Acute and Chronic Myocarditis

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Acute myocarditis, an inflammatory disease of the myocardium, has various causes, the most common being viral infection [1] (Table 6.1).

In acute myocarditis of viral origin, viruses enter the cardiomyocytes, causing cytopathic effects due to viral replication. This triggers a humoral and cellular response that includes immune reactions [1].

Acute myocarditis is characterized by edema and infiltration of pan T lymphocytes and macrophages; variable amounts of myocardial necrosis may occur [1–4].

While the precise incidence of acute myocarditis is unknown [1, 5–7], it is probably higher than generally thought. Indeed, myocarditis is often a collateral effect of influenza syndromes, and if it does not cause major symptoms, it is not diagnosed at all.

Acute myocarditis is one of the causes of sudden death in athletes, as demonstrated by Italian and USA research [8, 9] (Fig. 6.1). Some experimental studies in animals [10–12] suggest that physical activity during acute myocarditis increases the replication and aggressiveness of the virus. It follows that, in order to prevent sudden death, early identification of acute myocarditis in athletes is essential, so that the individual can rest and avoid exercise. In real life, however, during febrile

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Table 6.1 Causes of myocarditis (From Caforio A et al. 2013, modified)

Infectious	
Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, etc.
	DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, etc.
Rickettsial	*Coxiella burnetii* (Q fever), etc.
Spirochetal	*Borrelia* (Lyme disease), *Leptospira* (Weil's disease)
Bacterial	*Staphylococcus*, *Streptococcus*, *Pneumococcus*, etc.
Fungal	*Aspergillus*, etc.
Protozoal	*Trypanosoma cruzi*, *Toxoplasma gondii*, etc.
Parasitic	*Trichinella spiralis*, etc.
Immune-mediated	
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, etc.
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, colchicine, etc.
Alloantigens	Heart transplant rejection
Toxic	
Drugs	Amphetamines, cocaine, ethanol, etc.
Hormones	Pheochromocytoma, etc.
Etc.	
Other	

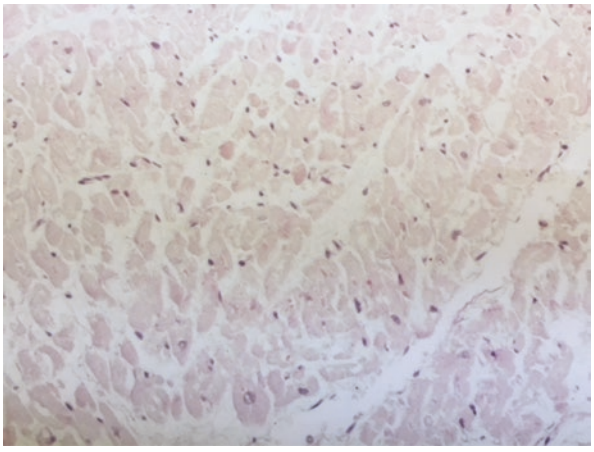


Fig. 6.1 Male, 25 years old, soccer player who suddenly died during physical training. The autopsy revealed an acute myocarditis. Istologic finding is reported which shows a diffuse infiltration of lymphocytes

syndromes, athletes frequently treat their symptoms aggressively with anti-inflammatory drugs and resume physical training as soon as possible.

Sudden death during myocarditis can occur both at rest and during effort and is determined by rapid and often polymorphic ventricular tachycardia, which may degenerate into ventricular fibrillation (Figs. 6.2 and 6.3).

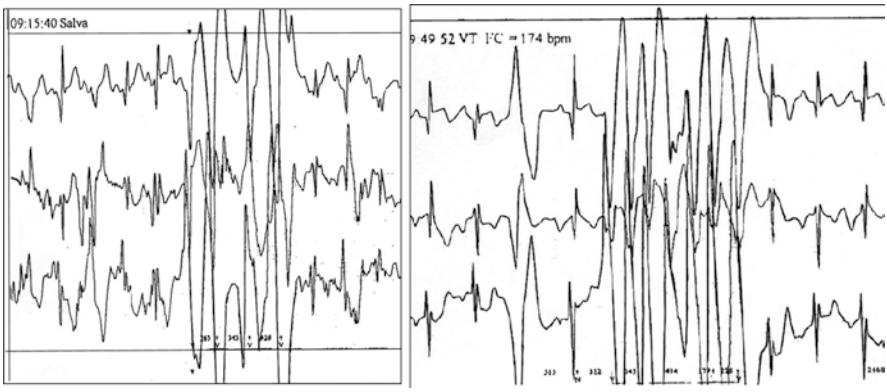


Fig. 6.2 Male, 21 years old. Syncope during soccer. Holter monitoring showed fast, polymorphic non-sustained ventricular tachycardia. A few days later, he suddenly died during a football match. Autopsy revealed acute myocarditis

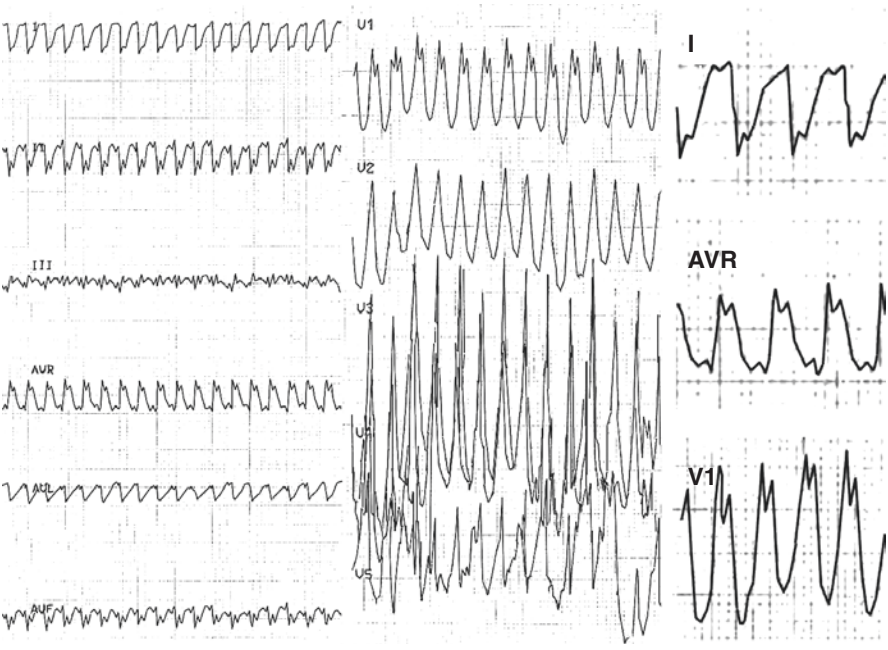


Fig. 6.3 Male, 14 years old. During a febrile episode, he experienced palpitations and pre-syncope. The ECG performed in the hospital showed fast ventricular tachycardia (VT). Note the morphology of QRS: RBBB with superior axis oriented towards aVR. This morphology indicates that VT arose from the infero-lateral part of the left ventricle

6.1 Clinical and Electrocardiographic Findings

The disease generally begins with fever and may present in many different ways, ranging from mild symptoms to chest pain, palpitations, etc. [1]. Only a few patients present with left ventricular dysfunction; in these cases, the disease can cause heart failure. In some cases, syncope and/or cardiac arrest may occur as a consequence of cardiac arrhythmias (see above).

The diagnosis of myocarditis is generally reached on the basis of a clinical suspicion and alterations of the electrocardiogram (ECG) [13–20].

In the acute phase, the ECG frequently shows ST elevation in infero-lateral leads (Fig. 6.4a). Of note, the presence of ST elevation in the clinical setting of pericarditis is a sign of concomitant myocarditis. Indeed, the pericardium has no electrical activity. ST elevation in myocarditis may resemble transmural myocardial infarction (STEMI). However, the electrophysiological mechanism of ST elevation in the two conditions is different, and some important differences are present. During STEMI, a transmural ischemic injury is determined by thrombotic occlusion of a coronary artery. Consequently, major modifications of monophasic action potential (MAP) occur in this area, i.e., reduction in the voltage and duration of MAP, which extends transmurally in the affected area.

Thus, in the case of STEMI, an "ST vector" is generated which is oriented from the normal myocardium (opposite to the ischemic myocardium) to the affected area; this creates ST elevation in leads which explore the ischemic myocardium and ST depression in reciprocal leads [21].

In myocarditis, ST elevation is determined by modifications of MAP that are similar to those seen in STEMI (reduction of voltage and duration) but are localized mainly in intramyocardial and subepicardial layers, while the subendocardium is frequently not involved or less involved.

This phenomenon determines an electrical gradient between the subendocardial and subepicardial myocardium, creating an "ST vector" orientated from the endocardium to the epicardium. This vector is recorded as ST elevation in leads exploring the affected area [22] (Fig. 6.5). In myocarditis, there are no reciprocal leads recording ST depression. The only exception may be an ST depression in aVR, as this lead explores the cavity of the left ventricle and records the negative part of the ST vector (Figs. 6.4a and 6.5).

Despite these differences, the differential diagnosis between myocarditis and STEMI may sometimes be difficult, and coronary angiography may be required.

In addition to ST elevation in the acute phase of myocarditis, QRS modifications may also occur: low and/or fragmented voltages, axis deviation, and also Q waves, which can mimic acute myocardial infarction (Fig. 6.6a, b). All these alterations may be due to edema and/or transient cell injury or may be the consequence of definite necrosis. In the first cases, these alterations are transient (Fig. 6.6a–c), while in the last case they persist chronically. In the subacute phase (i.e., 12–24 h after the acute episode), T-wave inversion occurs in the same leads in which ST elevation was previously recorded (Fig. 6.4b).

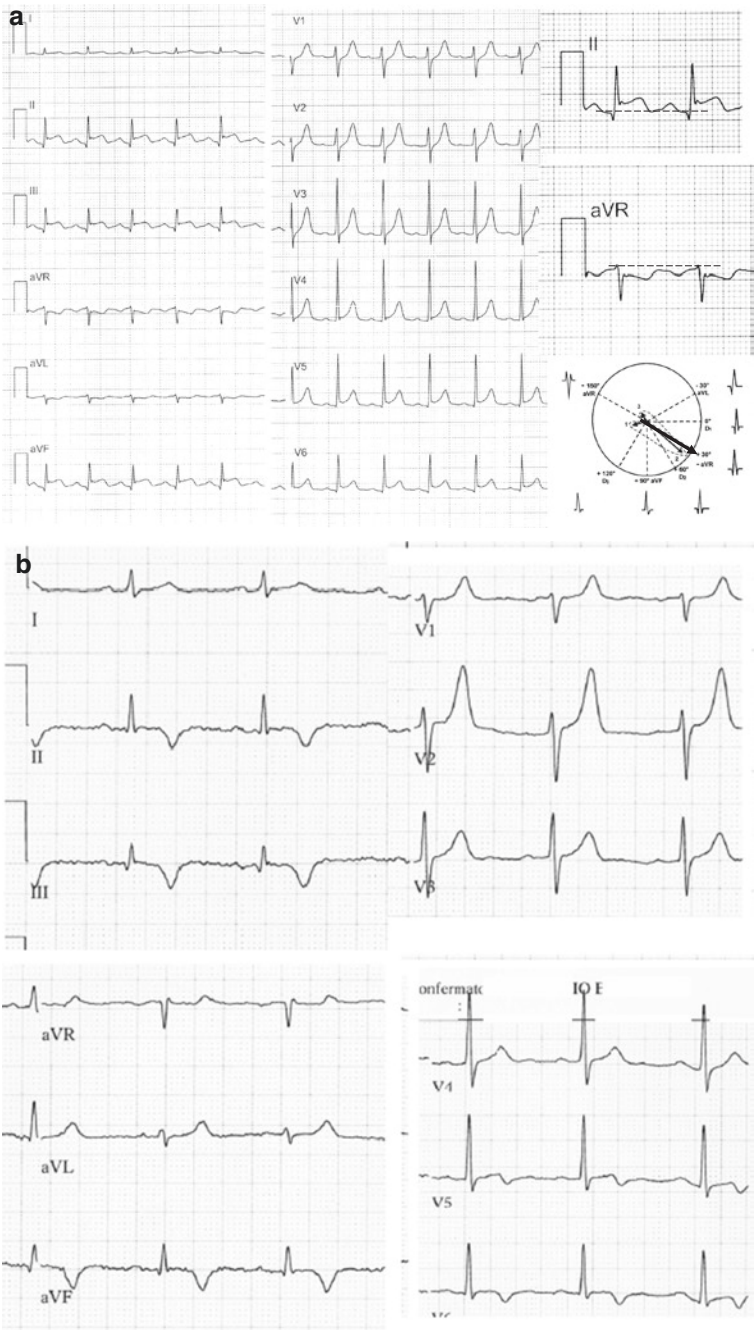
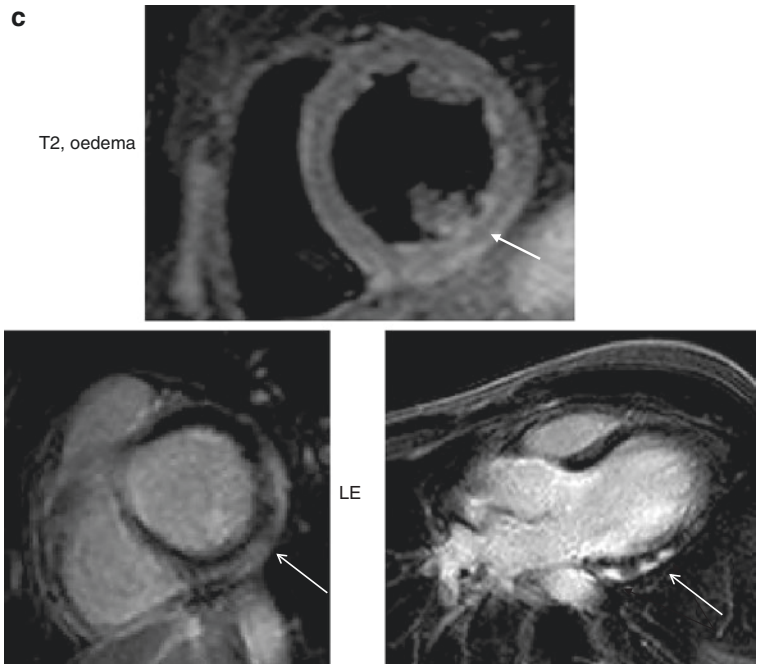


Fig. 6.4 (**a**) Acute myocarditis. The ECG shows ST elevation in infero-lateral leads (II, III, aVF, V5–V6) and ST depression in aVR. (**b**) Same case as in (**a**). ECG recorded after 48 h. Note negative T waves in infero-lateral leads (II, III, aVF, V5–V6). (**c**) Same case as in (**a**, **b**). CMR performed after 48 h. Edema (top) and LE (bottom) can be observed



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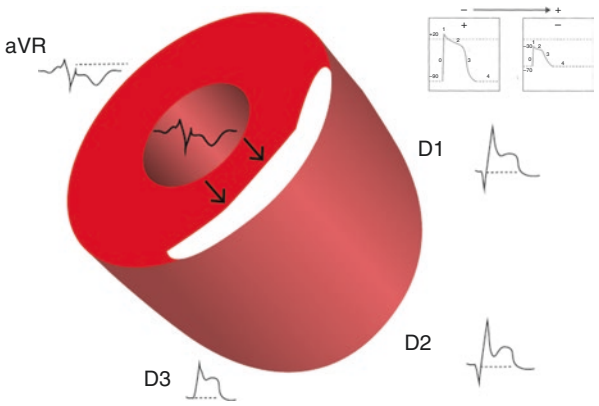


Fig. 6.5 Elecrophysiological mechanism of ST elevation in acute myocarditis. During myocarditis, ST elevation is determined by modifications of monophasic action potential similar to those seen in STEMI (reduction of voltage and duration); these are localized mainly in intramyocardial and subepicardial layers, while the subendocardium is frequently not involved or less involved. This phenomenon determines a gradient between the subendocardial and subepicardial myocardium, creating an "ST vector" orientated from the endocardium to the epicardium. This vector is recorded as ST elevation in leads exploring the affected area. In aVR, ST depression may be recorded, as this lead explores the cavity of the left ventricle and records the negative part of the ST vector

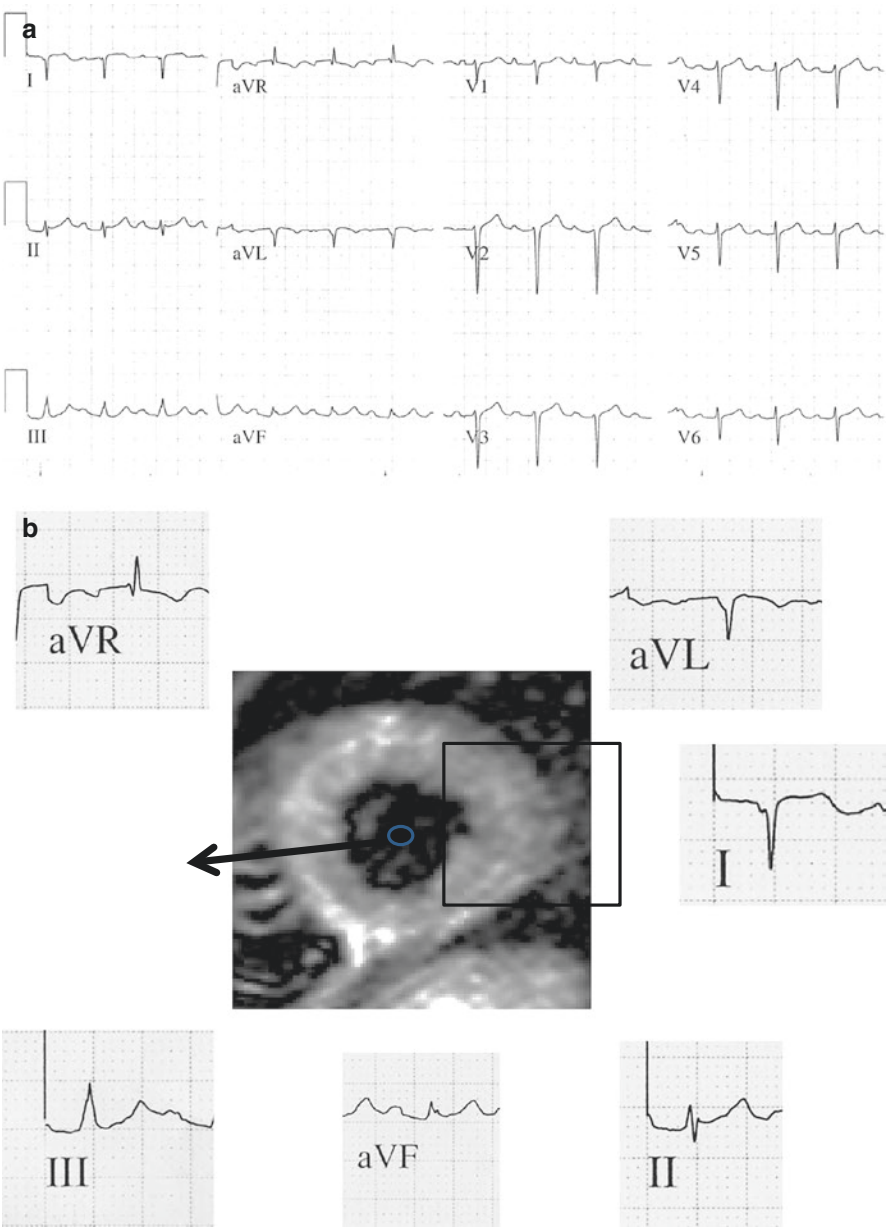


Fig. 6.6 (**a**) Male, 52 years old. Acute myocarditis. The ECG recorded on admission shows ST elevation in I-aVL, right axis deviation, Q waves in I-aVL, and poor R wave progression in precordial leads. (**b**) Same case as in (**a**). CMR performed in the acute phase shows marked edema, particularly in the high lateral wall of the left ventricle. Edema is probably the cause of Q waves in leads (I, aVL) exploring this area. (**c**) Same case as in (**a**, **b**). The ECG performed 6 months later shows normalization of the ECG and, in particular, the disappearance of Q waves in I-aVL

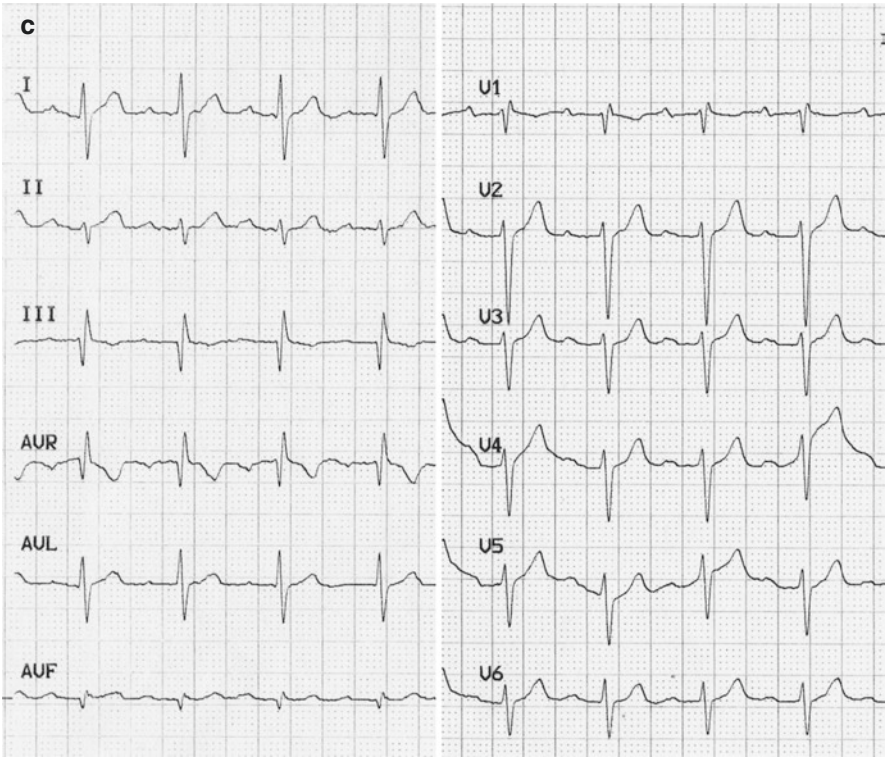


Fig. 6.6 (continued)

The electrophysiological mechanism of T-wave inversion does not have an experimental basis. Nevertheless, T-wave inversion is correlated with the persistence of edema and is probably determined by prolongation of action potential duration.

In patients with Lyme disease or giant cell myocarditis, AV block can develop.

In myocarditis, myocardial damage is documented by the increase of serum enzymes (CK, CKMB, troponins).

Not all patients with myocarditis are medically examined in the acute phase. Some are examined only days or weeks later. In these cases, the suspicion of myocarditis should be aroused in the presence of a clinical history of fever and chest pain and of the new appearance of negative T waves in the ECG.

6.2 Additional Instrumental Findings (Imaging Techniques and Endomyocardial Biopsy)

In many cases of myocarditis, particularly in mild forms, the echocardiogram does not yield useful information. In other cases, depending on the degree of inflammation, regional wall motion abnormalities and systolic dysfunction with preserved

ejection fraction may be present. In rare fulminant myocarditis, the echocardiogram reveals a non-dilated, thickened and hypocontractile left ventricle, as the intense inflammatory response results in massive interstitial edema and loss of contractility [1].

Recently, cardiovascular magnetic resonance (CMR) imaging has been introduced into clinical practice; this provides noninvasive tissue characterization of the myocardium and can efficaciously support the diagnosis of myocarditis. Indeed, in addition to evaluating volumes and contractility, CMR is able to identify both edema and tissue damage. Edema is identified by T2-weight images; myocardial damage is recognized by means of gadolinium late enhancement (LE) (Fig. 6.4c).

Edema is generally present in subepicardial layers and causes an increase in myocardial thickness. CMR visualizes edema as white images within the dark normal myocardium (Figs. 6.4c and 6.6c). Gadolinium, which is injected intravenously, reaches the myocardial interstitium but does not enter the cells. After a few minutes, however, it disappears from both the vessels and the interstitium.

The persistence of gadolinium LE in the acute phase of myocarditis may be related to pathological membrane permeability of the cells involved in inflammation or to cellular necrosis. LE appears in CMR images as white areas within dark normal myocardium (Fig. 6.4c).

In the acute phase of myocarditis, LE is found in over 70% of patients [23]. It is localized in the infero-lateral wall in about 35% of cases, in the anteroseptal wall in about 35%, and in other segments in 15%; in the remaining cases, no LE is detected [23]. According to some authors [23], in acute myocarditis, the localization of LE in the anteroseptal wall has a long-term negative prognostic significance.

Endomyocardial biopsy (EMB) is considered the gold standard for the diagnosis of definite myocarditis. EMB shows histological findings typical of myocarditis and helps to identify the etiology and type of the inflammation (e.g., giant cell, eosinophilic myocarditis, sarcoidosis) [1]. In addition, EMB can guide treatment in subjects infection-negative who need immunosuppression. In clinical practice, however, particularly in mild forms of myocarditis, EMB is not necessary for diagnosis, nor does it change the usual treatment; it is therefore not routinely performed. In contrast, EMB is recommended in complicated forms and/or when diagnosis is uncertain.

6.3 Athletes with Fever: What to Suggest to Sports Physicians

As stated above, in an athlete with fever, it is prudent to stop physical activity, training included. If a suspicion of myocarditis arises, an ECG should be performed; assays of cardiac troponins and creatine kinase may be useful, although, when normal, they do not exclude myocarditis (their normality simply indicates the absence of acute necrosis).

When myocarditis is very probable, an echocardiogram and CMR should be performed.

6.4 Long-Term Outcome of Myocarditis: Chronic Persistence of Inflammation and Residual Fibrosis

The evolution of the disease after the acute phase is quite variable, and it may be useful to monitor this by repeating CMR during follow-up. CMR repeated in hospitalized patients 6 months after the acute phase [24] shows complete recovery in about 10% of cases, with the disappearance of both edema and LE. In about 75% of cases, fibrosis can be detected by means of LE persistence. Finally, in about 15% of cases, both edema and LE are present during follow-up, indicating the persistence of inflammation [24].

It is important to remember that the site and distribution of fibrosis due to myocarditis are different from those seen in other diseases. For example, fibrosis of ischemic origin is transmural or subendocardial, while fibrosis due to myocarditis is generally localized in the subepicardial layers and/or is patchy in intramyocardial layers (Fig. 6.7).

6.5 Clinical and Prognostic Significance of Chronically Residual Fibrosis

Clinical experience teaches that, in patients with ventricular arrhythmia and no obvious heart disease, fibrosis is often detected by CMR and may be the consequence of a previous undetected myocarditis.

In these cases, the QRS morphology of ventricular ectopies is generally RBBB-like, with an upward-oriented axis often pointing toward aVR [22]. On the basis of this morphology, it can be deduced that ventricular ectopic beats originate from the infero-lateral wall of the left ventricle. In these cases, CMR detects fibrosis in the same site (Fig. 6.8a–c). Thus, fibrosis is presumably the cause of ventricular arrhythmias.

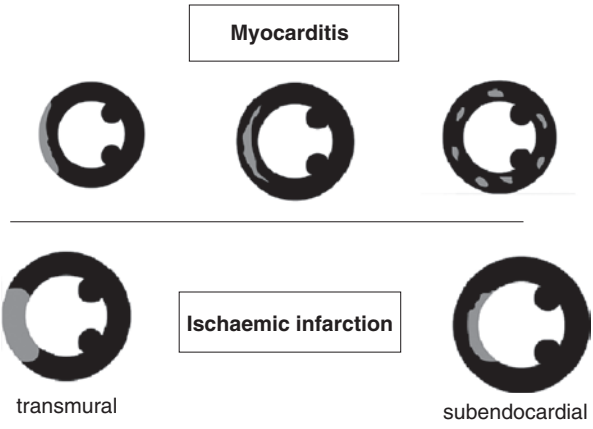


Fig. 6.7 Different localizations of fibrosis (as detected by CMR) in myocarditis and in ischemic heart disease. Top: myocarditis; bottom: ischemic infarction. In myocarditis, LE may be localized at the epicardial level or intramurally. In postinfarction fibrosis of ischemic origin, LE is transmural or localized at the endocardial level

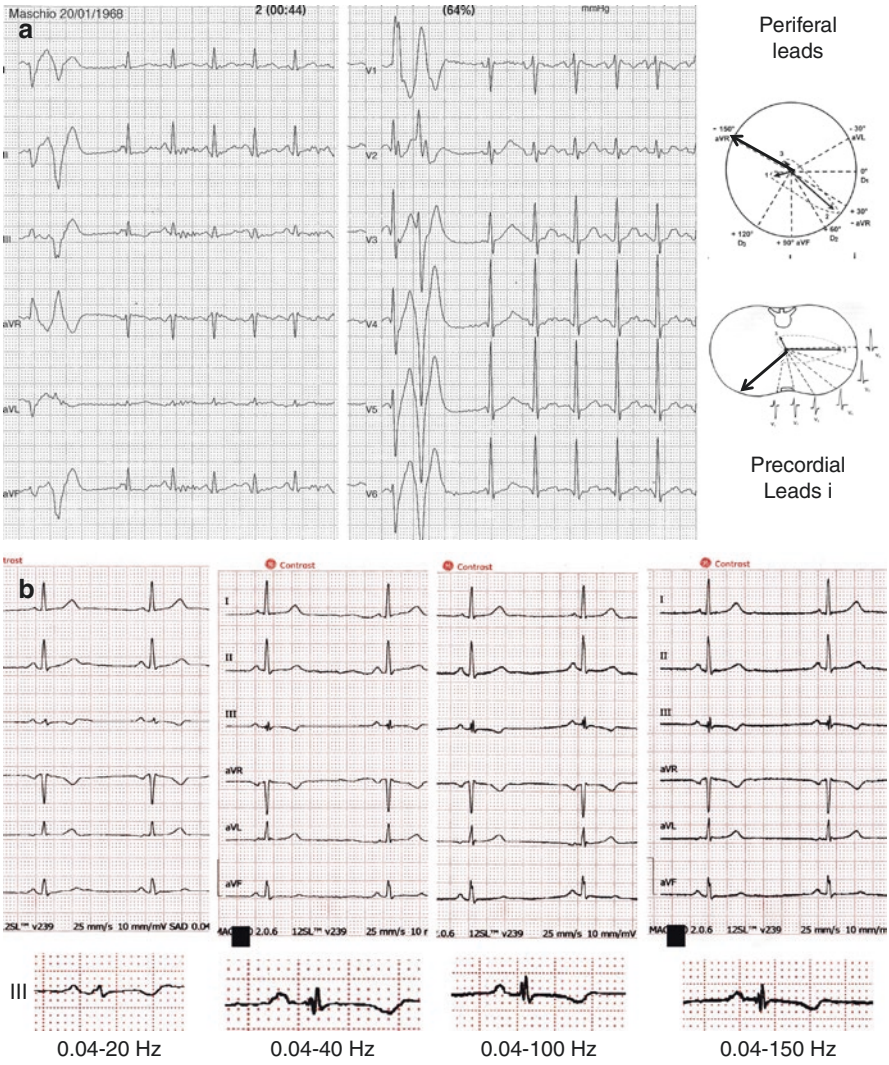


Fig. 6.8 (**a**) Male, 48 years old. ECG during effort shows ventricular premature beats with RBBB-like QRS morphology with upward-oriented axis pointing toward aVR [22]. On the basis of this morphology, it can be deduced that ventricular ectopic beats originate from the infero-lateral wall of the left ventricle. (**b**) Same case as in (**a**). Particular of peripheral leads with different low-pass filters. It can be noted that, when low-pass filters of 0.04–20 Hz are used, no fragmented potentials are recorded. In contrast, fragmented and high-frequency potentials are recorded by using low-pass filters between 0.04–40 Hz and 0.03–150 Hz. (**c**) CMR after gadolinium confirms the presence of fibrosis in the infero-lateral wall of the left ventricle

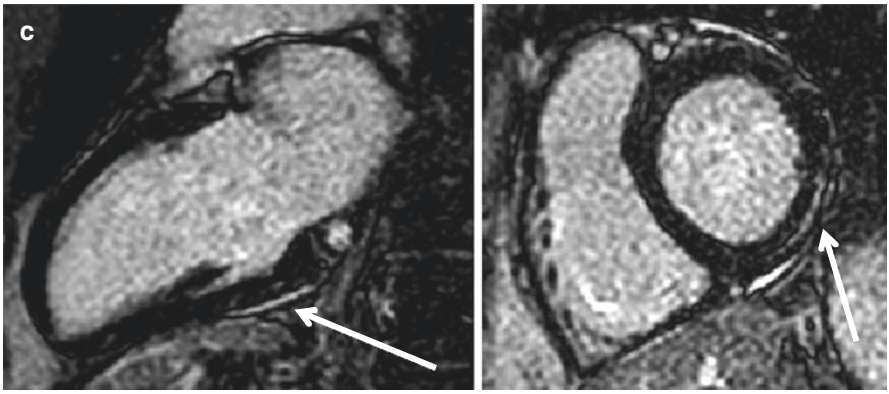


Fig. 6.8 (continued)

Despite these observations, the incidence of ventricular arrhythmias in subjects with post-myocarditis fibrosis is poorly known. Some authors [24] suggest that, during long-term follow-up (7–8 years), patients with residual fibrosis 6 months after the acute phase have a higher incidence of ventricular arrhythmias (VA) than those without fibrosis on CMR.

In such patients, cardiac events (including heart failure and/or malignant VA) have been reported to occur in 11.5% of cases, and in particular, a negative prognostic correlation with the extent of fibrosis has been found. It therefore follows that prudence is recommended in subjects with extensive fibrosis and alarming VA.

In contrast, we do not yet have enough information to establish the risk of patients with limited residual fibrosis and no VA or non-repetitive VA.

6.6 When ECG Suggests the Presence of Fibrosis

Fibrosis of limited extension may produce no ECG signs. Both in myocarditis and in other pathologies (e.g., myocardial infarction) if fibrosis is extensive and diffuse, low voltages, fragmented potentials, and terminal notches can be observed [24–29] (Figs. 6.8b and 6.9a–c). These ECG signs are related to loss of myocardium and delayed activation of peripheral areas, owing to the barriers constituted by fibrotic tissue (Fig. 6.10).

However, it must be stressed that low voltages and fragmented potentials may be recorded if low-pass filters are used in ECG [26]. Indeed, if low-pass filters less than 25–30 Hz (i.e., 0.04–20 Hz) are used, fragmented potentials at high frequency may be eliminated together with artifacts (Fig. 6.8b). In contrast, these potentials may be well recorded by using low-pass filters between 40 and150 Hz (i.e., 0.04–40 or 0.04–150 Hz). In addition, if fibrosis is extensive and compact, Q waves may be recorded in lateral leads or tall R waves in V1, as in ischemic fibrosis. Finally,

fibrosis may produce negative T waves (Fig. 6.11a, b), as a result of late activation of epicardial areas, by inverting the repolarization vector between the endocardial and epicardial myocardium (Fig. 6.12).

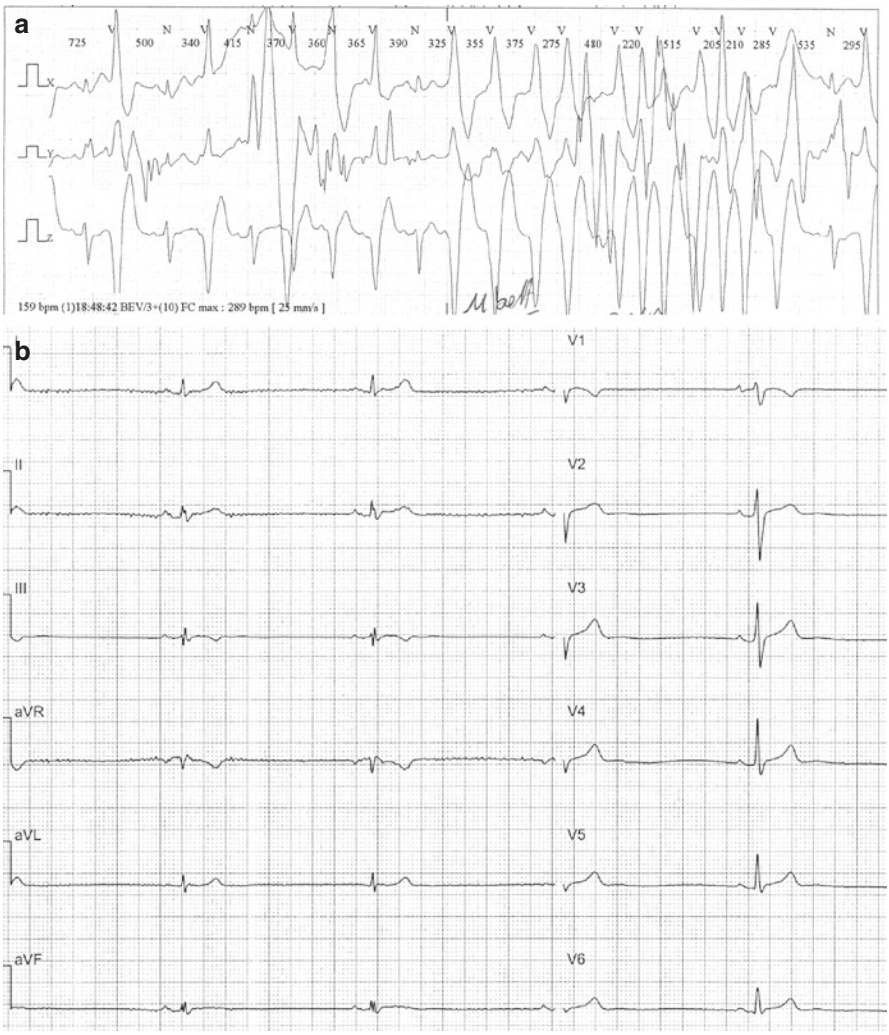
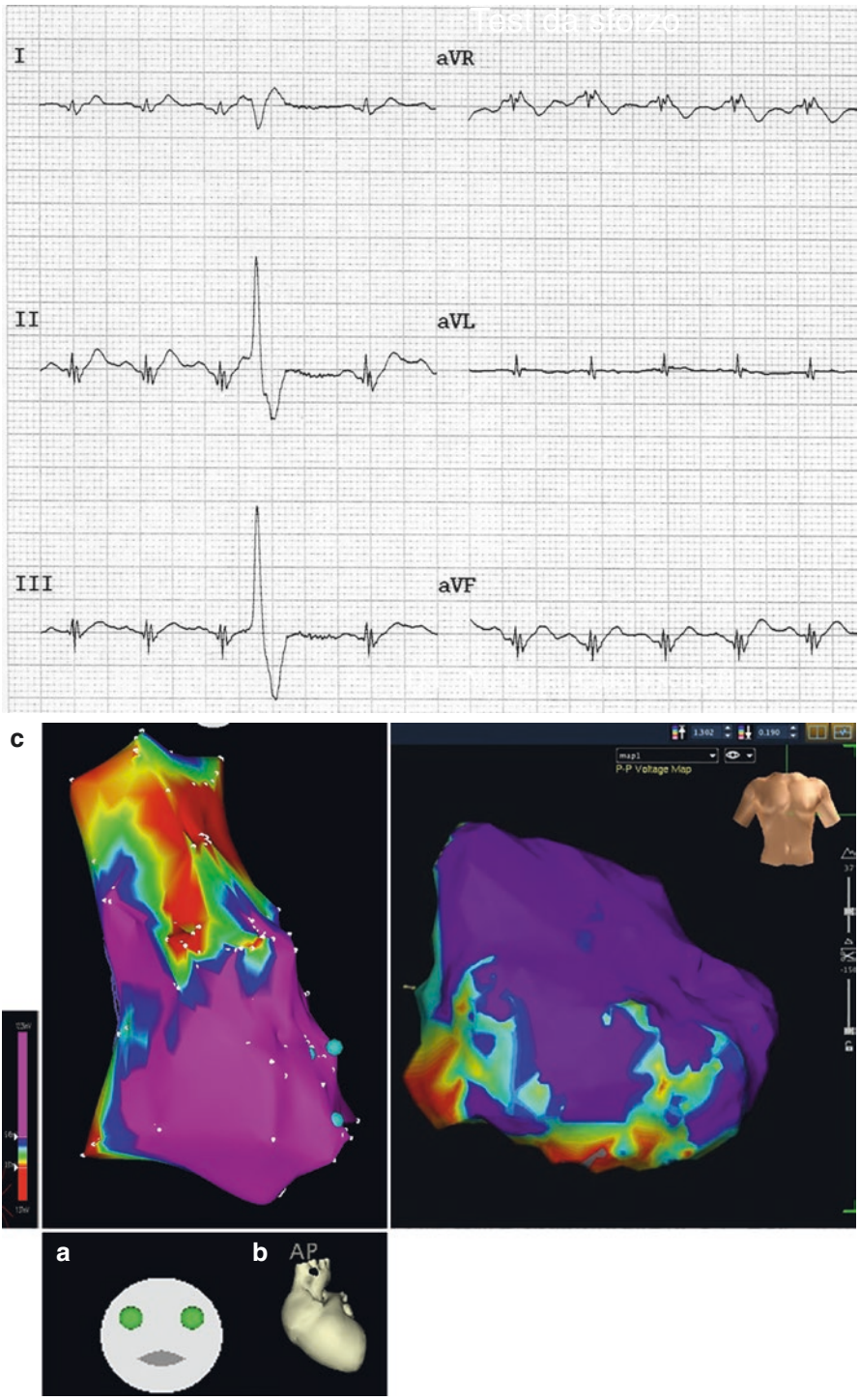


Fig. 6.9 (**a**) Male, 32 years old. Professional soccer player. Holter monitoring performed after a syncope during effort shows polymorphic fast non-sustained ventricular tachycardia (**a**). The basal ECG shows low-voltage QRS in peripheral leads (**b**). (**b**) Same case as in (**a**). During effort testing, fragmented WRS complexes are recorded in II, III, and aVF. (**c**) Same case as in (**a**, **b**). Voltage mapping of the right ventricle (**a**, endocardial) and left ventricle (**b**, epicardial). Diffuse areas of low voltage are documented in both ventricles, which were confirmed by CMR. Biopsy revealed chronic active myocarditis and isolated a virus: HHV6



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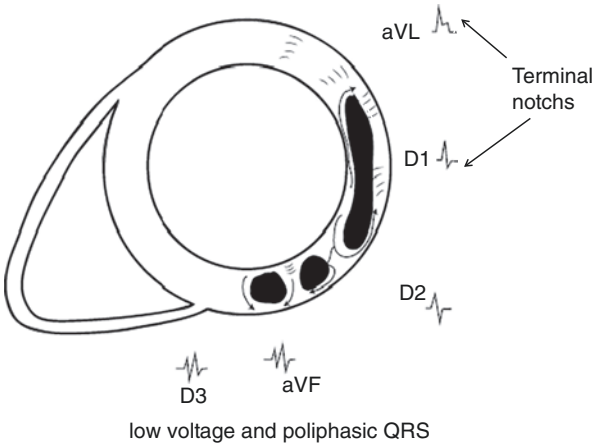

Fig. 6.10 Electrophysiological mechanisms of low-voltage, fragmented potentials, and potentials and notches of QRS complexes determined by fibrosis. For explanations, see text

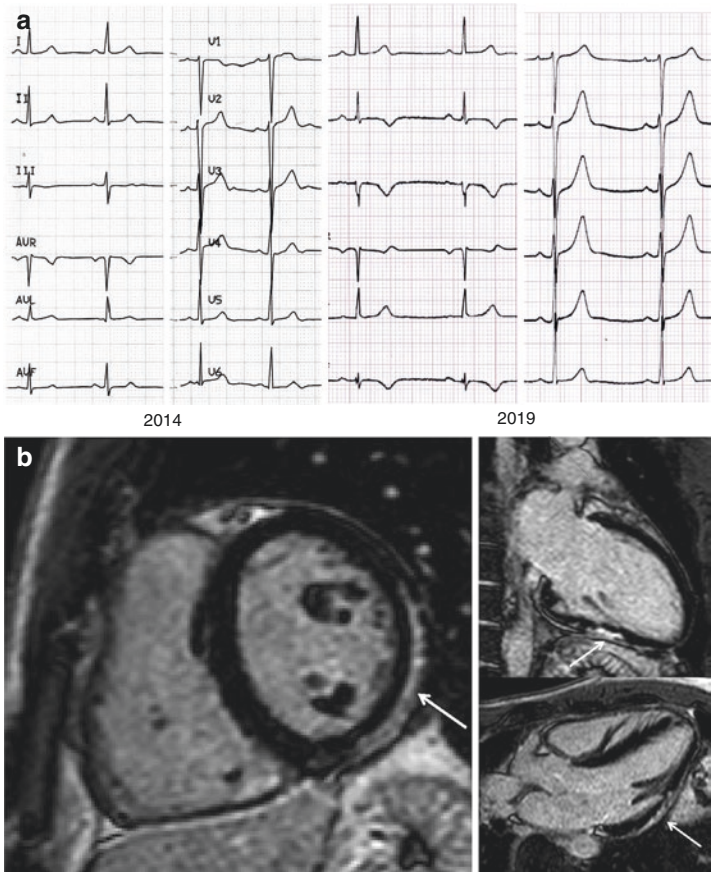

Fig. 6.11 (**a**) Male, 23 years old. He had suffered persistent chest pain 3 months earlier. ECG showed negative T waves in inferior leads, which had been absent 5 years earlier. The ECG aroused the suspicion of previous myocarditis. See also (**b**). (**b**) Same case as in (**a**). CMR confirmed post-myocarditis fibrosis, showing LE in the infero-lateral wall of the left ventricle (arrows)

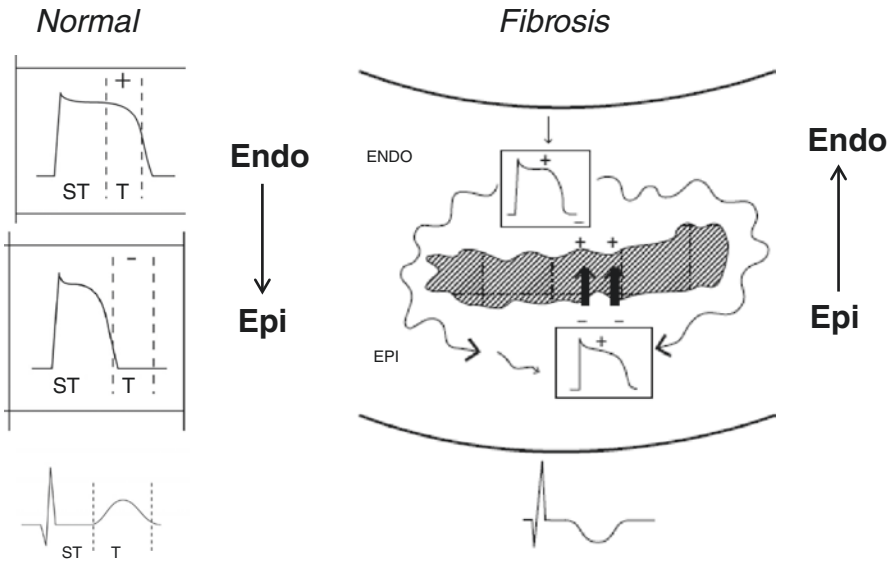

Fig. 6.12 Electrophysiological mechanism of negative T waves in post-myocarditis fibrosis. Fibrosis may produce negative T waves as a consequence of late activation of epicardial areas, inverting the repolarization vector between the endocardial and epicardial myocardium

6.7 Sport Eligibility After Myocarditis

In the absence of fibrosis on CMR and of VA during effort testing and Holter monitoring, eligibility for sport should not be denied. By contrast, it should be denied in the presence of extensive residual fibrosis and significant VA (frequent VPBs, repetitive phenomena). In the case of subjects with limited residual fibrosis and no significant VA, what to do is controversial; eligibility should probably not be denied, as long as strict clinical and instrumental controls are implemented during follow-up.

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