Myocarditis
Heart and Metabolism is a quarterly journal focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and non-ischemic heart disease.
EDITORIAL
Myocarditis ............................................................ 2
G. Jackson

ORIGINAL ARTICLES
Myocarditis: the causes ............................................ 3
U. Kühl
Management of myocarditis ........................................ 8
C. El Amm and L. T. Cooper
Differentiating infarction from myocarditis ................. 13
E. Pozo and J. Sanz
Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy .................. 18
A. Frustaci and C. Chimenti
Metabolic remodeling as a target preventing myocardial dysfunction:
focus on trimetazidine ........................................... 22
A. N. Parkhomenko and O. S. Gurjeva

CASE REPORT
Multimodality imaging of Churg–Strauss myocarditis ........... 27

REFRESHER CORNER
Myocarditis: inflammatory and endocrine causes ................ 31
A. L. P. Caforio

HOT TOPICS
Takotsubo cardiomyopathy: a possible metabolic disorder .......... 36
M. Zeb, B. Naheed, F. Irshad, T. Edwards, I. M. Ali and F. Witherow

GLOSSARY ............................................................. 41
G. D. Lopaschuk
Myocarditis presenting acutely is an inflammatory disease of the myocardium. The estimated incidence varies from 3 to 6% and a diagnosis is made difficult by the fact that myocarditis often presents subclinically and unexpectedly. It may well be a cause of sudden unexplained cardiac death, particularly in young people. While the principal etiology in developed countries is viral, the underlying cause may not easily be identified. Dr Kühl addresses the issue in detail in his article. Clinically, if a patient presents with a sudden onset of symptoms of chest pain or heart failure with or without arrhythmias, and when other causes have been excluded, myocarditis must always be considered, particularly if there is coexistent viral illness, for example influenza [1]. Alternatively, the patient may have been taking drugs that are known to be linked to hypersensitivity reactions, for example penicillin. There are no specific points in the examination of the patient, but there may well be signs of heart failure. The collection of physical signs and patient symptoms, combined with chest pain or the presentation of dyspnea that is not recognized to be reflecting ischemic heart disease, should alert the physician to the possibility of myocarditis as an etiology. Drs Cooper and El Amm elegantly discuss the management of myocarditis that takes these parameters on board. Importantly, they widen the differential diagnosis so that treatment can be precisely targeted at the cause [2].

Clearly, the differentiation of myocarditis from myocardial infarction is clinically immediately and subsequently important prognostically. The value of early and late immunosuppressive therapy is debated by Frustaci and Chimenti. They make the point that immunosuppressive therapy may be effective in a significant number of patients, as confirmed with endomyocardial biopsy, but it has always been difficult to differentiate an effective drug therapy from the natural history of the disease. Furthermore, immunosuppressive treatment of virus-positive myocarditis has been associated with an adverse outcome and should be avoided in patients who do not exhibit biopsy-confirmed exclusion of viral invasion [3].

Although myocarditis is relatively uncommon, it can be quite devastating to the younger person, transforming them over a 24–48 hour period from physical fitness to major disability and even sudden death. In short, we desperately need a more reliable imaging technique. It is interesting to speculate as to whether trimetazidine, because of its metabolic action, may be an important drug in myocarditis as it has already proved to be an effective drug in cardiac failure patients [4].

Finally, we must not forget that there are other causes of myocarditis separate from viral illnesses. Whatever the cause, a complete survival rate has been documented in only 25–56% of cases. Mortality appears to be related to the manifestations of cardiomyopathy, particularly cardiac failure and sudden cardiac death. The implantable cardioverter defibrillator as well as anti-failure treatment and anti-arrhythmic treatment does potentially, if initiated early, reduce the mortality rate. While there is more to myocarditis than the specific complication of a viral illness, this edition of Heart and Metabolism, as well as addressing the commonest cause of myocarditis (viral), also widens the arena not only to the alternative causes but how to detect and manage them.

REFERENCES
Introduction
The term myocarditis describes inflammatory disorders of the heart muscle of varied infectious and noninfectious origin. It can be caused by any kind of infection, drugs, toxic substances, or may be associated with autoimmune conditions (Table I). Viruses are the main cause in developed countries while bacteria or other infectious agents predominate in the etiology of myocarditis in rural countries [1]. The actual incidence of virus-induced myocarditis or virus-associated cardiomyopathy is not well established because viral heart disease may not be apparent, is difficult to diagnose and can vary with different viruses as a function of circulating virus populations. Chronic myocardial inflammation may be caused by persisting organ infections, toxic agents or distinct physical conditions, may persist as a post-infectious condition, or be associated with systemic autoimmune conditions [2].

The clinical presentation of myocarditis ranges from mild “flu-like” symptoms or persisting physical disability with no hemodynamic consequences to congestive heart failure, ventricular dysfunction, arrhythmias and sudden cardiac death. In the absence of structural heart diseases myocarditis accounts for approximately 10% of recent-onset cardiomyopathy in adults and this figure may be higher in children. Early fulminant disease is still associated with a high mortality rate despite timely admission to intensive care. Patients
who survive the critical phase have a fairly good prognosis and survival from myocarditis is approximately 60–70%. In the remaining patients progressive chronic heart failure and unpredictable sudden cardiac death remain a serious concern, often occurring years after the initial clinical event and sometimes despite complete recovery of myocardial function in the meantime.

Acute infectious myocarditis

Etiologies of acute infectious myocarditis include viruses, protozoa, bacteria, or fungi, but often the underlying cause cannot be identified. Apart from enteroviruses, which traditionally have been considered the most common agent in myocarditis and dilated cardiomyopathy (DCM), distinct genotypes of erythroviruses including parvovirus B19 (B19V), human herpesvirus type 6 (HHV6), adenoviruses, HIV, cytomegalovirus, herpes simplex type 2 virus and hepatitis C virus, and many others have been identified with varying degrees of frequency (Table I) [3, 4]. Chagas’ disease, which can present acutely as in fulminant myocarditis, or progress insidiously into a chronic cardiomyopathy with symptomatic heart failure, is still one of the most common causes of DCM worldwide. The causative organism is the protozoa Trypanosoma cruzii, which is prevalent in endemic regions in the world, most notably in South America.

Infectious agents such as viruses are often processed in lymphoid organs and may proliferate within immune or other cells, eg, lymphocytes or macrophages. They subsequently achieve target organ infection through hematogenous or lymphangitic spread. The early phase of myocardial disease is initiated by infection of cardiac myocytes, fibroblasts, or endothelial cells through receptor-mediated endocytosis.

Enteroviruses and adenoviruses enter the heart as a secondary target organ and infect and injure cardiomyocytes after binding to the Coxsackie adenoviral receptor [5]. In contrast to such newly acquired infections, which target and injure cardiac cells at any age, B19V is acquired by the majority of patients in childhood and, due to the virus receptor distribution, persists lifelong within bone marrow and the vascular endothelial precursor cells (EPC) in more than 70% of individuals over 60 years of age [6]. Permanent infection of the vascular endothelium in adults thus does not

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| Trypanosoma cruzi |

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Abbreviations

B19V: parvovirus B19; DCM: dilated cardiomyopathy; HHV6: human herpesvirus type 6

Table I Etiological agents causing myocarditis. EBV, Epstein–Barr virus; HHV6, human herpesvirus type 6; HSV, herpes simplex virus.
generally occur from newly acquired B19V infection, which constitutes a rare event in adults, but through endogenous B19V-infected bone marrow-derived endothelial progenitor cells, which are released into the bloodstream during vascular repair [7]. Similarly, HHV6 is commonly acquired during the first 2 years of life, and also persists in latent form for life. In heart tissue, HHV6 genomes are detected in vascular endothelial cells, cardiomyocytes and infiltrating interstitial cells [8]. Unique among human herpesviruses, the HHV6 genomes can furthermore become integrated into the human genome (ciHHV6) and can be transmitted by means of germline chromosomal integration, in which they have similar prevalence and result in the potential for virus gene expression in every cell [9]. ciHHV6 affects approximately 0.2–0.8% of human populations.

At the time of the first onset of symptomatic heart disease, most common acute viral infections clinically present as myocarditis often with infarct-like presentation or unexpected onset of acute heart failure. The resulting type and extent of myocardial compromise and hence the prognosis of the disease depend on the nature of the offending infectious agent, the affected cardiac structures, and the degree of irreversible myocardial lesions caused by cytolytic viruses or the innate and adaptive anti-infectious immune responses [1, 2]. For clinical management and with respect to pathogenicity and prognosis it has to be taken into consideration that those viruses that do not infect cardiomyocytes constitute distinct disease entities at least in the short run. Therefore, despite a similar clinical and histological presentation, B19V and HHV6-associated myocarditis in adults should not be considered in the same way as newly acquired enteroviruses, adenoviruses or other cardiotropic infections that rapidly destroy contractile cardiac tissue.

**Pathogenicity**

For many viruses the exact cardiac infection site and the underlying pathogenic mechanisms are unknown, and most information on the distinct phases of viral heart disease is derived from enteroviral infections. Myocarditis can be considered to have three phases in its pathophysiology. The first is the viral phase, followed by the immunological response phase, followed by the cardiac remodeling phase [1, 10]. A direct virus-related cytolysis of cardiomyocytes can already be detected before any inflammatory infiltrate develops. After this enterovirus RNA is predominantly located in areas showing focal inflammatory cell infiltrates and myofibre necrosis (Figure 1 (b, c)). This indicates that during early disease direct lytic infection of myocytes rather than an autoimmune reaction is responsible for myocarditis.

The innate and adaptive antiviral immune responses initiate a further step in the development of virus-associated myocarditis [1, 10]. It is activated to eliminate as many virus-infected cardiac cells as possible to control the infection [11]. In addition to the early virus-mediated injury, this immune-mediated virus clearance from infected cardiomyocytes takes place at the expense of a further destruction of myocardial tissue that is not capable of regeneration (Figure 1 (c)) [12].

The antiviral immune response then has to be modulated by negative controls in order to prevent excessive tissue damage and organ dysfunction. Inflammation resolves the majority of cases (>70%) after successful virus clearance or suppression of transcriptional activation of the virus. Even after complete resolution of inflammation, however, tissue damage that has developed in the early stages may contribute to later tissue remodeling and progression of the disease (Figure 1 (e, f)). The degree of remodeling of the heart following cardiac injury affects cardiac structure and function and determines the difference between appropriate healing or the development of post-infectious DCM [11, 13].

**Chronic myocarditis and inflammatory cardiomyopathy**

**Acquired viral cardiomyopathy**

A virus-associated cardiomyopathy develops if, due to an inadequate immune response, the acquired virus is not cleared successfully or if transcriptional virus activity persists. Viral persistence can expose the host to persistent antigenic trigger and chronic immune activation resulting in chronic myocarditis. A smoldering inflammatory process, characterized by diffuse low grade infiltrates of lymphocytes, macrophages and enhanced tissue expression of cell adhesion molecules, is detectable in about 40% of patients with chronic enteroviral or adenoviral infection [14]. A similar frequency and value of inflammation is also detected in the myocardial tissue of patients with B19V and HHV6 infections [15, 16]. Transcriptionally
active B19V infection is associated with an altered cardiac expression of genes that encode proteins of the antiviral immune response and mitochondrial energy metabolism [17]. This may also be responsible for prolonged B19V-associated intramyocardial inflammation and impairment of myocardial function, which, in the long run, affect the outcome of patients [7, 17]. Histologically, interstitial fibroses and scars indicate chronic myocardial alterations caused by both the persisting virus and chronic immune cell activation (Figure 1 (e, f)).

**Post-infectious chronic myocarditis**

The presentation of viral antigens that evokes an antiviral immune response, which aims at viral elimination, is not necessarily detrimental to the heart. However, this immune response is a “double-edged sword”: molecular mimicry and genetically predisposing conditions can secondarily target cryptic myocardial antigens [18]. In the case of postviral (auto)immunity, this immune response continues despite successful elimination of the viral genome. In addition, organ-specific cellular (auto)immunity antibodies that crossreact with myocardial antigens and are cross-linked by Fc-receptors at the myocyte surface may contribute to impairment of cardiac function [19]. In addition, cardiodepressive cytokines induced by the immune system can directly impair cardiac contractility. While the pathogenic relevance of autoantibodies has been questioned in the past as epiphenomena of the immune response, recent experiments with stimulating antibodies directed against the second extracellular β1-receptor loop and positive results from immunoadsorption studies have indicated a causative role for autoantibodies in DCM.

**Noninfectious myocarditis**

Giant cell myocarditis (GCM, Figure 1 (d)), acute eosinophilic myocarditis and granulomatosous inflammatory processes such as cardiac sarcoidosis are rare but clinically important acute inflammatory heart muscle diseases often of unknown etiology. The majority of patients present with acute heart failure on the first encounter. These myocarditis subtypes have a high mortality rate if not diagnosed and treated in time [2].

Many medications have been implicated in contributing to hypersensitivity myocarditis [1]. Symptomatic myocarditis with fever, skin rash, peripheral eosinophilia and sinus tachycardia can occur in an unpredictable fashion following the ingestion of a particular drug that may be new to the patient’s regimen, or that they have previously ingested and been exposed to for quite some time. Drugs may induce myocardial inflammation by either direct toxic effects on heart tissue or by inducing hypersensitivity reactions, which

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**Fig. 1** Diagnostic evaluation of inflammation in a myocardial biopsy specimen (histology and immunohistology). (a) Normal myocardium; (b) borderline-myocarditis with low-grade focal lymphocytic infiltration; (c) acute lymphocytic myocarditis with focal cell infiltrates and necrosis of myocytes; (d) giant cell myocarditis with focal cell infiltrates and necrosis (N) of myocytes; (e) mild post-infectious interstitial fibrosis; (f) severe postinflammatory dilated cardiomyopathy with hypertrophy of the cardiomyocytes and pronounced fibrosis/scarring. Magnification x200.
are often associated with eosinophilic myocarditis (Table I) [20]. Eosinophils are also observed in myocardial inflammatory processes that are associated with Churg–Strauss vasculitis or hypeeosinophilic syndromes, vaccination for several diseases or are caused by helminthic and parasitic infections (Table I).

Conclusion

Myocarditis most commonly results from an external inflammatory trigger, such as viruses or drugs, inducing a host immune response, which may range from a minimally transient response to fulminant overwhelming inflammation. Lymphocytic myocarditis is the most common form of myocarditis reported in the USA and western Europe, and virus infections are considered the most common cause of this acquired inflammatory heart disease. Severe myocarditis will lead to myocardial damage from the presence of inflammatory cell infiltrate and cytokine activation, with some contribution directly from virus-mediated cell death. These processes can severely depress cardiac function. Viruses and other acute infectious agents are usually cleared from the host by the immune system in 1–4 weeks; however, in some instances, the infectious agent genome can persist in the host myocardium for months or years, constituting a nidus for chronic inflammatory response, and a known risk factor for a worse prognosis.

Acknowledgment: Some research projects used as the basis for the review article were funded by the German Research Foundation in the context of Sonderforschungsbereich-Transregio (SFB-TR19), inflammatory cardiomyopathies.

REFERENCES

Definition and etiology

Myocarditis refers to the clinical, imaging, biochemical and histological manifestations of myocardial inflammation. The cardinal feature of myocardial inflammation is an abnormally high number of effector lymphocyte subsets and macrophages associated with myocyte damage. The clinical syndromes associated with myocarditis include myopericarditis, sudden death and heart failure resulting from immune-mediated myocardial damage. Common findings in myocarditis include stiffening and contractile impairment of the ventricles, conduction system disease and a heightened risk of ventricular arrhythmias, particularly during exercise.

The histological definition of myocarditis is classically represented by the Dallas criteria, proposed by a consensus panel of cardiovascular pathologists in 1986 [1]. These criteria define myocarditis as an inflammatory cellular infiltrate in the heart with or without myocyte necrosis and/or degeneration of adjacent myocytes. In the past two decades immunohistochemical criteria that include the increased expression of class II (HLA-DR) antihuman leukocyte antigens and heightened numbers of CD3, CD4, CD8 or CD68-positive inflammatory cells have increased the sensitivity of endomyocardial biopsy (EMB) for the diagnosis of myocarditis [2]. Markers of complement deposition that are commonly seen in humeral allograft rejection have recently been found in patients with cardiomyopathy, suggesting persistent activation of innate immune pathways [3].

Myocarditis may result from a myriad of cardiac infections and noninfectious triggers such including toxins, chest irradiation and rarely even vaccines [4]. In the setting of systemic inflammation myocarditis can...
develop in association with autoimmune disorders such as lupus erythematosus, hypersensitivity reactions or idiopathic hypereosinophilic syndrome [5, 6]. The most commonly identified cause of myocarditis is an upper respiratory tract or gastrointestinal virus infection. The most common viruses identified in heart biopsies from patients with acute myocarditis are currently parvovirus B19 and human herpes virus 6 [7]. Because most data on viral cardiomyopathy were gathered from case series in Europe and North America, the prevalence of viral disease as a proportion of heart failure in much of Africa, Asia and South America remains unknown. In specific regions of the developing world, rheumatic carditis after streptococcal A infection and Chagas’ disease from Trypanosoma cruzi remain important causes of myocarditis and heart failure [8].

Pathogenesis
The pathogenesis of myocarditis can be simplified into a phase of acute injury, a subsequent innate and adaptive immunological response and finally a transition either to chronic cardiomyopathy with fibrotic scar or to recovery (Figure 1) [9]. Genetic factors strongly impact susceptibility to and outcome of myocarditis in mice, but specific genes that influence human disease have not been identified [10]. In enteroviruses, variations in the 5′ region of the viral genome influence replication efficiency and virulence [11].

In models of enteroviral myocarditis, virus-mediated acute myocyte damage elicits an innate immune response that includes the recruitment of natural killer cells and proinflammatory cytokines through an inflammasome-mediated pathway [12]. The innate response develops into an antigen-specific immune response, which leads to successful virus clearance. In many cases the immune reaction downregulates and immune homeostasis is restored with no lasting cardiac damage. However, in a minority of cases the virus and/or the inflammatory reaction persists and contributes to cardiomyopathy and a syndrome of heart failure. Up to 30% of myocarditis cases progress to chronic cardiomyopathy [13]. Autoantigens such as cardiac myosin can mediate this chronic myocardial damage through molecular mimicry with viral antigens [14]. The opportunity for therapeutic intervention in clinical medicine is presently limited to the later phases of this disease model.

Management
In 2013 the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases published a position statement on the management and therapy of myocarditis [15]. In their paradigm, management of patients who have persistent cardiomyopathy resulting from acute myocarditis depends on the presence or absence of myocardial infection and inflammation. Patients with viral infection may be considered for antiviral therapies. Patients with inflammation and no virus infection may benefit from immunosuppressive or immunomodulatory therapies [16]. Patients with neither evidence of viral genomes nor inflammation and whose ejection fraction is less than 40% should be treated with guideline-based heart failure therapy. An EMB is required to determine whether inflammation or infection is present.

The ESC position statement recommends that a standard 12-lead ECG and a transthoracic echocardiogram be performed in all patients with clinically suspected myocarditis. Although there are no ECG changes sufficiently specific to diagnose myocarditis, the presence of QRS prolongation is an independent negative predictor of survival [17]. The echocardiogram is valuable to exclude valvular or pericardial heart disease. Echocardiographic findings predictive of lower transplant-free survival are lower left ventricular ejection fraction and impaired right ventricular function [18].

Myocardial damage occurs in about a third of patients with pericarditis [19]. In patients with pericarditis, a troponin rise and normal left ventricular function the term “myopericarditis” is used. In patients with pericarditis and more severe myocardial dysfunction, the term “perimyocarditis” has been suggested. The overall likelihood of death or heart failure is quite low in patients with myopericarditis [20]. Non steroidal anti-inflammatory drugs and colchicine are probably safe for the treatment of pericarditis even with elevated troponin if the ejection fraction is normal, but should be avoided in more severe cases with systolic heart failure.
Avoidance of competitive athletics is recommended in all patients with myocarditis and myocardial pericarditis for at least 6 months. Return to athletics requires re-evaluation of heart function and an assessment of arrhythmic risk usually with a Holter monitor and/or an exercise ECG [21].

Cardiac magnetic resonance imaging (MRI) is useful to distinguish ischemic from nonischemic myocarditis.
cardiomyopathy. An expert panel recommended that both T1 and T2-weighted imaging be used to obtain optimal sensitivity and specificity when myocarditis is suspected [22]. When gadolinium contrast imaging is not feasible, T1 mapping is an emerging tool that can be used as a criterion for the detection of acute myocarditis with a reported sensitivity of 91% [23].

Radionuclide imaging in unexplained cardiomyopathy is limited to several uncommon clinical scenarios. Resting perfusion imaging combined with $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$FDG) positron emission tomography (PET) can be helpful in the diagnosis of cardiac sarcoidosis. $^{18}$FDG uptake is increased in myocardial granulomas in regions with a matched decrease in perfusion. In regions of scar from previous inflammation, a matched decrease in $^{18}$FDG and perfusion tracers in a non coronary distribution may be seen. Extrathoracic sites of active sarcoidosis and changes in $^{18}$FDG uptake following immunosuppression can also be tracked with PET imaging [24].

Mechanical circulatory support with ventricular assist devices or extracorporeal membrane oxygenation support is beneficial as a bridge to transplantation or recovery in adults and children with fulminant myocarditis and profound shock [25]. Cardiac transplantation is also an effective therapy for patients with myocarditis who have refractory heart failure, and survival after transplantation is similar to survival in adults for other causes of cardiac transplantation [26]. The outcome following transplantation in children may be worse than for other causes of dilated cardiomyopathy (DCM) if myocarditis is the cause of transplantation [27].

The role of transvenous EMB in the management of cardiomyopathy remains controversial. However, the 2013 position statement from the ESC Working Group on Myocardial and Pericardial Diseases and the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of heart failure disagree on the routine use of EMB in unexplained DCM [15, 28]. Histology and immunohistology are required to confirm inflammation, and viral genome analysis is a common method to infer active viral infection, but when do the data from EMB change prognosis and management?

In certain clinical scenarios, unique data from EMB will impact prognosis and therapy. Consensus generally exists that EMB-confirmed sarcoidosis will change management by the use of immunosuppressive therapy in most cases. Lymphocytic myocarditis predicts successful bridging to recovery after left ventricular assist device in adults [29] and the long-term risk of allograft rejection in children [27]. Viral genomes on EMB have been associated with increased risks of left ventricular dysfunction, heart transplantation or death [30–31]. The literature regarding the prognostic value of viral genomes to predict heart transplantation or death is mixed [32].

Since the 2013 ACCF/AHA guideline for the management of heart failure was published, a case series from Johns Hopkins Hospital reported results from 851 patients who underwent right ventricular EMB from 2000 to 2009 [33]. Overall, 25.5% of EMB provided a diagnosis and 22.7% of EMB changed the clinical course. The authors concluded that EMB is useful in acute-onset unexplained cardiomyopathy. However, the usefulness of EMB in chronic DCM was low. Recent reports suggest that left ventricular EMB has a greater diagnostic utility than right ventricular EMB in disorders that primarily affect the left ventricle [34, 35].

**Future directions**

The MRI patterns of epicardial and/or mid-myocardial signal abnormality can identify nonischemic myocarditis or scar, but neither MRI nor $^{18}$FDG PET can identify specific causes and cellular types such as giant cell or eosinophilic myocarditis. However, perfluorocarbons such as $^{19}$fluorine can specifically detect macrophages, granulocytes and dendritic cells in murine myocarditis. A recent study by van Heeswijk et al [36] demonstrated that the perfluorocarbon $^{19}$fluorine can be detected using 9.4T cardiac MRI in a mouse model of autoimmune myocarditis. Translation of this and similar imaging agents under investigation to the clinical arena should allow for the noninvasive detection of myocarditis in settings where EMB is not readily available.

Emerging therapies to prevent the progression of acute myocarditis to chronic DCM may focus on patient-specific immune reactions. For example, T helper type 17 cells are increased and T regulatory cells are decreased in mice with myocarditis [37]. The persistence of this or other immunophenotypes may identify subsets of myocarditis patients who are at risk of chronic heart failure and who may benefit from tailored immunotherapy. Clinical trials of protein A immunoadsorption, a cyclic peptide that binds anti-β1-receptor antibodies and specific anticytokine strategy studies are underway or planned [38].
REFERENCES

Differentiating infarction from myocarditis

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Abstract
Myocarditis can resemble an acute coronary syndrome (ACS), even an ST-segment elevation myocardial infarction. Furthermore, when a coronary angiogram reveals no significant disease, differential diagnosis can be challenging. Endomyocardial biopsy is still the gold standard for the diagnosis of myocarditis; however, its invasive character and limited sensitivity restrict its generalized application to all patients. Both echocardiography and cardiac serum biomarkers may be normal in the setting of ACS or myocarditis, and when abnormal lack enough specificity to differentiate reliably between the two entities. Nuclear techniques have high sensitivity but modest specificity for the detection of myocarditis, and have the additional limitations of availability and radiation exposure. Cardiac magnetic resonance (CMR) has emerged as a leading modality in the noninvasive diagnosis of myocarditis due to its ability to detect myocardial edema, hyperemia, necrosis and fibrosis in a safe and reproducible fashion. In patients with an ACS-like presentation but normal coronary arteries, CMR is useful not only to differentiate acute myocarditis from an ischemic event but also to identify alternative etiologies. Heart Metab; 2014;62:13–17

Keywords: Cardiac imaging techniques; cardiac magnetic resonance; differential diagnosis; myocardial infarction; myocarditis.

General considerations
Clinical manifestations of myocarditis range from the absence of symptoms to cardiogenic shock, including acute myocardial infarction (MI)-like syndrome. Given the availability of highly effective strategies in acute coronary syndrome (ACS), it is mandatory to rule out coronary artery disease as a potential cause, commonly with invasive angiography. However, the presence of normal coronary arteries neither confirms the diagnosis of myocarditis nor rules out ACS. The gold standard for the diagnosis of myocarditis is endomyocardial biopsy (EMB) [1]. Nonetheless, major disadvantages include its invasive character and poor sensitivity, probably related to patchy sampling and imperfect reproducibility of histological criteria [2].

These limitations highlight the need for reliable noninvasive diagnostic tools; however, the most common approaches lack enough specificity to warrant dependable differential diagnosis. Electrocardiographic findings are neither specific nor sensitive, and myocarditis can be accompanied by ST-segment elevation mimicking an acute MI as well as other ST-segment and T-wave changes, Q-waves, ventricular arrhythmias, or conduction abnormalities [3]. Serum biomarkers of myocardial injury may or may not be elevated in either syndrome, depending on the severity of myocardial damage and the time of testing in relation to the course of the disease. Additional serological testing if infectious or immune myocarditis is suspected also has limited diagnostic value [1].
Imaging techniques play an important role in the diagnosis of acute myocarditis and its differentiation from ACS. Cardiac magnetic resonance (CMR) in particular has emerged as the most reliable modality due to the combination of tissue characterization capabilities and a good safety profile.

Echocardiography
The role of echocardiography is limited as there are no specific signs of myocarditis, and segmental wall motion abnormalities resembling ACS may be detected [4]. Nonetheless, echocardiography can still provide relevant information beyond biventricular function. While increased sphericity and left ventricular (LV) volume are common in active acute myocarditis, fulminant forms usually demonstrate normal LV diameter with increased wall thickness [5]. A transient increase in LV wall thickness during the acute phase has been correlated with the presence of myocardial edema in histopathology [6].

Nuclear imaging
There are limited data regarding the diagnostic accuracy of nuclear imaging in myocarditis, with overall high sensitivity although modest specificity. Radionuclide examinations have been largely replaced by CMR due to restricted availability, poorer spatial resolution and the inherent risk from radiation exposure.

An early study compared gallium-67 \(^{67}\text{Ga}\) scintigraphy to EMB for the detection of myocarditis in 68 patients with dilated cardiomyopathy [7]. \(^{67}\text{Ga}\) showed high sensitivity (83%) and specificity (86%), but the positive predictive value was poor (36%), probably due to the low incidence of myocarditis (8%) in this population. In addition, \(^{67}\text{Ga}\) can accumulate in acute MI [8], although a small case series has shown the feasibility of detecting acute myocarditis presenting as ACS [9].

The identification of myocyte necrosis using a monoclonal antibody labeled with indium-111 \(^{111}\text{In}\) and directed towards myosin was first validated in MI [10]. The diagnostic accuracy was then determined in biopsy-confirmed myocarditis [11, 12], showing outstanding sensitivity (83–100%) but limited specificity (31–53%). These results could partly be explained by the high percentage of acute dilated cardiomyopathy without histological evidence of myocarditis that showed a positive scan [13]. Furthermore, antimyosin scintigraphy could demonstrate diffuse, heterogeneous isotope uptake in acute myocarditis versus intense, localized accumulation in MI (Figure 1) [14].

Cardiac magnetic resonance

Cardiac magnetic resonance diagnosis of myocarditis
Beyond the evaluation of global and segmental biventricular function and pericardial effusion, the ability of CMR to characterize histological changes of myocarditis relies on the detection of interstitial edema, hyperemia and capillary leakage, cardiomyocyte necrosis and myocardial fibrosis with specific sequences [15] (Figure 2). T2-weighted imaging can be used to detect the presence of myocardial edema both in inflammatory and ischemic diseases. In ACS, edema is typically localized to the territory of the culprit vessel [16]. In myocarditis, edema may be either segmental or diffuse, which justifies the quantification of myocardial signal intensity in comparison with a reference tissue like skeletal muscle [17]. A signal intensity ratio of 2 or greater has shown an average sensitivity, specificity and diagnostic accuracy of 70% [15].

Regarding contrast-enhanced CMR, the presence of vasodilatation, hyperemia and capillary leakage during the acute phase can be evaluated with early gadolinium enhancement (EGE) [18]. A relative increase in myocardial signal intensity early after contrast administration indicates diffuse expansion in the gadolinium volume.

**Fig. 1** Antimyosin scintigraphy. (a) Diffuse isotope uptake (white arrows) is noted in a patient with viral myocarditis. (b) Localized uptake (black arrow) is seen in a patient with an inferior myocardial infarction. Images courtesy of Dr. Jagat Narula, The Mount Sinai Hospital, New York, USA.

**Abbreviations**
ACS: acute coronary syndrome; CMR: cardiac magnetic resonance; EGE: early gadolinium enhancement; EMB: endomyocardial biopsy; \(^{67}\text{Ga}\): gallium-67; \(^{111}\text{In}\): indium-111; LGE: late gadolinium enhancement; LV: left ventricular; MI: myocardial infarction
of distribution, with an average sensitivity of 74%, specificity of 83% and diagnostic accuracy of 78% [15]. Late gadolinium enhancement (LGE) imaging may reveal focal areas of contrast accumulation secondary to cellular necrosis and/or replacement fibrosis. The characteristic pattern of LGE in myocarditis is patchy or multifocal in a subepicardial or intramyocardial distribution, often involving the lateral wall [19]. This feature is not pathognomonic but is clearly distinct from ischemic heart disease, which typically presents with subendocardial or transmural LGE within a coronary artery territory (Figure 3). It should be taken into account that LGE requires a large enough area of focal myocyte necrosis or fibrosis, which probably explains why this technique is less sensitive (59%) but more specific (86%) than edema and EGE imaging [15].

Two studies evaluated the accuracy of individual tissue-based markers (edema, hyperemia and necrosis) or their combinations in patients with clinically diagnosed acute myocarditis compared with healthy controls [17], or patients with suspected chronic myocarditis undergoing EMB [20]. Both investigations concluded that combinations of two CMR criteria increase performance with pooled sensitivity, specificity and accuracy of 67%, 91% and 78%, respectively [15]. Therefore, recommendations for CMR diagnosis of myocarditis, also known as the Lake Louise consensus criteria, have been issued [15], considering a scan positive for myocarditis if two from the three tissue characterization parameters are present (Table I).

In a retrospective analysis of 131 patients with possible acute myocarditis undergoing CMR and EMB, the combination of the three criteria demonstrated a sensitivity of 39%, specificity of 93% and accuracy of 63% [21]. A recent prospective study [22] in 132 patients with acute or chronic myocarditis tested the Lake Louise criteria using EMB as the reference. A good diagnostic accuracy (79%) was confirmed when the study was performed within the first 14 days after symptom onset, whereas performance decreased to 52% if CMR was carried out later. This finding highlights the relevance of early CMR evaluation if acute myocarditis is clinically suspected.

Differential diagnosis between myocarditis and acute coronary syndrome

CMR is helpful in differentiating myocarditis from ACS in patients with acute chest pain. In 55 patients with unclear presentation and a final clinical diagnosis, all patients with MI (n = 31) had a subendocardial perfusion defect with a corresponding subendocardial or transmural area of LGE, while all but one patient with myocarditis (n = 24) had normal perfusion and a non-ischemic LGE pattern [23]. In a series of 64 patients with acute presentation and probable myocarditis,
In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial inflammation if two or more of the following criteria are present:

- Regional or global myocardial signal increase (≥2) on T2-weighted images.
- Increased global enhancement ratio between myocardium and skeletal muscle (≥4) or absolute myocardial enhancement (≥45%) on early gadolinium-enhanced T1-weighted images.
- At least one focal lesion with nonischemic distribution in inversion recovery-prepared T1-weighted LGE sequences (this finding is consistent with myocyte injury or scar).

A repeat CMR study 1 or 2 weeks after the initial CMR study is recommended if:

- None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical suspicion.
- Only one of the criteria is present.

Left ventricular dysfunction or pericardial effusion provide additional supportive evidence for myocarditis.

**Table 1** Lake Louise CMR diagnostic criteria for myocarditis. Adapted from Friedrich et al [15]. CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement

<table>
<thead>
<tr>
<th>Myocarditis (%)</th>
<th>ACS (%)</th>
<th>Other (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baccouche et al [28]</td>
<td>82</td>
<td>81</td>
<td>4</td>
</tr>
<tr>
<td>Leurent et al [29]</td>
<td>107</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>Assomul et al [30]</td>
<td>64</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>Monney et al [24]</td>
<td>79</td>
<td>81</td>
<td>13</td>
</tr>
<tr>
<td>Gerbaud et al [31]</td>
<td>130</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Steen et al [32]</td>
<td>29</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td>Lauradogolila et al [33]</td>
<td>80</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>Stensaeth et al [34]</td>
<td>49</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table II** Diagnosis in CMR studies for patients with acute chest pain, elevated troponin and no significant coronary stenosis. ACS: acute coronary syndrome; CMR: cardiac magnetic resonance.

CMR is especially useful in the setting of acute chest pain, positive ECG and/or cardiac enzymes, and normal/inconclusive coronary angiograms [27]. In this setting, a number of studies (Table II) [24, 30–35] have demonstrated the ability not only to differentiate ACS from acute myocarditis, but to identify alternative etiologies such as Takotsubo cardiomyopathy or pulmonary embolism. We believe that in such patients a typical CMR is diagnostic for myocarditis and confirmatory EMB can be avoided. Nonetheless, EMB can be considered even in these cases given the relevant information influencing prognosis and therapeutic management that may be derived from tissue analysis [1]. Indeed, CMR and EMB including immunohistochemistry and viral genomic analysis appear to be complementary, and the combination allowed for an etiological diagnosis in 95% of patients in one study [28].

**Conclusions**

Myocarditis may mimic ACS, and conventional tests lack enough specificity for adequate differential diagnosis. CMR can noninvasively depict distinct abnormal tissue patterns (edema, hyperemia and myocyte necrosis/fibrosis) in each entity. Nuclear imaging is an alternative approach, although hampered by radiation and limited specificity. While beyond the scope of this paper, novel multimodality molecular contrast agents designed to target ligands involved in myocardial metabolism, necrosis, apoptosis and inflammation [29] promise to increase further our ability to detect and differentiate ischemic and inflammatory cardiac disorders in the near future.

**Acknowledgment:** Eduardo Pozo has received a grant for a fellowship in advanced cardiovascular imaging from Fundación Alfonso Martín Escudero, Madrid, Spain.
REFERENCES

Introduction
Myocarditis is an inflammatory disease of the heart caused by viral, bacterial and fungal infection, systemic diseases, autoimmune dysregulation, drugs and toxins. From the clinical point of view it ranges from subclinical paucisymptomatic forms to life-threatening arrhythmias, cardiogenic shock and sudden death.

Although in about 40% of cases acute myocarditis may resolve spontaneously [1], in the remaining patients it evolves to a chronic phase as a consequence of an abnormal immune response, with
Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy

ventricular dilation, reduced contractility and clinical progression to heart failure.

Despite the advancement of diagnostic techniques in defining the etiology of myocarditis, a specific standardized treatment is not yet available. This is mainly related to the still unknown mechanisms regulating the normal or abnormal host immune response leading either to virus elimination and spontaneous resolution of the inflammatory process or to an immune-mediated damage persisting with or without viral clearance. In addition, the type of infectious agent and its prevalent mechanism of cell damage (i.e., directly cytopathic or immune-mediated) could also affect the evolution of the myocardial inflammation.

In particular, the use of immunosuppressive treatment for lymphocytic myocarditis is still controversial, both in children [2, 3] and in adults [4, 5] presenting with either cardiac arrhythmias [6] or heart failure [7]. Indeed, in the absence of specific markers of eligibility for this treatment, a large trial by Mason et al. [5] in the past produced misleading results showing the absence of an evident improvement of survival in myocarditis patients treated with immunosuppressive drugs compared with placebo. For this reason the use of immunosuppressive therapy is still confined to the treatment of eosinophilic [8], granulomatous [9] and giant-cell myocarditis [10], as well as lymphocytic myocarditis associated with connective tissue diseases [11] or with the rejection of a transplanted heart. More recently, Wojnicz et al. [12] in a randomized placebo controlled study suggested that an upregulation of HLA antigens in the myocardial tissue of patients with lymphocytic myocarditis may identify a homogeneous subgroup of inflammatory dilated cardiomyopathy sustained by an autoimmune mechanism of damage, and may represent a marker of susceptibility to the treatment. However, in that study the presence of a viral genome in the myocardium was not investigated.

Our group in retrospective and prospective studies has identified the characteristics of patient responders to an immunosuppressive therapy and the cellular and molecular mechanisms of cardiac recovery after immunosuppression.

Retrospective study

In a retrospective study, the virological and immunological profiles of patients with active lymphocytic myocarditis and chronic heart failure, responders and non responders to immunosuppressive therapy, were analyzed [13]. Forty-one patients with a histological diagnosis of active myocarditis and characterized by progressive heart failure with an ejection fraction (EF) of less than 40%, lasting over 6 months in spite of conventional supportive therapy were studied. They received immunosuppressive therapy including 1 mg/kg a day of prednisone for 4 weeks followed by 0.33 mg/kg a day for 5 months and 2 mg/kg a day of azathioprine for 6 months. Patients were classified as responders if they had a decrease of at least one New York Heart Association (NYHA) class and an improvement in EF of 10% or greater compared with baseline measures, and non responders if NYHA class and EF failed to improve or deteriorated or in the presence of major events such as cardiogenic shock, heart transplantation or cardiac death. Among the 41 patients, 21 responded with a prompt improvement of EF and showed evidence of healed myocarditis at control biopsy. Conversely, 20 patients failed to respond, and 12 of them remained stationary, three underwent a cardiac transplantation and five died, showing a histological evolution towards a dilated cardiomyopathy. Retrospective polymerase chain reaction (PCR) on frozen endomyocardial samples and evaluation of circulating cardiac autoantibodies on patient sera showed that non responders had a high prevalence of viral genomes in the myocardium (85%) and no detectable autoantibodies in the serum, whereas 90% of responders were positive for autoantibodies, with only three (15%) presenting with viral genomes on PCR analysis. Among the non responders the myocardial persistence of enterovirus and adenovirus or their combination was associated with the worst clinical outcome. These data indicate in the absence of cardiac viral genomes a prerequisite for the clinical use of immunosuppression, while they also suggest a potential impact of antiviral agents for patients with virus-positive inflammatory cardiomyopathy.

Prospective study

To confirm this result in a prospective manner, we performed a randomized, double-blind, placebo
controlled single-center trial enrolling patients with myocarditis and chronic heart failure, and submitting all patients with no evidence at PCR of a myocardial viral infection to immunosuppressive treatment [15]. Eighty-five patients were treated with prednisone 1 mg/kg a day for 4 weeks followed by 0.33 mg/kg a day for 5 months and azathioprine 2 mg/kg a day for 6 months (43 patients, group 1) or placebo (42 patients, group 2) in addition to conventional therapy for heart failure. The primary outcome was the 6-month improvement in left ventricular (LV) function. Group 1 showed a significant improvement in the left ventricular ejection fraction (LVEF) and a significant decrease in LV dimensions and volumes compared with baseline (Figure 1(a, b)). In particular, 38 out of 43 patients on immunosuppressive therapy (88%) showed an improvement in cardiac function and dimensions. The remaining five patients maintained a stable clinical picture and cardiac function parameters. Remarkably, even patients with severe advanced disease (LV end-diastolic diameter up to 90 mm and LVEF of 20%) significantly improved, being able to resume their previous work. The duration of heart failure did not correlate with the extent of recovery. None of the group 2 patients at the 6-month follow-up showed an improvement in LVEF, which significantly worsened compared with baseline. In particular, 35 of 42 group 2 patients (83%) showed further impairment of cardiac function, while the remaining seven patients remained the same. No major adverse reaction was registered as a result of immunosuppression. Histological analysis showed active myocarditis with diffuse inflammatory infiltrates associated with focal necrosis of the adjacent myocytes (meeting the Dallas criteria), with interstitial and focal replacement fibrosis in most of the left and right ventricular specimens from all patients (Figure 1(c)). The infiltrates included mainly activated T cells (CD45RO positive, CD3 positive) with a moderate amount of cytotoxic lymphocytes (CD8 positive) and macrophages (CD68 positive).

Morphometric analysis showed no differences in terms of the extent of fibrosis and the amount of inflammatory cells between group 1 and group 2 patients. Control histology at 1 and 6 months showed, in the 38 group 1 patients who improved with immunosuppression, a healed myocarditis with disappearance of the inflammatory infiltrates associated with interstitial and focal replacement fibrosis (Figure 1(d)). In the five group 1 patients who did not improve, myocardial inflammation reduced or disappeared in the control biopsies, but some degenerative changes in myocardiocytes were observed. In group 2 patients, control biopsies were not dissimilar from baseline, showing persistence of myocarditis as well as expansion of interstitial and replacement fibrosis.

The results of this trial confirmed the positive impact of immunosuppression on the recovery of LV function in a high rate (88%) of patients with virus-negative inflammatory cardiomyopathy. Remarkably, a striking improvement occurred even in patients with extreme LV dilatation and dysfunction. In this group of patients myocardial inflammation was most likely the result of an immune-mediated injury towards segregated (ie, myosin) or new antigens shared with viral components (ie, antigenic mimicry). Lack of response in 12% of cases suggests the presence of viruses that had not been screened for or mechanisms of damage and inflammation not susceptible to immunosuppression. With regard to undetected viral genomes, metagenomic assessment of myocardial virome, including DNA and RNA extraction from PCR-negative endomyocardial biopsies and the use of the GS-FLX platform, may identify new infectious agents and provide indications for a more selective administration of immunosuppressive therapy.

Cellular mechanisms of cardiac recovery

Cell mechanisms of cardiac recovery in patients with inflammatory cardiomyopathy treated with immunosuppression were analyzed, including cell death, activation of cell proliferation and reconstitution of cell myofilibrar content [16] to clarify the impact of cell repair against cell proliferation or the possible contribute of cell death.
inhibition. Ten responders, all showing the presence of circulating cardiac autoantibodies and the absence of viral genomes in the myocardium at PCR analysis, and 10 non responders, characterized by the worsening of LV dysfunction, the absence of circulating cardiac autoantibodies and by the presence of myocardial viral genomes [13] were retrospectively studied in order to analyze the cellular events associated with the opposite clinical outcome. Transmission electron microscopy studies showed in all patients before treatment large cytoplasmic areas apparently empty or filled with fine granular material as the result of the reduction of myofibrillar content (myofibrillolysis). After 6 months of immunosuppressive treatment, in responders myofibrillar mass and architecture recovered while in the myocytes of non responders there was a further reduction of myofibrillar content. Myocardiacocyte apoptotic and necrotic cell death were greater in baseline biopsies of responders and non responders than in controls, showing that myocyte loss is an important mechanism of myocardial damage in myocarditis with cardiac dysfunction. Importantly, after 6 months of effective immunosuppressive therapy, apoptosis and necrosis decreased by 85% and 62%, respectively, while they further increased by 42% and by 46%, respectively, in follow-up biopsies of non responders. The number of cycling myocytes in baseline myocardial tissue of both responders and non responders was greater than in controls and significantly increased after immunosuppression in both groups, suggesting that in chronic myocarditis, as in other forms of heart failure, there is an activation of myocyte regeneration in the attempt to compensate cell loss.

Conclusion

Immunosuppressive therapy is an important resource in the management of chronic virus-negative inflammatory cardiomyopathy. Lack of identification of new or unconventional viral agents remains a major limit of this therapeutic approach explaining the minor cohort of non responders. Future objectives will be the development of molecular programmes (ie, metagenomic assessment of myocardial virome) able to assess elusive genome sequences.

Source of funding: This study has been supported by grant RF-2009-1511346 and by grant RBFR081CCS from the Italian Ministry of Health.

REFERENCES

Metabolic remodeling as a target preventing myocardial dysfunction: focus on trimetazidine

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Abstract
During the past decade significant declines in cardiovascular mortality have been observed due to the wider use of reperfusion and the optimization of medical therapy. Although rates of procedural success are high in patients with acute and chronic ischemic heart disease, improvement in heart function is not always achieved due to reperfusion injury, microvascular obstruction and the no-reflow syndrome. Insufficient oxygen supply and lack of metabolic adaptation lead to the activation of a complex cascade of reactions including increased reactive oxygen species production, activation of oxidative stress, cellular damage, triggering of apoptosis, progressive cell loss and deposition of extracellular collagen matrix. These mechanisms lead to heart remodeling and progression of heart failure, and have similar features to those of nonischemic cardiopathy. Malicious metabolic remodeling may be prevented by protective mechanisms such as ischemic preconditioning, heart metabolism switch to more efficient energy substrate utilization and transfer. Therefore, adjunctive metabolic medical therapy is being recognized as a reasonable therapeutic option. Of the available therapies, trimetazidine is one of the most effective drugs with confirmed clinical benefits. The mechanisms of heart protection targeted by trimetazidine are quite complex and are reviewed in this article. ▷ Heart Metab; 2014;62:22–26

Keywords: Cardiomyopathy; ischemia; metabolic remodeling; reperfusion; trimetazidine.

Introduction
Despite advances in the management of patients with ischemic heart disease, the greater accessibility of timely invasive and surgical care and a decline in mortality outcomes are still not always satisfactory. The importance of adjunctive therapies targeting different mechanisms of alteration in heart metabolism is being increasingly recognized.

Reperfusion is usually associated with a rapid reintroduction of coronary blood flow into the ischemic region, and may cause the activation of a complex enzymatic cascade of reactions leading to additional cellular damage and myocardial cell loss, finally resulting in heart remodeling, the development of ischemic cardiomyopathy and heart failure. Heart remodeling is a complex process involving “genome expression, molecular, cellular and interstitial changes that are manifested clinically in changes in size, shape and function of the heart after cardiac injury” [1]. Mechanisms decreasing cellular wall permeability and preventing cellular damage by optimization of heart metabolism, switching energy substrate from fatty acid utilization towards glucose oxidation and reducing oxidative stress are currently being studied. Therefore
an understanding of metabolic cascades triggered by ischemic insult help to develop means of acute and long-term therapeutic cardiac protection.

Among the available drugs with cardioprotective properties, trimetazidine (1-[2,3,4-trimethoxy-benzyl] piperazine dihydrochloride) is one with clinical efficacy. Recent large acute myocardial infarction (MI) registry data (KAMIR) suggest survival benefits and a reduction in the incidence of new MI in patients treated with trimetazidine [2]. The drug has antianginal effects and shows clinical benefit in patients with recurrent angina, although its direct impact on heart contractility and vascular resistance is disputable [3, 4]. Trimetazidine has complex potential targets among which are oxidative stress, inflammatory pathways and endothelial function, and it improves heart rate variability in patients with ischemic cardiopathy suggesting a broader spectrum of indications [5].

**Heart metabolism and trimetazidine**

Trimetazidine is a selective 3-ketoacyl-coenzyme A thiolase inhibitor reducing free fatty acid (FFA) oxidation. Inhibition of FFA oxidation shifts metabolism towards glucose oxidation. Glucose is more efficient than FFA and requires less oxygen for equivalent ATP production. Glucose uptake is regulated inversely by FFA.

In general, heart function depends largely on oxygen supply/demand and energy metabolism. Energy metabolism could be briefly described as three major cascades of reactions: substrate utilization, high energy phosphate production by oxidative phosphorylation and energy transfer and utilization [6]. Substrate utilization mainly involves FFA uptake and oxidation and to a lesser extent glycolysis. Energy transfer starts in the mitochondria where ATP is transformed.

**Abbreviations**

CRP: C-reactive protein; FFA: free fatty acid; MI: myocardial infarction; mPTP: mitochondrial permeability transition pore; ROS: reactive oxygen species; TNFα: tumor necrosis factor alpha

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**Fig. 1** Mechanisms of myocardial protection and applications of trimetazidine. CHF, congestive heart failure; FFA, free fatty acid.
to phosphocreatine and ADP. Phosphocreatine leaves the mitochondria and enters the cytosol where reformation of ATP is catalyzed and free creatine re-enters the mitochondria [6]. Phosphorylation is important for energy-dependent Ca\(^{2+}\) sensitivity and cycling, and Ca\(^{2+}\)-dependent Ca release is one of the cornerstones of contraction. It activates myofilaments by binding to troponin C, which influences the interaction between actin and myosin. Then Ca\(^{2+}\) is removed back to the sarcoplasmatic reticulum by Ca\(^{2+}\)-ATPase and outside the cell by the Na/Na exchanger in the presence of K\(^+\)/Na\(^+-\)ATPase. In settings of myocardial ischemia inhibition of Na\(^+\) may occur due to energy deficit and results in intracellular Na\(^+\) and Ca\(^{2+}\) overload and enhanced production of reactive oxygen species (ROS) and intracellular acidosis.

Importantly, in low-flow states and in heart failure patients trimetazidine influences all three cascades of reactions: energy source utilization by FFA oxidation antagonism; energy transfer and utilization maintaining phosphocreatine concentrations; intracellular ATP, reducing intracellular Na\(^+\) and Ca\(^{2+}\) load and diminishing intracellular acidosis [7].

Adaptation and maladaptation
Heart metabolism is flexible and exhibits a great extent of adaptation. Under physiological conditions an increase in glycogen oxidation and prolonged glucose and lactate oxidation is observed and FFA metabolism is not greatly affected. In pathological conditions, such as ischemia, diabetes switch to fatty acid metabolism is present. Depletion of adaptation capabilities in settings of increased oxygen demand or decreased coronary blood flow leads to metabolic remodeling when the heart loses the flexibility of metabolism switch from one to another energy source. During ischemia long-chain saturated fatty acid oxidation is associated with diminished myocyte function and may induce apoptosis. Alternatively, enhanced glucose uptake and glucose transporter overexpression reduces ischemia-induced apoptosis [8].

Diminished coronary perfusion leads to decreased oxygen consumption and activation of maladaptive pathways. Reversible changes occur in hibernating myocardium with preserved viability and reduced oxygen demand. Short-term hibernation is associated with reduced Ca responsiveness while prolonged hibernation may result in fetal gene expression and metabolic switch from fat to glucose metabolism, glycogen accumulation and changes in cells signaling, an increase in the number of dysfunctional mitochondria, collagen deposition, macrophage infiltration, fibrosis, depletion of sarcomeres and activation of cell loss mechanisms. More profound changes occur in stunned myocardium and result from inhibition of Na-K-ATPase, an increase in intracellular Na\(^+\) and Ca\(^{2+}\) overload and stimulation of ROS production and depression of contractile function in near normal coronary flow. ROS production may be opposed to some extent by trimetazidine. Electronic paramagnetic resonance spectroscopy revealed that cardiac oxygen radical production at defibrillation was reduced by trimetazidine independently of direct scavenger effects [9].

Necrotic and apoptotic cell loss, inflammation, endothelial function and myocardial protection with trimetazidine
Ischemia, hibernation, stunning and cell damage may coexist. In response to prolonged ischemia a complex cascade of changes in cell metabolism and signaling may lead to myocardial injury and trigger further structural remodeling. Ischemia-associated heart remodeling involves different mechanisms, such as necrotic or apoptotic cell loss due to atherothrombosis and secondary to coronary microembolization and microvascular dysfunction in the presence of patent epicardial flow. Microvascular obstruction after reperfusion and activation of the expression of abnormal genes are leading to apoptotic cell loss, electrophysiological remodeling and inflammation with leukocyte infiltration. In viable cardiomyocytes adjacent to microinfarct zones the overexpression of tumor necrosis factor alpha (TNF\(\alpha\)) triggering apoptosis is observed [10]. Microvascular dysfunction may occur after reperfusion and it is characterized by diminished microvascular tissue perfusion, injury, microthrombosis and extravascular compression of capillaries [11].

Necrotic cell loss results from a no-flow state or reperfusion injury and is remarkable for an increase in mitochondrial membrane permeability, cell swelling, lysis and the fragmentation of cell structures and activation of inflammatory pathways. Apoptotic cell death occurs in low-flow states and may be triggered by severe energy depletion and ATP deficit and also by reperfusion injury. Apoptosis follows either intrinsic mitochondria-mediated or extrinsic membrane-mediated pathways. Oxidative stress and the accumulation of ROS and Ca\(^{2+}\) overload contribute to caspase activation. The intrinsic
pathway involves these mechanisms impacting voltage-anion channel-gated functioning of the mitochondrial permeability transition pore (mPTP). mPTP opening is caused mainly by reperfusion and facilitates a release in cytosol apoptosis-inducing factors [12]. The extrinsic pathway is receptor-mediated and may be activated by oxidative stress late after reperfusion.

These metabolic changes may be attenuated by protective mechanisms. It has been proved that repetitive short episodes of ischemia may induce more effective adaptation to subsequent ischemia by receptor-mediated ischemic preconditioning. Ischemic preconditioning is being executed by mitochondrial mKATP channel opening and the prevention of mPTP opening [13, 14].

Trimetazidine influences mitochondrial membrane permeability and apoptotic cell loss diminishing oxidative stress and inhibiting mPTP opening, and also reduces caspase 3 activity [15]. The prevention of necrotic cell loss and limitation of inflammatory cascades may also be achieved using trimetazidine before reperfusion [16]. In several studies it has been demonstrated that pretreatment with trimetazidine limits the effects of myocardial ischemia during percutaneous angioplasty [17]. The efficacy of trimetazidine in terms of the prevention of ischemia–reperfusion injury may be attributable to the lowered generation of ROS and activation of “defensive” signaling pathways [18]. The drug administered before reperfusion ameliorates myocardial injury by activation of the pro-survival Akt enzyme and p38 mitogen-activated protein kinase [19].

Attenuating extensive tissue injury the drug also reduces the systemic inflammation associated with reperfusion. Kuralay et al reported that in patients with coronary artery disease undergoing percutaneous intervention, 3 days’ pretreatment with trimetazidine (60 mg/day) was associated with lower levels of C-reactive protein (CRP), TNFα and nitrites, suggesting an anti-inflammatory effect [16]. In experimental studies, trimetazidine inhibited neutrophil accumulation after myocardial ischemia and reperfusion and reduced neutrophil-mediated injury [9, 20].

In excessive cytokine (TNFα, IL-1, IL-6), chemokine and platelet activation, complement-mediated cascades may enhance myocardial injury and dysfunction. TNFα may act by “immediate” and “late” nitric oxide (NO)-dependent pathways [21]. Alterations in NO synthesis regulation and sensitivity, downregulation of eNOS and progressive endothelial dysfunction increase in vasoconstrictive endothelin 1 release, resulting from reperfusion damage and no-reflow phenomenon are important contributors to myocardial dysfunction. Di Napoli et al demonstrated in an experimental study beneficial effects of trimetazidine on eNOS expression partially preventing the progression of these mechanisms [22].

Changes in cell shape and functional properties, cell loss, collagen deposition in the extracellular matrix and fibrosis are attributable to ischemic and non-ischemic heart remodeling; therefore, the heart protection mechanism to some extent shares similar features in ischemic and dilated cardiomyopathy. Major factors contributing to cell injury and the extent and reversibility of dysfunction are the severity of the ischemic episode, the presence of preconditioning, time to reperfusion along with other influences such as environmental factors and comorbidities (eg, diabetes or glucose intolerance). It has been reported that in patients with chronic ischemic heart disease trimetazidine exhibits anti-inflammatory properties. In a study of patients with ischemic dilated cardiomyopathy CRP-levels remained unchanged in the trimetazidine arm during the 18-month period of follow-up, whereas in controls a progressive increase in CRP was registered [23]. Similarly, in diabetes patients with idiopathic dilated cardiomyopathy steady levels of CRP were registered at 6 months after study initiation in the trimetazidine group as opposed to a significant CRP increase in controls. It should be noted that in that study therapy with trimetazidine was associated with a decline in N-terminal pro brain natriuretic peptide levels, improvement in left ventricular contractility and prolonged 6-minute walk test [24]. The better performance of trimetazidine in diabetes patients with idiopathic dilated cardiomyopathy may be partly explained also by the extracardiac effects of the drug, which beyond cardiac FFA oxidation impacts whole body insulin sensitivity countering the myocardial damage of insulin resistance, as was hypothesized by the authors [25].

In addition, the beneficial effects of trimetazidine on heart remodeling in the prevention of nonischemic cardiopathies may be potentially associated with the inhibition of pressure overload-induced cardiac fibrosis through the NADPH oxidase–ROS–connective tissue growth factor signaling pathway [26].

Complex effects of trimetazidine also include electrophysiological effects, such as a reduction of Q–T interval dispersion, beneficial effects on heart rate variability in
patients with ischemic cardiopathy, which may result from an improvement of ATP-dependent signaling and from a reduction in cardiac fibrosis [27, 28]. In summary, in patients with acute and chronic ischemic heart disease, nonischemic dilated cardiopathy associated with low-flow states or deep metabolic heart remodeling, in addition to traditional therapy, adaptive metabolic treatment is a reasonable option [29]. Trimetazidine is a drug with established clinical benefits and a complex mechanism of action, switching heart metabolism from FFA to more effective glucose metabolism, preventing reperfusion injury, activation of inflammatory cascades, endothelial dysfunction, apoptosis, diminishing heart fibrosis and also structural and electrophysiological remodeling.

REFERENCES

5. Gunes Y, Guntekin U, Tuncer M, Sahin M (2009) Improved left heart metabolism from FFA to more effective glucose metabolism, preventing reperfusion injury, activation of inflammatory cascades, endothelial dysfunction, apoptosis, diminishing heart fibrosis and also structural and electrophysiological remodeling.

Multimodality imaging of Churg–Strauss myocarditis

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Abstract
A 26-year-old man presented with a 1-month history of hemoptysis, fever and chest pain. Investigations revealed a peripheral blood eosinophilia along with focal areas of lung consolidation on radiographic imaging. Subsequent echocardiography confirmed cardiac involvement, with a reduction in systolic function and a speckled appearance of the myocardium. The patient was diagnosed as having eosinophilic granulomatosis with polyangiitis and was treated with intravenous cyclophosphamide and corticosteroids. He made an excellent recovery and was subsequently discharged 4 weeks later. We present the radiographic and cardiac imaging findings of this condition along with a review of the value on cardiac screening in this patient population. ■ Heart Metab; 2014;62:27–30

Keywords: Cardiac magnetic resonance; Churg–Strauss syndrome; echocardiography; eosinophilic granulomatosis polyangiitis; myocarditis.

Introduction
A 26-year-old man with a history of asthma presented to our institute with a 1-month history of intermittent hemoptysis, pleuritic chest pain and night sweats. Clinical examination revealed a tachycardia of 112 beats per minute and pyrexia of 37.9°C. The full blood count demonstrated an elevated total white cell count \((16.4 \times 10^9)\) with an abnormally elevated eosinophil count of \(8.2 \times 10^9\). Serum biochemistry was normal apart from elevated serum troponin T measurement of 1366 ng/L. Given the clinical findings, the patient underwent an urgent 12-lead ECG and a chest X-ray. The ECG showed saddle-shaped ST-segment elevation suggestive of pericarditis, while the chest X-ray showed patchy consolidation in the left mid zone and coarse reticular marking in the mid zones bilaterally (Figure 1).

A computed tomographic pulmonary angiogram excluded the presence of pulmonary emboli but confirmed the presence of extensive lung parenchymal changes. The proximal airways were dilated with some opacification and distal dilatation. In addition, there was associated thickening of the bronchi and multifocal areas of ground glass opacification (Figure 2). These findings were suggestive of pulmonary hemorrhage along with eosinophilic pneumonia.

A subsequent transthoracic echocardiogram confirmed concomitant pericardial and myocardial involvement (Figure 3). There was a mild pericardial effusion and the myocardium was thickened (14 mm) with a heterogeneous speckled appearance indicative of edema. Left ventricular systolic function was mildly reduced at 40% and there was evidence of reduced long axis function.
Immunology demonstrated an elevated serum IgE level of 902 KU/L (normal range 0–81). There were no myeloperoxidase, anti proteinase-3, glomerular basement membrane, extractable nuclear antigens or antineutrophil cytoplasmic antibodies (ANCA). Given the elevated eosinophil count, elevated serum IgE level and imaging findings, a diagnosis of Churg–Strauss syndrome with myocardial involvement was made. The patient was promptly started on corticosteroids, an angiotensin converting enzyme (ACE) inhibitor and a β-blocker. Unfortunately, shortly thereafter he developed a right foot drop secondary to partial right common peroneal nerve damage, which initiated the start of intravenous cyclophosphamide. A cardiac magnetic resonance (CMR) scan performed 1 week later showed an improvement in systolic function to 55% and confirmed the myocardial involvement suggested by the transthoracic echocardiogram. On T2-weighted imaging there was evidence of circumferential enhancement indicative of myocardial edema. Following the administration of gadolinium, patchy areas of late enhancement were noted within the apex, anterior, septal and inferior walls with a transmurality of 25%. In addition, there were patches of intramyocardial late gadolinium enhancement within the mid ventricular septal and inferior walls (Figure 4).

The patient remained in hospital for a further 4 weeks during which his symptoms gradually improved. He was discharged home 5 weeks after his initial presentation. At follow-up 3 months later, he had received six infusions of cyclophosphamide, was on a reducing dose of prednisolone and was being maintained on an ACE inhibitor and β-blocker. His chest X-ray (Figure 5) and echocardiographic findings (Figure 6) had resolved and his foot drop had improved.

**Fig. 1** Chest X-ray. Initial chest X-ray showing patchy areas of consolidation within the lower lobe of the left lung (white arrows).

**Fig. 2** Computed tomography pulmonary angiogram showing (a) multifocal areas of ground glass opacification with more focal consolidation and (b) peripheral ground glass changes seen within the lower lobe of the left lung (black arrows).

**Fig. 3** Transthoracic echocardiogram showing thickening of the left ventricular walls, a “speckled” texture to the myocardium in the parasternal long axis (a) and apical four-chamber views (b). (c) A pulsed Doppler sample taken at the tips of the mitral valve leaflets demonstrating restrictive diastolic filling of the left ventricle. (d) A reduction in myocardial systolic velocity at the lateral mitral valve annulus indicative of reduced longitudinal axis function. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
In 1951, Churg and Strauss described a syndrome characterized by asthma and a “strikingly uniform clinical picture of fever and eosinophilia, and symptoms of cardiac failure, renal damage and peripheral neuropathy resulting from vascular embarrassment in various systems and organs” [1]. This entity was known as “Churg–Strauss syndrome” for many years but this has now been replaced by “eosinophilic granulomatosis with polyangiitis” (EGPA) [2].

The American College of Rheumatology has identified six criteria for the disease [3]. When at least four of these six criteria are met (asthma, eosinophilia >10%, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities and extravascular eosinophil infiltration) a vasculitis can be classified as being EGPA with a sensitivity of 85% and specificity of 99.7% [3]. EGPA is classically described as having three main sequential phases [4]. The first phase, or prodromal phase, usually consists of allergic rhinitis, nasal polyposis and airway irritability. The second phase, or eosinophilic phase, is characterized by peripheral blood eosinophilia organ involvement. The third phase, or vasculitic phase, is accompanied by clinical manifestations as a result of systemic necrotizing vasculitis.

Discussion

Cardiac involvement

Cardiac involvement can occur in up to 62% of patients with EGPA [5] and is more common in ANCA-negative patients [6, 7]. Cardiac manifestations include restrictive or dilated cardiomyopathy, myocarditis, arrhythmias, valvular abnormalities, arrhythmias and sudden death. Dennert et al studied
32 consecutive patients in remission and found that 62% of patients had evidence of cardiac involvement. Clinical symptoms were present in 25%, major ECG abnormalities in 13%, echocardiographic abnormalities in 50% and CMR abnormalities in 62% of patients. The commonest ECG abnormality was the presence of T-wave changes (50%), while on echocardiography wall motion abnormalities (41%). CMR imaging was concordant with the echocardiographic findings in demonstrating wall motion abnormalities in 47% of patients. In addition, there was evidence of regional fibrosis in 22% and global fibrosis in 25% of patients. Fibrosis was only found in patients who had other cardiac abnormalities, and there was a good agreement between echocardiography and CMR imaging when fibrosis was excluded (sensitivity 88% and specificity 81%, respectively).

In general, the prognosis of EGPA is considered to be good, with an overall 10-year survival rate of 81–92% [8]. Up to 50% of EGPA mortality is caused by cardiac involvement, with up to 39% of patients dying during the acute phase of the disease [8]. In a recent study of 383 patients with EGPA followed up for a mean duration of 66.8 months, cardiac involvement determined by clinical evaluation, an ECG and echocardiography remained the greatest predictor of death with a hazard ratio of 4.11 (95% CI 1.96–8.60) [6]. Although there remains considerable interest in the detection of subclinical cardiac involvement with CMR and positron emission tomography, further longitudinal studies are required to determine their prognostic value [9]. Until these data are available, early clinical, ECG and echocardiographic screening is indicated for all patients with EGPA to detect early cardiac involvement.

**Treatment**

The choice of initial therapy is usually determined by the patient’s prognostic profile, as defined by the five-factor score (FFS) [10]. This includes cardiac, gastrointestinal and central nervous system involvement with proteinuria greater than 1 g/24 hours and creatinine greater than 140 μM/L. Patients with an FFS score of 1 or greater usually have a worse prognosis and are treated with corticosteroids and immunosuppressants. Corticosteroids are usually used in isolation for patients with an FFS score of 0. Although remission rates remain high with this approach, controversy still exists as to how many pulses of intravenous cyclophosphamide should be used, and relapse rates remain high for those patients receiving reducing doses of corticosteroids alone. There are no systematic trials evaluating the use of ACE inhibitors and β-blockers in EGPA-associated cardiac involvement.

**Conclusions**

The current case reports the multimodality imaging findings of a patient who presented with EGPA and demonstrates the value of early echocardiographic screening in these patients to identify early cardiac involvement to guide treatment.

**REFERENCES**

Myocarditis: inflammatory and endocrine causes

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Abstract
Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentations. In patients with mild symptoms and no or little ventricular dysfunction, myocarditis may resolve spontaneously without specific treatment. However, in up to 30% of cases, biopsy-confirmed myocarditis can progress to dilated cardiomyopathy and is associated with a poor prognosis. Myocarditis can also present as a life-threatening condition or with sudden cardiac death. Prognosis in myocarditis patients varies according to the clinical presentation, the underlying etiology and pathogenesis, and particularly in immune-mediated forms, such as giant cell myocarditis, or myocarditis in systemic extra-cardiac autoimmune conditions, the prognosis is poor. A 2013 European Society of Cardiology task force has introduced new criteria for clinically suspected myocarditis and proposes consideration for endomyocardial biopsy (including histological, immunohistochemical and molecular biological analysis) as well as autoantibody serum testing in clinically suspected cases, to identify those patients in whom specific therapy is appropriate. Heart Metab; 2013;62:31–35

Keywords: Autoimmunity; diagnosis; dilated cardiomyopathy; endomyocardial biopsy; myocarditis.

Introduction
In the 1996 World Health Organization/International Society and Federation of Cardiology classification of the cardiomyopathies [1] and the 2013 European Society of Cardiology (ESC) task force report on myocarditis [2], myocarditis is defined as an inflammatory disease of the myocardium, diagnosed on endomyocardial biopsy (EMB), inflammatory cardiomyopathy as myocarditis in association with cardiac dysfunction (Table I) [3, 4]. Inflammatory and endocrine causes are listed among the specific cardiomyopathies in some [1, 2], but not all classifications [5, 6]. Causes of inflammatory cardiomyopathy or myocarditis are detailed in the 2013 ESC task force report on myocarditis [2]. The 2013 ESC task force criteria define etiological subsets as follows:

- Viral myocarditis: histological evidence of myocarditis associated with positivity by polymerase chain reaction (PCR) on EMB for one or more of the viruses.
- Autoimmune myocarditis: histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies.
- Viral and immune myocarditis: histological myocarditis with positive viral PCR and positive cardiac autoantibodies. In these patients a follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac autoantibodies, eg, postinfectious autoimmune disease.
Here we will deal with classic and rare endocrine causes of myocarditis or inflammatory cardiomyopathy.

**Etiology and pathogenesis**

Infectious agents, systemic diseases, endocrine diseases, drugs and toxins can cause myocarditis [1, 2, 7–11]. Molecular techniques, mainly reverse transcriptase PCR suggest that viral infections are a common cause of myocarditis in western countries [1, 2, 7–13]. Autoimmune myocarditis may occur with exclusive cardiac involvement or in the context of autoimmune disorders with extracardiac manifestations, eg, sarcoidosis, hypereosinophilic syndrome, scleroderma and systemic lupus erythematosus. In human myocarditis there is evidence of viral and autoimmune mechanisms, acting in individuals with or without a predisposing genetic background [2, 9, 14, 15]. Progression from myocarditis to dilated cardiomyopathy (DCM) may occur in patients who cannot eliminate the infective agents [2, 12] or have developed pathogenic serum cardiac autoantibodies directed against myocardial autoantigens [2, 9, 14, 15].

**When to suspect myocarditis: the 2013 ESC task force criteria**

Inflammatory cardiomyopathy/myocarditis is a challenging diagnosis in cardiology and needs a high level of suspicion; clinical presentation is polymorphic [2]. To aid the clinician in the identification of myocarditis, the ESC myocarditis task force has introduced new criteria for clinically suspected myocarditis [2]. Clinically suspected myocarditis is defined by the presence of more than one clinical presentation and more than one diagnostic criterion from different categories, in the absence of:

- Angiographically detectable coronary artery disease (CAD; coronary stenosis ≥50%).
- Known pre-existing cardiovascular disease or extracardiac causes that could explain the syndrome (eg, valve disease, congenital heart disease, etc.). Suspicirion is higher with a higher number of fulfilled criteria.
- If the patient is asymptomatic more than two diagnostic criteria should be met.

Key points in the medical history include the following:

- In relation to the family history, it is suggested to enquire about familial DCM, other cardiomyopathy, sudden cardiac death and autoimmune and infectious subtypes.
- In relation to the patient’s history, it is suggested to enquire about recent (days to 2 weeks) upper respiratory or gastrointestinal suspected viral syndrome, allergy, other autoimmune diseases, previous clinically suspected or confirmed myocarditis, heavy alcohol intake, consumption of drugs and toxic substances (eg, cocaine), vaccines, travel to places where specific cardiotropic infection is possible or endemic (eg, Brazil, Argentina and Chile for Chagas’ disease), proximity with domestic

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**Abbreviations**

CAD: coronary artery disease; CMR: cardiac magnetic resonance; DCM: dilated cardiomyopathy; EMB: endomyocardial biopsy; ESC: European Society of Cardiology; LGE: late gadolinium enhancement; PCR: polymerase chain reaction

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**Myocarditis (WHO/ISFC) [1, 2]:**

Inflammatory disease of the myocardium diagnosed by established histological and immunohistochemical criteria.

**Inflammatory cardiomyopathy (WHO/ISFC) [1, 2]:**

Myocarditis in association with cardiac dysfunction.

**Dilated cardiomyopathy (ESC; WHO/ISFC) [1, 2, 6]:**

DCM is a clinical diagnosis characterized by dilation and impaired contraction of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease.

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**Table I** Definitions. DCM, dilated cardiomyopathy; ESC, European Society of Cardiology; WHO/ISFC, World Health Organization/International Society and Federation of Cardiology.
animals, conventional coronary risk factors, etc. The aim is to search for as well as exclude possible treatable causes (e.g., drug-related toxicity or hypersensitivity). Most patients will have “idiopathic” or presumed viral myocarditis. The ESC task force clinical presentations [2] include one or more of the following:

- Acute coronary syndrome-like, with or without normal global or regional left ventricular and/or right ventricular dysfunction on echocardiography or cardiac magnetic resonance (CMR), with or without increased troponin T/troponin I (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 CAD and known causes of heart failure.
- Chronic heart failure, with heart failure symptoms (with recurrent exacerbations) of more than 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.

The ESC task force diagnostic criteria [2] include one or more of the following features from categories 1 to 4:

1. ECG/Holter/stress test features: newly abnormal 12-lead ECG and/or Holter and/or stress testing, any of the following: 1 to 3 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, supra-ventricular tachycardia.


3. Functional and structural abnormalities on cardiac imaging (echo/angiography/CMR): new, otherwise unexplained left ventricular and/or right ventricular structure and function abnormality (including incidental finding in apparently asymptomatic individuals): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi.

4. Tissue characterization by CMR: oedema and/or late gadolinium (LGE) enhancement of classic myocarditic pattern (according to Lake–Louise criteria) [16].

Role of noninvasive cardiac imaging

Echocardiography defines morphology and biventricular function, but it is not specific. It may be normal or similar to DCM. Pericardial effusion may be present, as well as segmental wall motion abnormalities. Apical left ventricular aneurisms suggest Chagas’ disease. In fulminant myocarditis there may be a slight increase in left ventricular wall thickness and a mildly dilated severely hypokinetic ventricle [2].

Indium antimyosin antibody and $^{67}$gallium nuclear imaging are rarely used (limited availability of tracers, poor spatial resolution, radiation issues) [2].

CMR imaging defines the morphology and biventricular function of the heart and provides tissue characterization. Myocardial edema is assessed on T2-weighted CMR images, hyperemia/capillary leak on myocardial early gadolinium enhancement ratio, and necrosis/fibrosis on LGE. LGE is typically subepicardial, localized in inferolateral and less frequently in anteroseptal left ventricular segments, and may be focal or diffuse in distribution. The best overall diagnostic accuracy (78%) is found by the combination of all three tissue-based CMR parameters, but correlative data with EMB are still based on low numbers. CMR does not differentiate viral from non-viral myocarditis [16].

Role of endomyocardial biopsy

In patients fulfilling the diagnostic criteria for clinically suspected myocarditis, the ESC myocarditis task force recommends selective coronary angiography and EMB, including conventional histology, as well as immunohistochemistry and PCR detection of infectious agents [2, 7]. This recommendation also applies to patients with an acute coronary syndrome-like presentation, not included in the American Heart Association/American College of Cardiology/Heart Failure Society of America scientific statement on EMB [17]. EMB confirms the diagnosis of myocarditis and identifies the underlying etiology and type of inflammation (e.g., giant cell, eosinophilic myocarditis, sarcoidosis), which imply different treatments and
prognosis [1, 2, 9]. EMB is also the basis for safe (infection-negative) immunosuppression [2, 9, 18]. If EMB is performed by experienced teams, its complication rate is low (0–0.8) [2, 9, 19].

**Natural history and management**

**Potential long-term complications**

Myocarditis of suspected viral etiology resolves in approximately 50% of cases in the following 2–4 weeks, but about 25% will develop persistent cardiac dysfunction and 12–25% may deteriorate acutely and either die or progress to end-stage DCM with a need for heart transplantation [2]. Risk stratification based on standard clinical and diagnostic markers is poor; biventricular dysfunction at presentation has been reported as the main predictor of death or transplantation [2, 9, 13]. Giant cell myocarditis is associated with a poor prognosis [2, 9]. Prognosis may also be worse in selected forms with multisystem involvement. The detection of selected viral genomes on EMB or of chronic inflammation by immunohistology may have independent prognostic value but further confirmation is required [2, 9, 13]. Fulminant myocarditis has been associated with a good prognosis [2].

**Standard treatment**

Inflammatory cardiomyopathy should be treated in keeping with current heart failure and arrhythmia guidelines. Patients with fulminant myocarditis or with hemodynamic compromise in spite of optimal medical management need intravenous inotropic agents and/or mechanical circulatory support as a bridge to recovery or transplantation [2]. Aerobic activity should be restricted for 6 months, and re-introduced gradually [2].

**Etiology-directed treatment**

Antibiotic or antiviral therapy should be instituted if appropriate or available in specific infectious forms [2]. Hypereosinophilic inflammatory cardiomyopathy often responds to withdrawal of the offending agent (eg, drugs, toxic substances) or to treatment of the underlying cause (eg, parasitic infection), but steroids are often needed [2].

The 2013 ESC task force recommends immunosuppressive therapy in infection-negative giant cell myocarditis, in cardiac sarcoidosis and in inflammatory cardiomyopathy/DCM associated with other extracardiac autoimmune diseases [2, 20]. The immunosuppressive regimen should be tailored to the patient [2]. Immunosuppressive therapy may also be used in selected virus-negative patients with exclusive cardiac involvement, particularly if they are cardiac autoantibody positive and do not respond to standard heart failure therapy, but double-blind placebo controlled multicenter randomized studies in patients with defined viral or autoimmune cardiomyopathy/DCM are not yet available [2, 9].

**Pheochromocytoma as a rare endocrine cause of myocarditis**

Pheochromocytomas are primarily benign tumours originating from neuroectodermal chromaffin cells within the adrenal medulla, abdomen or within the plexus of sympathetic adrenergic cells, 10% of cases are familial. It may coexist with medullary thyroid carcinoma or hyperparathyroidism, in multiple endocrine neoplasia syndrome type II, due to a mutation in the RET proto-oncogene. In multiple endocrine neoplasia IIB pheochromocytomas coexist with medullary thyroid carcinoma and mucosal neuromas on the lips and tongue. Pheochromocytomas may also be associated with neurofibromatosis or with cerebellar or retinocangiomas in von Hippel–Lindau disease. Diagnosis requires the demonstration of increased norepinephrine or epinephrine or its metabolites in serum and blood. Quantitative 24-hour urinary metanephrines are useful. Treatment is surgical.

Cardiovascular findings include: headache, palpitation, excess sweating, chest pain, weight loss, hypertension with associated orthostatic hypotension, due to episodic excess catecholamine secretion. There are case reports of cardiomyopathy, as well as autopsy reports of histological myocarditis in patients with previously diagnosed or undiagnosed pheochromocytomas. ECG shows left ventricular hypertrophy and strain pattern.

**Management**

Preoperative management requires 7–14 days of α-adrenergic blockade, usually with prazosin or phenoxycbenzamine. β-Blockade is contraindicated before α-adrenergic blockade. If necessary for control of supraventricular arrhythmia or incessant tachycardia β1-selective agents such as atenolol are preferred. If surgery is not feasible, metyrosine can decrease catecholamine synthesis and improve cardiovascular signs and symptoms.
Conclusion
Historically, myocarditis has been considered a rare and poorly understood condition, a conundrum with polymorphic clinical presentation and variable prognosis ranging from spontaneous resolution to progressive heart failure and death. Prognosis in myocarditis patients varies according to the clinical presentation, the underlying etiology and pathogenesis. Diagnosis of certainty and diagnosis of specific etiopathogenetic forms of myocarditis can only be achieved by EMB. A 2013 ESC task force [2] has introduced new criteria for clinically suspected myocarditis and proposes consideration of EMB (including histological, immunohistochemical and molecular biological analysis) as well as autoantibody testing in clinically suspected cases, to identify those patients in whom specific therapy is appropriate, particularly immunosuppression for infection-negative forms.

REFERENCES

Takotsubo cardiomyopathy: a possible metabolic disorder

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Abstract
Takotsubo cardiomyopathy is considered a transient nonischemic cardiomyopathy of possible metabolic etiology. Based on the morphology of the left ventricle and presumed etiology, this condition has been described using several different names including transient left ventricular apical ballooning, ampulla cardiomyopathy, stress-induced cardiomyopathy, neurogenic stunned myocardium, broken heart syndrome and acute catecholamine cardiomyopathy. The term “takotsubo” means octopus trap and is derived from the Japanese to describe the characteristic appearance of the left ventricle in this condition. In the typical or classic form of takotsubo cardiomyopathy the apical and mid-segment contractile function of the left ventricle is depressed with compensatory hyperkinesis of the basal part thus acquiring an octopus trap or balloon shape during systole. However, several other forms have also been described. The left ventricular dysfunction is not confined to any single area of the coronary artery and the coronary angiogram typically shows nonobstructive coronary arteries. The exact etiology is not known; however, abnormal catecholamine metabolism and response is believed to be the most likely explanation. Preceding emotional and physical stress is recognized in at least 30% of patients. The clinical presentation is acute and mimics ST-elevation myocardial infarction due to symptoms of chest pain, electrocardiographic changes and raised troponin. The widespread availability of primary percutaneous coronary intervention and awareness of takotsubo cardiomyopathy has led to an increasing number of patients being diagnosed with this condition. The treatment is supportive, the prognosis is excellent, and the left ventricular dysfunction is transient, and most patients make a full recovery without myocardial fibrosis or any long-term sequelae. ▪ Heart Metab; 2014;62:36–40

Keywords: Acute catecholamine cardiomyopathy; ampulla cardiomyopathy; broken heart syndrome; neurogenic stunned myocardium; stress-induced cardiomyopathy; takotsubo cardiomyopathy; transient left ventricular apical ballooning.

Introduction
Takotsubo cardiomyopathy (TC) is considered a transient nonischemic cardiomyopathy of possible metabolic etiology in origin [1]. This condition was first described by a case series of five Japanese patients in 1991 [2]. Takotsubo is a Japanese term that means octopus trap [3]. This name has been used due to the systolic appearance of the left ventricle found in the classic form of takotsubo cardiomyopathy, which is characterized by a reversible non contractile left ventricular (LV) apex with a compensatory hyperdynamic basal part in the presence of nonobstructive coronary
Mehmood Zeb

Takotsubo cardiomyopathy: a possible metabolic disorder

arteries (Figure 1) [3]. As a result of the appearance of the left ventricle this condition is also known as transient apical ballooning syndrome, or apical cardiomyopathy [1]. Clinically, TC is indistinguishable from acute coronary syndrome (ACS) due to acute cardiac sounding chest pain, ST segment changes on a 12-lead ECG and elevated cardiac enzymes [1]. However, the main distinguishing characteristic in the acute setting is the absence of epicardial coronary occlusion and the transient nature of LV dysfunction in the long term. Therefore TC is a diagnosis of exclusion, and in most cases it is mandatory to exclude obstructive coronary artery disease [4, 5].

The concept that LV dysfunction might result from physical or emotional stress, in the absence of overt myocardial ischemia, has started to gain more widespread acceptance [5]. Following its initial description, TC was increasingly recognized and given a multitude of names that reflected both the presumed etiologies and pathological findings. These included transient LV apical ballooning [4], neurogenic stunned myocardium [6], ampulla cardiomyopathy [7], stress-induced cardiomyopathy [8], broken heart syndrome [9] and acute catecholamine cardiomyopathy [10].

Since its first description the presentation of TC has gradually increased; MEDLINE searches for the terms apical ballooning, ampulla cardiomyopathy, takotsubo cardiomyopathy and takotsubo cardiomyopathy between 1989 and 2013 demonstrated a significantly increased frequency of publications in the past 5 to 10 years.

Types of takotsubo cardiomyopathy

In classic TC the LV apex is non contractile, with a hyperdynamic basal part; however, several other forms have also been described including “mid ventricle takotsubo cardiomyopathy” found in 17% of cases [11, 12], in which mid ventricular contractile function is impaired, but the apex and base remain hyperdynamic. However, in the third type “basal or reverse takotsubo cardiomyopathy” the basal ventricle is non contractile with a hyperdynamic apex. In about 30% of cases both the left and right ventricle is affected, giving the appearance of dilated cardiomyopathy [12].

Prevalence

The diagnosis of TC is made in approximately 1–2% of all cases of suspected acute myocardial infarction [13], although this estimate may be low because of underrecognition. In our experience 5.7% of patients presenting with features of ACS are diagnosed with TC [1]. Park et al demonstrated echocardiographic evidence of TC in 28% of intensive care patients, although that study was limited by the absence of coronary angiography [14].

TC has a higher prevalence among postmenopausal women and women with anorexia nervosa [15, 16]. The diagnosis of TC has become more frequent most probably due to increasing awareness and access to cardiac catheterization [1].

Pathophysiology

The exact cause of TC is unknown. However, several hypotheses exist to explain the mechanism and pathophysiology of this disease.

Physical or emotional stress and catecholamine excess

The onset of TC is often preceded by emotional, physical stress, or critical illness; for example, an increased

Abbreviations

ACS: acute coronary syndrome; LV: left ventricular; TC: takotsubo cardiomyopathy

Fig. 1  (a) Left ventriculogram in systole showing no contraction in the apical region and apical ballooning. (b) Left ventriculogram in diastole demonstrating no difference in apical shape in comparison to systole. (c) Cardiac catheterization revealing unobstructed left coronary system. (d) Cardiac magnetic resonance showing left ventricle in systole, clearly demonstrating lack of contraction at apex and ballooning of left ventricle (typical octopus pot-like appearance). Reproduced from Zeb et al. [1] with permission from BMJ Publishing Group Ltd.
incidence of the syndrome was noticed after earthquakes in Japan [17]; a clearly recognized stressor is found in at least 30% of patients [18]. Therefore, it is speculated that abnormal catecholamine dynamics related to emotional stress may be playing a role in the pathogenesis of TC. This hypothesis has been extensively studied [1]. In a recent retrospective study, Giavarini et al reported that pheochromocytomas and paragangliomas may present as acute takotsubo-like cardiomyopathy in 11% of cases [10]. Wittstein et al demonstrated significantly elevated catecholamine levels in the plasma of patients with TC in comparison to normal individuals and patients with acute myocardial infarction with heart failure [19]. The authors also demonstrated persistently elevated level of catecholamines for more than a week while the plasma half-life is only few minutes. Kume et al demonstrated excessive catecholamine release from the hearts of patients with TC [20]. Abraham et al demonstrated the development of all variants of TC in nine patients following intravenous epinephrine and dobutamine infusion, supporting the concept that catecholamines play a role in the genesis of TC [21]. In addition, drugs with sympathetic effects have also been associated with TC [21]. Several mechanisms have been proposed to explain the catecholamine-mediated cardiotoxicity, eg, multiple coronary arteries spasm or microvascular dysfunction, direct catecholamine-mediated myocardial dysfunction, endothelial dysfunction and intracellular calcium overload, resulting in damage to myocytes [1]. A catecholamine-induced disorder in glucose metabolism has been suggested on the basis of decreased LV apical 18F-fluorodeoxyglucose uptake on positron emission tomography of 15 patients with the apical variant of TC [22]. Increased LV apex endocardial surface area due to trabeculations and the presence of higher concentrations of β-adrenergic receptors in the apical versus basal myocardium have been proposed to be responsible for abnormal response and akinesis of the apex. However, this hypothesis fails to explain mid cavity and basal TC, unless in the future an abnormal distribution of these receptors is demonstrated in other forms of TC [1]. These observations support the hypothesis that, during times of stress when epinephrine is the main circulating catecholamine, regional differences in epinephrine-sensitive β2-receptors could explain the myocardial response to the catecholamine surge seen in TC.

Lyon et al demonstrated overexpression of β1-adrenergic receptors in LV myocardium of mice subjected to supraphysiological epinephrine concentrations [23], which has been shown to have a negative inotropic effect on cardiomyocytes, possibly due to intracellular signal trafficking switch from Gs protein to Gi protein. This signal switching is also known to have a protective effect against apoptosis [24]. Ellison et al also demonstrated myocyte damage and sparing of cardiac stem cells by acute β-adrenergic overload, which could provide an insight into a potential mechanism for the rapid recovery of myocardial function [25].

Other hypotheses

Myocarditis as a cause of TC is not well supported by the data. Viral titers do not rise after the initial event, and biopsy findings are not suggestive of myocarditis. Cardiac magnetic resonance imaging of a limited number of patients has shown no evidence of myocarditis or infarction [1]. Multiple epicardial coronary artery spasm as a cause of TC is not strongly supported by the literature, despite isolated reports. The presence of persistent ST segment changes in patients with TC, even when coronary angiography shows no spasm, also goes against this hypothesis.

The reason why cardiomyopathy occurs predominantly in postmenopausal women is also unexplained. However, the deficiency in estrogen activity may play a role, supported by the evidence of estrogen supplementation attenuating TC in an animal model, and the influence of sex hormones on endothelial function [26]. Interestingly, a study of 72 individuals (47% women) with subarachnoid hemorrhage reported that LV wall motion abnormality occurred only in women [27].

Cardiac syndrome X is also common in postmenopausal women, and endothelial dysfunction is thought to affect the underlying pathophysiology [28, 29]. A genetic component is suggested by the observation of the occurrence of TC in two sisters and in a mother–daughter pair [1, 30]. However, comprehensive DNA sequence analysis failed to show any association between functional variants of the genes encoding various types of adrenoceptors and TC [30].

At present there is no evidence to suggest a difference in the pathophysiology of various morphological forms of TC; however, a common mechanism is suggested by the finding of two morphological variants in the same individual [31] and the finding of multiple morphological variants with epinephrine or dobutamine infusion [21].
Histology
In one study the biopsy findings of myocardium consisted of mononuclear cell infiltrate and contraction band necrosis [19]. However, in another study histological analysis of myocardium of patients with TC demonstrated disorganization of contractile and cytoskeletal proteins, infiltration by mononuclear lymphocytes and macrophages in most cases, with increased extracellular matrix proteins, glycogen accumulation in the absence of apoptosis and autophagy. After functional recovery, most of these changes showed nearly complete reversibility [32]. These findings are not similar to the pathological changes observed in the stunned myocardium, which suggests that TC is a separate entity [33].

Clinical features and diagnosis
The presentation of TC is indistinguishable from ACS, most patients present with chest pain (68%) and breathlessness (17%), but approximately 4% of patients present with cardiogenic shock and 1.5% present with ventricular fibrillation. Physical examination may be normal or show signs of heart failure [1, 18]. The classic ECG appearance consists of ST-segment elevation mimicking acute anterior ST-segment elevation myocardial infarction in about 70–80% of cases. T-wave abnormalities are present in 64%, pathological Q-waves in about 32% of cases; however, loss of R-wave amplitude has also been reported [1, 18]. To date no specific ECG markers have been identified to differentiate between TC and ACS. A small rise in troponin is present in most patients [1, 18].

Coronary angiogram is the most discriminating test showing normal or near normal coronary arteries; however, left ventriculography shows the pathognomonic appearance of LV dysfunction, which should be considered in all patients who presents with troponin-positive chest pain and unobstructed coronary arteries [1]. Echocardiogram is helpful for the visualization of acute LV dysfunction and future recovery. Cardiac magnetic resonance imaging shows the typical LV dysfunction and excludes myocarditis [34].

Recent studies have also proposed investigations to exclude pheochromocytoma and paragangliomas.

Complications
The reported complication rate is about 19%. Cardiogenic shock is the most common severe complication, occurring in 6.5% of patients. Other complications include LV-thrombus formation (4%), cerebrovascular accident (1.6%), ventricular tachycardia (1.6%), atrial fibrillation (1%), ventricular fibrillation (0.5%) and ventricular septal defects (0.5%). Recurrence of the syndrome is infrequent, experienced only by 3.5–10% of patients [1, 18, 35].

Treatment
The treatment of TC is supportive. Initial treatment is based on an assumed clinical diagnosis of ACS. The combination of aspirin, cardioselective β-blockers and angiotensin-converting enzyme inhibitors is advocated during the period of LV dysfunction [36]. However, there are no randomized trials to guide the optimum treatment. Due to the possible abnormal response to excessive catecholamines the use of β-blockers is considered beneficial [34]. This is also supported by evidence from animal model studies of TC that have demonstrated resolution of ST-segment elevation by combined α and β-adrenoceptor blockade [37]. Furthermore, Uchida et al demonstrated that α and β-adrenoceptor blockers might play a role in the prevention of stress-induced cardiac dysfunction [38]. It has also been suggested that the use of β-blockers might reduce the LV outflow tract obstruction associated with hyperdynamic basal contraction [36].

Prognosis
Although in most cases TC has a benign natural history, with an overall inhospital mortality rate of 1.1–3.2%, individuals presenting with severe heart failure, pulmonary edema and cardiogenic shock are at high risk [35].

Conclusion
The incidence of TC is increasing most probably due to increasing awareness and increasing access to emergency coronary angiograms designed for primary percutaneous intervention. The exact pathophysiology is less well understood; however, the available evidence suggests a cardiotoxic effect of excess catecholamines. Physical and emotional stress has been widely blamed for the excessive catecholamine surge in many cases, even though a clearly recognized stressor is found in less than 30% of patients [18]. Treatment is supportive. Fortunately, in the majority of cases, the outlook is benign and the LV dysfunction is self-limiting.
REFERENCES

ATPase
An ATPase is a protein that utilizes the hydrolysis of ATP as an energy source to drive the process of primary active transport in which ions are transported against a concentration gradient, or electrical potential.

NT-proBNP
The N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) is an inactive, 76-amino acid peptide derived for the cleavage of the 108-amino acid prohormone, proBNP, to the active hormone BNP, a 32-amino acid peptide. NT-proBNP is a sensitive biomarker of cardiac dysfunction, and can serve as a prognostic indicator in patients with stable coronary artery disease.

Reverse transcriptase
A reverse transcriptase is a type of enzyme responsible for the synthesis of DNA that is complementary to a single-stranded RNA template. The process of reverse transcription is critical to the life-cycle of retroviruses.

Autoantibody
An autoantibody is an antigen-binding protein synthesized by the immune system (ie, B cells) that recognizes the body’s normal constituents as “non self”/foreign. Autoantibodies can attack these normal constituents leading to inflammation and tissue damage, and are central contributors to the pathophysiology of autoimmune diseases.

Autoantigen
An autoantigen is a substance that, despite being a normal tissue component, is recognized by the immune system (ie, B cells and T cells) as “non self”/foreign and is subjected to an inappropriate cell-mediated and/or humoral immune attack resulting in autoimmunity.
In the next issue:
Diet and the heart

EDITORIAL
Eat your heart out!
*M. Marber*

ORIGINAL ARTICLES
Nutrient signalling and cardiovascular aging
*M. Vinciguerra*

Does diet alter cardiovascular risk?
*R. Estruch*

Epicardial adipose tissue - a simple marker of obesity or a complex mediator of cardiovascular disease?
*R. Rajani*

Gut microbes and cardiometabolic risk
*M. Nieuwdorp*

Trimetazidine effects on diet and the heart
*R. Ferrari*

CASE REPORT
Resolution of metabolic syndrome after bariatric surgery
*R. Mukherjee*

REFRESHER CORNER
Basic food composition - is it just sugar and fat?
Add salt
*T. Sanders*

HOT TOPICS
Effects of bariatric surgery on the heart
*O. Rider*

GLOSSARY
*G. D. Lopaschuk*