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Giovanni A. Tavecchia
ASST Grande Ospedale Metropolitano Niguarda, Giovanni.Tavecchia@ospedaleniguarda.it

Iside Cartella
ASST Grande Ospedale Metropolitano Niguarda, Iside.Cartella@ospedaleniguarda.it

Enrico Ammirati
ASST Grande Ospedale Metropolitano Niguarda, enrico.ammirati@ospedaleniguarda.it

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Editorial

Future Perspectives in Acute Myocarditis Complicated by Cardiogenic Shock

Giovanni Amedeo Tavecchia, MD[1,2]; Iside Cartella, MD[1,2]; Enrico Ammirati, MD, PhD[1]
[1]De Gasperis Cardio Center, and Transplant Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[2]University of Milano Bicocca, Milan, Italy

Email: Enrico.ammirati@ospedaleniguarda.it

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Abstract

Acute myocarditis is an inflammatory disease of the myocardium with a highly variable clinical course. Fulminant myocarditis (FM) represents the most threatening scenario with hemodynamic compromise and cardiogenic shock at presentation. Despite medical advances and the availability of promising mechanical circulatory support (MCS), FM is burdened by a dismal prognosis. Early referral to tertiary hospitals with MCS facilities and prompt diagnosis with endomyocardial biopsy are critical steps toward optimal management. Moreover, beyond supportive care, the prevention of irreversible myocardial damage with immunomodulating therapies must be proven in clinical trials. In this editorial, we briefly describe current evidence and future perspectives regarding the management of myocarditis complicated by cardiogenic shock.

Keywords: cardiogenic shock, fulminant myocarditis, immunosuppression, endomyocardial biopsy

Background

Acute myocarditis (AM) is an inflammatory disease of the myocardium of recent onset, which could be triggered by infections, drugs, toxic substances, and abnormal immunoreactivity.[1-3] Its clinical presentation is highly variable, ranging from a mild self-limiting syndrome to a severe life-threatening condition.[4] Similarly, the course of patients with myocarditis is heterogeneous, varying from partial or full recovery to advanced heart failure (HF) requiring a durable left ventricular (LV) assist device (LVAD) or heart transplantation (HTx).[5] Clinically aggressive forms of myocarditis are labeled as fulminant myocarditis (FM) and are characterized by an acute-onset clinical presentation with hemodynamic compromise, cardiogenic shock, and/or fatal arrhythmia.[2,6]

Diagnosis

During the last decade, the measurement of high-sensitivity cardiac troponin and the use of cardiac magnetic resonance imaging (CMRI) has allowed the diagnosis of non-complicated forms of AM non-invasively with high accuracy.[7] However, endomyocardial biopsy (EMB) is the reference standard for diagnosing myocarditis and should be performed in selected clinical scenarios.[8,9] EMB is an invasive procedure and carries a considerable risk of cardiac complications if performed in low-volume centers (up to 9%), whereas the risk is relatively low (1-2%) if performed in experienced centers.[8,10] To date, EMB is essential in discriminating between specific histology, such as giant cell myocarditis (GCM), eosinophilic myocarditis, and lymphocytic myocarditis. The use of EMB is highly recommended in

patients with FM or AM with rapidly progressing HF, in whom information derived from histology is essential for optimal management (eg, immunosuppressive treatment in GCM or eosinophilic myocarditis).[1,9]

Cardiogenic Shock

Cardiogenic shock is a low-cardiac-output state resulting in life-threatening end-organ hypoperfusion and hypoxia.[11] According to the Lombardy registry, the incidence of cardiogenic shock in a cohort of 443 patients with definite AM demonstrated by CMRI or histology is 8-9%.[5] Meanwhile, cardiogenic shock can occur in 38.9% of COVID-19-associated AM cases.[12] Patients with FM have a high rate of events,[13] with a 60-day rate of death or HTx as high as 28% based on a large international cohort.[5] These data are consistent with the United States administrative data, which documented a significant increase in the incidence of cardiogenic shock over time (from 7% in 2005 to 12% in 2014) and a strong relationship between hemodynamic compromise at presentation and long-term prognosis.[14] In patients presenting with FM and cardiogenic shock, supportive measures play a key role in ensuring adequate tissue perfusion and oxygenation. Initial treatment often requires mechanical ventilation, inotropic agents, and vasopressors, as recommended by consensus documents on the management of cardiogenic shock.[11] Of note, it should be kept in mind that high doses of vasoactive agents could be detrimental by increasing myocardial oxygen consumption and reducing the probability of myocardial recovery.[4,15] Use of a pulmonary artery catheter can be useful to guide treatment escalation and/or wean patients with AM and cardiogenic shock.

Temporary Mechanical Circulatory Support

In patients unresponsive to maximal pharmacological therapy, temporary mechanical circulatory supports (t-MCS) should be considered. The United States administrative data has shown a growth in the use of t-MCS among AM patients between 2005 and 2014, from 4.5% to 8.6%.[14] This trend was significant for all devices except for the intra-aortic balloon pump (IABP), the most frequently used support. Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is still the most extensively used advanced t-MCS in patients with profound cardiogenic shock (SCAI class D-E) and guarantees full cardiorespiratory assistance with survival rates in FM ranging from 56% to 87%.[10,11] Nevertheless, it is well known that V-A ECMO increases LV afterload, and venting strategies, such as vasodilators and/or IABP implantation, may be required to prevent LV distension and pulmonary edema.

In this setting, the role of the Impella® system (Abiomed) has emerged over time. It has been postulated that the presence of LV overload could worsen myocardial inflammatory reaction and that the axial flow pump, by directly unloading the LV, could exert anti-inflammatory disease-modifying effects.[16,17] Before using the Impella® system, three conditions should be fulfilled: 1) right ventricular function should be preserved, 2) LV thrombosis should be excluded to avoid systemic embolism, and 3) the LV cavity should have adequate size to avoid the suction phenomenon. Nevertheless, the multicenter cVAD registry on microaxial flow catheter (Impella®) used for FM (34 patients from 2009 to 2016) showed an in-hospital survival of 62%, similar to other registries on t-MCS;[18,19] furthermore, 29% of patients required the transition to another MCS.[20]

Heart Transplantation and Left Ventricular Assist Devices

If a patient cannot be weaned from t-MCS after 2 or 3 weeks, HTx or a durable LVAD may be considered. HTx survival is similar to that of patients with other types of HF (5-year survival rate of 78% for patients with myocarditis versus 77% for those with nonischemic cardiomyopathy and 74% for those with ischemic cardiomyopathy). Nevertheless, higher rates of early cellular rejection (16% versus 5%) and relapses of GCM in transplanted hearts have been reported.[21]

Immunosuppressive Treatment

The role of immunosuppressive therapy is well-established for treating GCM, eosinophilic myocarditis, cardiac sarcoidosis, and FM associated with systemic autoimmune diseases.[2] Regarding lymphocytic post-viral FM, the role of immunosuppressive therapies remains controversial.[22] Current evidence, mainly derived from patients with chronic inflammatory cardiomyopathy, suggests that immunosuppressive treatment should be administered in patients with high inflammatory markers and without a viral genome on myocardial samples.[23] However, the role of the viral genome in guiding the treatment is not well-established, and the majority of evidence suggests that virus-triggered immune-mediated reactions are the principal cause of cardiomyocyte injury rather than direct virus-mediated cell injury.[3] Molecular mimicry between cardiac and viral antigens could be a possible mechanism of myocardial injury in virus-triggered AM. Moreover, a growing body of evidence indicates that viruses such as PVB-19 and HHV6 may be found in the EMB of patients without myocarditis.[24] These findings indicate that the presence of viruses in the setting of AM may not represent an absolute contraindication to immunosuppressive treatments. Though not supported by evidence from clinical trials, current recommendations in our center consider intravenous gamma globulin administration in pediatric patients (single-infusion regimen of 0.5–2 g/kg) and steroids in adults (eg, methylprednisolone 1 g daily for 3 days,

followed by oral prednisone 1 mg/kg daily with gradual tapering) if high suspicion of immune-mediated FM exists.[22] To elucidate the role of immunosuppression in FM and complicated AM, randomized controlled trials are needed. The MYocarditis THerapy With Steroids (MYTHS) trial (ClinicalTrials.gov identifier: NCT05150704), is an ongoing international randomized, single-blind pragmatic trial, that is randomizing 288 patients with FM or AM complicated by HF and impaired LV ejection fraction (< 41%) to pulse corticosteroid therapy (methylprednisolone 1g IV daily for 3 days) on top of standard therapy and maximal supportive care versus placebo. The trial will evaluate a combined primary endpoint defined as the time from randomization to the first event occurring within six months, including (1) all-cause death, (2) HTx, (3) LVAD implantation, or (4) the need for an upgrade of the t-MCS, or (5) a ventricular tachycardia/fibrillation treated with direct current shock, or (6) first rehospitalization due to HF or ventricular arrhythmias or advanced atrioventricular block. The trial started enrollment in October 2021 with an estimated duration of 3–4 years.[22]

Future Directions

A pivotal goal for the future is to reduce mortality rates of FM. In contrast with a previous report,[25] it is now well established that FM has poor in-hospital outcomes.[5,13] To reduce in-hospital mortality, prompt referral of patients with FM to hub centers and EMB performance is crucial. Histologic confirmation of specific FM etiologies (GCM and eosinophilic myocarditis) is of utmost importance for the timely start of immunosuppressive treatments and, thus, prevention of irreversible myocardial injury. The role of immunosuppressive treatment in lymphocytic FM needs to be clarified since there is a lack of standardized management. For this reason, we believe that the MYTHS trial could provide further insights regarding the potential beneficial effects of corticosteroids in lymphocytic FM. Eventually, regarding t-MCS, the role of axial flow pumps such as the Impella® system is growing, and the potential anti-inflammatory effects of direct LV unloading deserve consideration. An international network of tertiary centers experienced in cardiogenic shock and AM can help solve these unsolved questions.

Disclosures

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