was associated with mutations of some genes encoding the potassium channels (KCNH2, KCNQ1, KCNJ2). These genes are involved also in the pathogenesis of LQTS (in particular LQT1 and LQT2), but on the contrary, in SQTS, the mutations are responsible for a gain of function of the potassium channels. In few patients with SQTS, mutations in the genes CACNA1C and CACNB2 (encoding the alpha- and beta-subunits of the L-type calcium channel of the myocardium) responsible for a loss of function of the channel were identified. These genes are usually involved also in the pathogenesis of Brugada syndrome (in particular manifesting with type 1 ECG pattern).

The different genotypes correspond to different phenotypes and different channel's function disturbances (loss or gain of function), and they manifest with different ECG patterns [31–35].

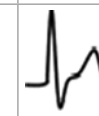
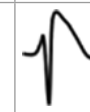
The classification of the different forms of short QT syndrome according to the gene's mutations, the channel involved, and the ECG expression is summarized in Table 25.3.

Clinical Presentation

The clinical onset of the SQTS is unpredictable and extremely variable.

Relying on the data available up to now and taking into account the largest series of cases (29 subjects) published by Giustetto in 2006 [23], cardiac arrest seems to be the most frequent manifestation (34 %) and is often the first clinical presentation (28 %). In that series, syncope was present in 24 % of patients and palpitations in 31 % of patients with frequent documentation of

Table 25.3 Summary table of genes and channels involved, channel's function modifications and ECG patterns in SQTS

	Gene	Channel	Function disturbance	ECG
SQTS1	KCNH2	IKr	Gain	
SQTS2	KCNQ1	IKs	Gain	
SQTS3	KCNJ2	IK1	Gain	
SQTS4	CACNA1C	ICaL	Loss	
SQTS5	CACNB2B	ICaL	Loss	

atrial fibrillation or flutter also in young patients. For this reason, it is important to consider SQTS as a differential diagnosis when a lone atrial fibrillation is found in young patients and in children. However, in that series, the median age of presentation was 30 years with a wide range between 4 months and 62 years [23].

Diagnosis

Considering the rarity of the syndrome, a univocal definition of the diagnostic criteria does not exist. According to the latest HRS/EHRA/HPRS consensus document [36], a diagnosis of SQTS can be made:

- If a QTc interval ≤330 ms is present, measured avoiding bradycardia and tachycardia and using Bazett's formula
- If a QTc interval <360 ms is present, associated with at least one among pathogenic mutation, family history of SQTS, history of familiar sudden cardiac death at age ≤40 years, and VT/VF in absence of structural heart disease

Therapy

Because of the small series and few data available, there is a lack of evidence regarding the clinical management of patients with SQTS. The ICD implantation in patients who survive cardiac arrest or experimented sustained ventricular tachycardia is obvious considering the high lethality of this syndrome, but the issue is more questionable when talking about primary prevention. The hardest point is doing a correct risk stratification without strong risk factors confirmed up to now.

Quinidine and sotalol are the two drugs used up to now exploiting their ability in prolonging QT interval. However, quinidine has proven to be effective in prolonging QT interval only in patients with SQTS, while sotalol could be effective in the other subtypes [37–39].

For these reasons, the authors of the latest HRS/EHRA/HPRS consensus document [36] conclude that the most reasonable management is:

- ICD implantation (recommended, Class I) in symptomatic patients with a diagnosis of SQTS who survived cardiac arrest and/or

have documented spontaneous sustained VT with or without syncope
- ICD implantation (considered, Class IIb) in asymptomatic patients with a diagnosis of SQTS and a family history of SCD
- Quinidine (considered, Class IIb) in asymptomatic patients with a diagnosis of SQTS and a family history of SCD
- Sotalol (considered, Class IIb) in asymptomatic patients with a diagnosis of SQTS and a family history of SCD

Finally, it is important to remember the primary importance of an appropriate ICD programming to avoid inappropriate shocks due to oversensing of tall T waves present in the ECG pattern of SQTS.

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Catecholaminergic Polymorphic Ventricular Tachycardia: A Challenging Case of "Epilepsy"

26

Laura Cipolletta

26.1 Introduction

Cardiac channelopathies are potentially malignant conditions caused by mutations in the channels that alter ion transit across the cardiac myocyte cell membrane. The clinical presentation of these mutations is variable, ranging from isolated abnormalities on electrocardiogram (ECG) to sudden cardiac death.

26.2 Case Report

A 17-year-old boy was referred to the cardiology clinic by a neurologist for evaluation of potential arrhythmia. He was treated for resistant focal epilepsy for 4 years. During a typical event, he fell off, with generalized shaking, lasting several minutes. Then he gasped and in few seconds later he appeared to stop breathing. He also had a period of incoherent speech, followed by sleepiness lasting for several hours. He suffered from urinary incontinence during episodes. These events occurred approximately every month, although they had increased in frequency over the past 2 months.

The episodes were triggered by anxiety and never occurred during physical efforts, although he had no active lifestyle.

Several anticonvulsant medications were not effective, so inpatient EEG monitoring was performed. EEG demonstrated frequent, independent, temporal intermittent rhythmic delta activity, indicating an increased risk for focal seizures; however, the typical episode was not recorded during admission. A second EEG recorder captured a typical event. It showed a high-amplitude diffuse slowing waves (suggestive of extracerebral artifact), followed by an abrupt, and diffuse, attenuation lasting 60 s, and finally a slow recovery to diffuse polymorphic delta frequencies. There was no ECG recording during the episode. The EEG pattern suggested cerebral hypoperfusion, so the patient was referred to a cardiologist. At admission to the cardiology department, he became anxious and lost consciousness.

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Medical History and Cardiovascular Risk Factors

- No cardiovascular risk factor; his family history of structural heart disease, syncope, or sudden cardiac death was unremarkable.
- 2010: diagnosis of focal epilepsy unresponsive to antiepileptic agents.

Allergies

None

Medications

Valproic acid

Vital Signs

- Temperature: 36 °C
- Heart rate: 90 bpm
- Arterial blood pressure: 100/60 mmHg
- Respiratory rate: 16 breaths/min
- Oxygen saturation: 100 %

Physical Examination

- General appearance: Well developed, well nourished, alert, and cooperative
- Lungs: Clear to auscultation and percussion without rales, rhonchi, wheezing, or diminished breath sounds
- Cardiovascular: Normal S1 and S2. No S3, S4, or murmurs. Regular rhythm. No peripheral edema, cyanosis, or pallor. Warm and well-perfused extremities
- Abdomen: Positive bowel sounds. Soft and nondistended. No guarding or rebound. No masses

Routine Laboratory Test

Tests were normal (hemoglobin 13.4 g/dl, white blood cells 6,290/mmc, creatinine 0.7 mg/dl, potassium 3.9 mEq/l, sodium 140 mEq/l, magnesium 1.8 mg/dl).

Instrumental Examination

Basal ECG was normal with several PVC.

The loss of consciousness corresponds to the onset of polymorphic VT on telemetry ECG monitoring (Figs. 26.1 and 26.2) and spontaneously the VT converted to sinus rhythm with frequent premature ventricular complexes (PVCs) after a brief period of cardiopulmonary resuscitation.

Clinical Course and Therapeutic Management

This event was similar to his typical episodes. During his hospital stay, he was treated with a beta-blocker (propranolol 3 mg/kg/die) with no further episodes.

Genetic testing revealed a mutation in the cardiac ryanodine receptor gene (RyR2), consistent with CPVT.

26.3 Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Epidemiology

The prevalence of CPVT is about 1:10,000. The mean age of onset is between 7 and 9 years, although later onset has been reported. Approximately 30 % of patients have a family history of stress-related syncope, seizure, or SCD before age 40 years. There is a high level of penetrance of the disease (75–80 %) [1].

Clinical Presentation

Syncope triggered by exercise or emotion is the typical clinical presentation of CPVT patients and sometimes a reproducible, stress-related,

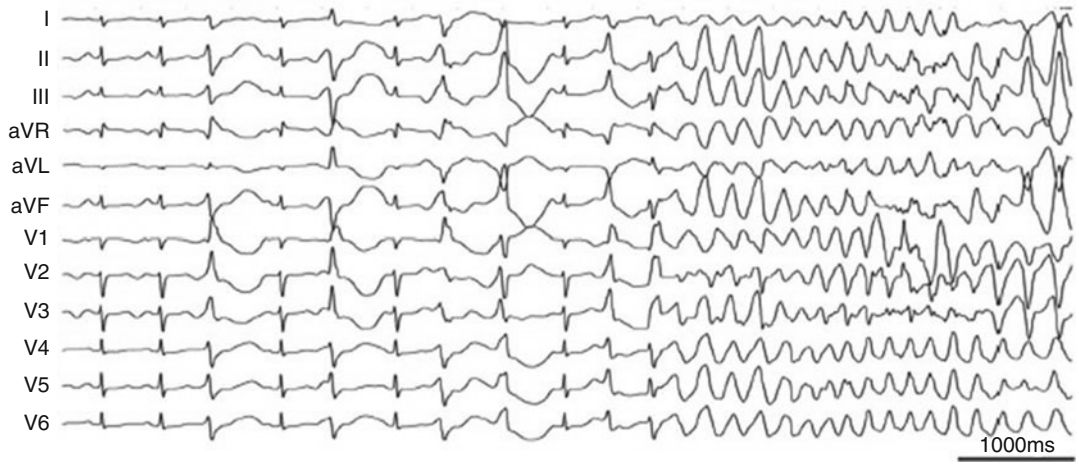

Fig. 26.1 Onset of polymorphic VT symptomatic for syncope, converted to sinus rhythm after cardiopulmonary resuscitation

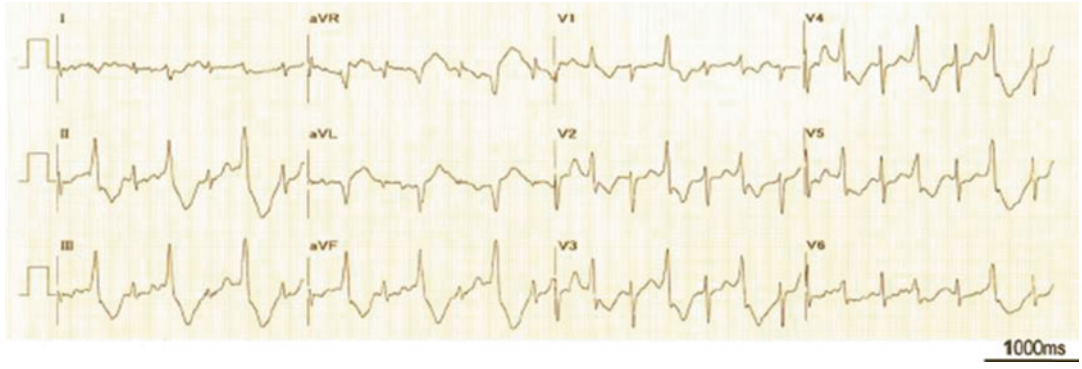

Fig. 26.2 Restoration of sinus rhythm with frequent monomorphic PVCs

bidirectional VT in the absence of a structural heart disease or QT interval prolongation could be documented. CPVT appears as one of the most malignant forms of ventricular arrhythmia. By age 40, almost 80 % of untreated CPVT patients develop symptoms (syncope, VT, or VF), and overall mortality is 30–50 % [2]. The first manifestation of the disease can be SCD in a significant number of cases [3].

Electrocardiographic Features

Brugada-like ST elevation, QT interval abnormalities, and atrioventricular and intraventricular conduction defects are absent in resting ECG of patients with CPVT. Ventricular arrhythmia distinguishing CPVT is characterized by alternating QRS axis with 180° rotation on a beat-to-beat basis ("bidirectional VT"). However, this typical arrhythmia is not observed in all patients. With increasing exercise workload, a progressive worsening of arrhythmias is a characteristic feature of CPVT. A heart rate of 110–130 beats/min is the cutoff to the appearance of ventricular arrhythmias during exercise stress testing, initially as polymorphic PVCs. Then, the complexity and frequency of arrhythmias progressively worsen as workload increases: ventricular bigeminy, run of polymorphic PVCs, and polymorphic or bidirectional VT. Bidirectional VT may degenerate into polymorphic VT and VF, if exercise is

not quickly stopped. On the recovery phase, VT rate and VT duration progressively diminish until arrhythmias disappear. During exercise, at a range of heart rates similar to or slower than that of ventricular arrhythmias, isolated premature atrial complexes, nonsustained supraventricular tachycardia, and short runs of AF usually are observed [3, 4].

Diagnosis of CPVT

Resting ECG, echocardiography, and EP testing frequently are completely normal. CPVT diagnosis is clinically based on symptoms (syncope or aborted SCD), family history, and response to exercise or isoproterenol infusion. Holter monitoring, exercise, and drug provocation demonstrated ventricular arrhythmias in more than 80 % of patients. Not infrequently, syncopal episodes are considered as vasovagal in origin, and no further workup is performed. If the loss of consciousness is associated with convulsions, as it happened in our case, it may be misdiagnosed as epileptic seizures if a prolonged circulatory arrest resulted in brain ischemia [1].

When a syncopal episode induced by exercise or emotion occurs in a child or in a young patient with a normal resting ECG and no structural heart disease, CPVT should be hypothesized [1, 3].

The most important test for diagnosis of CPVT is the exercise stress test that induces ventricular arrhythmias in at least 80 % of CPVT patients. When the sinus rate exceeds an individual threshold rate (usually at 110–130 beats/min), VT typically appears. A diagnostic and highly reproducible marker of CPVT is the progressive worsening of arrhythmias during exercise. Intravenous infusion of catecholamines (e.g., isoproterenol or epinephrine) can also provoke progressive ventricular arrhythmias [2, 4]. After a first syncopal episode, if a high suspicion of CPVT exists, repeated exercise stress test is fundamental to avoid delay in the diagnosis [4]. Also, when a maximal exercise stress test is difficult, continuous ambulatory monitoring may reveal arrhythmias typical for CPVT. In some cases, an implantation of a loop recorder could be reasonable [1, 4]. Invasive EP testing is of no value in the diagnosis or risk stratification in patients with CPVT. Programmed electrical stimulation is not useful to arrhythmia induction [1, 3]. Genetic testing should be performed in all definitive CPVT probands (see Fig. 26.3).

Genetics of CPVT

Mutations in genes that encode for Ca^{2+} regulatory proteins are the principal cause of CPVT. The genetic variants of CPVT that have been described are the following: an autosomal dominant trait (CPVT1, most common) caused by mutations in the RyR2 gene and a recessive form (CPVT2, rare) associated with homozygous mutations in the CASQ2 gene [1].

RyR2 is the major calcium release channel of the sarcoplasmic reticulum, mediating excitation–contraction coupling. RyR2 mutations are present in approximately 50–70 % of patients with CPVT. Typical CPVT mutation of RyR2s shows gain-of-function defects following channel activation by PKA phosphorylation (in response to beta-adrenergic stimulation), leading to an uncontrolled Ca^{2+} release from the sarcoplasmic reticulum during electrical diastole that increases the diastolic membrane depolarizations (DADs) and triggers arrhythmias [2].

Another sarcoplasmic reticulum Ca^{2+} buffering protein associated with RyR2 is CASQ2 that plays an important role in the control of Ca^{2+} release from the sarcoplasmic reticulum to the cytosol. The hypothesis is that some of these mutations compromise CASQ2 synthesis and reduce expression or provoke complete absence of CASQ2 in the heart and others cause expression of defective CASQ2 proteins with abnormal regulation of cellular Ca^{2+} homeostasis [2, 3].

Mechanism of Ventricular Arrhythmias in CPVT

The central pathogenic abnormality in CPVT results from abnormalities in the control of sarcoplasmic reticulum Ca^{2+} release. The L-type Ca^{2+}

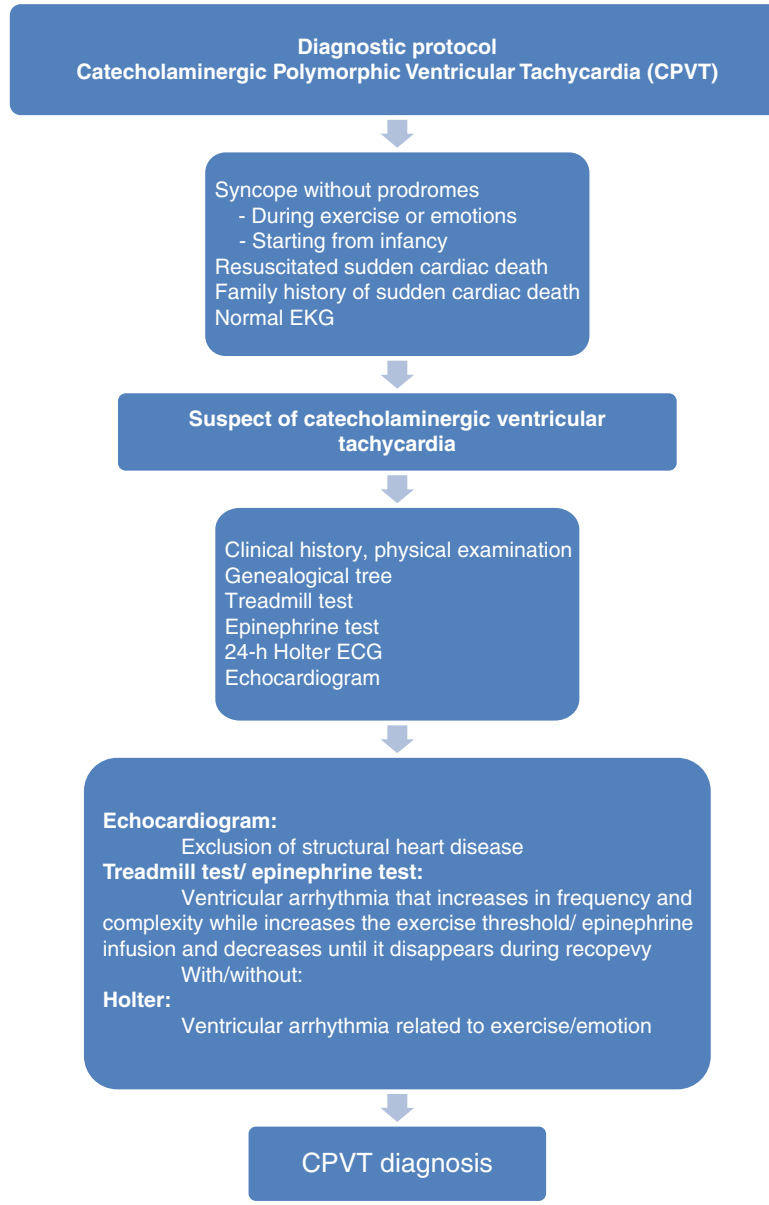

Fig. 26.3 Diagnostic protocol of catecholaminergic polymorphic ventricular tachycardia

channels in the cell membrane permit Ca^{2+} influx during the action potential plateau that triggers more Ca^{2+} release (Ca^{2+} transients) from the sarcoplasmic reticulum into the cytosol via activation of Ca^{2+} release channels (RyR2). This amplifying process, known as Ca^{2+}-induced Ca^{2+} release, causes a quick raise in cytosolic Ca^{2+} concentration to an optimal level required for binding of Ca^{2+} to troponin C and induction of contraction [5]. During diastole, the sarcoplasmic/endoplasmic reticulum calcium adenosine triphosphatase (SERCA) resequesters most of the surplus Ca^{2+} in the cytosol into the sarcoplasmic reticulum, controlled by the phosphoprotein phospholamban. Additionally, to balance the Ca^{2+} that enters with the Ca^{2+} current, Na^{+}–Ca^{2+} exchanger extrudes from the cell some of the Ca^{2+}.

RyR2 mutations alter the physiological properties and function of RyR2 using some molecular mechanisms not fully understood. It has been

suggested that the binding affinity of RyR2 for the regulatory protein calstabin-2 is reduced by CPVT mutations in RyR2. The closed conformational state of the RyR2 channel is stabilized by calstabin-2, which enables the channel to close completely during diastole (at low intracellular Ca^{2+} concentrations) and prevents aberrant Ca^{2+} leakage from the sarcoplasmic reticulum, ensuring muscle relaxation. The binding affinity of calstabin-2 is worsened by PKA phosphorylation (induced by beta-adrenergic stimulation) of the mutant RyR2 channels, increasing the probability of an open state at diastolic Ca^{2+} concentrations. So, diastolic Ca^{2+} leak from the sarcoplasmic reticulum during stress or exercise is the result of the incomplete closure of the mutant RyR2 channel during diastole [1, 6]. Other groups have suggested that in CPVT the mutated RyR2 channel is more sensitive to luminal (sarcoplasmic reticulum) Ca^{2+}. So under baseline conditions, where sarcoplasmic reticulum load is normal, there is no Ca^{2+} leak, but under beta-adrenergic (sympathetic) stimulation, sarcoplasmic reticulum Ca^{2+} concentration raises above the reduced threshold, causing Ca^{2+} to leak out of the sarcoplasmic reticulum. A third hypothesis for RyR2-related CPVT is that the intermolecular interactions between discrete RyR2 domains necessary for proper folding of the channel and self-regulation of channel gating are impaired by the mutations in RyR2 [6].

The most important Ca^{2+} storage protein in the sarcoplasmic reticulum is calsequestrin (CASQ2) and forms a part of a quaternary complex with RyR2, triadin, and junction, which play a major role in regulating intracellular Ca^{2+}. Calsequestrin, as a high-capacity, low-affinity Ca^{2+}-binding protein, is able to bind luminal Ca^{2+} during diastole, buffering Ca^{2+} within the sarcoplasmic reticulum and preventing diastolic Ca^{2+} release via RyR2 to the cytosol. For effective termination of sarcoplasmic reticulum Ca^{2+} release and prevention of spontaneous Ca^{2+} release during diastole, the control of RyR2s by luminal Ca^{2+} is required. CASQ2 mutations lead to diminished Ca^{2+} signaling refractoriness and generation of arrhythmogenic spontaneous Ca^{2+} releases [6]. The main arrhythmogenic mechanism in CPVT is DADs and triggered activity because the bidirectional ECG pattern of this VT corresponds to the arrhythmias related with intracellular Ca^{2+} overload and the DADs documented during digitalis toxicity. Mutations in RyR2 or CASQ2 lead to the activation of the Na^{+}–Ca^{2+} exchanger enhanced by cytosolic Ca^{2+} overload. This mechanism generates a net inward current (the so-called transient inward current) that provokes DADs and if they reach the threshold for Na^{+} channel activation can trigger abnormal beats [1, 3]. Low-amplitude DADs usually are not clinically significant. A decrease in the initiating cycle length probably is the most important factor that leads subthreshold DADs to reach threshold; indeed fast heart rates increase both the amplitude and rate of the DADs. Moreover, catecholamines can facilitate the development of DADs because the stimulation of beta-adrenergic receptors and subsequently cAMP increases the L-type Ca^{2+} current and leads to an increase in transsarcolemmal Ca^{2+} influx and intracellular Ca^{2+} overload; also the enhancement of the activity of the Na^{+}–Ca^{2+} exchanger increases the likelihood of DAD-mediated triggered activity; finally, the enhancement of the uptake of Ca^{2+} by the sarcoplasmic reticulum leads to a greater amount of Ca^{2+} stored in the sarcoplasmic reticulum and the subsequent major release of Ca^{2+} from the sarcoplasmic reticulum during contraction. The increased susceptibility to ventricular arrhythmias in CPVT patients during exercise and emotional stress is associated with increased sympathetic stimulation and higher heart rates.

Sometimes in CPVT, spontaneous Ca^{2+} release and DADs can happen without Ca^{2+} overload. For example, mutations in RyR2 or CASQ2 provoke defective Ca^{2+} signaling that lowers the sarcoplasmic reticulum Ca^{2+} threshold for spontaneous Ca^{2+} release below the normal baseline level causing the so-named "perceived" Ca^{2+} overload [6].

Mechanism of the Bidirectional Morphology of Ventricular Tachycardia

The EP mechanisms leading to the characteristic bidirectional morphology of the VT are not fully understood. Some of the proposed mechanisms are the following: changes in conduction

direction from a single ventricular focus, one VT focus that triggers another focus, and firing from double ventricular foci (i.e., the right and left apical portions of the heart) [2, 6].

Others showed that left posterior inferior origin accounts for the majority of cases. Additionally, the site of origin of bidirectional VT has been recognized in the Purkinje network, with alternating firing from the right and left branches of the Purkinje fibers [3].

A recent experimental model identified a "ping-pong" mechanism as etiology of ventricular arrhythmias in CPVT, so in different regions of the His–Purkinje system (HPS) or ventricles, DAD-induced triggered activity develops at different heart rate thresholds. First, if the heart rate rises above a certain threshold, ventricular bigeminy appears from a single site in the HPS or ventricular myocardium. Ventricular bigeminy shortens the R–R cycle length that induces DAD-triggered beats from a second focus within the HPS, with the latter reciprocally activating PVCs from the first focus; this process is repeated back and forth, in a ping-pong pattern. The bidirectional VT characteristic of CPVT is produced by the "reciprocating bigeminy" from the two sites. When three or more sites concurrently develop bigeminy, the result is the development of polymorphic VT, whereas when repetitive DADs generate a run of triggered activity from a single site, the result is the development of monomorphic VT [7].

Differential Diagnosis

The first step is the exclusion of other inherited arrhythmogenic cardiac disorders that can cause malignant ventricular tachyarrhythmias. Measure of QT interval excludes the diagnosis of SQTS (if QTc interval less than 320 ms) or LQTS (if QTc interval more than 450 ms). The first syncope in CPVT patients more often occurs during childhood, whereas clinical symptoms of LQTS typically start around puberty.

Furthermore, the typical arrhythmia in CPVT patients is bidirectional VT with a beat-to-beat 180° rotation of the QRS complex, in contrast to the torsades de pointes (characterized by the twisting of the points of the QRS complexes), frequent in LQTS patients [1–3].

Bidirectional VT can also occur in patients with type 7 LQTS (LQT7, Andersen–Tawil syndrome) linked to mutations in the KCNJ2 gene, which may be considered a CPVT phenocopy, particularly in patients with Andersen–Tawil syndrome having borderline QT interval prolongation. SCD is rare among Andersen–Tawil syndrome and KCNJ2 mutation carriers [8]. Furthermore, typical of Andersen–Tawil syndrome are the extracardiac features such as periodic paralysis and facial dysmorphism [1–3].

Ankyrin-B syndrome can also manifest with catecholamine-mediated ventricular arrhythmias. Cardiac ankyrin-B is a structural membrane adapter protein encoded by ANK2 gene. Loss-of-function mutations result in increased intracellular concentration of Ca^{2+} and a greater risk of fatal arrhythmia. This syndrome has been categorized under LQTS (LQT4), but the QT interval prolongation is inconsistent and the degrees of cardiac dysfunction and arrhythmias observed (including bradycardia, sinus arrhythmia, idiopathic VF, adrenergically mediated VT, and SCD) are variable, so ankyrin-B syndrome is considered as a different clinical entity compared to classic LQTS.

The typical ECG pattern and the structural abnormalities of the RV distinguish ARVD from CPVT despite the development of exercise-provoked arrhythmias. The typical arrhythmia in ARVD is monomorphic VT with a left bundle branch block (LBBB) pattern that is totally different from the polymorphic PVCs or VT in CPVT [4].

In contrast to CPVT, arrhythmias in Brugada syndrome appear usually at rest or during sleep so patients with Brugada syndrome do not manifest polymorphic PVCs on physical effort. Moreover, Brugada syndrome shows the characteristic ST segment elevation in the precordial ECG leads at baseline and after provocation testing with Na^+ channel blockers, absent in CPVT [4].

Risk Stratification

Because of the relatively small number of patients, reported risk stratification for SCD in CPVT is difficult. CPVT patients with prior

cardiac arrest and those in whom pharmacological therapy does not suppress are considered at high risk for SCD. Programmed electrical stimulation typically fails in inducing ventricular arrhythmias and is of no value for risk stratification. Furthermore, the predictive value of inducibility of ventricular arrhythmias by catecholamine infusion or exercise for risk stratification has not been confirmed.

Pharmacological Therapy

The first line of treatment for CPVT is beta-blockers and should be promptly initiated to prevent the occurrence of ventricular tachyarrhythmias. Untreated CPVT has a poor prognosis, so drug therapy is indicated for all clinically diagnosed patients and also for all silent carriers of a CPVT mutation. The most widely used beta-blockers are nadolol (1–2.5 mg/kg/day) and propranolol (2.5–3.5 mg/kg/day). Intravenous propranolol is the treatment of choice for acute management of CPVT (Table 26.1).

Exercise stress testing and Holter monitoring can help determine the adequate beta-blocker dosage for arrhythmia control, but the absence of exercise-provoked arrhythmias does not completely exclude the risk of arrhythmia recurrence, and the maximum tolerated dose of beta-blockers should be prescribed to optimize control of arrhythmias with the aim of avoiding the achievement of the threshold rate for CPVT [3, 4].

Recent studies demonstrate that the addition of flecainide to beta-blocker therapy can effectively reduce exercise-induced ventricular arrhythmias in CPVT patients not controlled by beta-blocker therapy alone [9]. Direct blockade of RyR2 channels and reduction of Ca^{2+} spark amplitude rather than Na^{+} channel blockade mediate the flecainide effects [10].

Limited data suggest that verapamil (an inhibitor of RyR2) can be an alternative option for the treatment of CPVT. Also, verapamil used in combination with beta-blockers can provide additional protection. However, there is no conclusive

Table 26.1 Treatment of catecholaminergic polymorphic ventricular tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) – treatment
Genotype, if available
Beta-blockers (BB) at maximum tolerated doses:
In patients with CPVT clinical diagnosis (Class I indication, level of evidence: C) [11]
In patients without clinical symptoms of CPVT but with genetic diagnosis of CPVT during childhood (Class IIa indication, level of evidence: C) [11]
In patients with CPVT and genetic diagnosis in adult age without any symptoms of tachycardia (Class IIb indication, level of evidence: C) [11]
Nadolol 40 and 80 mg:
Kids: 1–2.5 mg/kg/die, q.d. Adults: maximal doses 160 mg/die, q.d.
Propranolol:
Kids: 2.5–3.5 mg/kg/die, t.i.d. (every 8 h) Adults: 160 mg/die (q.d.)
Treadmill test could help titrate beta-blocker doses (target heart rate of <85 % of maximum heart rate, significant reduction of ventricular arrhythmia burden during exercise test)
Left thoracic sympathectomy [2–4]
Kids with syncope during beta-blocker therapy, to delay/avoid ICD implantation ICD patients with frequent ICD therapy (ATP/shock/electrical storm)
Flecainide [9]:
On top of maximum tolerated doses of beta-blockers and ICD [patients with high burden of complex ventricular arrhythmias in the exercise test during follow-up or frequent ICD therapy (ATP/shock/electrical storm)] Doses: 150–200 mg/die; range: 100–300 mg/die
ICD: CPVT + resuscitated sudden cardiac death (Class I indication, level of evidence: C) [11]
ICD + BB in CPVT patients with syncope and/or sustained VT during treatment with BB (Class IIa indication, level of evidence: C) [11]
Absolute contraindication to competitive sports [13]
Relative contraindication to recreational sports [13]
Avoid other arrhythmia triggers: loud noises, emotional stress
If the patient is implanted with ICD: periodic follow-up to monitor recorded arrhythmias or ICD therapy
Urgent medical consultation in case of syncope or nocturnal agonal respiration
Evaluation recommended to first-degree family members

evidence for recommending verapamil alone or in combination with beta-blockers because of the small number of patients and the limited follow-up and also its impact on prognosis is not known [4].

Implantable Cardioverter Defibrillator

ICD therapy is recommended for CPVT patients who have survived a cardiac arrest or those who continue to have symptoms (syncope or sustained or hemodynamically unstable VT) despite adequate beta-blocker therapy [11].

Approximately half of ICD recipients experience an appropriate shock to terminate VT during 2 years of follow-up. It is important to maintain the maximum tolerated dose of beta-blockers in ICD patients to help reduce the risk of arrhythmic storms and ICD shocks [1, 2].

Catheter Ablation

When ventricular arrhythmias are triggered by monomorphic PVCs, catheter ablation of the focus of PVCs may be attempted to reduce the burden of arrhythmias and ICD shocks. The initiating beat of VT usually shows an LBBB–inferior axis pattern, suggestive of a ventricular outflow tract origin [12].

Sympathetic Denervation

Small case series suggest the effectiveness of left cardiac sympathetic denervation in patients with recurrent symptoms despite beta-blocker therapy or those experiencing intractable arrhythmic storms or frequent ICD shocks [2].

Participation in Sports

All CPVT patients with documented exercise- or isoproterenol-induced VT should avoid all competitive sports. A less restrictive approach may be possible for the genotype-positive/phenotype-negative (asymptomatic, no inducible VT) athlete [13].

Family Screening

After a diagnosis of CPVT in a family member because of the severe clinical manifestations and high mortality of CPVT, it is important to study both first- and second-degree relatives to find potential CPVT patients [14]. Exercise testing and Holter monitoring are used for screening family members. Moreover, some CPVT patients may not have arrhythmias in the exercise stress test during early childhood, but later in life, a change in the phenotype may occur. Therefore, follow-up with repeated exercise stress tests is indicated. When a gene mutation has been identified in the proband, genetic testing is recommended to screen family members [3].

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Part IX

Miscellanea

Sudden Cardiac Death

27

Laura Cipolletta

27.1 Introduction

Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are defined as the sudden cessation of cardiac activity with hemodynamic collapse, usually due to sustained ventricular tachycardia/ventricular fibrillation (VT/VF). Patients with structural heart disease especially coronary heart disease are defined at greater risk.

An intervention (e.g., defibrillation) or a spontaneous reversion to sinus rhythm is defined as SCA (or aborted SCD), and if the patient dies, the event is called SCD [1]. However, typically the term SCD is used to describe both fatal and nonfatal cardiac arrest occurring 1 h from symptom onset.

The specific causes of SCA vary with patient age and different kinds of population studied. Most commonly ventricular fibrillation (VF) in the setting of structural heart disease causes hemodynamic collapse and subsequently SCA.

The underlying cardiac disease and the rapidity of resuscitation maneuvers (defibrillation) are the determinant factors to establish the outcome following SCA. The insufficient cerebral blood flow due to SCA mostly results in loss of consciousness within seconds to minutes. There are usually no premonitory symptoms. If symptoms are present, they are nonspecific such as weakness, chest discomfort, shortness of breath, and palpitations [2].

27.2 Case Report

A 17-year-old female patient was admitted to hospital after an episode of SCA that ensued during physical activity. The electrocardiogram (ECG) recorded during the episode showed a pulseless VT (Fig. 27.1).

Medical History and Cardiovascular Risk Factors

- Ebstein anomaly and severe pulmonary stenosis; her family history of structural heart disease, syncope, or sudden cardiac death was unremarkable.
- 2014: She had undergone surgical tricuspid valve replacement with a biological prosthetic valve and cavopulmonary anastomosis.

Allergies

None

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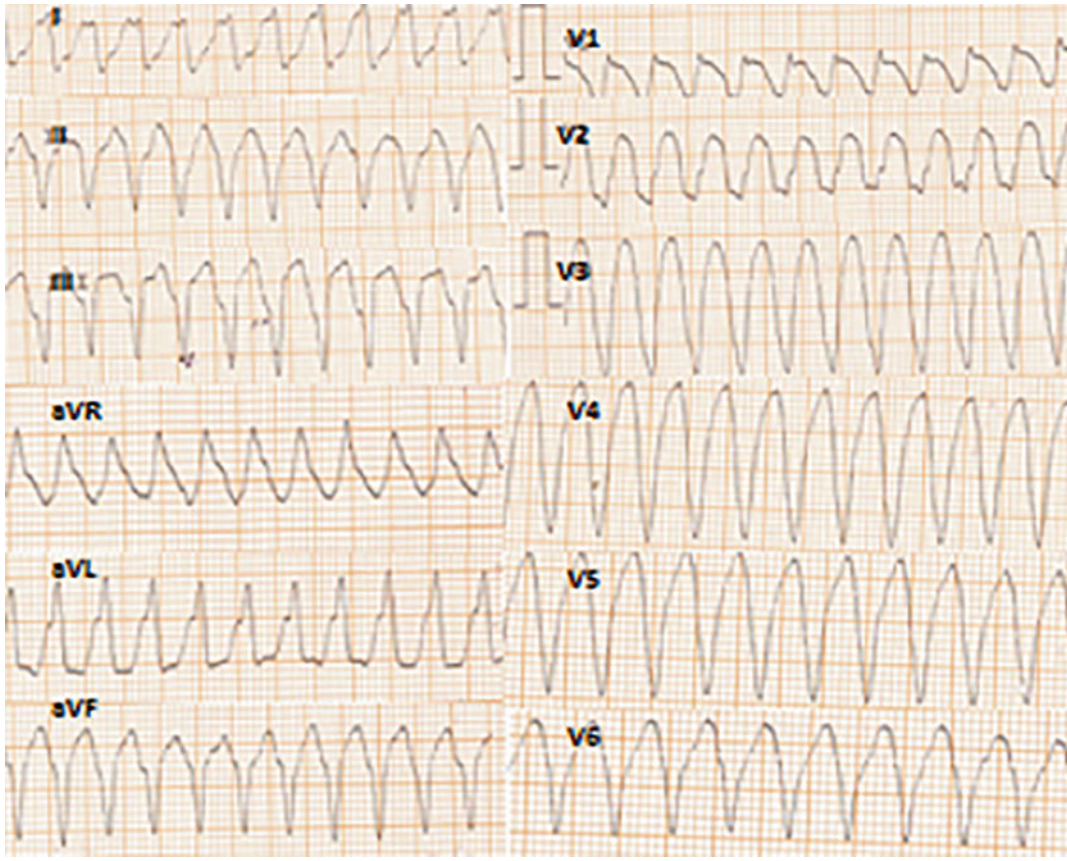

Fig. 27.1 Onset of polymorphic VT symptomatic for syncope, converted to sinus rhythm after cardiopulmonary resuscitation

Medications

None

Vital Signs

- Temperature: 36.8 °C
- Heart rate: 80 bpm
- Arterial blood pressure: 110/70 mmHg
- Respiratory rate: 18 breaths/min
- Oxygen saturation: 92 %

Physical Examination

- General appearance: Well developed, well nourished, alert, and cooperative
- Lungs: Clear to auscultation and percussion without rales, rhonchi, wheezing, or diminished breath sounds
- Cardiovascular: Normal S1 and S2. No S3 and S4. Systolic murmur 2/6 at Erb's point. Regular rhythm. No peripheral edema, cyanosis, or pallor. Warm and well-perfused extremities
- Abdomen: Positive bowel sounds. Soft, nondistended. No guarding or rebound. No masses

Routine Laboratory Test

Tests were normal (hemoglobin 12.8 g/dl; white blood cells 9680/mmc; creatinine 0.82 mg/dl; potassium 3.7 mEq/l; sodium 138 mEq/l; magnesium 1.7 mg/dl).

Instrumental Examination

Basal ECG after DC shock was normal with incomplete right bundle branch block and specific abnormalities of repolarization.

The loss of consciousness was caused by a monomorphic pulseless VT (Fig. 27.1), converted to sinus rhythm by external DC shock after a brief period of cardiopulmonary resuscitation.

Figure 27.2 shows the magnetic resonance of the patient. The right ventricle was severely enlarged, with a papyraceous right ventricular wall.

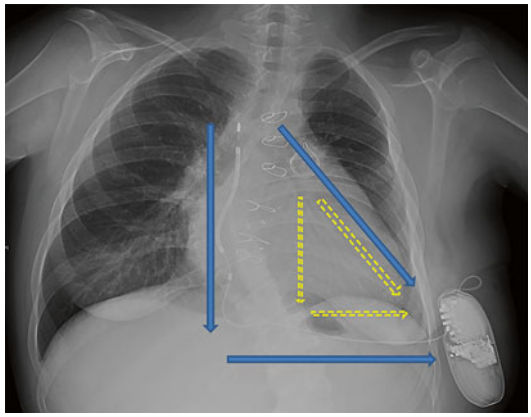

Fig. 27.2 Cardiac magnetic resonance

Clinical Course and Therapeutic Management

During hospital stay, she was treated with a beta-blocker (propranolol 3 mg/kg/day) with no further episodes. Genetical analysis and exercise test ruled out polymorphic ventricular tachycardia as the etiology of the VT.

The VT episode was treated with an external direct current cardioversion, and the patient was then referred to our center to attempt a VT ablation. Unfortunately, the fact that the right ventricle (RV) was papyraceous and the free ventricular wall was thin would have exposed the patient to a high risk of catheter perforation.

Because transvenous implantable cardioverter defibrillator (ICD) implantation had the same risk of cardiac perforation and access to the right cardiac chambers had been made unfeasible by cavopulmonary anastomosis, subcutaneous (S)-ICD implantation was considered. In assessing the patient's adequacy for S-ICD implantation, the morphology of the QRS was screened to avoid T-wave oversensing. Because of the bizarre morphology of the QRS attributable to severe dilatation of the RV, QRS screening was performed with the left arm electrode placed to the right side of the xiphoid process. Under local anesthesia and conscious sedation, the catheter was inserted

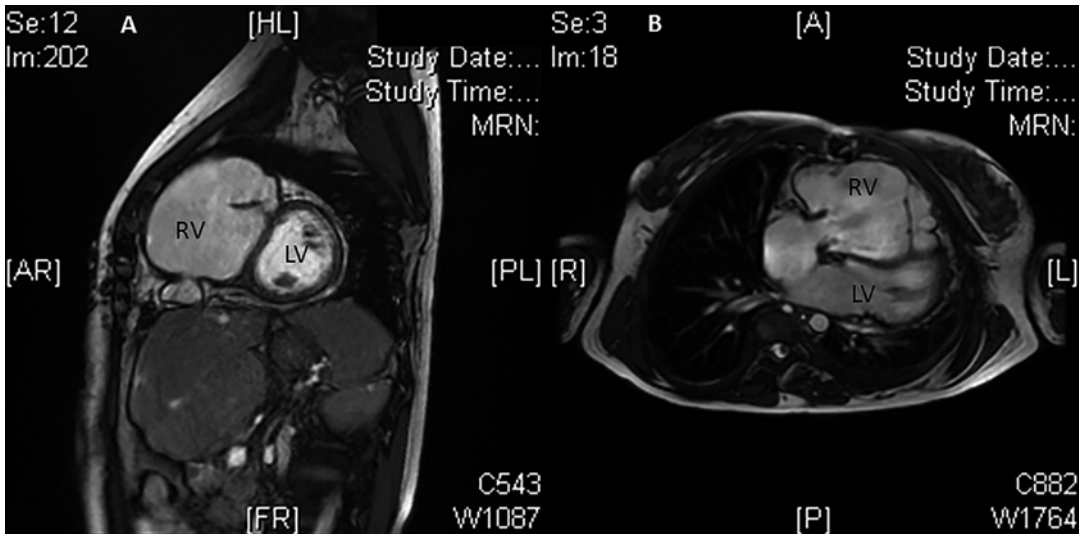

Fig. 27.3 Chest X-ray of S-ICD implant

subcutaneously from the pocket in the left midaxillary region to the right side of the xiphoid process. The tip was then advanced up to the manubriosternal junction, 1 cm to the right of the midsternal line (Fig. 27.3). At the end of the procedure, a defibrillation test was performed: Clinical VT was induced, correctly sensed, and treated after 12.5 s with a 65 J shock (conventional polarity configuration). At 2-month follow-up examination, the patient did not have any complications, and no significant events were recorded.

27.3 Sudden Cardiac Death

Definitions

Various criteria have been used to define SCA and SCD in the medical literature [3]. It is difficult to find a specific definition for several main reasons: First of all, only two-thirds of events are witnessed, making the diagnosis difficult to establish; secondly, the cardiac rhythm at clinical presentation is unknown in many cases, so it is not possible to restrict the definition of SCA to documented cases of VF; finally, the suddenness of death is generally defined by the duration of symptoms prior to SCA, but in approximately one-third of cases, the duration of symptoms is not clearly defined.

For these reasons, the criteria proposed do not rely upon the cardiac rhythm at the time of the event. The criteria focus on the sudden pulseless event occurred out of hospital and on the absence of a noncardiac condition (e.g., pulmonary embolism, intracranial hemorrhage, central airway obstruction) as the cause of cardiac arrest.

The following definitions of SCA and SCD were presented by the 2006 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS):

> Sudden cardiac arrest is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death. Cardiac arrest should be used to signify an event as described above, that is reversed, usually by CPR and/or defibrillation or cardioversion, or cardiac pacing. Sudden cardiac death should not be used to describe events that are not fatal [1].

Epidemiology

SCD accounts for approximately 15 % of the total mortality in the industrialized countries [4].

The incidence of SCD increases as a function of advancing age. The prognosis of patients experiencing SCA varies significantly according to the initial rhythm, although the outcome remains poor, despite advances in the treatment of heart disease.

The incidence of experiencing SCA is increased by age, sex, and underlying cardiac disease [5]. Indeed, men are two to three times more likely to experience SCA than women. In the Women's Health Initiative, 161,808 postmenopausal women were followed for an average of 10.8 years, and the incidence rate of SCD was 2.4 per 10,000 women/year, and nearly one-half of women who experienced SCD did not have prior clinically recognized coronary heart disease [6].

The presence of clinically recognized heart disease and of coronary heart disease (CHD) risk factors, respectively, increases six- to tenfold and two- to fourfold the risk of SCA [7].

Etiology

SCA is more frequent in male with structural heart disease, especially CHD. The most frequent cause of SCA is CHD that amounts up to 70 % of SCAs. It is possible that SCA occur during an acute coronary syndrome (ACS) such as in patients with a chronic, stable CHD [8]. Usually in this setting, prior myocardial damage and scar act as a substrate for SCA. On the contrary, SCD occurs more commonly in the absence of an identifiable acute cardiac event.

Ten percent of cases of out-of-hospital SCA is represented by other forms of structural heart disease, both acquired and hereditary. Examples of such disorders include the following:

1. SCD is responsible for approximately one-third of deaths in heart failure and cardiomyopathy.

2. Left ventricular hypertrophy due to hypertension or other causes.
3. Myocarditis.
4. Hypertrophic cardiomyopathy.
5. Arrhythmogenic right ventricular cardiomyopathy.
6. Congenital coronary artery anomalies.
7. Mitral valve prolapse.

Data from different reports documented approximately 10–12 % of cases of SCA among subjects without structural heart disease, under age 45, while a lower value of about 5 % has been described when older patients are included [9, 10].

Hereditary factors that contribute to coronary heart disease risk have been thought to operate nonspecifically for the SCD syndrome. However, several studies have identified mutations and relevant polymorphisms along the cascade from atherogenesis to plaque destabilization, thrombosis, and arrhythmogenesis, each of which is associated with a risk of a coronary event.

SCA in the absence of apparent structural heart disease can occur in different settings:

1. Brugada syndrome
2. Idiopathic VF
3. Congenital or acquired long QT syndrome
4. Arrhythmogenic right ventricular cardiomyopathy
5. Catecholaminergic polymorphic VT
6. Familial SCD of uncertain cause
7. Wolff-Parkinson-White syndrome

A major role in the pathogenesis of SCA, in addition to the presence of the above underlying disorders, is played by acute superimposed triggers. These include ischemia, autonomic nervous system activation, psychosocial factors, electrolyte disturbances (particularly hypokalemia and hypomagnesemia), and the proarrhythmic effect of some antiarrhythmic drugs. The mortality is highest in the first month after acute myocardial infarction (MI) in patients with ejection fraction (EF) of less than 30 % [1].

In addition, direct trauma over precordium precipitated SCA that results from commotio cordis.

The cumulative risk of SCD has been estimated at 15–20 % of adults with aortic stenosis, with the risk being higher in symptomatic patients and equal to or less than 5 % in asymptomatic patients. Mitral valve prolapse is usually non-life-threatening, and its link with SCD has never been definitely demonstrated. Reported SCD rates in patients with Wolff-Parkinson-White (WPW) syndrome have been 0.15 %, due in most to the development of atrial fibrillation (AF) with a rapid ventricular response that degenerates to VF. Genetic influences modulate the risk of SCD in the setting of CHD. The Paris Prospective Study I, analyzing more than 7,000 men followed for an average of 23 years, found that a parental history of SCD increased the relative risk of SCD for offspring to 1.8, without elevating the risk for MI. When both parents had SCD, the relative risk for SCD in offspring was 9.4. Genetic influences may act through multiple mechanisms, such as modulation of the substrate, atherothrombosis, electrogenesis impulse propagation, neural control, and regulation [1].

Some individuals can have inherited abnormalities that are not manifest until triggered by an external event. For example, autonomic modulation associated with certain types of activity, as well as drugs that affect cardiac repolarization, can convert a subclinical genetic abnormality to SCD. Among the genetic factors, the most common are DNA variants called "polymorphisms" that may be present in a large proportion of the population and create susceptibility for SCD. Single nucleotide polymorphisms (SNPs) are DNA variants that can be associated with a functional consequence. For example, a polymorphism identified in the alpha 2b adrenergic receptor is associated with an increased risk of MI and SCD [1]. Nevertheless, to create a risk for SCD, a combination of polymorphisms

in different genes may be required, interacting with a specific trigger or substrate, because millions of SNPs are present in the DNA of each individual [1].

Risk Factors

An increased risk of SCA is associated with a number of clinical characteristics and other factors among patients without prior clinically recognized heart disease [11, 12]. Coronary heart disease and SCA have a lot of risk factors in common. These include family history of myocardial infarction, hypertension, dyslipidemia, diabetes mellitus, obesity, cigarette smoking, and physical inactivity [13, 14].

The risk of SCA in patients with coronary heart disease is strongly related to current cigarette smoking and the number of cigarettes smoked per day. In the Nurses' Health Study, 101,018 women were followed for 30 years, and current smokers had a significantly greater risk of SCD than women who had never smoked (adjusted hazard ratio 2.44, 95 % CI 1.80–3.31), and the risk was increased even among women who smoked 1 to 14 cigarettes per day (adjusted hazard ratio 1.84, 95 % CI 1.16–2.92) [15]. In this study, the risk of SCD declined over time in a linear fashion after quitting smoking, reaching the same risk of SCD as never smokers 20 years after quitting [15].

The risk of SCA is particularly high among current smokers and declines rapidly after stopping smoking, to reduce the risk of SCA and a multitude of other complications.

During and up to 30 min after strenuous exercise, the risk of SCA is transiently increased compared to other times [16]. In fact, the actual risk during any one episode of vigorous exercise is very low (1 per 1.51 million episodes of exercise) [17]. Also, the magnitude of the transient increase in risk during acute exercise is lower for people who perform regular exercise compared with people for whom exercise is unusual [16, 17].

Data from long-term exercise intervention trials among apparently healthy persons that focus upon major disease end points are absent. Anyway, regular exercise should be encouraged for the primary prevention of coronary heart disease and consequently SCA. Despite a small transient increase in risk during and shortly after strenuous exercise, rate of SCD is lower among exercisers compared with sedentary men [17]. A reduced risk of SCD is associated with a lower resting heart rate and increased heart rate variability, characteristics which developed after regular exercise.

Patients should be advised to pay attention to possible symptoms of coronary heart disease, even if they are trained exercisers.

Hypertrophic cardiomyopathy, anomalous coronary artery of wrong sinus origin, myocarditis, and arrhythmogenic right ventricular cardiomyopathy [18, 19] are an exception to the lower overall risk associated with intensive exercise that occurs in patients with certain, often unrecognized underlying heart diseases.

A family history of SCA, which could be associated with myocardial infarction, is related to a 1.5- to 1.8-fold increased risk of SCA [20]. Traditional risk factors that tend to aggregate in families, such as hypercholesterolemia, hypertension, diabetes mellitus, and obesity, do not explain the increase in risk. However, it is likely that interactions of mutations or polymorphisms in specific genes and environmental factors influence this risk.

Elevated serum C-reactive protein (CRP) is also associated with an increased risk of SCA [21]. Higher serum concentrations of CRP could be an expression of chronic inflammation that has been implicated as a risk factor for cardiovascular diseases (including acute coronary syndromes and stroke).

Heavy alcohol consumption (six or more drinks per day) or binge drinking increases the risk for SCD [22, 23]. In fact, moderate alcohol intake (e.g., one to two drinks per day) is related to a reduction of the risk of SCD [22].

Clinical observations have suggested that acutely stressful situations could have a possible relation with a higher risk of SCA. For example, major disasters, such as earthquakes and war, result in a rapid transient increase in the rate of SCA in populations [15]. Social support from

others may reduce the risk associated with stressful life events.

Excessive caffeine intake has been investigated as a potential risk factor for SCA [24], but no significant association with SCA has been found.

After a myocardial infarction, elevated plasma nonesterified fatty acid (free fatty acid) concentrations were associated with ventricular arrhythmias and SCD [25]. However, in the Cardiovascular Health Study, in a population-based cohort of older adults [26], nonesterified fatty acids were not associated with SCD. Moreover, in a population-based case-control study among people without prior clinically recognized heart disease, cases of SCA had higher concentrations of trans isomers of linoleic acid in red blood cell membranes [27].

In contrast, in several studies, a higher dietary intake and higher plasma levels of long-chain n-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid) are associated with a lower risk of SCD [28].

Mechanisms of Sudden Cardiac Death

The rhythm most often recorded at the time of sudden cardiac arrest is VF. Previous studies suggest that up to 80 % occur via this mechanism and up to 20 % are attributed to bradyarrhythmias, including advanced atrioventricular (AV) block and asystole [1]. Bayes de Luna et al. [31] reported that in 157 ambulatory patients who had SCD while undergoing Holter recording, 62.4 % had VF, 16.5 % had bradyarrhythmias, 12.7 % had torsades de pointes, and 8.3 % had primary VT. The true incidence of bradyarrhythmias is not easy to understand since a rhythm beginning as VF may appear to be asystole during the first ECG recording. Advanced AV block or significant bradycardia can provoke VF. It is difficult to identify clearly the electrophysiological mechanism responsible for SCD. Mechanisms may be multifactorial and are different depending on the specific cardiac abnormality, and a rhythm can begin via one mechanism and proceed via a different one.

Class I and III antiarrhythmic agents were not able to reduce total and SCD mortality in patients at risk for SCD [30]. In fact, both classes do not direct their actions on cardiac muscle or specialized conducting tissues that have been shown effective for prevention of SCD. Beta-blockers, ACE inhibitors, angiotensin receptor-blocking agents, lipid-lowering agents, spironolactone, and fibrinolytic and antithrombotic agents were judged likely effective especially in primary prevention. Since SCD is for the most part the result of a ventricular tachyarrhythmia, these drugs act on the biochemical, ischemic, and fibrotic processes that underlie the onset or maintenance of life-threatening ventricular arrhythmias.

The mechanisms of cardiac arrest are represented by electromechanical dissociation, asystole and heart block, and VF. More permanent changes could also occur, such as plaque rupture, but it is likely that transient factors interact with a fixed substrate to precipitate the arrhythmia. The possibilities include physical activity, transient ischemia, hypoxia, stretch, ion channel abnormalities, pH and electrolyte changes, inflammation, neuroendocrine actions, and drugs.

Management

The acute management of survivors of SCA includes the following:

1. Identification and treatment of acute reversible causes
2. Evaluation for structural heart disease
3. Evaluation for primary electrical diseases in patients without identifiable arrhythmic triggers or cardiac structural abnormalities
4. Neurologic and psychologic assessment
5. Evaluation of family members in selected patients with a suspected or confirmed heritable syndrome

Noninvasive Management

ECG

A noninvasive evaluation is recommended with resting 12-lead ECG in all patients who are evaluated for ventricular arrhythmias (class I, level of evidence: A). It allows to identify various congenital abnormalities associated with ventricular arrhythmias and SCD (e.g., LQTS, SQTS, Brugada syndrome, ARVC) but also other ECG modifications, such as those due to electrolyte disturbances, or evidence suggesting underlying structural disease, such as bundle branch block; Q waves indicative of ischemic heart disease, ventricular hypertrophy, or infiltrative cardiomyopathy; and AV block. QRS duration and repolarization abnormalities are both independent predictors of SCD. A QRS duration greater than 130 ms has been associated with increased mortality in patients with a reduced LVEF (equal to or less than 30 %). Prospective studies have also reported an association between ST-segment depression or T-wave abnormalities and increased risk of cardiovascular death and SCD in particular [1]. QTc greater than 440 ms has been demonstrated to predict cardiovascular death with adjusted relative risk of 2.1 [31]. Some data suggest that the correlation between QTc and survival could be "J shaped." So, also relatively short QTc intervals have also been associated with increased risk. The definition of short QT syndrome as a QTc less than 300 ms has been proven to be an independent predictor of SCD [32].

Exercise Testing

Among noninvasive evaluation, exercise testing is useful in patients with known or suspected exercise-induced ventricular arrhythmias, including catecholaminergic VT (class I, level of evidence: B).

T-Wave Alternans (TWA)

It is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias (class IIa, level of evidence: A).

Other Noninvasive ECG Techniques

Also other noninvasive ECG techniques such as signal-averaged ECG (SAECG), heart rate variability (HRV), baroreflex sensitivity, and heart rate turbulence may be useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias (class IIb, level of evidence: B) [1].

Echocardiography

Echocardiography is recommended for the subset of patients at high risk for the development of SCD, such as those with dilated, hypertrophic, or RV cardiomyopathies, AMI survivors, or relatives of patients with inherited disorders associated with SCD (class I, level of evidence: B).

Invasive Tests

Coronary Angiography

Coronary angiography can be useful in evaluating the presence of significant obstructive CHD in patients with life-threatening ventricular arrhythmias or in survivors of SCD, who have an intermediate or greater probability of having CHD by age, symptoms, and gender (class IIa, level of evidence: C).

Electrophysiological Study (EPS)

Invasive tests such as EPS were required in the primary prevention of SCD in patients with the same characteristic of patients enrolled in MADIT, MUSTT, and BEST-ICD trials [1]. Inducibility of VT in patients with NSVT on Holter monitoring identified a population at high risk for VT/VF and ICD use in the MADIT trial [33]. Lower heart rate, lower EF, and a longer interval between MI and an EPS correlate with higher inducibility. In patients with ischemic heart disease, asymptomatic NSVT, and an EF less than 40 %, inducibility of sustained VT identifies patients at high risk of subsequent VT. Persistent inducibility while receiving antiarrhythmic drugs predicts a worse prognosis. Patients in whom amiodarone

suppressed VT inducibility or slowed VT to a mean cycle length of greater than 400 ms had 30 % higher mortality compared with patients who did not respond to amiodarone and had an ICD [1].

In dilated cardiomyopathy (DCM), EPS has a low predictive value and low inducibility [1].

EPS is not useful in long QT syndrome (LQTS) and hypertrophic cardiomyopathy. His role is not yet clear in Brugada syndrome because of the lack of large randomized studies and a uniform protocol [1].

In arrhythmogenic right ventricular cardiomyopathy (ARVC), EPS is useful to guide ablation [1].

Management of Cardiac Arrest

Cardiac arrest is described as an abrupt loss of effective blood flow that causes immediate loss of consciousness and leads immediately to death if untreated.

The most common electrical mechanisms for cardiac arrest are VF and pulseless VT but also could be a severe bradyarrhythmias, asystole, or pulseless electrical activity. Survival probabilities are better for VT/VF at first presentation than for bradyarrhythmias or asystole.

A rapid response time is the major determinant of survival. So cardiopulmonary resuscitation (CPR) should be started immediately after contacting a response team (class I, level of evidence: A).

In an out-of-hospital setting, if an automatic external defibrillator (AED) is available, shock therapy should be administered according to the guidelines on CPR (class I, level of evidence: C).

Reversible causes and factors contributing to cardiac arrest should be managed during advanced life support, such as management of mechanical factors, hypoxia, electrolyte disturbances, and volume depletion (class I, level of evidence: C).

If no CPR is initiated, the decrease in cardiac arrest survival is about 7–10 % per minute and 3–4 % per minute with CPR. On the contrary, when immediate defibrillation is available, with response time of less than 30 s, such as in monitored intensive care units and EP laboratories, survival from VF is greater than 90 % [34].

Synchronized cardioversion is used for unstable monomorphic VT, while high-energy unsynchronized shocks at defibrillation doses treat unstable polymorphic VT and VF. Monomorphic-tolerated VT generally is converted to sinus rhythm by monophasic waveform cardioversion synchronized shocks at initial energies of 100 J or higher.

The general aims of advanced life support are to establish hemodynamically effective cardiac rhythm, to optimize ventilation, and to maintain and support the restored circulation.

Epinephrine, 1 mg intravenously, is administered and followed by repeated defibrillation attempts at 360 J. Epinephrine may be repeated at 3–5-min intervals with defibrillator shocks in-between doses, but high-dose epinephrine does not provide added benefit [35].

Bradyarrhythmic events or pulseless electrical activity could be precipitated by metabolic and transient factors that must be controlled. Simultaneously, the rescuer should correct the chemistry of the blood focusing on ventilation (i.e., improved oxygenation, reversal of acidosis, and improvement of the underlying electrophysiological condition). Metabolic acidosis of cardiac arrest is corrected by adequate oxygenation of the blood, but sometimes additional correction can be achieved by intravenous administration of sodium bicarbonate. Excessive quantities can be deleterious. Possible reversible causes, particularly for bradyarrhythmia and asystole, should be considered and/or treated promptly, such as pulmonary embolus, acute MI, hypovolemia, hypoxia, cardiac tamponade, tension pneumothorax, acidosis, drug overdose, hypothermia, and hyperkalemia [1].

Primary Prevention

Primary prevention of SCA is tailored according to the different categories of patients, such as general population, patients surviving an acute

myocardial infarction, patients with heart failure and cardiomyopathy, and patients with one of the congenital disorders associated with an increased risk of SCA (e.g., Brugada syndrome, congenital long QT syndrome, WPW).

General Population

Two approaches could be applied to reduce the risk of SCA in the general population: screening and risk stratification to identify individuals who may benefit from specific interventions (e.g., stress testing, screening ECGs) and behavior that target the underlying disorders that predispose to SCA and reduce the risk in any individual (e.g., smoking cessation or other lifestyle modifications).

- *Screening and risk stratification:* In patients with known elevated risk of SCA (e.g., patients with a prior myocardial infarction), further risk stratification can identify subgroups that benefit from specific therapies, such as an ICD. On the contrary, in the general population without known cardiovascular disease, routine screening with 12-lead electrocardiography, exercise stress testing, or Holter monitoring hardly or ineffectively identifies populations at an increased risk of SCA.

Key point in risk stratification of the general population could be the following:

- *Identifying risk factors for cardiovascular disease* according to standard guidelines
- *Screening for coronary heart disease* in selected patients

Routine additional testing for the SCA risk stratification is not recommended.

A complex topic matter of debate is the preparticipation evaluation of athletes. There are conflicting opinions regarding the appropriateness of screening and, if so, the optimal screening evaluation, such as with an electrocardiogram or echocardiogram.

- *Risk factor reduction*: As mentioned above, the majority of the traditional risk factors associated with coronary heart disease are also associated with SCA.

Thus, reduction of these risk factors may affect the incidence of SCA in the general population. Such interventions include:

- Effective treatment of hypercholesterolemia
- Effective treatment of hypertension
- Heart-healthy diet
- Regular exercise
- Smoking cessation
- Moderation of alcohol consumption
- Effective treatment of diabetes

There is no definitive evidence that risk factor reduction in the general population lowers the rate of SCA. On the contrary, several studies have demonstrated that treatment of risk factors can lower total cardiovascular and coronary mortality. Reduction of cardiovascular risk factors may reduce SCA rates as well because the majority of CHD mortality is due to SCD.

In observational studies of populations at low cardiovascular risk, greater dietary fatty fish intake was associated with lower cardiac mortality [36]. This benefit is partially due to a reduced risk of SCD. From these results, subsequent randomized trials evaluated the benefit of fish oil supplements in high-risk populations [37].

The benefit of pharmacologic doses of n-3 polyunsaturated fatty acids is little compared to the intake of one to two servings of fatty fish per week. The pharmacologic use of fish oil supplements should be restricted to patients with refractory hypertriglyceridemia in whom the periodic monitoring of apolipoprotein B levels is recommended [37].

Post-myocardial Infarction

The risk of SCA is increased in patients who have had a myocardial infarction (MI), and this risk varies significantly according to a number of factors.

The strategies to the prevention of SCA in such patients include the following:

- *Standard medical therapies:* Both beta-blockers and ACE inhibitors (or angiotensin II receptor blockers) reduce overall mortality after an MI and are routinely administered. These agents also lower the incidence of SCD.
- *Risk stratification:* To identify those patients at the highest risk of SCA.
- *ICD implantation in selected patients:* ICD therapy is recommended for primary prevention to reduce SCD in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30–40 %, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and have a reasonable expectation of survival with a good functional status for more than 1 year (class I, level of evidence: A) [1].

In patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF of less than or equal to 30–35 %, are NYHA functional class I on chronic optimal medical therapy, and have a reasonable expectation of survival with a good functional status for more than 1 year, implantation of an ICD is reasonable (class IIa, level of evidence: B) [1].

Heart Failure and Cardiomyopathy

Patients with heart failure and left ventricular systolic dysfunction, regardless of the etiology, are at an increased risk of SCA. Primary prevention with an ICD is recommended in selected patients with either ischemic or nonischemic cardiomyopathy (NICM). ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF less than or equal to 30–35 %, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and have a reasonable expectation of survival with a good functional status for more than 1 year (class I, level of evidence: B) [1].

Ventricular arrhythmias and SCD are common in patients with symptomatic acute and chronic HF and LV systolic dysfunction. In the setting of acute HF, ventricular arrhythmias may be poorly tolerated and early cardioversion should be performed, rather than attempting pharmacological termination of arrhythmia.

In addition, standard medical therapies for HF (beta-blockers, ACE inhibitors or angiotensin II receptor blockers, and aldosterone inhibitors such as spironolactone or eplerenone) may lower the risk of SCA [1].

Secondary Prevention

ICD Therapy

An implantable cardioverter defibrillator (ICD) is the preferred therapeutic modality in survivors of SCA. The ICD does not prevent the recurrence of malignant ventricular arrhythmias, but it effectively terminates these arrhythmia recurrences.

ICD patients who have frequent arrhythmia recurrences and device discharges may benefit from adjunctive therapies, such as antiarrhythmic drugs or catheter ablation.

Coronary revascularization reduces the risk of SCD in patients with VF when evidence of acute myocardial ischemia is documented to precede the onset of VF (class I, level of evidence: B) [1]. With evidence of prior MI and significant LV dysfunction, if coronary revascularization cannot be realized, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have a reasonable expectation of survival with a good functional status for more than 1 year (class I, level of evidence: A) [1].

In patients with LV dysfunction due to prior MI with hemodynamically unstable sustained VT, receiving chronic optimal medical therapy, with a reasonable expectation of survival for more than 1 year, ICD is the effective therapy to reduce SCD (class I, level of evidence: A) [1].

ICD therapy is recommended for secondary prevention of SCD in patients who survived VF or hemodynamically unstable VT or VT with syncope and who have an LVEF less than or equal to 40 %, who are receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 year (class I, level of evidence: A) [1].

Amiodarone is a reasonable therapy to reduce symptoms due to recurrent hemodynamically stable VT for patients with LV dysfunction due to prior MI who cannot have or refuse to have an ICD implanted (class IIa, level of evidence: C) [1].

ICD implantation is a reasonable treatment of recurrent ventricular tachycardia in patients post-MI with normal or near-normal ventricular function who are receiving chronic optimal medical therapy and who have a reasonable expectation of survival with a good functional status for more than 1 year (class IIa, level of evidence: C) [1].

Antiarrhythmic Drugs

Antiarrhythmic drugs are less effective than an ICD for secondary prevention of SCD. Thus, their use is limited to the adjunctive role in frequent ventricular arrhythmia recurrences or in patients who do not want or are not candidates for an ICD (e.g., due to marked comorbidities or end-stage heart failure with a life expectancy less than 1 year).

Amiodarone, sotalol, and/or other beta-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias in optimally treated patients with HF (class I, level of evidence: C) [1].

Curative catheter ablation or amiodarone may be considered in place of ICD therapy to improve symptoms in patients with LV dysfunction due to prior MI and recurrent hemodynamically stable VT whose LVEF is greater than 40 % (class IIb, level of evidence: B) [1].

Congenital Heart Disease

ICD implantation is indicated in patients with congenital heart disease who are survivors of cardiac arrest after exclusion of any reversible causes. ICD implantation is indicated in patients who are receiving chronic optimal medical therapy and who have a reasonable expectation of survival with a good functional status for more than 1 year (class I, level of evidence: B) [1].

Congenital heart disease represents a spectrum of anatomical and physiological defects with an intrinsic risk of arrhythmias and late SCD. Overall, congenital heart defects are the principal cause of infant mortality (less than 1 year of age) in the industrialized world. About all defects can now be repaired or palliated, with greater than 1 million worldwide long-term survivors after surgery for congenital heart disease [38].

Due to the low incidence of late SCD in postoperative congenital heart disease patients, prospective randomized clinical trials do not exist to identify either risk factors for SCD or the role of primary prevention therapies.

During infancy and childhood, greater than 75 % of deaths in patients with congenital heart disease are in-hospital events, during the perioperative period [39].

The remaining deaths often occur in patients with other congenital anomalies in an out-of-hospital setting.

Beyond 20 years of age, a progressive increase in the incidence of sudden and total cardiac mortality occurs in postoperative congenital heart disease patients [40].

Congenital heart defects associated with the greatest risks of late SCD are tetralogy of Fallot, D- and L-transposition of the great arteries, aortic stenosis, and functional single ventricle [41].

The additional factors most likely associated with an increased risk of SCD due to ventricular arrhythmias appear to be volume overload due to pulmonary insufficiency and QRS duration greater than 160 ms [42]. EPS for risk stratification in these patients is not useful, in part due to variable study protocols and response to such testing [1].

The mechanism of SCD appears to be atrial flutter with 1:1 AV conduction, followed by myocardial ischemia resulting in polymorphic VT or VF or progressive ventricular dysfunction that results in ventricular arrhythmias [42]. Moreover, a positive response to EPS, independent of the clinical indica-

tion, may identify patients with a high risk of late SCD [42]. Also, there are non-arrhythmic causes of late sudden death in postoperative patients, including cerebral or pulmonary embolism, endocarditis, and aneurysm rupture [40].

Coronary artery abnormalities are another class of congenital anomalies that may result in SCD. The most common congenital coronary artery anomaly leading to SCD in the young is anomalous origin of the left coronary artery from the right sinus of Valsalva. The mechanism of SCD is that acute angulation of the coronary ostium or compression of the left coronary artery on the region between the aortic wall and RVOT results in acute myocardial ischemia and the subsequent VT or VF. The risk of SCD is greatest during the first three decades of life. Diagnosis may be difficult because only one-third of patients have exertional syncope or angina. Coronary angiography is needed to definitive diagnosis and the treatment is surgical revascularization. Similar risks for SCD have also been defined for anomalous origin of the right coronary artery from the left sinus of Valsalva [41].

Anomalous origin of the left coronary artery from the pulmonary artery generally is manifested during the first month of life. Myocardial ischemia and dysfunction develop with the normal decline in pulmonary vascular resistance when coronary perfusion is shunted to the pulmonary circulation. The diagnosis is echocardiographic during infancy, and the definitive treatment is surgical reimplantation of the left coronary ostium [41].

Ablation

First of all, ablation is indicated in patients who are at low risk for SCD, who are drug intolerant, or who do not wish long-term drug therapy and have sustained predominantly monomorphic VT that is drug resistant (class I, level of evidence: C) [1]. Secondly, it is indicated in patients with bundle branch reentrant VT (class I, level of evidence: C) [1]. Thirdly, it is indicated as adjunctive therapy in patients with an ICD who are receiving multiple shocks as a result of sustained VT that is not manageable by reprogramming or changing drug therapy or who do not wish long-term drug therapy (class I, level of evidence: C) [1]. Finally, ablation is indicated in patients with WPW syndrome resuscitated from sudden cardiac arrest due to rapidly conducted atrial fibrillation causing VF (class I, level of evidence: B) [1].

Less evidence exists regarding ablation of Purkinje fiber potentials that may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology (class IIb, level of evidence: C) [1].

Also ablation of asymptomatic PVCs may be considered when the PVCs are very frequent to avoid or treat tachycardia-induced cardiomyopathy and when PVCs are trigger of untolerated VT/VF [1] (class IIb, level of evidence: C).

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The Role of Home Monitoring

28

Laura Cipolletta and Jenny Ricciotti

28.1 Case Report

A 42-year-old Caucasian man suffering from type 1 Brugada syndrome was referred to our department in 2007 after an episode of palpitations followed by syncope while driving his car. The electrocardiogram (EKG) showed a type 1 Brugada syndrome pattern, and further history revealed two syncopal episodes 2 years later during fever. When asked about sudden cardiac death in his family, he reported that a maternal uncle had died at age of 40 for unknown reasons.

A transvenous single-chamber implantable cardioverter defibrillator (ICD), St. Jude Fortify VR, equipped with a ventricular electrocatheter system was implanted, and the patient was subsequently discharged in stable condition.

At the time of implantation, ventricular sensing with a stable intrinsic amplitude of 11 mV without T-wave sensing was achieved. The ICD was programmed with a VT detection zone at 179 bpm with only monitoring and no therapy and a second detection zone at 214 bpm, with antitachycardia pacing (ATP) during charging and shock at 36/40/40 J for three times.

Subsequent follow-up was organized with outpatient visits every 6 months; in addition, starting from February 2011, when the ICD generator was replaced at the end of battery life, the patient was equipped with a remote monitoring system (St. Jude Medical Merlin.net) that can record data relative to arrhythmic events and technical details of the device and leads and transmit regularly to the cardiology center (on average, 1 transmission/month, plus any additional transmission in case of detected alarm episodes).

The patient had never received ICD therapy over 6 years' follow-up; all functional and lead integrity parameters were normal during all the follow-up visits.

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In the summer of 2013, we received a nonprogrammed remote transmission with an alert of many episodes of tachyarrhythmia, marked as supraventricular and ventricular, both sustained and nonsustained, with consequent ICD therapy deliveries. By examining all the transmissions in detail, we can see how the delivered therapies resulted inappropriately and recognition of arrhythmias was incorrect.

What Are the Possible Causes for Inappropriate ICD Therapy?

- Supraventricular arrhythmias with rapid ventricular conduction
- Abnormal sensing (and esp. oversensing with double T-wave counting)
- Lead malfunction
- Electromagnetic interference

Figure 28.1 shows an episode interpreted as ventricular tachycardia (VT)/ventricular fibrillation (VF) with delivery of ATP during charging of the capacitors; indeed the beats marked as VF correspond to deflections of high amplitude, not constantly present, identifiable as noise in the ventricular channel.

Noise and artifacts can lead to oversensing and cause inappropriate ICD therapies; they can be classified into different types:

- *External noise* (e.g., magnetic interference) usually present on all sensing channels, constant and regular, with high frequency (~50–60 Hz)
- *Myopotential noise* with high frequency and low and constant amplitude, which can vary with respiration
- *Internal noise*, due to problem in the lead conductors with high-frequency and highly variable amplitude, which occurs intermittently, separated by periods of isoelectric baseline and typically on one lead/channel

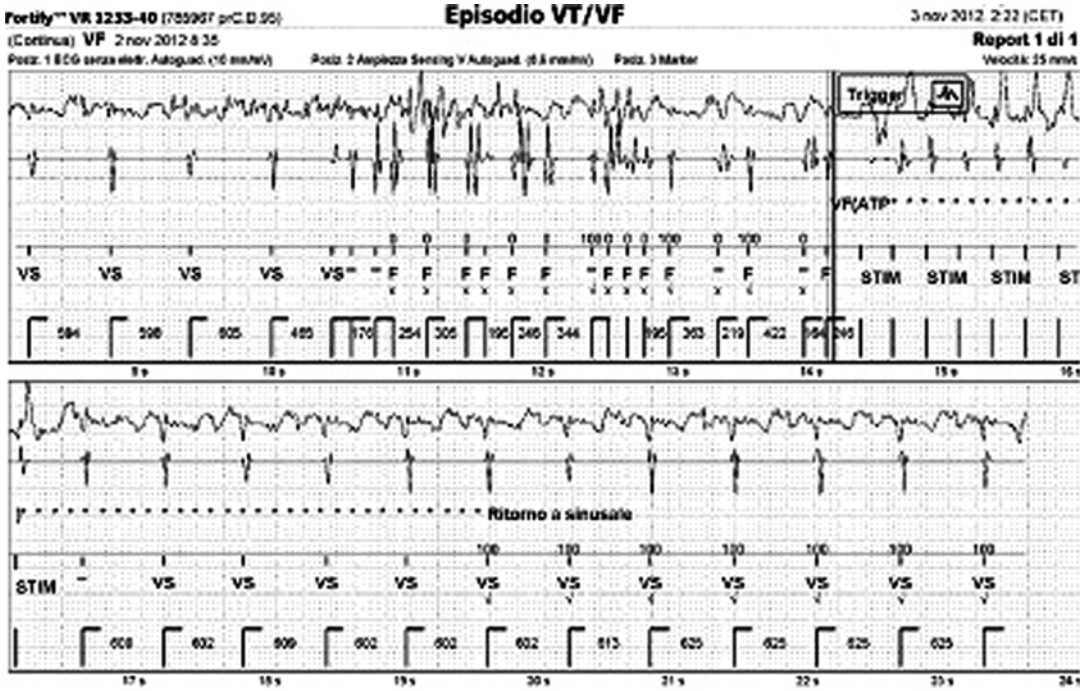

Fig. 28.1 Episode marked as VT/VF. The far-field electrogram (A) is present on the *top*, the near-field ventricular sense channel (V) is present in the *middle* tracing, and the marker channel is on the *bottom*

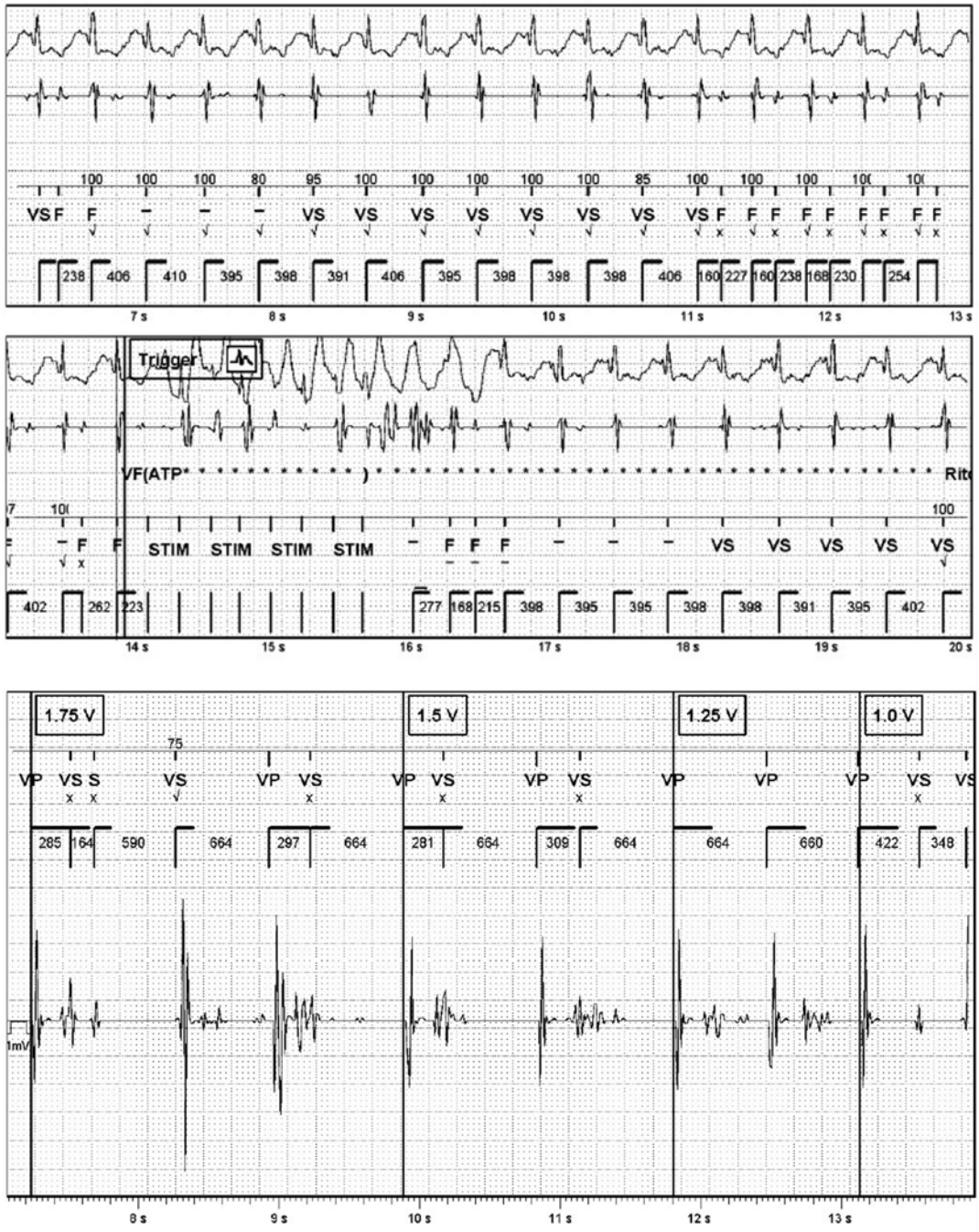

Fig. 28.2 VF episode secondary to T-wave oversensing (*top*). Capture test (*bottom*)

The episodes marked as VF are likely to be an artifact with the characteristics of high amplitude and low frequency, not constant but intermittent, which suggest a problem in the integrity of ventricular lead.

Figure 28.2 shows another episode labeled as VF, inappropriately treated with ATP, and capacitors charging subsequently aborted; in reality it is not a real VF but an oversensing phenomenon from double T-wave counting.

The patient was called for an ambulatory visit. During ICD interrogation, the anomalies already showed with remote monitoring were confirmed, the usual tests were performed, and the parameters of sensing, pacing, and ventricular lead impedance (sensing 11.7 mV, impedance pacing 460 Ω, shock impedance 50 Ω) were evaluated. It was noticed that each paced ventricular beat was followed by artifacts recorded on ventricular channel; that confirmed the malfunction of the device (Fig. 28.2). Furthermore the noise could be reproduced by isometric maneuvers and with pocket manipulation.

After confirmation of ICD system malfunction, the patient was hospitalized in the cardiology clinic.

Medical History and Cardiovascular Risk Factors

No cardiovascular risk factor. Hiatal hernia. Thalassemia trait

Allergies

No allergy is referred by the patient.

Social History

The patient works as an employer. Does not smoke or drink alcohol. He never used illicit drugs.

Medications

He was not on any medication.

Vital Signs

Temperature 36.4 °C, heart rate 75 bpm, blood pressure 120/80 mmHg, respiratory rate 16 breaths per minute, and oxygen saturation in ambient air 97 %

Physical Examination

- Weight 70 kg, height 167 cm, and estimated body mass index (BMI) of 25.
- *General:* alert, awake, and oriented.
- *Skin*: normal in appearance, texture, and temperature; no rashes; no lesions; no erythema.
- *Head, eyes, ears, nose, and throat:* normal.
- *Neck*: no abnormal adenopathy in the cervical or supraclavicular areas. Thyroid gland is normal without masses. No carotid bruit and no jugular venous distention.
- *Cardiovascular:* Regular rate and rhythm; S1 and S2 normal; no murmurs, rubs, or gallops heard; point of maximal intensity nondisplaced and nonsustained; and no hepatojugular reflux.
- *Lungs:* Lungs are clear to auscultation and percussion bilaterally and no alterations in tactile fremitus.
- *Abdomen:* The abdomen is symmetrical without distention; bowel sounds are normal in quality and intensity in all areas. No masses or splenomegaly noted; liver span is 6 cm by percussion.
- *Extremities:* No cyanosis, clubbing, or edema noted. Peripheral are normal in all areas.
- *Neurologic:* Cranial nerves II–XII are normal. Motor and sensory examination of the upper and lower extremities is normal. Reflexes are normal and symmetrical bilaterally in both extremities.

Routine EKG at Rest (Fig. 28.3)

Conclusions: sinus rhythm, normal atrioventricular conduction, and type 1 Brugada syndrome pattern saddleback in V2.

All the routine laboratory tests were performed, including complete blood count, liver and renal functions, electrolytes, thyroid function, and lipid concentrations—all resulted normal.

Echocardiography

Tricuspid Aortic Valve with Normal Valve Opening. Normal size of aortic bulb, ascending

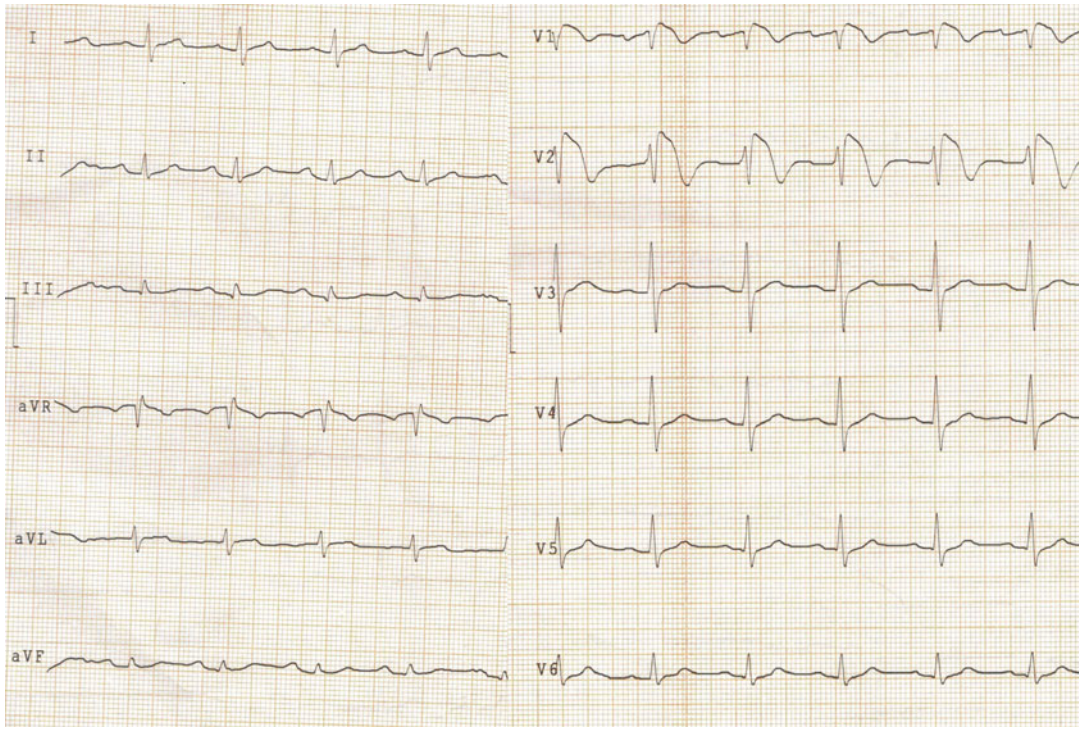

Fig. 28.3 EKG. Conclusions: sinus rhythm, normal atrioventricular conduction, type 1 Brugada syndrome pattern saddleback in V2

aorta, aortic arch, and abdominal aorta. Left atrium of normal size (LA diameter M-mode = 30 mm, area 14 cm^2). Right atrium was normal (area 4c = 14 cm^2). Prolapse of the anterior mitral leaflet. The tricuspid valve was normal.

Normal Dimensions and Thicknesses of the Left Ventricle. Normal contractile function (ejection fraction 60 % with Simpson's biplane method) and normal wall motion. Right ventricle of normal size and with normal contractile function (TAPSE = 29 mm). Inferior vena cava of normal size (13 mm), with normal collapse during inspiration. The pericardium is normal. Color Doppler: mild mitral regurgitation. Normal diastolic function. Minimal tricuspid regurgitation. PAPs about 20 mmHg.

There are a lot of factors that should be weighed in the management of a failed ICD lead.

First, the suspected mechanism of lead failure should be evaluated; for this reason to exclude a macroscopic failure of the lead, a fluoroscopy was made, which showed no images related to fractures or insulation defects of the conductors.

Given the sensing defect of the ventricular lead, we have reprogrammed sensitivity parameters, in order to reduce the oversensing phenomenon; when sensitivity parameters of an ICD are changed, it is always advisable to perform a defibrillation threshold test (DFT).

During the DFT (Fig. 28.4) after the first shock at 2 J to induce VF, some noise entered the ventricular channel hiding the real VF; when the noise has stopped, the VF signal was very low and unclassified beats were recorded. The shock was effectively delivered late by the device, and during the pacing post-shock, every paced beat was followed by noise and ICD began to recharge already the capacitors. To avoid that other inappropriate shocks were delivered, ICDs were turned off.

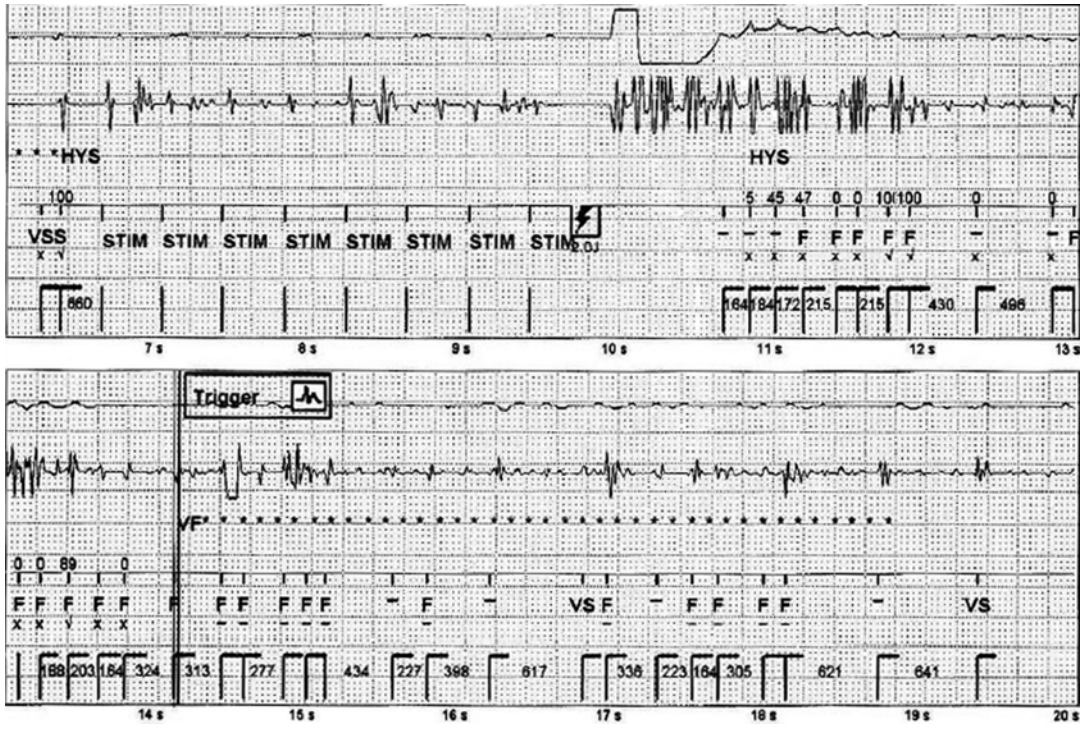

Fig. 28.4 Defibrillation threshold test

What Are the Treatment Options in Case of Malfunction of an ICD Ventricular Lead?

1. *Add a new pace/sense lead alone*, leaving in place the old lead, if the shock circuit is working correctly. This may be the appropriate strategy in older patients, patients with multiple comorbidities, or patients for whom lead extraction is prohibitively high risk. The disadvantages of adding new leads without removal of the failed leads include multiple leads crossing the tricuspid valve, lead-to-lead interaction, and an increased risk of future lead-related problems. If lead extraction became necessary in the future, the complexity and risks would be higher with more leads.
2. *Lead extraction.* The 2009 Heart Rhythm Society consensus recommendations for the extraction of a nonfunctional, noninfected ICD lead [1] are reported in Fig. 28.5. The extraction procedure has a high morbidity with possible fatal complications (cardiac or vascular avulsion, cardiac tamponade, pulmonary and systemic embolism, retained ICD lead fragments, lead dislodgement, or damage to other existing leads). Passive fixation leads and dual-coil leads may be more difficult to extract because of increased adhesions.

Management in every case needs to be individualized.

In our case, given the young age of the patient, with no comorbidities, with a long life expectancy, and with an average time from the

Non Functional Leads
Class I
1. Lead removal is recommended in patients with life threatening arrhythmias secondary to retained leads or lead fragments. *(Level of evidence: B)*
2. Lead removal is recommended in patients with leads that, due to their design or their failure, may pose an immediate threat to the patients if left in place. (e.g. Telectronics ACCUFIX J wire fracture with protrusion) *(Level of evidence: B)*
3. Lead removal is recommended in patients with leads that interfere with the operation of implanted cardiac devices. *(Level of evidence: B)*
4. Lead removal is recommended in patients with leads that interfere with the treatment of a malignancy (radiation/reconstructive surgery). *(Level of evidence: C)*
Class IIa
1. Lead removal is reasonable in patients with leads that due to their design or their failure pose a threat to the patient, that is not immediate or imminent if left in place. (e.g. electronics ACCUFIX without protrusion) *(Level of evidence C)*
2. Lead removal is reasonable in patients if a CIED implantation would require more than 4 leads on one side or more than 5 leads through the SVC. *(Level of evidence C)*
3. Lead removal is reasonable in patients that require specific imaging techniques (e.g. MRI) and can not be imaged due to the presence of the CIED system for which there is no other available imaging alternative for the diagnosis. *(Level of evidence: C)*
Class IIb
1. Lead removal may be considered at the time of an indicated CIED procedure, in patients with non-functional leads, if contraindications are absent. *(Level of evidence C)*
2. Lead removal may be considered in order to permit the implantation of an MRI conditional CIED system. *(Level of evidence: C)*
Class III
1. Lead removal is not indicated in patients with non-functional leads if patients have a life expectancy of less than one year. *(Level of evidence C)*
2. Lead removal is not indicated in patients with known anomalous placement of leads through structures other than normal venous and cardiac structures, (e.g. subclavian artery, aorta, pleura, atrial or ventricular wall or mediastinum) or through a systemic venous atrium or systemic ventricle. Additional techniques including surgical backup may be used if the clinical scenario is compelling. *(Level of evidence: C)*

Fig. 28.5 Indications to transvenous lead extraction in patients with nonfunctional leads [1]

implantation of the lead, we decided to proceed with the extraction. The procedure was performed under local anesthesia by an interventional cardiology in the electrophysiology lab with a cardiac surgeon on standby. After lead isolation with an excimer laser sheath system, its removal was performed without complications.

Few days later, the patient underwent implantation of a subcutaneous ICD (S-ICD, Cameron Health). This new type of cardioverter defibrillator was approved in 2012 by the FDA; it is implanted subcutaneously without using intracardiac and intravascular leads.

The indications for implant of an S-ICD are the same as a transvenous ICD, excluding the need for pacing for bradycardia and recurring ventricular tachycardia (VT) that is reliably terminated with antitachycardia pacing (ATP).

For these reasons, it is therefore particularly indicated for young patients, with an active lifestyle and a long life expectancy, at risk of sudden cardiac death due to ven-

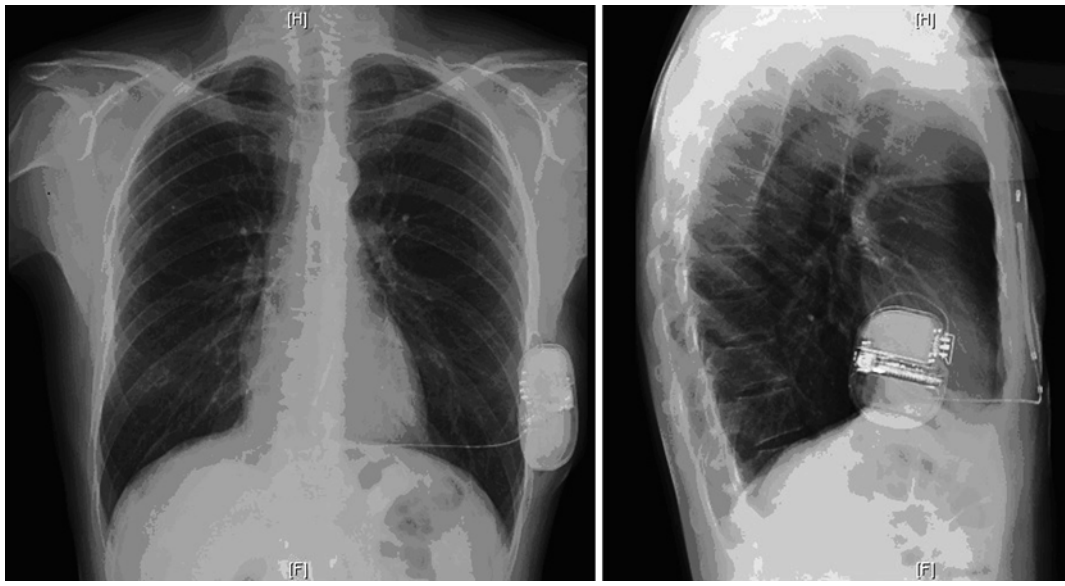

Fig. 28.6 Chest X-ray postimplantation of the S-ICD (posteroanterior and lateral views)

tricular tachyarrhythmias, as in the genetic arrhythmogenic syndromes (Brugada syndrome, long and short QT syndrome, and other channelopathies).

After the implantation, a chest X-ray was performed that confirmed the correct placement of the S-ICD system (Fig. 28.6).

The patient was discharged in stable condition.

Conclusion

Inappropriate therapies delivered from the ICD, due to the malfunction of ventricular lead, treated with transvenous lead extraction and implant of the new S-ICD. Home monitoring was crucial for early defect detection.

28.2 Home Monitoring

Introduction

Routine device follow-up assessment at regular intervals is required after implant of an electronic device (PMK or ICD) [2]. The purpose of these assessments is to evaluate the patient and the device control. Traditionally, device follow-up clinic is designated to realize these assessments. In the last years, a new technology such as the remote monitoring (RM) is developed and permits surveillance and device assessment from any location of the patient. RM is important to facilitate early diagnosis of arrhythmia and evaluate earlier than in-office visit problems with the device or leads. Now, in the international guidelines, RM of implantable devices has been indicated as a new standard for patient follow-up, and it has been defined as an alternative to the large part of scheduled follow-up visits [3].

Types of Remote Monitoring Systems

Home Monitoring™ (Biotronik)

It was introduced first in 2001. This technology automatically permits the transmission of data on a daily basis at fixed intervals and soon after a clinically relevant event has occurred. It is wireless and does not require patient action. The surveillance parameters can be individualized. This function of the system can be summarized in three steps:

1. The first step is the communication between the implanted generator and the patient device, named CardioMessenger (CM). On the scheduled time, the patient must be from 20 cm to 2 m far from the CM to ensure successful transmission.
2. The second step is the delivery of the CM message to the service central, via GSM/GPRS cellular. A specific website shows the device periodical report of the Biotronik Home Monitoring® system that includes the intracavitary EKG. At the top, the mark channel is visualized, and at the bottom, the electrocardiograms are observed. The system automatically performs the following transmissions: (1) Every 24 h, at a physician-scheduled time, the device sends a transmission containing the data recorded along the last 24 h that is forwarded by CM to the service center. (2) A message is immediately sent when a serious cardiac event or change happens in the device parameters.
3. In the third step, the physician receives a report issued from the service center, named CardioReport, that is possible to consult in an Internet-based secure webpage. The physician, from any computer, will have access to whole information related to the event and to the device and leads, which will have the following characteristics:

- Home page: that allows the physician to rapidly visualize patients who need more attention
- Consolidated report (CardioReport), continuously updated
- Control and recognition of changed events and the possibility to recognize alert changes
- Fields to add comments and remarks, which relate to both the patient and his/her clinical history
- Time line: history of detailed events on a time line

CareLink® Network

With this system, data from the device, via a common telephonic connection, are sent to a ser-

vice center. The physician enters a personal username and password in a specific website to access to data sent. A transmission is made by the patient connecting the RM device to the telephone plug to establish the first connection with the cardiac implantable electronic device (CIED) and pressing the button to start the data transfer. The CareLink® website immediately allows the consultation of exactly the same actualized data observed in the office. It is always possible to consult every transmission from the file archive on the website. All more recent Medtronic CIED are compatible with CareLink®. The parameters showed in the website are the following:

- Complete program of the CIED
- Initial report
- 21 s of EGM recorded at the moment of sending data
- Battery voltage and estimated remaining life of CIED
- Percentage of pacing
- Atrioventricular conduction
- Atrial and ventricular impedance
- Atrial and ventricular automatic threshold
- High ventricular rate episodes
- High atrial rate episodes
- Transthoracic impedance

It is possible to program manually automatic transmissions at intervals not shorter than 21 days. The OptiVol™ sensor incorporated in the CareLink™ network measures the drop of intrathoracic impedance upon intrapulmonary fluid accumulation. Yu et al. demonstrated that the impedance drop preceded the onset of clinical heart failure symptoms by a mean of 15 days [6]. This feature is a powerful tool to prevent heart failure hospitalizations in CRT and ICD patients if medical therapy is adjusted quickly on an outpatient basis.

One of the first randomized studies that confirmed the clinical value of CareLink™ network is the PREFER study that enrolled 980 patients randomized 2:1. The primary endpoint was to evaluate remote pacemaker interrogation for the earlier diagnosis of serious events compared with traditional transtelephonic monitoring and routine in-person evaluation. After 12 months' follow-up, the use of remote pacemaker interrogation detected actionable events that are potentially important more quickly and more frequently than transtelephonic rhythm strip recordings [7].

Several other clinical studies showed the benefits related to the use of RM such as the reduction of outpatient clinic workload, better patient quality of life, improved implanted system surveillance, and continuous patient monitoring to early detect harmful clinical events and to improve patient outcome [8–12].

Latitude (Boston Scientific)

This system also utilizes wireless transmission from the device to a communicator and then to a central repository. From there, the data is made available on an Internet platform. As with the other systems, the Internet site is the same as the respective manufacturers' programmer in order to make the system easier. With this system scheduled appointments for remote controlling can be programmed. Additionally, a red light on the communicator prompts the patient to initiate on-demand transmission if an alert has been detected. Furthermore, the Latitude System optionally allows for connection of a blood pressure cuff and a weighing scale for ambulatory monitoring of heart failure patients.

Merlin.net® (St. Jude Medical)

The implant system is provided through wireless telemetry, and follow-up is provided through the RF Merlin@home® transmitter, which receives the DirectCall® messages. The monitoring system sends daily data (DirectAlerts®) that are exported to a database. A patient can start the interrogation pressing the start button of the Merlin@home® system that has status lights for both the transmitter and the transmission in one icon and connects to a telephonic line. The status of the implanted device is checked on a daily basis to send notification to the physician through e-mail, text message, phone call, or the Internet.

SMARTVIEW® (Sorin Group)

It is the most recent RM system, approved by FDA in 2013. The device communicates with an at-home unit that transmits stored data about device

function system to the patient and appropriate clinicians. Using this information, a cardiologist can monitor disease progression and determine whether the implant needs to be reprogrammed. Installation of the SMARTVIEW remote monitoring system at the patient's home is assisted by a dedicated help desk provided by Sorin.

Clinical Utility

Early AF Episodes Detection

Rhythm disturbances can readily be identified in all of these devices allowing early detection of the development of atrial fibrillation. Arrhythmia-related severe adverse events, caused by long-lasting undetected atrial fibrillation, may be avoided by the early detection of atrial fibrillation occurrence as soon as arrhythmia has been stored in the device memory because of the prompt clinical reaction of the physician. That is particularly meaningful in asymptomatic patients, because this permits timely decisions concerning antithrombotic or anticoagulant therapy [22]. Remote monitoring has been also associated with a reduced hospitalization rate for atrial fibrillation and a potential lower risk for stroke [12].

Heart Failure Monitoring

The majority of these patients suffer from concomitant heart disease, reduced left ventricular ejection fraction, and symptomatic heart failure. Thoracic impedance can be measured with these implanted devices and has been considered as a surrogate marker of pulmonary congestion. When a current is passed between the intracardiac lead and the generator, the impedance to the conduction of this current is inversely related to the fluid content of the lungs. In a validation study, Yu et al. [6] found that the impedance started to decrease 15 days prior to worsening heart failure symptoms. In a more recent study of HF patients, Abraham et al. showed that the sensitivity of intrathoracic impedance monitoring was far superior to daily weight monitoring for predicting worsening HF events [16]. On the contrary, the SENSE-HF trial failed to show utility of the same technology [17] and also revealed the unreliability of impedance testing early after implant. The sensitivity to predict HF events was at best 42 % with a positive predictive valve of 38 %. The DOT-HF trial [18] studied the clinical utility of the OptiVol to track changes in intrathoracic impedance. All-cause mortality and rehospitalizations did not change from control to impedance-monitored therapy. The OptiVol is being used to provide physicians with wireless alerts of threshold deviations for worsening cardiac status in the OptiLink-HF trial [19]. To increase the predictive ability of a diagnostic algorithm, Whellan et al. in the PARTNERS-HF trial [20] combined more device variables. Utilizing data from an independent dataset, the authors identified a fluid index >100 Ω days or any two of the following as criterion: (1) long atrial fibrillation duration, (2) rapid ventricular rate during atrial fibrillation, (3) a high (≥60) fluid index, (4) decreased patient activity, (5) high night heart rate, (6) low heart rate variability, (7) low CRT pacing, or (8) ICD shocks. Patients with positive device diagnostics had a hazard ratio of 5.5 (95 % CI 3.4–8.8; $P<0.0001$) of HF hospitalization with pulmonary congestion within a month. More recently, Landolina et al. [10] in the EVOLVO study randomized 200 patients with a Medtronic wireless ICD/CRT-D along with the CareLink network; half had "remote transmission on," while the rest had "remote transmission off." In the control group, audible alerts were turned on with no transmission of data, while in the intervention group, all alerts were transmitted with no audible alerts. The primary endpoint was emergency department or urgent in-office visits, and the secondary endpoint was the number of visits related to worsening HF and arrhythmias or ICD-related events. Patients in the remote monitoring arm had significantly less events (0.59 vs. 0.93 events per year; incident rate ratio 0.65; 95 % CI 0.49–0.88; $P=0.005$). As expected for the directed intervention, the median time from the alert to ICD data review was 24.8 days for the standard care arm compared with 1.4 days in the remote monitoring arm. The audible alerts from the ICD/CRT-D devices did not make much of a difference. In fact, also prior studies have indicated that many alerts go unnoticed by patients [21].

PVC, NSVT, and Slow VT Episode Monitoring

Early detection of an high burden of PVC or NSVT/slow VT in CRT patients with heart failure allows for early treatment, pharmacological or ablative, of these conditions, and there is evidence that hospitalization rates can be reduced, as the biventricular pacing reduction and worsening heart failure could be prevented.

VT/VF Therapy

Remote monitoring permits to verify earlier device therapies and decide a strategy personalized for each patient. If the patient had only an appropriate shock, he will be reassured and hospital admission is avoided. In case of ≥ 2 shocks, the RM is useful to guarantee ER admission. RM has been also associated with less appropriate and inappropriate ICD shocks [12] explained by the early suppression of inappropriate therapies prompted by recurrent supraventricular tachyarrhythmias or by oversensing and prevention of appropriate therapies by the early introduction of antiarrhythmic measures.

Monitoring of Lead Performance

Five-year failure rates have been reported to be between 2 and 15 % [13], and lately problems with high-profile ICD lead performance (Medtronic Sprint Fidelis and St. Jude Medical Riata) have concerned the medical world [14]. For that purpose, some remote monitoring systems can report daily lead integrity measurements of more than 90 % of the time in most of cases [15]. However, lead alert system and CareLink helped to identify the major defibrillator lead problems experienced with Medtronic Sprint Fidelis lead [3]. Unfortunately, contrary to other reports, not always finding a lead failure with RM is possible. Several case reports warn that sometimes the Riata leads can fail to deliver therapy although normal electrical parameters have been recorded during in-office visits [4]. However, in the report of Hauser et al. [5], 87 % of the leads analyzed, in a late stage of disintegration, had shown electrical abnormalities, which may have been detected by remote monitoring. Remote monitoring offers help for the management of the huge workload that manufacturers' advisory causes. The findings in remote monitoring systems can be used to avoid clinical problems, but in their absence, nothing can be done [6, 7].

Early Identification of Device Troubleshooting

Oversensing, electromagnetic interferences, loss of capture, undersensing, pacemaker-mediated tachycardia, and prompt starting of therapeutic measures are used for the early identification of device troubleshooting [23].

Improving of Quality of Life

While ICDs are highly effective in lowering the rate of arrhythmic deaths in high-risk patients, the delivery of shocks, especially when repetitive, remains a major cause of discomfort, anxiety, depression, and poor quality of life. RM makes possible the very early detection of causes of appropriate and inappropriate ICD interventions and rapid implementation of preventive measures. This may confer important advantages for the quality of life of patient and device longevity [24].

Infrastructure and Organization of Remote Monitoring

Two-thirds of the centers in Europe do not have a specific unit for RM, and the RM program is a part of their traditional device follow-up clinics.

The organization for RM in Europe is based primarily on nursing with easy communication with the responsible physician for medical decisions. Many centers, however, conduct only sporadic reviews or have no specific protocol, so the risk exists that some events may be undetected and that the opportunity to adjust therapy may not be undertaken [25].

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Drug-Related Adverse Events

29

Simone Maffei and Jenny Ricciotti

29.1 Case Report

A 58-year-old woman presented to the emergency department accompanied by her family members for complaints of agitation and dyspnea. She had a history of bipolar disorder that required lithium, and there were no history of suicidal ideation, recent medication changes, and improper medication administration and no family history of sudden cardiac death. There were unknown cardiovascular risk factors or allergies. Home medication: only lithium (but the patient didn't remember the dosage of the drug).

According to the relatives, the patient had been suffering from gastroenteritis with significant diarrhea few days before.

Vital Signs and Physical Examination

- Temperature: 36.5 °C
- Heart rate: 36 beats per minute
- Blood pressure: 150/90 mmHg
- Respiratory rate: 22 breaths/min; oxygen saturation while breathing in ambient air, 97 %
- General: awake but agitated and disoriented with aimless movements
- Head, eyes, ears, nose, and throat: normocephalic, atraumatic, mucous membranes dehydrated, extraocular muscles intact, and pupils equally round and reactive to light and accommodation bilaterally
- Cardiovascular: regular bradycardia rhythm, S1 and S2 normal, and no pathological heart murmurs
- Lungs: no rales, rhonchi, or wheezes; no alterations in tactile fremitus; normal percussion
- Abdomen: overweight, no pulsatile masses, soft, nondistended/nontender, no hepatosplenomegaly, slightly sore upon deep palpation in the lower quadrants, and lively peristalsis
- Extremities: no cyanosis or clubbing, no edema, and dehydrated skin

Routine Laboratory Tests

- Complete blood count: mild neutrophilic leukocytosis (WBC 12.160/mmc); hemoglobin 12.4 g/dl

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- Hepatic function (GOT, GPT, γ-GT, ALP, and total, direct, and indirect bilirubin): normal
- Impaired renal function (creatinine 2.10 mg/ dl)
- Electrolytes: Na^+ 133 mEq/l and K^+ 3.4 mEq/l
- Myocardial necrosis markers: CK-MB 2.3 ng/ml and TnI 0.30 ng/ml
- Lithium level: 3.7 seq/l

A routine 12-lead resting ECG was performed (Fig. 29.1a–d).

ECG showed marked sinus bradycardia (heart rate was 36 b/min), normal atrioventricular and intraventricular conduction, and diffuse alterations of ventricular repolarization with negative T waves from V1 to V5; QTc = 435 msec.

What Are the Possible Causes of Agitation and Dyspnea in This Patient? Why Are There Sinus Bradycardia and Diffuse Alterations of Ventricular Repolarization?

- Acute coronary syndrome (ACS)
- Electrolyte disorders (hypokalemia, hyponatremia)
- Drug intoxication
- Exacerbation of renal failure

ACS is very unlikely because the patient didn't present chest pain, there was a little movement of cardiovascular enzymes (probably secondary to worsening of renal function), and an echocardiogram showed no alterations in the kinetics. Blood tests showed slight alterations of sodium and potassium that did not cause any electrocardiogram abnormalities.

Instead, there was a marked alteration of lithium levels (normal values, 0.6–1.2 mEq/L for chronic bipolar disorder; 1.0–1.5 mEq/L in the case of acute manic episode) that could explain both agitation state and ECG changes.

Retention of lithium is favored by all those conditions that may be associated with intravascular volume depletion.

In this case, gastroenteritis has led to a state of dehydration which resulted in the deterioration of renal function and an increase of lithium serum levels.

The patient was monitored and a fluid infusion was set up with saline to restore an adequate blood volume and hydration state.

After a few hours, there was a gradual reduction in blood creatinine and lithium levels with the regression of the electrocardiographic changes shown above (Fig. 29.2a–d).

The patient was discharged completely asymptomatic the next day, with a normal electrocardiogram and with good renal function. We advised a further psychiatric check for a possible optimization of the specific medical therapy.

Lithium

Lithium salts are still used in the prophylaxis and treatment of bipolar syndrome (manic–depressive) with a dose ranging from 1 to 1.5 g per day in the attack phase to 300–400 mg daily as a maintenance dose. Lithium is still considered the drug of choice in the treatment of patients with "affectivity bipolar," that is, for people who experience alternate phases and periods of sadness and hopelessness (depression) with periods of excitement and euphoria (mania).

Lithium salts have a narrow therapeutic index, and their use should always be subordinate to the possibility of periodic blood tests.

The daily dose of lithium should be individualized on the basis of the drug plasma levels. It is important to determine the plasma concentration of lithium (lithium levels) once per week for the first 2 months, once a month for the next 6–8 months, and once every 2–3 months during the maintenance phase of therapy. Lithium levels should be checked after each change of the dose.

Clinical signs of toxicity manifest themselves at concentrations of lithium levels equal to or higher than 1.5 mEq/l. The majority of patients reach levels of toxicity when intercurrent diseases (diarrhea, vomiting, heart failure, renal failure) or drug interactions (NSAIDs, ACE-I) are present.

Side Effects

Lithium can cause a number of side effects in various districts of the organism (see Table 29.1).

It is also known that lithium can cause various cardiac disorders, including conduction abnormalities. The mechanisms underlying these conduction defects are not clearly understood. A wide range of lithium toxicities have been observed, from severe bradycardia to arrhythmias. Direct effects on the sinus node and thyroid function abnormalities to underlie these side effects have been postulated. However, most previous cases of conduction abnormalities occurred in the setting of chronic lithium therapy or in patients receiving toxic levels of lithium [1].

Although most side effects occur at the supratherapeutic levels, there are several case reports of conduction abnormalities induced by lithium in patients at levels within the therapeutic range. This suggests a wide range of individual responsiveness to lithium [1].

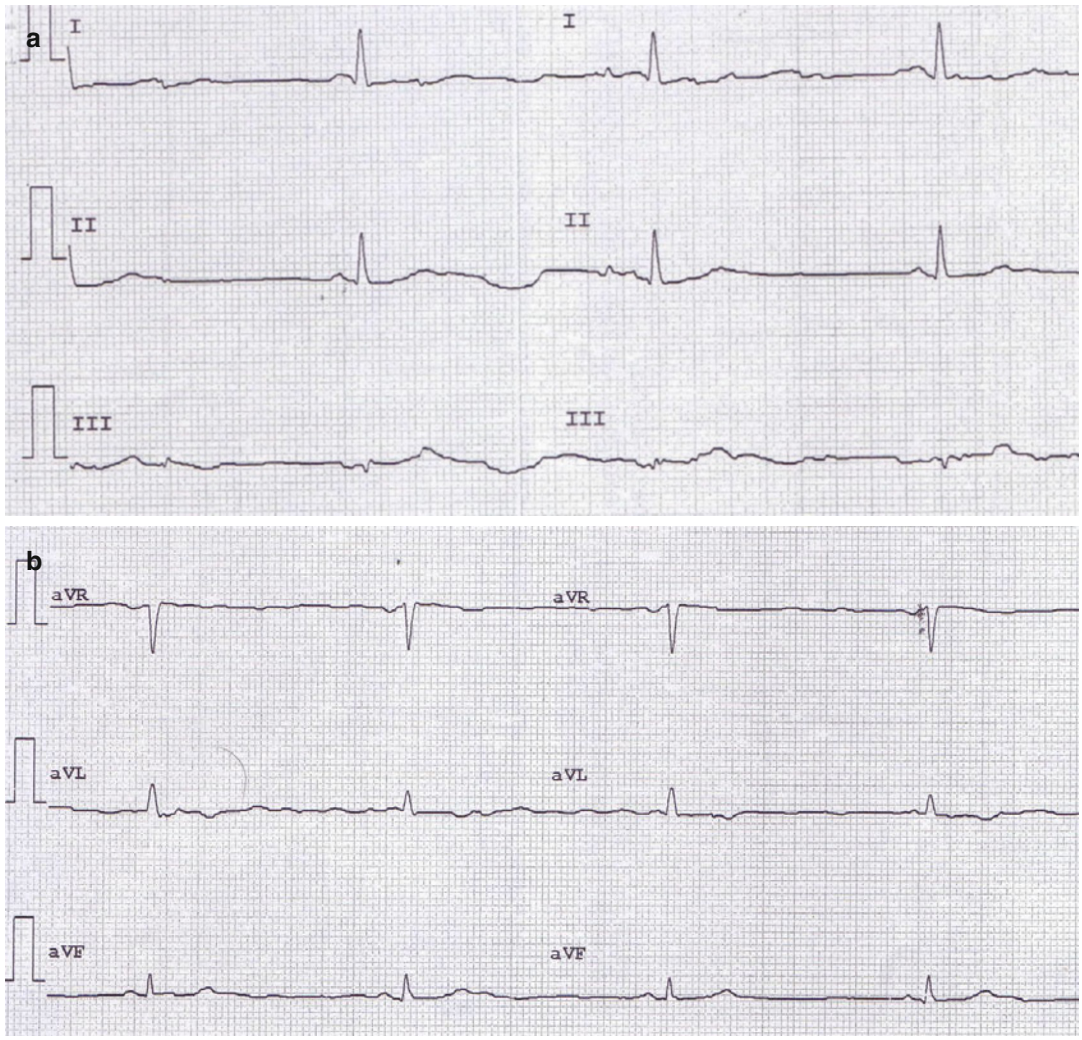

Fig. 29.1 (**a**–**d**) Image 1 ECG: sinus bradycardia, heart rate of 36 b/min, and negative T waves from V1 to V5

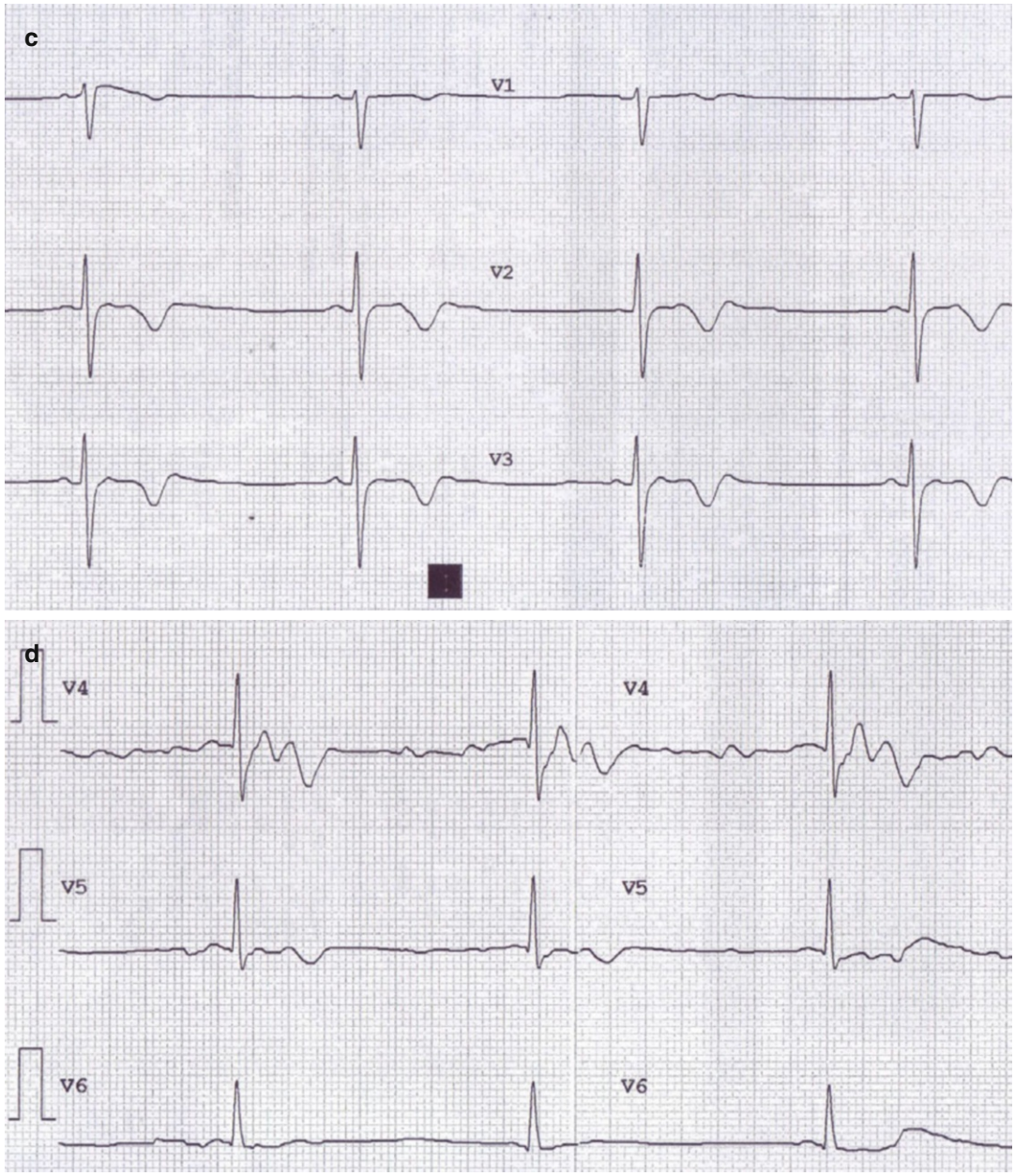

Fig. 29.1 (continued)

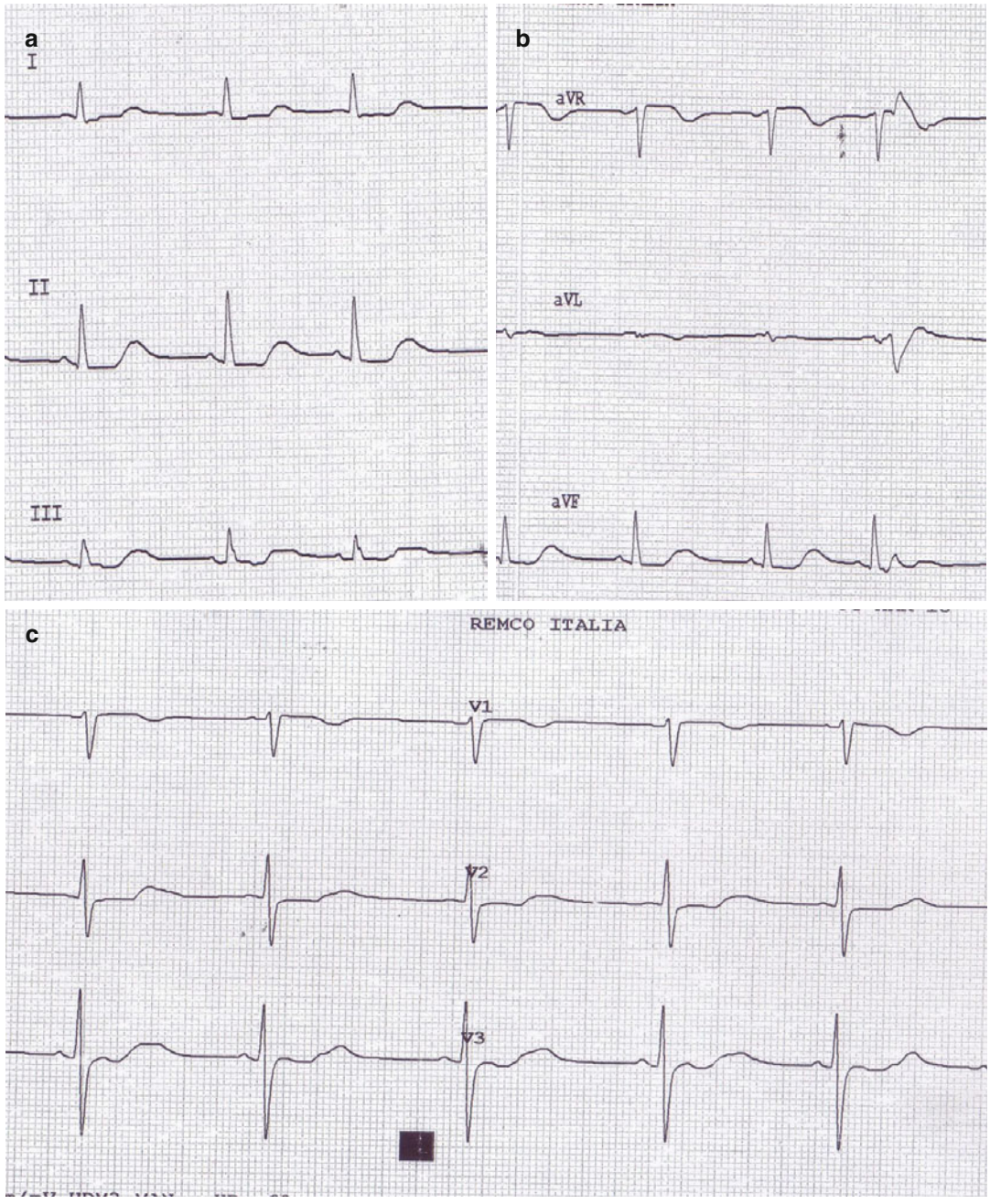

Fig. 29.2 (**a**–**d**) Image 2 ECG: reduction of previous electrocardiographic changes

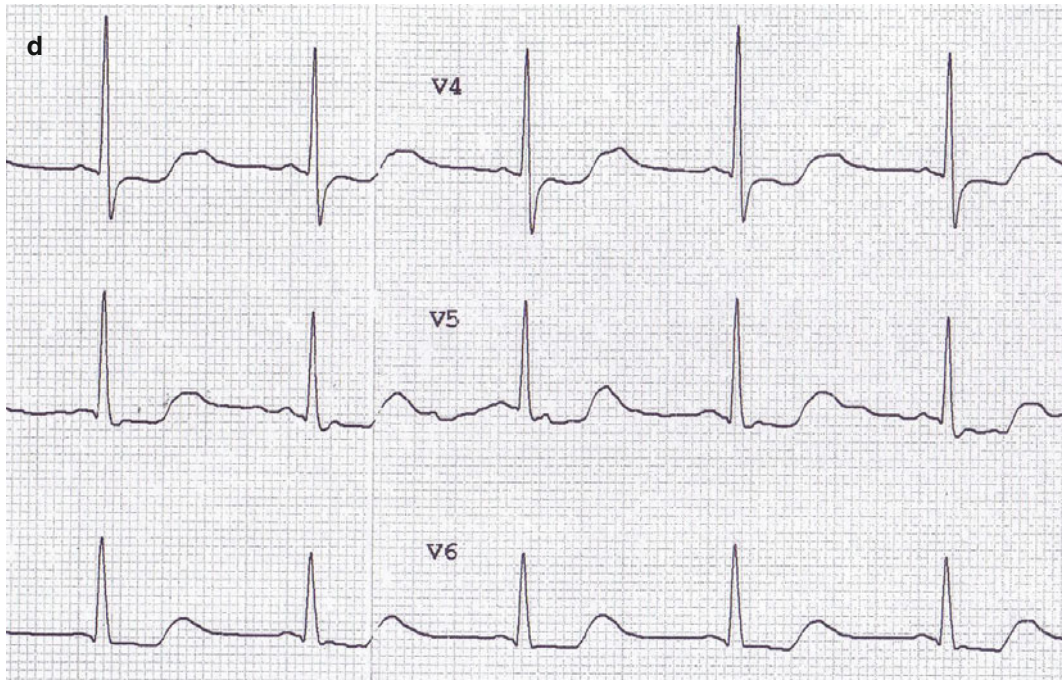

Fig. 29.2 (continued)

The major cardiovascular side effects of lithium include:

- Unmasking of Brugada syndrome
- Sinus node dysfunction
- Atrioventricular (AV) block
- Various arrhythmias (torsades de pointes, ventricular tachycardia, ventricular fibrillation)
- Asymptomatic electrocardiographic changes (changes in T waves characterized by flattening, isoelectrical changes, or inversion)
- Prolongation of the QT interval

Table 29.1 Lithium side effects

Side effects
Nervous system disorders
Absences, seizures, drowsiness, dizziness, fatigue, lethargy, psychomotor delays, confusion, restlessness, stupor, coma, tremors (twitching, clonic movements of the legs), ataxia, dry mouth
Nephrology
Decreased ability to concentrate urine, renal failure (rarely), diabetes insipidus
Endocrinological
Hypothyroidism, hyperparathyroidism, weight gain (insulin-like effect)
Sense organs
Taste changes, alteration of thirst
Teratogenic
Likely association with Ebstein's anomaly (avoid use during pregnancy)

29.2 Drug-Related ECG Adverse Events

Several drugs and toxins can act on the cardiovascular system, either at therapeutic level or secondary to overdose and poisoning. They may cause ECG abnormalities, heart rhythm disturbances, depression of myocardial contractility, and vasodilation.

There are two main mechanisms underlying the adverse cardiovascular effects of pharmacological and toxin agents:

- A direct action on ion channels: sodium (Na^+) channel blockers, outward potassium (K^+) channel blockers, calcium channel blockers (CCB), sodium–potassium adenosine triphosphatase (Na^+/K^+ ATPase) blockers
- Effects on the autonomic nervous system: vagal and sympathetic action and beta-adrenergic block

Drugs cause ECG changes also indirectly, determining electrolyte and acid–base imbalance. It must be remembered that many drugs produce effects resulting from the combination of several mechanisms.

Drugs and Toxins Acting on Ion Channels

Sodium Channel-Blocking Agents (Table 29.2)

During phase 0 of the action potential, the opening of fast sodium channels causes Na^+ influx and depolarization of cardiac cell membrane; this led to contraction of ventricular myocytes, which is expressed by QRS complex in ECG.

Inhibitors of fast Na^+ channels slow the rise of the depolarization in phase 0; in case of overdose, there is a progressive widening of the QRS complex, with the risk of heart block and ventricular arrhythmias. The depression of myocardial contractility is responsible for hypotension induced by these agents [2].

Class I antiarrhythmic drugs belong to this category.

Table 29.2 Sodium channel-blocking drugs

Cardiovascular drugs: class Ia antiarrhythmic drugs, class Ib antiarrhythmic drugs, class Ic antiarrhythmic drugs, verapamil, diltiazem, propanolol
Psychiatric drugs: carbamazepine, cyclic antidepressants, antipsychotics (loxapine), neuroleptics (thioridazine, mesoridazine), citalopram
Antihistamines (diphenhydramine)
Illicit drugs: cocaine
Other drugs: amantadine, chloroquine, hydroxychloroquine, orphenadrine, propoxyphene
Toxins: quinine, saxitoxin, tetrodotoxin

Class Ia antiarrhythmic drugs are quinidine, procainamide, and disopyramide. They are potent inhibitors of sodium channels and additionally determine a block of potassium channels.

At high plasma concentrations, conduction through the AV junction is slowed and the automaticity and refractoriness of His–Purkinje system are reduced; QT prolongation is the first sign in ECG and is related to the increased duration of the action potential in ventricular muscle fibers; with increasing doses, there is a progressive flaring of the QRS complex.

Sinus node dysfunction, varying degrees of AV block, ventricular arrhythmias, and torsades de pointes (TdP) can also occur; also during the first administrations, quinidine can cause TdP, in a dose-independent manner.

Quinidine and disopyramide at high doses have a potent negative inotropic effect, resulting in hypotension and shock. Toxic levels of quinidine are responsible for a syndrome known as cinchonism, with tinnitus, blurred vision, photophobia, confusion, delirium, and abdominal pain.

Procainamide toxicity is similar to that of quinidine but with less negative inotropic effects [3–5].

Class Ib antiarrhythmic drugs have a high affinity for sodium channels that are in the inactivated state, with a rapid binding kinetic on–off. They reduce the duration of the ventricular action potential but do not act on potassium channels and therefore do not affect the QT interval [6].

Since lidocaine easily crosses the blood–brain barrier, neurological effects are the first to appear

in the case of toxicity, with light-headedness, seizures, confusion, hallucinations, and comatose state. At cardiac level, there is a slowing of conduction and reduction in myocardial contractility, and with very high doses, asystole, advanced heart block, and refractory hypotension may occur [5].

Class Ic antiarrhythmic drugs (flecainide, propafenone, encainide) bind to sodium channels in the activated state. At high plasma concentrations, these agents have a potent negative inotropic effect; the PR interval and QRS duration are prolonged, and QT interval generally is not very affected.

Propafenone unlike the other drugs in this class also possesses subclinical beta-blocker properties [5].

Cyclic antidepressants block sodium channels in a manner similar to quinidine, slowing the rise of phase 0 of the action potential; in case of toxicity, an increase in duration of QRS and QT interval can occur, with a depression of myocardial contractility [6].

Block of the reuptake of catecholamines in the presynaptic nerve terminal and the antagonist effect on alpha-adrenergic receptors can cause hypotension. A study [7] suggested that an R wave in aVR $\geq$ 3 mm and a rightward terminal vector are predictive factors of cardiotoxicity from cyclic antidepressants and correlated with the risk of rhythm disturbances and seizures.

The initial management of all drug intoxication is based on circulatory and airway support.

The mainstay treatment of sodium channel blocker toxicity is the intravenous administration of sodium bicarbonate that increases the extracellular sodium concentration and blood pH.

Lidocaine is indicated in case of refractory ventricular arrhythmias. Gastric lavage and activated charcoal may be effective in limiting absorption if administrated early after drug ingestion (1–2 h).

Calcium Channel Blockers (CCB)

CCBs block (see Table 29.3) the transport of calcium ions into the cell from the extracellular space, inhibiting voltage-sensitive L-type Ca^{2+} channels; these channels are responsible for the generation of action potential in the pacemaker cells and for the contraction of smooth muscle cells of the peripheral vessel walls.

Table 29.3 Calcium channel blockers

Dihydropyridines	1st generation: nicardipine, nifedipine 2nd generation: felodipine, isradipine, nimodipine 3rd generation: amlodipine, nitrendipine 4th generation: lercanidipine, lacidipine
Phenylalkylamine	Verapamil
Benzothiazepine	Diltiazem
Diarylaminopropylamine ether	Bepridil

Verapamil and diltiazem have a major affinity for cardiac calcium channels and in toxic states may induce sinus node and AV node dysfunction and depression of myocardial contractility. Bradycardia, various degrees of AV blocks, and accelerated junctional rhythms are common, and in most severe cases, asystole is a possible complication; enlargement of QRS complex may be an expression of a ventricular escape rhythm or a consequence of sodium channel block with a delay in the depolarization phase 0.

At the systemic level, common manifestations are hyperglycemia and metabolic acidosis, nausea and vomiting, lethargy, confusion, dizziness, and slurred speech.

Dihydropyridines have a major affinity for vascular smooth muscle cells and, in overdoses, may produce vasodilation, with severe hypotension and reflex tachycardia with palpitations and flushing [5, 8].

Specific treatment of CCB intoxication involves intravenous administration of calcium salts (calcium gluconate), the use of glucagon that promotes calcium entry into cells, and the use of vasopressors and inotropes in case of hypotension and shock; also insulin therapy may be indicated, with a hyperinsulinemia/euglycemia protocol because it can improve inotropy and increase peripheral vascular resistance.

Potassium Channel Blockers

Important antiarrhythmic drugs, as amiodarone, dofetilide, sotalol, dronedarone, etc. (see Table 29.4), belong to this class. Drugs of this group block the outward flow of potassium from the cell into the extracellular space. The block in the output current of potassium slows the repolarization phase of the myocardium and prolongs the duration of action potential [9].

The most common ECG manifestation is the QT interval prolongation (QTc interval greater than 450 msec in men and 470 msec in women).

The delay of repolarization resulted in a lower potential difference at the two sides of the cardiac cell membrane; this can induce early afterdepolarization, triggered activity, and reentry phenomena with the risk of polymorphic ventricular tachycardia and TdP [10, 11].

In a patient with suspected QT prolongation induced by drugs, first, the possible cause must be withdrawn, and, second, any associated conditions such as the presence of electrolyte disturbances should be treated.

The intravenous administration of magnesium sulfate is able to reduce the occurrence of arrhythmias in the case of long QT; in the presence of episodes of TdP in patients who do not respond to such treatment, an overdrive pacing may be indicated [5].

Table 29.4 Potassium channel blocking drugs

Cardiovascular drugs: Class IA antidysrhythmics: disopyramide, quinidine, procainamide Class IC antidysrhythmics: encainide, flecainide, moricizine, propafenone Class III antidysrhythmics: amiodarone, dofetilide, ibutilide, sotalol Antianginal/vasodilators: bepridil, prenylamine, terodiline
Psychiatric drugs: Antipsychotics: chlorpromazine, droperidol, haloperidol, mesoridazine, pimozide, quetiapine, risperidone, thioridazine, ziprasidone Cyclic antidepressants: amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, maprotiline Other antidepressants: citalopram, venlafaxine Phenothiazines
Antimicrobials: Fluoroquinolones: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin Macrolides: clarithromycin, erythromycin Others: pentamidine, chloroquine, halofantrine, hydroxychloroquine
Antihistamines: astemizole, diphenhydramine, loratadine, terfenadine, hydroxyzine
Serotonin 5-HT4 receptor agonist: cisapride
Other drugs: Arsenic trioxide Probucol Synthetic opioids: levomethadyl *Opium alkaloids*: papaverine *Toxins*: quinine, organophosphates

Sodium–Potassium ATPase Blockers

Cardiac glycosides inhibit the sodium–potassium ATPase pump on the cell membrane; as a result, there is an increase in intracellular sodium and a secondary activation of the Na^+/Ca^{++} exchanger. This led to increased levels of intracellular calcium, with stimulation of contractile fibers in myocytes and a positive inotropic effect; they also increase vagal tone and slow AV conduction [12].

At therapeutic doses, digitalis induces a series of ECG signs known as "digitalis effect": flat or inverted T waves, ST segment depression, PR prolongation, and shortening of the QT interval with increased U-wave amplitude [13, 14].

In cardiac glycoside toxicity, electrocardiographic abnormalities are the result of increased automaticity and slow conduction in the AV node.

Different arrhythmias can be produced; the most frequent manifestations are atrial fibrillation with slow ventricular response, paroxysmal atrial tachycardia with block, accelerated junctional rhythm, ventricular ectopic complexes (bigeminal and trigeminal), and bidirectional ventricular tachycardia.

The treatment of severe digoxin toxicity consists in intravenous administration of digoxin-specific Fab fragments; they are able to restore the activity of the sodium–potassium ATPase pump, by displacing digoxin away from its receptors, leading to a rapid disappearance of signs and symptoms of intoxication [5].

Drugs and Toxins Acting on the Autonomic Nervous System

Beta-Blocker Antagonists

Pharmacodynamic properties of beta-blockers differ in relation to their affinity for beta-adrenergic receptor (see Table 29.5): block of β1 receptors has negative chronotropic and inotropic effects and reduces renin secretion, while inhibition of β2 receptors induces relaxation of smooth muscle cells in the vessels, bronchial apparatus, and gastrointestinal tract and influences glucose metabolism (inhibition of glycogenolysis and gluconeogenesis) [15].

The most common manifestations of beta-blocker toxicity include cardiovascular system symptoms, with disorders of the conduction system (sinus node dysfunction, various degrees of AV blocks, intraventricular conduction delay) and hypotension, secondary to altered myocardial contractility and block of peripheral receptors.

Sotalol is the only beta-blocker with class III antiarrhythmic properties, via blockade of potassium channels, causing an increase in the duration of repolarization phase, with QTc prolongation on ECG and risk of ventricular tachyarrhythmias and TdP. Also propanolol and acebutolol can induce prolongation of the QTc interval [16, 17].

Overdose with agents with intrinsic sympathomimetic activity can be expressed with hypotension and tachycardia.

Other manifestations of beta-blocker poisoning are bronchospasm, lethargy, coma, and hypoglycemia.

In the management of patients with beta-blocker intoxication, glucagon via IV infusion is used that induces an increase in cAMP levels and an influx of calcium in the intracellular space, secondary to the stimulation of a membrane receptor in a different site of action compared to that of beta-blockers. Other therapeutic interventions are the infusion of atropine, calcium, and catecholamines [5].

Other Drugs Acting on the Sympathetic Nervous System (Table 29.6)

Drugs acting on alpha-adrenergic receptors are classified as central and peripheral, with agonist and antagonist properties.

Alpha-2 central agonists (clonidine, α-methyldopa) and peripheral alpha-1 blockers (doxazosin, prazosin, terazosin) are principally used as antihypertensive drugs; overdose states can be associated with rhythm disturbances (sinus, atrial, junctional, and ventricular bradyarrhythmias; first-degree AV block; ventricular tachyarrhythmias), severe hypotension, and cardiac failure.

Table 29.5 Selectivity of beta blockers

Drug	β1-selectivity	ISA	α-Adrenergic blockade	Half-life (h)
Propanolol	–	–	–	3–5
Nadolol	–	–	–	10–20
Timolol	–	–	–	3–5
Pindolol	–	++	–	3–4
Labetalol	–	+	+	4–6
Carvedilol	–	–	+	7–10
Metoprolol	++	–	–	3–4
Atenolol	++	–	–	5–8
Esmolol	++	–	–	0.13
Acebutolol	+	+	–	8–12
Bisoprolol	++	–	–	9–12
Nebivolol	++	–	–	10–30

Abbreviations: *ISA* intrinsic sympathomimetic activity

Table 29.6 Sympathomimetic drugs and toxins

Drugs	Beta-adrenergic agonists (albuterol, dobutamine, epinephrine, isoproterenol, norepinephrine, ritodrine, terbutaline) Theophylline Ergot alkaloids Phenylpropanolamine and other over-the-counter sympathomimetics (decongestants containing phenylephrine, pseudoephedrine, ephedrine) Monoamine oxidase inhibitors Caffeine Chloral hydrate (sedative and hypnotic drug)
Illicit drugs	Cocaine Amphetamines Phencyclidine Delta-tetrahydrocannabinol (cannabis) Psilocybin and other hallucinogens Lysergic acid diethylamide
Toxins	Ethanol Hydrocarbon solvents (e.g., toluene, benzene, chloroform, etc.) Freon (and other fluorocarbon aerosols)

A lot of drugs and toxins can cause signs of hyperactivity of the sympathetic nervous system both centrally and peripherally, with positive inotropic and chronotropic stimulation (Table 29.6). At ECG, sinus tachycardia is very common; at high dosage, supraventricular and ventricular arrhythmias may also occur. Cocaine can induce vasospasm and platelet activation, causing myocardial ischemia and infarction also in young subjects with no other cardiovascular risk factors [18, 19].

Peripheral alpha-1 agonist drugs (imidazoline derivatives) are used as nasal decongestants; at high doses by topical administration, they can induce systemic toxicity, hypertension, and tachycardia.

Anticholinergic Toxicity

A lot of drugs, toxins, and other natural substances have anticholinergic properties: antihistamines, tricyclic antidepressants, antipsychotics (e.g., phenothiazines, clozapine, olanzapine), atropine, scopolamine, toxic plants from Solanaceae family containing belladonna alkaloids, and toxic mushrooms (*Amanita muscaria*).

At high dosage, they commonly induce sinus tachycardia, but in case of poisoning, we should assess for serious supraventricular and ventricular arrhythmias.

Clinical manifestations of anticholinergic toxic syndrome are flushing, dry skin and mucous membranes, mydriasis, altered mental status, sinus tachycardia with hypertension, and urinary retention [19].

Cholinomimetic Toxicity

The most common cause of toxicity from drugs and toxins with cholinomimetic properties is the intoxication with organophosphate and carbamate pesticides. Organophosphorus pesticides inhibit esterase enzymes (acetylcholinesterase) with consequent accumulation of acetylcholine and stimulation of acetylcholine receptors in synapses of the autonomic nervous system, central nervous system, and neuromuscular junctions.

In the early phase, tachycardia is present secondary to the stimulation of nicotinic receptors, followed by the development of bradycardia by the stimulation of muscarinic receptors; subsequently, even after a few days, in cases of severe intoxication, AV blocks and asystole may appear [5], with QT prolongation, ventricular tachycardia, and TdP.

Cases of myocardial infarction have been reported, secondary to parasympathetic hyperactivity with coronary vasospasm and direct damage of pesticides on the myocardium [19].

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30 Difficult Interpretation of ECG: Small Clues May Make the Difference. The Role of the P Wave

Alessandro Maolo and Daniele Contadini

30.1 Case Report

A 24-year-old woman suspected of scleroderma was referred to the clinic of internal medicine for clinical evaluation.

The patient presented with asthenia and mild dyspnea for moderate physical activity. She reported sleeping with just one pillow, and she had no episodes of nocturnal dyspnea. She had no syncope or presyncopal symptoms.

Physical Examination

- *General:* no fatigue, no acute distress, alert, awake, and oriented; well developed and well nourished
- *Neck:* supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- *Cardiovascular:* regular rate and rhythm, S1 normal, paradoxical splitting of the S2, and reduction of intensity at the apex. Mild systolic crescendo-decrescendo murmur at the second right intercostal space with no radiation, early low-pitched diastolic decrescendo murmur, and no pansystolic plateau murmur attributable to ventricular septal defect. Point of maximal intensity displaced to the center of the chest. No hepatojugular reflux and capillary refill less than 2 s.
- *Lungs:* rales at auscultation at the bases bilaterally, no rhonchi or wheezes, no egophony, no alterations in tactile fremitus, and normal percussion sounds
- *Abdomen:* mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, nondistended/nontender, no rebound or guarding, no costovertebral angle tenderness, and no hepatosplenomegaly
- *Extremities:* no cyanosis or clubbing and no peripheral edema

Electrocardiogram

A routine ECG was performed and is described as follows (Fig. 30.1a,b):

Regular RR interval with a heart rate of 75 bpm.

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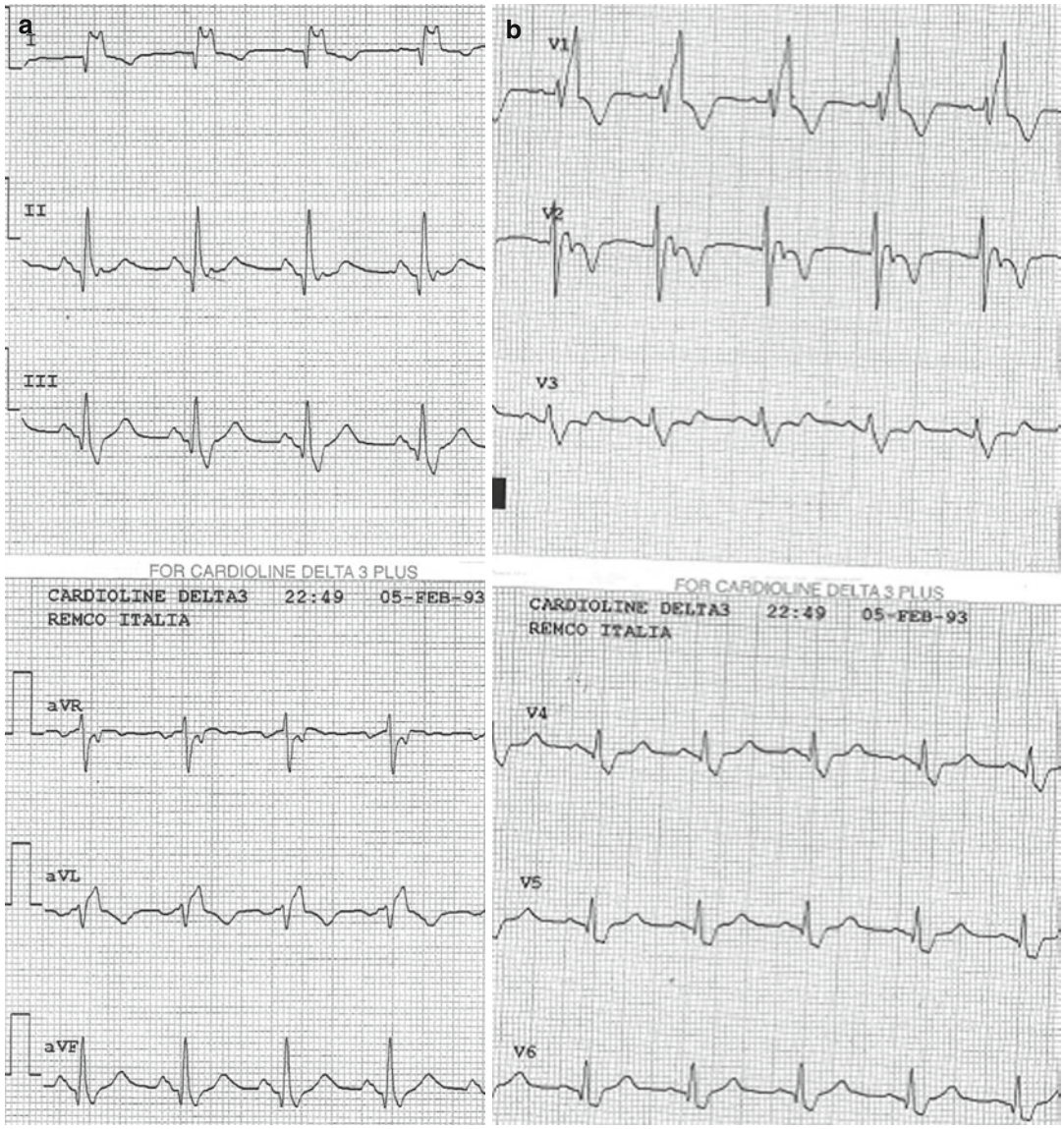

Fig. 30.1 (**a**, **b**) Standard 12-lead ECG at rest. See the chapter for the description

P wave is apparently increased in amplitude and duration; however, watching carefully, we can notice that the amplitude of the P wave doesn't reach a pathologic value. In fact the maximum amplitude is 0.20 mV in II lead. Also the duration is mildly prolonged, with the maximum P wave duration of 120 milliseconds (ms) reached in II lead. P wave morphology can be considered pathological: if we pay attention on the P wave in II, III, and aVF leads, we can notice that the first part is high and narrow and it's followed by a second part that is smaller and larger than the first one. This is a likely sign of biatrial enlargement. P wave axis is 90°, being negative in aVR and aVL leads, biphasic in I lead, and positive in II, II, and aVF leads. A negative P wave in aVL is something to think about.

PQ interval is normal (160 ms).

QRS complex is clearly enlarged (160 ms) with a normal amplitude. However, it decreases

progressively from V1 to V6. Looking at precordial leads, the morphology is typical for right bundle branch block. In the limb leads, the QRS complex has a strange morphology. A deep S wave, typical for RBBB, in I and aVL leads is missing, and the intraventricular and interventricular conduction disturbance seems to be more complex than in a simple RBBB. Also the "rS" morphology in aVR lead and the "rSR'" in aVL leads are not typical for RBBB. Axis is indeterminable.

Repolarization is not abnormal because this is secondary to the conduction disturbance. The QT interval measures 400 ms and the QTc 447 ms.

Conclusions

ECG shows sinus rhythm, normal heart rate, right and left atrial enlargement, normal atrioventricular conduction, right bundle branch block, and secondary repolarization's abnormalities.

Looking at a previous chest X-ray, something unexpected was found (Fig. 30.2).

The patient had a situs viscerum inversus with dextrocardia (please note the cardiac apex and the gastric bubble placed on the right side). Moreover, the patient had tetralogy of Fallot and underwent a surgical correction when she was a child.

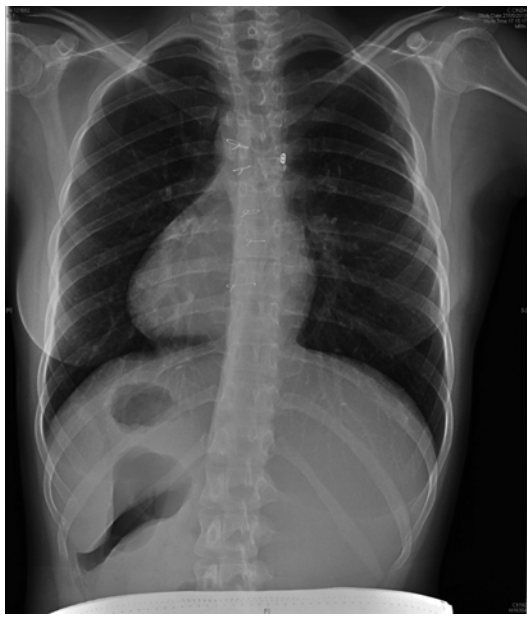

Fig. 30.2 Chest X-ray. Please notice the cardiac apex and the gastric bubble placed to the *right side*

Taking a new look to the previous ECG, we can now relate some findings with the anatomic abnormalities.

First of all, the axis of the P wave is not normal. The notch on the apex of the P wave is not a sign of an atrial enlargement. In fact in young people, the P wave duration can be normal up to 130 ms. The notch is a sign of interatrial conduction disturbance compatible also with the previous surgical intervention.

The previously diagnosed RBBB is a left bundle branch block. In dextrocardia, the morphological left bundle branch is placed on the right, and its conduction disturbance could be due to the interventricular septal defect that is always present in tetralogy of Fallot. The other intraventricular and interventricular conduction disturbances could be linked to the previous surgical intervention.

The atypical morphology of QRS complex in aVR and aVL leads can be related to dextrocardia too. In fact, in RBBB, "rSR'" and "qR" morphologies in aVR lead and a deep or large S wave in aVL lead are common findings, and in this case, the morphologies are inverted between the two leads.

By comparing the previous ECG with the following, it is visible that in the typical RBBB (ECG from another patient below), the QRS morphologies in aVR and aVL are switched (Fig. 30.3a,b).

A sign that could suggest the presence of dextrocardia is the decreasing amplitude of the QRS complex from V1 to V6 together with the negative P wave in aVL. This happens because the electrodes are placed on the left part on the chest and the electric signal from the heart is progressively going farther from the precordial leads, in particular from the left ones.

30.2 The Normal P Wave

P wave comes from the electrocardiogram sign of atrial depolarization. The impulse starts from the sinoatrial (SA) node and spreads to the right

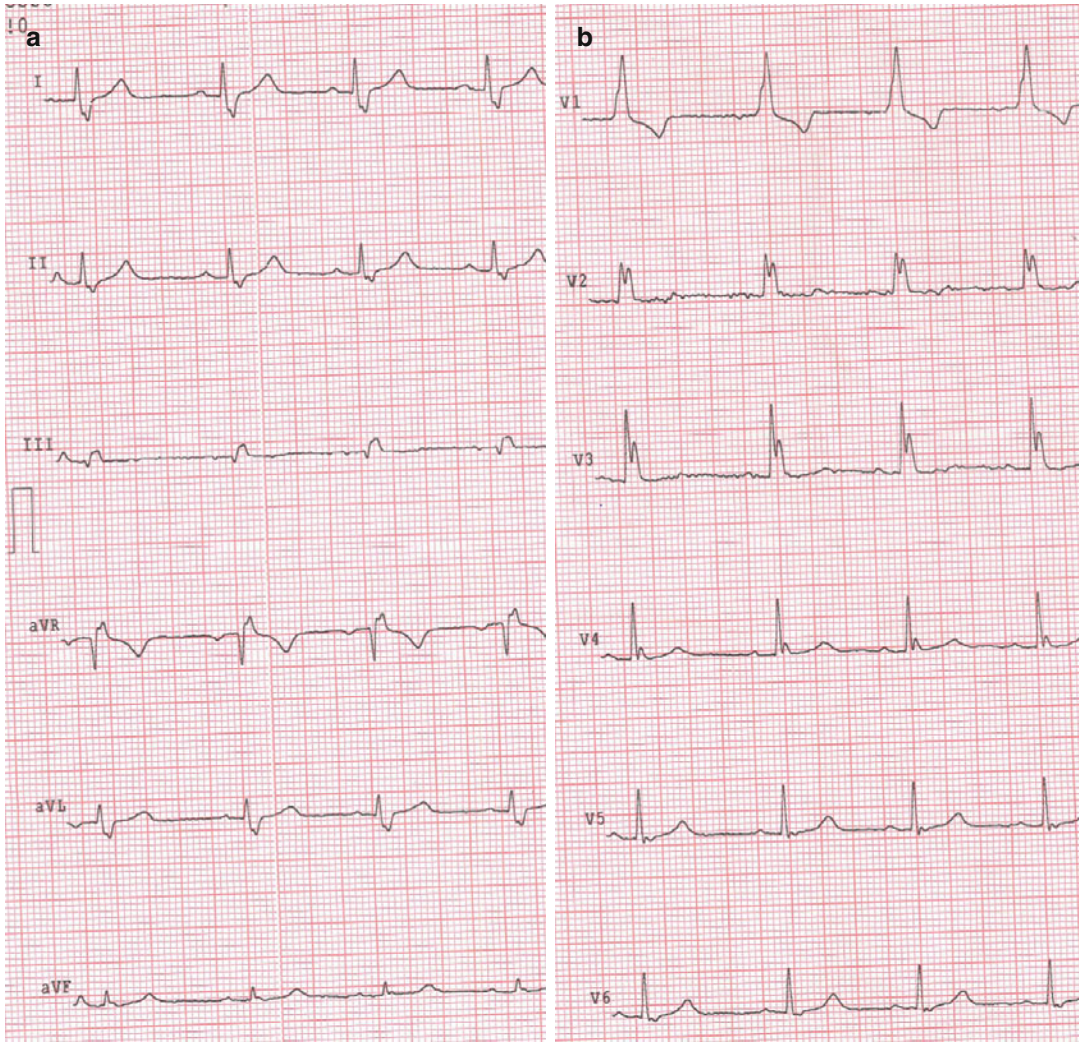

Fig. 30.3 (**a**, **b**) Standard 12-lead ECG at rest from another patient having a situs solitus and an RBBB. Please compare with the ECG in Fig. 30.1

atrium first and then through the interatrial septum to the left atrium.

Its normal duration varies from 70 to 140 ms even in normal subjects [1]. A P wave lasting more than 110 ms can be considered abnormal.

The P wave axis is the result of the electrical activation of the right atrium (directed anteriorly first and then posteriorly when involving the inferior wall) and of the left atrium (directed posteriorly). Therefore, on the limb leads, the normal P wave range is 0° to +75°. That's why the normal P wave is positive in I and II leads and always negative in aVR lead. Moreover, also in the precordial leads from V3 to V6, the P wave is generally positive. Conversely in V1 and V2, normal P wave is often diphasic and sometimes even negative.

Talking about the normal amplitude of the P wave, we have to say that it's affected by many factors such as the distance of electrodes from the heart and the level of atrial fibrosis. In the limb leads, a P wave inferior or equal to 0.25 mV or 25 % of the following R wave is considered as normal amplitude. In the precordial leads, the normal amplitude is a bit lower and doesn't exceed 0.15 mV [1].

30.3 Interatrial Conduction Delay

Atrial depolarization begins in the sinus node; from here, the electrical impulse goes through the internodal fascicles (fibers that connect sinus with the AV node). There are three bundles: the Bachman fascicle (anterior), the Thorel fascicle (in an intermediate position), and the Wenckebach fascicle (posterior). The last one conducts the impulse from the right to the left atrium, too. So, the atria activation begins from the right atrium and then reaches the left one. The normal duration of P wave is from 50 to 80 ms. A P wave duration superior to 110 ms is pathological and related to interatrial conduction delay. This condition is caused by a complete or partial interruption of the Bachman fascicle or other connecting atria fibers. Usually the interatrial conduction delay is associated with a modification of the axis of the terminal part of P wave. It is more negative (from −30° to −60°) with a caudal-cranial activation of the left atrium. This pattern of activation is visible as a biphasic P wave (positive-negative, with terminal negative component evident in inferior leads) lasting more than or equal to 100 ms. The interatrial conduction delay is highly specific of left atrium enlargement [1, 2].

30.4 P Wave Other Than That from the Sinus Node

The P wave is defined not to be sinusal when it originates from an ectopic focus that can be located in variable parts of the atria. A non-sinus P wave can be present as a premature atrial impulse (isolated or in pairs), as an ectopic atrial tachycardia (heart rate ≥ 100 bpm), or as an ectopic atrial rhythm (heart rate < 100 bpm).

In all these cases, the P wave has a different morphology and axis compared with the sinusal P wave. Analyzing its characteristics on the surface ECG can help us to identify the location of the ectopic focus, but it isn't always accurate. This variability depends on the possible presence of ectopic focus close to the sinus node and therefore originating P wave very similar to that present in normal sinus rhythm. Moreover, a single ectopic focus can cause P waves of different morphology related to the presence of intra-atrial or interatrial conduction disturbances. Likewise, ectopic P waves originating from different foci can have similar or the same morphology [1, 3].

Despite this wide variability, some ectopic foci are identifiable with fairly good precision. For example, if the ectopic impulse originates from a focus close to the AV node, a negative P wave can be visible in II, III, and aVF leads, while it is positive in aVL and aVR leads. On the contrary, if the ectopic focus is located in the left atrium, the P wave is negative in aVL and positive in aVR (similarly to the P wave in dextrocardia), while in the inferior leads, it can be positive or negative depending on the part of the left atrium in which the focus is placed.

30.5 Right Atrial Enlargement

Right atrial enlargement (RAE) is a common consequence of various cardiopulmonary diseases. As we already said, the atrial depolarization firstly involves the right atrium, so it is easy to understand that RAE alterations interest the initial portion of P wave with voltage increase but without modification in terms of P wave duration (Fig. 30.4a, b). Some typical P wave modifications can help to recognize RAE: P wave (or initial positive P wave deflection) > 0.15 mV (more specific ≥ 0.20 mV) in V1 and V2 leads; an initial positive part > 40 ms in V1 when P wave is biphasic in this lead; high and sharp P wave in inferior leads (II, III, aVF) ≥ 0.25 mV; and P wave axis ≥ +75° (it can reach +90° too). The last modification is very strictly associated with COPD. Sometimes the RAE correlated P wave modifications can be associated with QRS modification as increased voltages of right ventricle electrical vectors or delayed right ventricle depolarization [1, 2].

30.6 P Pulmonale

A P wave is defined "pulmonale" when it appears as a tall and peaked P wave in the inferior limb leads (II, III, and aVF) and

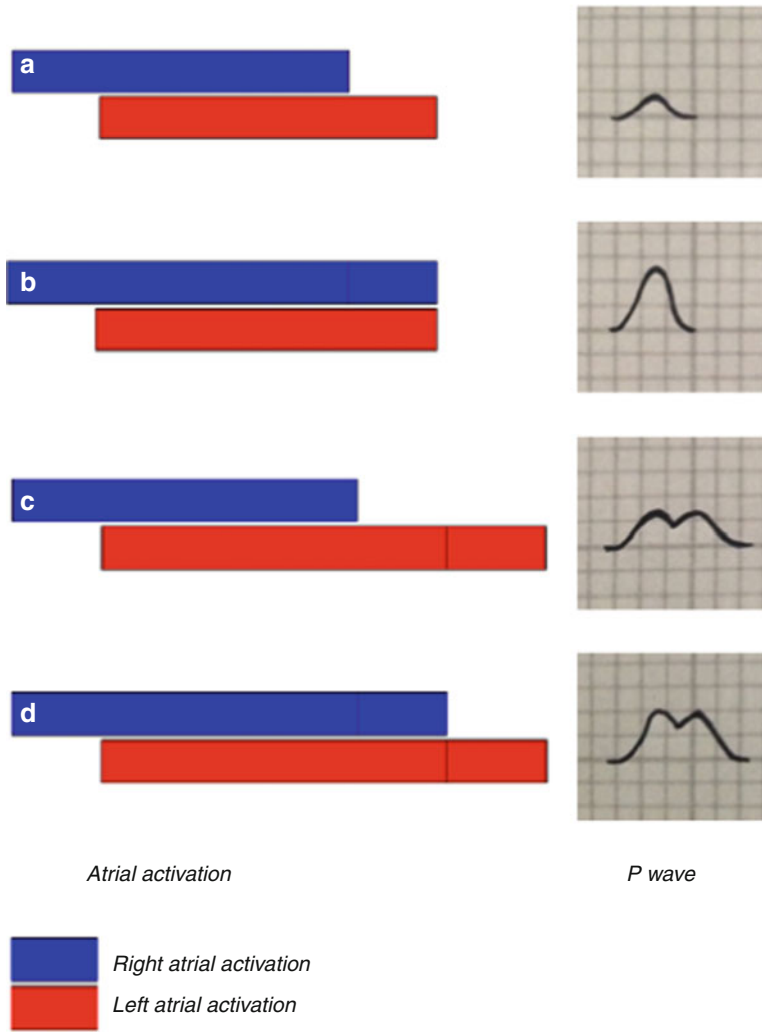

Fig. 30.4 Atrial activation and P wave morphology in normal atria (**a**), in right (**b**), left (**c**) and biatrial enlargement (**d**)

consequently having an axis superior to 70° [1]. This finding on the ECG has different correlations, but it's usually associated with pulmonary hypertension. The P pulmonale is most frequently associated with congenital heart disease such as tetralogy of Fallot, pulmonic stenosis, tricuspid atresia, or interatrial septum defects and interventricular septal defects in the presence of Eisenmenger syndrome. Furthermore, in patients with chronic cor pulmonale, this ECG pattern has an incidence of about 20 %. [1] As expected, the P pulmonale is a marker of chronic lung disease, but it is mostly associated with COPD and then pulmonary fibrosis. Moreover, severe COPD is responsible for alterations of the P wave axis more than its morphology. This axis deviation over 70° is due to the hyperinflation of lungs, always present in these kinds of patients.

Despite all, the P pulmonale pattern isn't strictly correlated with the increase of right atrial volume, and it can be present even in healthy subjects. In these cases, usually a sympathetic stimulation, resulting in a stronger and synchronous atrial contraction, or the vertical position of the heart can explain abnormalities in P wave axis and morphology similar to those present in the P pulmonale pattern [1].

30.7 Left Atrial Enlargement

Left atrial enlargement (LAE) is a common consequence of left ventricular or mitral valve diseases. The left atrial depolarization is the last part of atrial activation, so the LAE modifications involve the final component of P wave with duration's increase but without significant voltage alterations (Fig. 30.4a, c). Some typical P wave modifications can help to recognize LAE: P wave duration more than or equal to 120 ms in limb leads; left deviation of P wave axis more negative than +30°; and biphasic P wave in V1 with negative terminal component more than or equal to 40 ms and with a minimum of 1 mV bifid P wave (usually in dII, dI, aVL, V3, V4, V5, or V6), with an interval between the two peaks longer than 40 ms. A more peak-to-peak prolongation could be the sign of a mitral disease, often a severe stenosis. This pattern is also defined as P mitrale [1, 2].

30.8 Biatrial Enlargement

The P wave abnormality during biatrial enlargement can be simply considered as the summa of the RAE and LAE alterations (Fig. 30.4a, d). ECG findings could be a P wave duration more than or equal to 120 ms associated with an amplitude more than or equal to 2.5 mV; a diphasic P wave (positive-negative) in V1 with the positive component of at least 1.5 mV and a negative component longer than 40 ms with an amplitude of 1 mV or more; and the presence of notched P wave in left precordial leads and high P wave in right precordial leads [1, 2].

30.9 P Wave and Arrhythmias

The role of P wave in differential diagnosis of tachycardias has already been described in previous chapters. However, some P wave abnormalities during sinus rhythm can be useful as atrial fibrillation predictor. That concept will be discussed below.

P Wave Duration

A prolonged P wave can be related to echocardiographic findings of left or biatrial enlargement and consequently help us to identify patients with a high risk of developing atrial fibrillation. In a clinical trial of 660 patients, who underwent dual-chamber pacemaker implantation, P wave duration was measured using the standard 12-lead ECG (50 mm/s velocity). A P wave duration superior to 100 ms was identified in a group of patients with a higher risk for developing persistent atrial fibrillation and atrial fibrillation-related hospitalization [4].

The P wave duration analysis can be more accurate using signal-averaged ECG (SAECG). SAECG is a particular ECG technique using cardiac electric signals from many surface electrodes. The values measured with all the leads are averaged to minimize interference and to see even the smallest alterations. A prolonged signal-averaged P wave duration compared to the standard 12-lead ECG was found to be a more precise marker for the development of atrial fibrillation [5].

Other important findings detectable using SAECG are atrial late potentials. Late potentials are very-low-amplitude electric signals not visible with the standard 12-lead ECG. The QRS late potentials originally were studied to estimate the ventricular arrhythmia risk. Similarly the P wave (or atrial) late potential can be useful to stratify the risk for paroxysmal atrial fibrillation. Budeus et al. hypothesized that atrial late potentials found on P wave SAECG could have a role in the development of paroxysmal atrial fibrillation [6]. However, the predictive value of atrial late potentials has not been demonstrated univocally yet.

P Wave Dispersion

P wave dispersion is defined as the difference between the maximum and minimum durations of P wave measured on the standard 12-lead ECG. A significant high value of P wave dispersion could

be considered as the sign of abnormal atrial electrical impulse propagation. In the literature, the most used cutoff value for high P wave dispersion is considered to be 40 ms [7]. This value has been demonstrated to have a sensitivity of 83 % and a specificity of 85 % with a positive predictive value of 89 % in detecting subjects who had history of paroxysmal lone atrial fibrillation [8]. Calculating the P wave dispersion on the standard 12-lead ECG in 100 patients, it was found to be higher in patients who had a history of paroxysmal atrial fibrillation [8]. Moreover, other studies demonstrated that the P wave dispersion calculated on the standard surface ECG could be an effective predictor of atrial fibrillation development in postoperative period (after CABG) and in patients with hypertension [9, 10].

For a more accurate evaluation of P wave dispersion, SAECG was also used and some more precise markers were studied. In particular, P wave dispersion index (P wave duration standard deviation/P wave duration mean value ×100) calculated in 40 subjects was demonstrated to have an 83 % sensitivity and 81 % specificity values in the identification of patients with a history of paroxysmal atrial fibrillation [11].

The rationale for using P wave dispersion as a predictor of atrial fibrillation is that a high dispersion could be considered the electric sign of nonhomogeneous atrial conduction and consequently may reflect an electrical instability of the atria.

Nevertheless, the techniques used for ECG recording and P wave duration and dispersion measurement were not standardized in the different trials. Finally, we have to consider an interobserver and intraobserver variability that may affect accuracy and reliability of P wave dispersion as a noninvasive predictor of paroxysmal atrial fibrillation.

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