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Fulminant giant-cell myocarditis on mechanical circulatory support: Management and outcomes of a French multicentre cohort

Santiago Montero [a,i], Nadia Aissaoui [b], Jean-Marc Tadié [c], Philippe Bizouarn [d], Vincent Scherrer [e], Romain Persichini [f], Clément Delmas [g], Florence Rolle [h], Emmanuel Besnier [e], Alexandre Le Guyader [h], Alain Combes [a], Matthieu Schmidt [a,*]

[a] Medical Intensive Care Unit, iCAN, Institute of Cardiometabolism and Nutrition, Hôpital de la Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France
[b] Intensive Care Unit, U970, European Georges-Pompidou Hospital, Paris Descartes University, Paris, France
[c] Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France
[d] Cardiac Intensive Care Department, CHU Nantes, Nantes, France
[e] Rouen University Hospital, Department of Anaesthesiology and Critical Care, Rouen, France
[f] Medical–Surgical Intensive Care Unit, CHU de La Réunion, Felix-Guyon Hospital, Saint Denis, La Réunion, France
[g] Medical Intensive Care Unit, Rangueil Hospital, Toulouse, France
[h] Thoracic and Cardiac Surgery Department, CHU Limoges, Limoges, France
[i] Acute and Intensive Cardiovascular Care Unit, Department of Cardiology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute IIB-Sant Pau, Barcelona, Spain

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ABSTRACT

Aims: Giant-cell myocarditis (GCM) is a rare and often fatal form of myocarditis. Only a few reports have focused on fulminant forms. We describe the clinical characteristics, management and outcomes of GCM patients rescued by mechanical circulatory support (MCS).

Methods and results: The clinical features, diagnoses, treatments and outcomes of MCS-treated patients in refractory cardiogenic shock secondary to fulminant GCM admitted to eight French intensive care units (2002–2016) were analysed. We also conducted a systematic review of this topic. Thirteen patients (median age 44 [range 21–76] years, Simplified Acute Physiology Score II 55 [40–79]) in severe cardiogenic shock (median [range] left ventricular ejection fraction 15% [15–35%] and blood lactate 4 mmol/L) were placed on MCS 4 [0–28] days after hospital admission. Severe arrhythmic disturbances were frequent (77%), with six (46%) patients experiencing an electrical storm prior to MCS. Venoarterial extracorporeal membrane oxygenation was the first MCS option for 11 (85%) patients. GCM was diagnosed in five (38%) patients before transplant or death and treated with immunosuppressants; infections were the main complication (80%). Four patients died on MCS and no patient presented long-term survival free from heart transplant (nine patients, 69%). All transplanted patients were alive 1 year later and no GCM recurrence was reported after median follow-up of 42 [12–145] months.

Conclusion: Outcomes of fulminant GCMs may differ from those of milder forms. In this context, heart transplant might likely be the only long-term survival option.

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1. Introduction

Giant-cell myocarditis (GCM) is a rare and often fatal form of myocarditis that mainly affects young healthy subjects with no prior co-morbidities [1]. The latest cardiac imaging techniques and proactive search with repeated biopsies recently highlighted this rare aetiology [2] that may have various clinical onset characteristics. Indeed, congestive heart failure, atrioventricular block, ventricular tachycardia (VT) or even acute myocardial infarction-mimicking syndromes have been described so far, with variable symptom-onset-to-diagnosis intervals reported [1,3]. In the 1990s, landmark studies aiming to report incidence, clinical presentations and outcomes of this rare disease were mostly conducted by the International Multicentre GCM Registry group [1,4–7]. In their first report, nearly 90% of their patients were dead or transplanted 1 year after symptom onset [1]. More recent studies stressed the better outcomes obtained with combined immunosuppressants [2,3]. However, the aforementioned cohorts did not specifically report the clinical course, management and outcomes of the most severe forms, namely fulminant myocarditis that rapidly required mechanical

* Corresponding author at: Service de Réanimation Médicale, iCAN, Institute of Cardiometabolism and Nutrition, Hôpital de la Pitié–Salpêtrière, 47, bd de l'Hôpital, 75651 Paris Cedex 13, France.
E-mail address: matthieu.schmidt@aphp.fr (M. Schmidt).

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circulatory support (MCS). We describe, herein, a multicentre national experience with MCS-assisted fulminant GCM patients, and report their short- and long-term outcomes.

2. Patients and methods

2.1. Study population

Eighteen French cardiac, surgical or medical intensive care units (ICUs) with a MCS program were contacted to participate in the study. Each ICU retrospectively analysed its database and that of their Pathology Laboratory to identify all patients with 1) confirmed GCM diagnosis and 2) MCS support (i.e., venoarterial extracorporeal membrane oxygenation [VA-ECMO] or another ventricular assist device [VAD]). Histology samples were obtained by endomyocardial biopsy (EMB), apical sample at LVAD implantation, explanted heart histology or autopsy. GCM diagnosis required myocardial histology confirmation showing multinucleated giant cells with or without myocyte necrosis, associated with an inflammatory infiltrate comprised of lymphocytes, histiocytes and eosinophils (*Figure electronic supplemental material 1*). The time of diagnosis was defined as the day the pathologist confirmed GCM in a myocardial sample. MCS indications were defined as acute-refractory cardiovascular failure, with evidence of tissue hypoxia (e.g., extensive skin mottling or elevated blood lactate) concomitant with adequate intravascular volume status; severely diminished right ventricular or left ventricular ejection fraction (LVEF); low cardiac index (≤2.1 L/min/m^2); sustained hypotension despite high-dose catecholamine infusion (epinephrine ≥1 γ/kg/min or dobutamine ≥10 γ/kg/min + norepinephrine ≥1 γ/kg/min); or refractory electrical storm [8]. MCS-exclusion criteria were malignancies with fatal prognosis within 5 years or irreversible neurological pathologies and decisions to limit therapeutic interventions. Trained cardiovascular surgeons surgically inserted VA-ECMO cannulas with femoral–femoral cannulation as previously described [9,10]. An additional 7F catheter was systematically inserted into the femoral artery to prevent leg ischemia. Other MCSs used in our population were left ventricular assist device (LVAD), total artificial heart and biventricular MEDOS Assist System.

2.2. Pre-MCS data collection

At ICU admission, the following informations were collected for each patient: demographics (age, sex, body mass index), initial clinical characteristics and date of symptom onset. Admission disease-severity scores [Acute Physiology And Chronic Health Evaluation II (APACHE) [11], Simplified Acute Physiology Score (SAPS)II [12] and Sequential Organ Failure Assessment (SOFA) score [13]] were assessed during the first 24 h of admission, trying to obtain the predicted mortality according to severity at ICU admission (see table ESM-1 in the supplemental material for further details on severity scores). During the pre-MCS period, the inotrope score was defined as dobutamine dose (γ/kg/min) + [norepinephrine dose (γ/kg/min) + epinephrine dose (γ/kg/min)] × 100 [14]. Severity of illness was assessed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale [15]. Thus, the occurrence of cardiac arrest, laboratory tests, blood-gas analyses, electrocardiogram and echocardiographic parameters (LVEF and left ventricular dilation) were collected.

2.3. Outcome data

The main prognostic variables included ECMO-weaning or heart transplant, immunosuppressant use and related infections, survival to hospital discharge, 90-day survival, 1-year survival post-transplant and long-term survival (evaluated in July 2017). We also recorded: the total number mechanical ventilation (MV) days; ventilator-associated pneumonia (VAP); ICU and hospital lengths of stay; and in-ICU complications, e.g., severe haemorrhage, surgical wound or cannula infection, and requiring renal replacement therapy. Severe haemorrhage was considered life-threatening when intracerebral bleeding or haemorrhage resulting in substantial hemodynamic compromise required transfusion or increased vasopressor doses. In July 2017, survival and GCM-recurrence status were obtained for all survivors.

This investigation conforms with the principles outlined in the Declaration of Helsinki. In accordance with the ethical standards of our hospital's Institutional Review Board and French law, informed consent was not necessary for analyses of demographic, physiological and hospital-outcome data, because this retrospective observational study did not modify existing diagnostic or therapeutic strategies. The National Commission for Informatics and Liberties approved this study (no.1950673).

2.4. Literature review

We conducted a systematic MEDLINE-database literature review through the PubMed search engine with a global search strategy applying pre-specified selection with the terms "giant-cell myocarditis" or "giant-cell myocarditis" and "outcome". Our query was restricted to controlled or observational studies (retrospective and prospective) and case series focused, exclusively, on prognosis of GCM with more than five patients published before August 2017.

2.5. Statistical analyses

Results were expressed as numbers (%) or median [range]. Continuous variables were compared with Student's *t*-test or the Mann–Whitney *U* test, as appropriate, whereas categorical variables were compared with χ^2 tests. Analyses were computed using StatView v5.0 software (SAS Institute Inc., Cary, NC, USA) and a two-sided $P < 0.05$ defined significance.

3. Results

3.1. Study population

During the 15-year study period (2002–2016), 13 patients (7 males; median age 44 [21–76] years) from eight centres received MCS for fulminant GCM (Fig. 1). Two patients were retrieved to the referral ECMO centre on VA-ECMO. ICU admission, median SAPS II and SOFA scores were high, respectively, 55 [40–79] and 10 [4–19]. Two (15%) patients had pre-existing autoimmune disorders, i.e. hypothyroidism and vitiligo (Table 1). Seven (54%) patients were initially hospitalised for heart failure, while four (31%) had arrhythmic disorders. Throughout the GCM course, arrhythmic disturbances were frequent, with 10 (77%) patients having VT, ventricular fibrillation (VF), supraventricular arrhythmias or complete heart block. Six (46%) patients experienced an electrical storm. The coronary angiograms available for 11 (85%) patients were unremarkable.

VA-ECMO was the first MCS option for 11 (85%) patients, one patient received a biventricular MEDOS Assist system in 2002 and another a HeartMate II LVAD for inotrope-dependent dilated cardiomyopathy. One patient was bridged from VA-ECMO to a total artificial heart. Five (38%) patients suffered pre-ECMO cardiac arrest, with two (15%) of them cannulated during cardiopulmonary resuscitation (CPR). INTERMACS status for 11 (85%) patients was ≤2 (Table 2). All patients required hemodynamic support with vasoactive drugs, resulting in a median inotrope score of 10 [3–523] γ/kg/min at MCS cannulation. Pre-MCS median pH, blood lactate and LVEF were, respectively: 7.4 [7.0–7.6], 4 [1–11] and 15% [10–35%].

3.2. GCM diagnosis and treatment

Six (46%) patients underwent pre-MCS magnetic resonance imaging that confirmed the myocarditis diagnosis. EMBs were obtained from five (38%) patients: two of which were false-negatives. In addition, two other patients were diagnosed based on myocardial samples obtained during VAD implantation (i.e. total artificial heart and biventricular MEDOS Assist System). GCM-diagnosis confirmation was most frequently obtained by histological analysis of the explanted heart (*Figure electronic supplemental material 2*). Thus, only five (38%) patients were diagnosed prior to death or transplant, with three of them receiving at least one immunosuppressant. In addition, two more patients, whose disease was highly suspected clinically, were also treated with immunosuppressant drugs. Various combinations of ≥2 drugs were used, combining corticosteroids ($n = 3$), cyclosporine ($n = 2$), thymoglobulin ($n = 2$) or mycophenolate mofetil ($n = 1$) (more details about clinical characteristics, diagnostic approach and management of each patient can be found in Table 3). Among the five immunosuppressant-treated patients, four (80%) developed nosocomial infections (i.e., VAP and/or cannula infection); one of them died of septic shock secondary to *Clostridium difficile* colitis and multiresistant *Acinetobacter baumannii* cannula infection. Notably, none of them achieved sufficient LVEF recovery to be weaned-off MCS. Moreover, it is worth noting that two patients received levosimendan, and three underwent VT-substrate ablation after an electrical storm, with no LVEF recovery, and VT subsequently recurred in all of them.

3.3. Outcomes

ECMO-related complications and outcomes according to 90-day status are reported in Table 2. As expected, 90-day survivors had significant lower disease-severity scores at ICU admission, without any significant

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