How to improve therapy in myocarditis: role of cardiovascular magnetic resonance and of endomyocardial biopsy

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Histologically proven myocarditis has a polymorphic clinical presentation with 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 aetiology, 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 A high incidence of myocarditis has been reported in autopsy series among sudden cardiac death victims but these are not representative of the whole disease spectrum.4

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 (Table 1).2 Endogenous biochemical substances may also damage the cardiomyocytes, 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 auto-reactive clones are directed against cardiac self-antigens or neo-antigens with development of heart-specific autoantibodies (AHA).2 Conversely, the myocardium may be passively infiltrated and damaged by the proliferation of immunocompetent cells during systemic hyper-inflammatory reactions, such as in hypereosinophilia syndromes, auto-inflammatory 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 evolve through healing and recovery with or without residual scar, persistent cardiac damage and cardiomyocytes necrosis, metabolic stunning or apoptosis, and finally, interstitial or substitutive fibrosis.7

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 ischaemic damage associated with myocardial infarction (Table 2).7 Although the Dallas criteria are still part of the pathological diagnosis on EMB, they are nowadays insufficient to describe myocarditis.7

The 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 (Table 2).2,7 Aetiology-specific recommendations have been included in the 2013 European Society of Cardiology (ESC) expert consensus document on myocarditis (Table 2).2

Myocarditis presentation is heterogeneous ranging from pseudo-infarction with normal coronary arteries, to
unexplained acute, subacute or chronic heart failure with or without a dilated cardiomyopathy imaging phenotype, brady- or tachy-arrhythmias and syncope and sudden cardiac death, and cardiogenic shock.\textsuperscript{1–3}

Cardiac magnetic resonance (CMR) is a valid non-invasive option to characterize the inflamed myocardium by identifying oedema, early and late gadolinium enhancement. Lake Louise criteria have been proposed by an expert CMR consensus Task Force to get a diagnosis of myocarditis\textsuperscript{8} and these have also been recommended by the ESC 2013 myocarditis experts.\textsuperscript{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).\textsuperscript{8–11}

The combination of the CMR and EMB might allow a considerable improvement of the diagnostic sensitivity.\textsuperscript{9}

Cardiac magnetic resonance does not allow to exclude myocardial infections, thus it should not be considered the gold standard. Endomyocardial biopsy provides diagnosis of certainty, as well as aetiological and prognostic information, although it carries a risk, albeit low, of complications.\textsuperscript{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 (i) detection of giant cell or eosinophilic myocarditis and (ii) exclusion of infectious agents or viral genome in the myocardium of patients who may be candidates for immunosuppressive treatments (Table 2).\textsuperscript{2,7}

Recently, the 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 (Table 2) aiming at collecting homogeneous and comprehensive data, reducing controversies and better defining aetiology and prognosis in myocarditis (Table 2).\textsuperscript{2}

Treatment of myocarditis patients essentially stands on symptomatic treatment of signs and symptoms of cardiac disease and of haemodynamic impairment, and on aetiology-directed treatment.

Only based on experimental mouse models, non-specific anti-inflammatory therapy (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.\textsuperscript{2}

In the setting of infective myocarditis, antibiotics, antifungal agents, or anti-viral treatment may be used.\textsuperscript{2}

| Table 1 Aetiology of myocarditis |
|---------------------------------|
| **Infectious agents** | Bacterial: *Haemophilus Influenzae*, *Mycobacterium* (tuberculosis), *Mycoplasma pneumoniae*, and others (rare)  
   *Spirochaetal: Borrelia* (Lyme disease) and *Leptospira* (Weil disease)  
   *Fungal*: uncommon and mainly immunocompromised patients  
   *Protozoal*: *Trypanosoma cruzi* (common in South America) and others (rare)  
   *Parasitic*: rare  
   *Viral* (common):  
     RNA viruses: *coxsackievirus A and B*, echovirus, influenza A and B virus, respiratory syncytial virus, human immunodeficiency virus-1, and others (rare)  
     DNA viruses: *parovirus B19* (most common in recent German series), *adenovirus* (mainly paediatric cases), cymotegalovirus (immunocompromised patients), herpes simplex virus, *human herpes virus-6* (common in German patients, often in association with *parovirus B19*), Epstein-Barr virus, and others (rare) |
| **Drugs and toxics** | Drugs: amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin-2, trastuzumab, and clozapine  
   Heavy metals: copper, iron, and lead  
   Miscellaneous: scorpion sting, snake, and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, and sodium azide |
| **Immune mediated** | Autoimmune organ-specific (primary or post-infectious): *lymphocytic* (common) and *giant cell* (rare)  
   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, thyrototoxicosis, sarcoidosis, and Wegener’s granulomatosis  
   Allergic: miscellaneous: tetanus toxoid, vaccines, and serum sickness  
   Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, and amitriptyline  
   Alloantigenic: heart transplant rejection |

Adapted from Caforio et al.\textsuperscript{2}
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IV. Tissue characterization by cardiac magnetic resonance (CMR)

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)

e.g. post-infectious autoimmune.

Biopsy-proven (definite) myocarditis

- 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 (TnT/Tnl (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, and 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: I–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, and supraventricular tachycardia

  II. Myocardioctolysis 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, and endocardial 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, and family history of myocarditis

Table 2: European Society of Cardiology (ESC) task force criteria for clinically suspected and biopsy-proven myocarditis

| Category | Criteria |
|----------|----------|
| I. Electrocardiogram (ECG)/Holter/stress test features | - Newly abnormal 12-lead ECG and/or Holter and/or stress testing, any of the following: I–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, and supraventricular tachycardia |
| II. Myocardioctolysis markers (elevated cardiac troponins) | - Viral: histology (Hx) and immunoHx positive (pos), PCR pos for ≥ virus (recommended viral screen: enterovirus, influenza-virus, adenovirus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and human herpes virus 6) |
| III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR) | - Autoimmune: Hx and immunoHx pos, viral PCR negative (neg), with or without pos cardiac autoantibodies (aabs), and exclusion of other known inflammatory causes |
| IV. Tissue characterization by cardiac magnetic resonance (CMR) | - Viral and immune: Hx and immunoHx pos, viral PCR pos, and 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, infiltrative/storage disorders, and cardiac masses)

Adapted from Caforio et al.²

²N.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.
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. 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. Eosinophilic myocarditis needs immediate suspension of possible responsible pharmacological agents and is usually responsive to a cycle of high-dose steroid therapy. Biopsy-proven virus-negative autoimmune lymphocytic myocarditis treatment with immunosuppressive agents is now established. Finally, exercise avoidance should be prescribed to all patients until evidence of active myocarditis has resolved and the arrhythmic burden is well controlled.

Conflict of interest: none declared.

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