# HOW TO IMPROVE THERAPY IN MYOCARDITIS: ROLE OF CARDIOVASCULAR MAGNETIC RESONANCE (CMR) AND OF ENDOMYOCARDIAL BIOPSY

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***Abstract***

*Myocarditis represents an emerging challenge for physicians, due to its polymorphic clinical presentation and variable outcome, ranging from spontaneous resolution to sudden cardiac death or progression to dilated cardiomyopathy with a need for heart transplantation (in about a third of patients). Etiological forms include autoimmune, infectious (mainly viral), post-infectious autoimmune and toxic forms. In 2013 a European Society of Cardiology (ESC) expert consensus introduced specific criteria for clinically suspected myocarditis, e.g. in patients not undergoing EndoMyocardial Biopsy (EMB), and for EMB-proven myocarditis. According to ESC criteria Cardiac Magnetic Resonance (CMR) is part of diagnostic work-up and follow-up of myocarditis, but the diagnosis of certainty as well as etiological diagnosis requires EMB, applying histological, immunohistochemical, immunological and molecular techniques. Here we will review the contributions of EMB and CMR to conventional and etiology-directed treatment of myocarditis.*

Histologically-proven myocarditis has polymorphic clinical presentation and variable modality of onset, ranging from fulminant to acute, subacute or chronic arrhythmia or heart failure signs or symptoms, to asymptomatic biventricular dysfunction [1-3]. Prognosis is related to etiology, pathogenic mechanisms and severity of biventricular dysfunction at presentation [1-3]. However, studies on risk stratification and prognosis have provided no uniform conclusions, often due to a lack of diagnostic confirmation by EndoMyocardial Biopsy (EMB) [1-3]. Due to heterogeneity of both clinical presentation and diagnostic work-up, myocarditis frequency is also poorly documented [4]. A high incidence of myocarditis has been reported in autopsy series among sudden car-

diac death victims but these are not representative of the whole disease spectrum [4]. In this review the contributions of EMB and Cardiac Magnetic Resonance (CMR) to conventional and etiology-directed treatment of myocarditis are discussed.

## Etiopathogenesis

A complex interplay of environmental and genetic factors is likely to be responsible for myocarditis. Physical, chemical and microbiological agents may directly damage the myocardium, inducing an inflammatory reaction, e.g. toxic or infectious myocarditis (tab. I) [2]. Endogenous biochemical substances may also damage the cardiomyocyte, activating danger-related inflammatory pathways, such as in catecholamine-induced, or in thyrotoxicosis-associated myocarditis [2]. Genetic and epigenetic factors have also been implicated by modulating the immune response and cardiac susceptibility to damaging agents [5]. The inflammatory response may become inappropriate to the initial myocardial damage, because of hypersensitivity reactions or loss of self tolerance (autoimmune post-injury reactions) [2]. Autoimmune myocarditis may be isolated, e.g. organ-specific, or occur in the context of Systemic Immune-mediated Diseases (SIDs) [6]. In autoimmune myocarditis forms, specific autoreactive clones are directed against cardiac self-antigens or neoantigens with development of heart-specific autoantibodies (AHA) [2]. Conversely, the myocardium may be passively infiltrated and damaged by proliferation of immunocompetent cells during systemic hyper-inflammatory reactions, such as in hypereosinophilic syndromes, autoinflammatory diseases, septic shock or macrophage activation syndrome [6]. Some functional autoantibodies or toxic compounds may also directly impair metabolic and mechanical functions of the cardiomyocytes [2,6]. Regardless of the eliciting mechanisms, myocardial inflammation may lead to healing and recovery with or without residual scar, ongoing cardiac damage and cardiomyocyte necrosis, metabolic stunning or apoptosis and finally interstitial or substitutive fibrosis [7].

## Pathology

According to the 1986 Dallas Criteria, myocarditis is defined by the presence of an inflammatory infiltrate in the myocardium accompanied by degenerative and/or necrotic changes of adjacent cardiomyocytes not typical of ischemic damage associated with myocardial infarction (tab. II) [7]. Although the Dallas criteria are still part of pathological diagnosis on EMB, they are nowadays insufficient to describe myocarditis [7]. The requirements and protocols for pathological analysis of EMB have been updated by an international Task Force of the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP), including immunohistochemistry and molecular techniques for detection of most common cardiotropic virus genomes [7]. The new immunohistochemical and virological techniques improve sensitivity and specificity of EMB analysis and allow the differential diagnosis of infectious, and immune-mediated or autoimmune forms, which are infectious-negative (tab. II) [2,7]. These recommendations have also been in-

*Tabella I* - Etiology of myocarditis (adapted from ref. 2).

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|---|---|
| Infectious agents | *Bacterial:* Haemophilus influenzae, Mycobacterium (tuberculosis), Mycoplasma pneumoniae, others (rare)<br>*Spirochetal:* Borrelia (Lyme disease), Leptospira (Weil disease)<br>*Fungal:* uncommon, mainly immunocompromised patients<br>*Protozoal:* Trypanosoma cruzi (common in South America), others (rare)<br>*Parasitic:* rare<br>*Rickettsial:* rare<br>*Viral (common):*<br>*RNA viruses:* coxsackievirus A and B, echovirus, influenza A and B virus, respiratory syncytial virus, human immunodeficiency virus-1, others (rare)<br>*DNA viruses:* parvovirus B19 (most common in recent German series), adenovirus (mainly pediatric cases), cytomegalovirus (immunocompromised patients), herpes simplex virus, human herpes virus-6 (common in German patients, often in association with parvovirus B19), Epstein-Barr virus, others (rare). |
| Drugs and toxics | *Drugs:* amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, clozapine<br>*Heavy Metals:* copper, iron, lead<br>*Miscellaneous:* scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide,<br>*Hormones:* Pheochromocytoma<br>*Vitamins:* beri-beri<br>*Physical agents:* Radiation, electric shock. |
| Immune-mediated | *Autoimmune organ-specific (primary or post-infectious):* lymphocytic (common), giant cell (rare)<br>*Autoimmune associated with extra-cardiac autoimmune or immune-oriented disorders:* systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki's disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis<br>*Allergic:*<br>*Miscellaneous:* Tetanus toxoid, Vaccines, Serum sickness<br>*Drugs:* penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline<br>*Alloantigenic:* Heart transplant rejection. |

cluded in the 2013 European Society of Cardiology (ESC) expert consensus document on myocarditis (tab. II) [2].

## Clinical presentation, laboratory diagnostics and imaging

Myocarditis presentation is heterogeneous, ranging from pseudo-infarction with normal coronary arteries, to unexplained acute, subacute of chronic heart failure with or without a dilated cardiomyopathy imaging phenotype, brady or tachyarrhythmia and syncope and sudden cardiac death, cardiogenic shock [1-3]. It may also be mimicking other disease entities, such as myocardial infarction with normal coronary arteries (MINOCA) [8], and arrhythmogenic right ventri-

*Tabella II* - ESC Task Force Criteria for clinically suspected and biopsy-proven myocarditis (adapted from ref. 2).

*Defined by the presence of ≥1 clinical presentation (with or without ancillary findings) and ≥1 diagnostic criteria from different categories, in the absence of:*

- angiographically detectable coronary artery disease (coronary stenosis ≥50%)
- known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, etc.). Suspicion is higher with higher number of fulfilled criteria.
- If the patient is asymptomatic ≥2 diagnostic criteria should be met.

*Clinical presentations include ≥1 of the following:*

- Acute coronary syndrome-like, with or without normal global or regional Left Ventricular (LV) and/or Right Ventricular (RV) dysfunction on echocardiography or Cardiac Magnetic Resonance (CMR), with or without increased troponin (Tn)T/TnI (that may have a time course similar to acute myocardial infarction or a prolonged and sustained release over several weeks or months).
- New onset or worsening heart failure in the absence of Coronary Artery Disease (CAD) and known causes of heart failure.
- Chronic heart failure, with heart failure symptoms (with recurrent exacerbations) of >3 months duration, in the absence of CAD and known causes of heart failure.
- Life-threatening condition (including life threatening arrhythmias and aborted sudden death, cardiogenic shock, severely impaired left ventricular function), in the absence of CAD and known causes of heart failure.

*Diagnostic criteria include ≥1 of the following features from categories I to IV:*

*I. Electrocardiogram (ECG)/Holter/stress test features*
- newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following (see also figure 2): I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia.

*II. Myocardiocytolysis markers (elevated cardiac troponins).*

*III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR).*
- new, otherwise unexplained Left Ventricular (LV) and/or Right Ventricular (RV) structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional or global wall motion abnormalities, with or without ventricular dilatation, increased wall thickness, pericardial effusion, endocavitary thrombi.

*IV. Tissue characterization by cardiac magnetic resonance (CMR)*
- oedema and/or Late Gadolinium Enhancement (LGE) of classical myocarditic pattern (according to Lake-Louise criteria).
- *Ancillary findings:* fever (preceding 30 days), respiratory or gastrointestinal infection, previous myocarditis, peri-partum, personal or family history of allergy, systemic autoimmune disease, toxic agents, family history of myocarditis.

*Biopsy-proven (definite) myocarditis*

*The diagnosis of "Definite myocarditis" is based upon EMB confirmation of clinically suspected myocarditis, including conventional histology (Dallas criteria), as well as immunohistochemistry and Polymerase Chain Reaction (PCR) detection of infectious agents.*

*Histological definition (Dallas criteria):* "histological evidence of inflammatory infiltrates within the myocardium associated with myocyte degeneration and necrosis of non-ischaemic origin".

*Tabella II (segue)* - ESC Task Force Criteria for clinically suspected and biopsy-proven myocarditis (adapted from ref. 2).

| *Biopsy-proven (definite) myocarditis* |
|---|
| *Immunohistochemical criteria, abnormal inflammatory infiltrate defined as follows:* "≥14 leucocytes/mm$^2$ including up to 4 monocytes/mm$^2$ with the presence of CD 3 positive T-lymphocytes ≥7 cells/mm$^2$". |
| *Immunological criteria and myocarditis aetiology defined as follows:*<br>- Viral: histology (Hx) and immunoHx positive (pos), PCR pos for ≥virus (recommended viral screen: Enterovirus, influenzavirus, adenovirus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, human herpes virus 6)<br>- Autoimmune: Hx and immunoHx pos; viral PCR negative (neg); with or without pos cardiac autoantibodies (aabs); exclusion of other known inflammatory causes<br>- Viral and immune^: Hx and immunoHx pos; viral PCR pos; cardiac aabs pos. |
| *Absence of infectious agents identifies immune-mediated myocarditis and is the basis for safe (infection negative) immunosuppression.* |
| *EMB identifies specific myocarditis types (e.g. giant cell, eosinophilic, sarcoidosis) which imply different treatments and prognosis.* |
| *EMB provides differential diagnosis from diseases that may mimic myocarditis (arrhythmogenic right ventricular cardiomyopathy, Takotsubo cardiomyopathy, peri-partum cardiomyopathy, infitrative/storage disorders, cardiac masses).* |
| ^N.B. a follow-up EMB may identify persistent viral myocarditis, resolved myocarditis (Hx and virological), or persistent virus-negative myocarditis, e.g. post-infectious autoimmune. |

cular or left ventricular cardiomyopathy. A recent respiratory or gastrointestinal viral prodrome may or may not be present. ElectroCardioGraphic (ECG) findings may include tachy- and brady-arrhythmia, conduction abnormalities, non-specific repolarization changes. Concomitant pericardial involvement may be suspected by the finding of diffuse ST segment elevation on precordial leads [1-3].

Increased troponins do not distinguish between myocarditis and other causes of acute cardiac necrosis; in addition, lack of troponin rise does not rule out biopsy-proven myocarditis [2]. Markers of increased ventricular filling pressures, e.g. natriuretic peptides, are neither sensitive nor specific. Myocardial damage and dysfunction biomarkers, if abnormal at baseline, may be useful in documenting the clinical evolution of myocarditis and its response to therapy. In the appropriate clinical setting, laboratory investigation can be particularly helpful to confirm or exclude specific SIDs associated with myocarditis [6]. An indirect immunofluorescent assay is also available for the detection of serum AHA (fig. 1); the presence of these autoantibodies supports an autoimmune etiology for myocarditis [1,2].

Transthoracic echocardiography represents the first line imaging technique by providing hints for differential diagnosis (e.g. valvular disease) and morpho-functional characterization. A wide spectrum of ventricular morpho-functional abnormalities may be detected, ranging from regional wall motion abnormalities with a non coronary artery distribution, or diffusely hypokinetic non-dilated cardiomyopathy to a dilated cardiomyopathy [2,9]. Myocardial inflammatory edema, leading to an increase in wall thickness, may mimic hypertrophy [2]. Transthoracic echocardiography may also provide information on

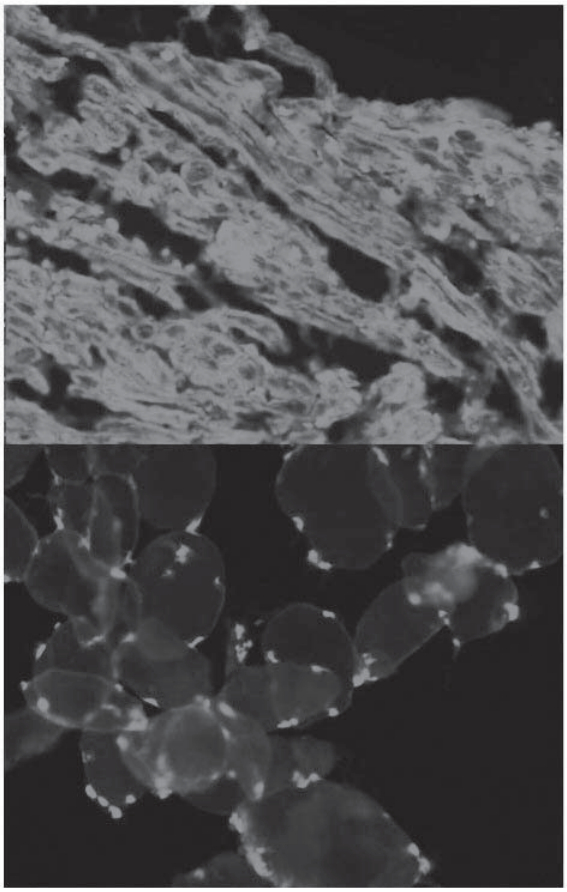

*Fig. 1.* Anti-Heart Aabs (AHA) pattern by indirect immunofluorescence test.
Top panel: Organ-specific AHA and Anti-Nuclear Aabs (ANA) pattern on human heart tissue: cytoplasmic diffuse staining of cardiac myocytes (organ-specific AHA pattern) and diffuse staining of the nuclei (non organ-specific ANA pattern) (x200);
Bottom panel (x200) on human skeletal muscle tissue: negative for AHA, positive for ANA.

concomitant pericardial or endocardial disease as well as additional findings suggesting a specific diagnosis (e.g., Libman-Sacks endocarditis in the setting of lupus myocarditis) [2,6] or endocavitary thrombus in the setting of acute eosinophilic myocarditis). In suspected myocarditis with infarct-like presentation, and with DCM it is necessary to exclude coronary artery disease [2,8]. CMR is a valid non-invasive option to characterize the inflamed myocardium by identifying edema, early and Late Gadolinium enhancement (LGE). Lake Louise Criteria have been proposed by an expert CMR consensus Task Force to get a diagnosis of myocarditis [10] and these have also been recommended by the ESC 2013 myocarditis experts [2]. Similarly to the Dallas criteria for EMB, it is now clear that also the Lake Louise criteria suffer from major limitations and new emerging CMR techniques are under intense research (T1- and T2-tissue mapping) [10-13].

When the patient suffers from a multisystem infective or inflammatory disease, signs of cardiac disease may herald the syndrome or appear in association with the signs and symptoms of extra-cardiac disease (e.g. nephritic syndrome, skin rash, etc.) [6]. In these cases the clinician should try to recognize etiological- or disease-specific patterns (e.g. DRESS syndrome, sarcoidosis, flu, etc.) to provide the best therapeutical approach. Multisystem inflammatory diseases may not be limited to the myocardium and the full cardiological clinical phenotype may result from the involvement of more than one cardiac structure (pericardium, endocardium and valves, coronary vessels) [6].

## Diagnostic issues

Due to its non-specific clinical presentation, myocarditis diagnosis can be challenging and might deserve a high level of suspicion. CMR and EMB do not reach the 100% sensitivity value compared to autopsy studies [10-13]. Moreover CMR positive predictive value for biopsy-proven myocarditis is influenced by clinical presentation patterns (ischemic-like vs. heart failure), since it fails to detect myocarditis in a considerable proportion of patients presenting with heart failure symptoms [12]. The combination of the CMR and EMB might allow a considerable improvement of the diagnostic sensitivity [11]. CMR does not allow to exclude myocardial infections, thus it should not be considered the gold standard. EMB provides diagnosis of certainty, as well as etiological and prognostic information, although it carries a risk, albeit low, of complications [2,7]. Therefore, a detailed histological, immunohistochemical and molecular genomic evaluation by EMB should never be withheld when it has the potential to change the therapeutic strategy, since it allows (a) detection of giant cell or eosinophilic myocarditis and (b) exclusion of infectious agents or viral genome in the myocardium of patients who may be candidates for immunosuppressive treatments (Table II) [2,7].

It should be noted that the pre-test probability of myocarditis as well as the positive and negative predictive values of clinical, EMB and CMR findings is largely unknown in defined clinical scenarios (e.g. in the context of SIDs). Therefore, at present clinical practice and diagnostic algorithms are admittedly mainly based on expert consensus from academic societies. For example, Cooper et al. back in 2007 proposed a list of scenarios for EMB use but such proposal did not take into account the current feasibility of immunosuppressive therapy and the key role of EMB for surveillance of autoimmune myocarditis in patients treated with immunosuppressive therapies (similar to EMB role for rejection surveillance in cardiac transplant patients) [14]. Japanese Experts stated that EMB is not mandatory to diagnose cardiac sarcoidosis when granulomatous disease has already been proven on extra-cardiac tissue samples [6]. At the same time, when diagnostic criteria are not fulfilled (e.g. seronegative autoimmune disease, isolated cardiac sarcoidosis, etc.), EMB may prove to be an essential aid to reach a final diagnosis and inform therapeutic strategy [2,6].

More recently, the European Society of Cardiology (ESC) Task Force on Myocarditis produced an expert consensus statement containing the set of criteria and the diagnostic algorithms for the diagnosis of clinically-suspected and biopsy-proven myocarditis (tab. II) aiming at collecting homogeneous and comprehensive data, reducing controversies and better defining etiology and

prognosis in myocarditis (tab. II) [2]. By combining clinical and diagnostic features, a clinician raises the suspicion of myocarditis (clinically-suspected myocarditis). To get a definitive and etiological diagnosis of myocarditis, a positive EMB should be obtained (biopsy-proven myocarditis). As such, EMB should be considered the ideal gold standard.

### *Subclinical disease*

All the above-described instrumental and biochemical findings may occasionally be present in the absence of clinically apparent disease, during cardiac investigation performed for other reasons (e.g. sport activity), raising the clinical suspicion of myocarditis. On the other hand, in the setting of SIDs, the role of cardiac screening in the absence of cardiac symptoms is not established [6]. Given the negative prognostic impact of cardiac involvement in most clinical scenarios, even when asymptomatic, a recent multidisciplinary ESC expert consensus group proposes that, whenever a clinical suspicion of active cardiac disease is raised in SIDs, any effort to get a detailed diagnosis should be made when it can have therapeutical consequences [6]. In fact, even when the disease appears in clinical remission, ongoing cardiac disease may still be detectable raising the question whether upgrade of immunosuppressive treatment is required or not [6].

## Treatment issues

Treatment of myocarditis patients essentially stands on symptomatic treatment of signs and symptoms of cardiac disease and of hemodynamic impairment, and on etiology-directed treatment. These aspects are constantly intermingled and require an interdisciplinary approach particularly in most severe cases or in the setting of SIDs. Most of current clinical practice is based on case reports and experts consensus. Only in some clinical scenarios (myocarditis in the setting of SIDs, sarcoidosis and organ-specific virus-negative myocarditis) high-quality evidence is available to dictate the general therapeutic approach.

### *Standard cardiological support therapy*

Supportive/symptomatic therapy is different in hemodynamically stable versus unstable patients. Unstable patients require intensive care unit admission for pharmacological inotropic and/or anti-arrhythmic treatment or mechanical support [2]. Stable patients may require anti-arrhythmic or heart failure therapy according to current guidelines [2]. Escalation of supportive therapy is required when the clinical picture evolves to hemodynamic deterioration as well as careful downgrading may be required in the recovery phase, either spontaneous or treatment-induced.

### *Anti-inflammatory therapy*

Only based on experimental mouse models, non specific anti-inflammatory therapy (NSAIDs or low-dosage steroids) is not recommended in myocarditis patients without histological confirmation, owing to the risk of hampering viral clearance in cases of viral myocarditis [2].

*Etiology-driven therapy*

A) In the setting of infective myocarditis, antibiotics, anti-fungal agents or anti-viral treatment may be used [1]. In HIV patients with biopsy-proven infectious myocarditis, control of HIV replication by antiviral agents may be the only way to allow heart recovery by clearance of opportunistic infections [2].

B) In SIDs with biopsy-proven non-infectious myocarditis, therapies able to down-modulate systemic immune-reactivity should be offered in order to achieve complete remission [6]. Growing evidence suggests that heart involvement may be an adverse prognostic marker in this setting and possibly justifies increased and prolonged use of immunosuppressive agents [6]. Rapidly acting pharmacological agents (e.g., steroids, cyclophosphamide, high-dose intravenous immunoglobulins, rituximab, anakinra, canakinumab, infliximab, etanercept, tocilizumab) are in principle promising candidates for treating rapidly progressive phases of the disease [6]. Anyway, further study is needed to define whether escalating or de-escalating immunosuppressive strategies, based on results of seriate measurement of cardiac damage markers and imaging studies, are better in inducing remission and prevent relapses. Maintenance therapy with traditional steroids sparing agents (azathioprine, methotrexate, mycophenolate, etc.) is then prescribed on the base of disease-specific recommendations.

C) Giant cell myocarditis is the most aggressive form of isolated autoimmune myocarditis. High-grade immunosuppression should be instituted as soon as the diagnosis is established, to prevent exitus or need for cardiac transplant [2]. Immunosuppression is maintained life-long; if the patient is transplanted, giant cell myocarditis can relapse on the graft and may respond to more aggressive immunosuppressive approach also including biological agents [2]. Eosinophilic myocarditis needs immediate suspension of possible responsible pharmacological agents and is usually responsive to a cycle of high dose steroidal therapy [2].

D) Biopsy-proven virus-negative autoimmune lymphocytic myocarditis treatment with immunosuppressive agents is now established [2]. Frustaci et al. demonstrated that a careful selection of patients candidable to immunosuppressive treatment is essential to meet the primary end points of recovery of left ventricular ejection fraction and immunohistochemical remission [15]. In the TIMIC trial patients with a clinical history of heart failure of 6 or more months duration (when spontaneous recovery of ventricular function becomes progressively more unlikely) were randomized to standard cardiological supportive therapy or to a trial with steroids (1 mg/kg/die for 1 months, than taper) and azathioprine (2 mg/kg/die) on top of standard cardiological therapy. Partial or complete recovery was obtained in immunosuppressed patients. These results have been subsequently reproduced by other European observational studies [16]. The role of immunosuppressive therapy in myocarditis patients with heart failure symptoms' duration of less than six months or with infarct-like presentation and unobstructed coronary arteries or in the setting of arrhythmic presentation has not been standardized, but case reports suggest similar efficacy [17,18].

Finally, exercise avoidance should be prescribed to all patients until evidence of active myocarditis has resolved and the arrhythmic burden is well controlled [2]. Consultation with arrhythmia specialists and sport physicians may be advisable in difficult cases.

## Conclusion

Myocardial inflammatory diseases represent a rapidly expanding field of cardiovascular medicine and research. We are just starting to appreciate the complex clinical approach to these disorders and define met and unmet needs in their diagnosis and treatment. An interdisciplinary work team of cardiologists, pathologists, clinical immunologists, rheumatologists and rehabilitation professionals is required to answer the increasing demands of treatment and support.

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