

Rapid onset of fulminant myocarditis portends a favourable prognosis and the ability to bridge mechanical circulatory support to recovery

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Abstract

OBJECTIVES: Fulminant myocarditis with cardiogenic shock is fatal without mechanical circulatory support. Once haemodynamic stability has been established with a ventricular assist device (VAD), the decision to wait for myocardial recovery as opposed to listing for an orthotopic heart transplant (OHT) can be difficult. We have undertaken this study to establish the criteria for determining the need for heart transplantation following VAD implant for fulminant myocarditis.

METHODS: A total of 442 VADs were implanted between 1993 and 2011. Twenty-four VADs were implanted for fulminant myocarditis with refractory cardiogenic shock. We retrospectively analysed the variables and the pathology for this cohort. Patients who had a full recovery of myocardial function and subsequent VAD explant (Explant) were compared with those bridged to OHT. There was one acute death.

RESULTS: There was no difference in the past medical history between the groups. Explant patients had a more acute onset of heart failure with a median of 7 days between the onset of symptoms and VAD implant, when compared with 22 days for OHT ($P = 0.01$). A rapid recovery in myocardial function was seen in the Explant group, with recovery of myocardial function (ejection fraction = $53 \pm 24\%$) in 14 ± 7 days. Myocardial function was sustained for 5 years following the VAD explant. The female gender favoured myocardial recovery and VAD explantability. Two patients had giant cell myocarditis, neither of whom had a recovery of function, and they were bridged to heart transplant with a VAD.

CONCLUSIONS: Fulminant myocarditis is a fatal condition without mechanical support. The rapid onset of symptoms is associated with a complete recovery of myocardial function and VAD explant. The absence of rapid recovery of myocardial function should prompt listing for a heart transplant.

Keywords: Myocarditis • Ventricular assist device • Heart failure • Myocardial recovery

INTRODUCTION

Acute myocarditis is a rare, yet potentially fatal disease process. The vast majority of patients present with subclinical, non-specific symptoms and can often be managed medically [1, 2]. The presentation with haemodynamic instability and cardiogenic shock, clinically classified as fulminant myocarditis, is a rare condition associated with a high mortality without aggressive intervention [3]. In the modern era of mechanical circulatory support, the survival of this patient population is excellent, with early support in the form of either ventricular assist devices (VADs) or extracorporeal membrane oxygenation (ECMO). While some patients may recover myocardial function and be successfully weaned from mechanical support with excellent long-term myocardial function [4], a significant proportion of patients with fulminant myocarditis will require either destination VAD support or, more commonly,

orthotopic heart transplantation (OHT) as a result of biventricular failure. The decision between waiting for myocardial recovery or listing a patient for heart transplant can be both unclear and challenging and remains poorly studied.

Though a diagnosis of giant cell myocarditis has been clearly demonstrated to correlate with a lack of recovery of myocardial function [5, 6], biopsy samples are often non-diagnostic for myocarditis. The incidence of a positive biopsy in clinically diagnosed myocarditis is as low as 10% [7]. Moreover, the majority of patients do not present with giant cell myocarditis, but rather with a less aggressive process. We undertook this study to elucidate the decision tree associated with managing patients with fulminant myocarditis. We hypothesized that patients with more aggressive and acute presentations of the disease were more likely to recover myocardial function, obviating the need for subsequent OHT.

METHODS

Study design

A retrospective review of a prospectively collected database was performed for all patients undergoing implantation of a VAD at a single institution between 1993 and 2011 (total patients = 442). The patients with refractory fulminant myocarditis with subsequent cardiogenic shock, defined as those patients with myocardial dysfunction refractory to high-dose vasopressors and requiring mechanical circulatory support, were identified ($n = 24$). The cohort of patients requiring VADs for refractory fulminant myocarditis was stratified into two groups: those with sufficient myocardial recovery to warrant VAD explantation (Explant group, $n = 11$) and those with persistent myocardial dysfunction who were successfully bridged to the OHT ($n = 12$). There was one acute death secondary to multisystem organ failure. The preoperative patient demographics, comorbidities, duration and type of symptomatology, pathology, laboratory values of hepatic and renal function, intraoperative variables and postoperative outcomes were retrospectively compared between the two groups. In addition, myocardial function using the echocardiographic data was also compared between the groups at three time intervals: initial presentation, immediately prior to the VAD explant and long-term follow-up.

Implantation of ventricular assist device

All patients were placed on cardiopulmonary bypass for implantation of the VAD. Median cardiopulmonary bypass times were 120 min for the Explant group and 122 min for the OHT group ($P = NS$). Patients either underwent implantation of an isolated left ventricular assist device (LVAD) or biventricular assist device (BIVAD) based on the patients' right ventricular function as assessed by pulmonary artery pressure, right atrial pressure and intraoperative transesophageal echocardiography. VADs implanted in the Explant cohort included: Thoratec (Pleasanton, CA, USA) paracorporeal ventricular assist device (PVAD)

biventricular VAD ($n = 7$), TCI (Thermo Cardiosystems, Woburn, MA, USA) IP pneumatic LVAD/Abiomed (Danvers, MA, USA) BVS 5000 right ventricular assist device (RVAD) ($n = 2$), Thoratec PVAD LVAD ($n = 1$) and Thoratec HeartMate II LVAD ($n = 1$). VADs implanted in the OHT cohort included: Thoratec PVAD BIVAD ($n = 6$), Thoratec HeartMate XVE LVAD ($n = 1$), TCI IP LVAD ($n = 1$), TCI VE electric LVAD ($n = 3$) and TCI IP LVAD/Abiomed RVAD ($n = 1$). One patient underwent the biventricular implant of Abiomed BVS 5000 VADs and subsequently expired secondary to a presumed embolic major brainstem cerebrovascular infarct. The decision between isolated single ventricle or biventricular support was based on an echocardiographic assessment of right and left ventricular functions as well as invasive haemodynamics. Severe right ventricular (RV) dysfunction, elevated central venous pressure (CVP), minimal difference between CVP and diastolic pulmonary artery pressure (< 5 mmHg) and low right ventricular stroke work index supported the need for an concomitant right ventricular support. Additionally, in the later subset of patients, a scoring system that we devised to evaluate the need for right ventricular support was also incorporated into our decision-making [8]. Many of these patients were in incessant ventricular tachycardia, mandating the need for biventricular support.

Ventricular assist device weaning protocol

When patients were believed to be candidates for VAD explant, a weaning protocol was initiated. All patients underwent a serial echocardiographic analysis of biventricular function, mitral regurgitation and aortic valve opening at regular intervals in the intensive care unit. A combination of normal biventricular function and continuous aortic valve opening provided evidence of myocardial recovery and the potential for VAD explants. According to our protocol, all patients who are possible candidates for recovery are given an additional bolus of systemic heparinization. At this stage, the VAD flows are slowly reduced to minimal levels. A transoesophageal echocardiogram of the biventricular function is performed while reducing the VAD flow. Patients are placed on low-dose inotropes (epinephrine and/or milrinone), as needed. If a patient is believed to be a candidate for VAD explant, they are transported to the operating room (OR). In the OR, they are heparinized to an activated clotting time of 400 s and the VAD flows are weaned to the minimal levels again. If the patient tolerates this withdrawal of support, they are placed on cardiopulmonary bypass for the removal of the VAD. Closure of the ventricular apical cannulation sites was performed with interrupted pledgeted horizontal mattress sutures reinforced with a second running haemostatic suture line. Aortic and/or pulmonary artery grafts are cut short and oversewn with a 4-0 Prolene suture.

Statistical analysis

Statistical analysis was performed using SPSS, version 18.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was utilized for the comparison of the continuous data and the Fisher's exact test was utilized for the comparison of the categorical data. The comparative measurements for quantitative variables are expressed as medians with interquartile ranges. The data within a single group are presented as mean \pm standard deviation. A P -value of < 0.05 was considered statistically significant for all analyses.

Table 1: Patient demographics

	Explant ($n = 11$)	OHT ($n = 12$)	P
Male (%)	18.2	75.0	0.01
Duration of symptoms (days)	7.0 (4.3–15.8)	22.0 (12.5–30.0)	0.01
Hospital length of stay (days)	31.0 (28.5–37.0)	57.0 (42.5–108.3)	0.02
Age (years)	37.0 (25.0–48.0)	40.5 (21.0–54.8)	0.64
Ejection fraction on presentation (%)	5.0 (5.0–10.0)	7.5 (5.0–10.0)	0.57
Preoperative bilirubin (mg/dl)	1.0 (0.3–1.9)	0.7 (0.6–1.1)	0.80
Preoperative creatinine (mg/dl)	0.9 (0.6–1.3)	1.4 (1.0–1.9)	0.07
Cardiopulmonary bypass time (min)	120.0 (94.0–168.0)	122.0 (107.0–145.8)	0.81

Continuous data expressed as medians with interquartile ranges.

RESULTS

Preoperative variables

There was no difference in preoperative variables between the 'Explant' and 'OHT' groups, with the exception of gender and duration of symptoms (Table 1). No significant differences in the preoperative past medical history were elucidated. All patients demonstrated a marked myocardial dysfunction as noted by a severely diminished ejection fraction on presentation (median = 5 and 7.5% for the Explant and OHT groups, respectively, $P = \text{NS}$). Patients in the Explant group demonstrated a more rapid progression of cardiovascular collapse from the onset of symptoms (median values: Explants = 7 days vs OHT = 22 days; $P = 0.01$). Infectious symptoms included fevers, malaise and productive cough. As demonstrated in Table 1, a significantly lower percentage of patients in the Explant cohort were male (18.2 vs 75.0%, $P = 0.01$). Both of the patients with a pathological demonstration of giant cell myocarditis failed to recover myocardial function, and required a subsequent transplant.

Myocardial recovery

A rapid recovery of myocardial function was demonstrated in patients who underwent successful VAD explants (14 ± 7 days). It was remarkable to note that even patients with incessant ventricular tachycardia regained a normal sinus rhythm. A lack of rapid myocardial recovery was associated with unsuccessful myocardial recovery and the need for a subsequent heart transplant. Myocardial function in the Explant cohort increased from $9 \pm 4\%$ on presentation to $53 \pm 24\%$ immediately following explants. Myocardial function appeared preserved in the patients followed for 5 years or longer. It appears that the rapid onset of symptoms, rapid recovery of myocardial function and female gender all favour myocardial recovery.

DISCUSSION

The majority of patients who present with myocarditis can be successfully managed medically and do not present with cardiovascular shock [2]. A small subset of patients with myocarditis will go on to develop haemodynamic instability and cardiogenic shock. Numerous reports in the past have demonstrated successful haemodynamic support of patients with cardiovascular collapse from myocarditis with either isolated LVAD or BIVAD support [4, 9, 10]. Similar to our study, excellent survival has been uniformly demonstrated if a VAD is inserted prior to end-organ damage [11]. In the present era, with the availability of highly durable and safe pulsatile and continuous flow VADs, we advocate the early implant of a VAD with early evidence of rapid deterioration of myocardial function in order to avoid end-organ damage, namely hepatic and renal failures. VAD implant can both allow unloading of the heart while awaiting potential myocardial recovery as well as preserving end-organ function.

Numerous reports from our centre as well as others have demonstrated increased mortality with subsequent conversion of an LVAD to biventricular support when compared with simultaneous RVAD implant; therefore, we have chosen an aggressive

approach to RVAD implantation [12–14]. If there is any question of the need for long-term right ventricular support, in the acute setting, we advocate utilizing a pulsatile device, so that a right ventricular device can be added to the same platform. Particularly in the acute setting, optimal right ventricular function is critical to minimize CVP and eliminate end-organ venous congestion. Several metrics have been proposed to assess right ventricular function and predict the need for biventricular support as opposed to isolated left ventricular support [8, 15, 16]. In our experience, we have found cardiac index, right ventricular stroke work index, preoperative RV dysfunction, creatinine, systemic blood pressure and prior cardiac surgery to be predictors for the need for RVAD [8]. Elevated CVP with low pulmonary artery and systemic blood pressures has also been a fairly reliable predictor of severe RV dysfunction and the need for RVAD. If RVAD support is unexpectedly required following continuous flow LVAD implant, a temporary RVAD may be utilized to try and recover enough right ventricular function to support the long-term continuous flow LVAD function while awaiting heart transplant [17, 18]. Any patient who receives a VAD for myocarditis should be thought of as a potential transplant candidate, as such, haemostasis is paramount, and blood transfusions should be limited in order to avoid the sensitization of antibodies and potential organ rejection or a positive antibody crossmatch.

Many centres are utilizing ECMO to haemodynamically support a patient with cardiogenic shock with end-organ damage and concerns about hepatic recovery [19, 20]. Additionally, in the patient population that is in extremis and cannot tolerate transport to the OR for VAD implant, ECMO can be rapidly instituted at the bedside. Haemodynamic stability can be rapidly established and myocardial recovery can be successfully achieved with an ECMO circuit. Once reversibility of end-organ damage has been demonstrated, ECMO can subsequently be converted to VAD support. If myocardial recovery is not established within 5 days of the institution of an ECMO, consideration should be given to conversion to VAD support in order to allow physical rehabilitation of the patient [21]. Alternative temporary mechanical support strategies could include utilizing the Centrimag, Tandem Heart or similar short-term continuous flow devices to support a patient who may rapidly recover myocardial function. Based upon our data, patients who present with a rapid progression of heart failure following the onset of symptoms, may be candidates for temporary short-term support. Given the lack of understanding of the patient cohorts presenting with myocarditis who could potentially recover function, we chose to implant the long-term devices in these patients. But, in the future, we will give strong consideration to utilizing temporary devices in the patients who present with a rapid onset of symptoms and cardiogenic shock. These devices are less invasive and hence impose less stress on the patient.

As demonstrated in this study, the rapid progression to fulminant myocarditis necessitating mechanical circulatory support favours the subsequent rapid recovery of myocardial function. We were surprised to find an increased rate of myocardial recovery in our female patients who presented with non-giant cell myocarditis. This gender difference is very interesting and may potentially imply a genetic predisposition to recover the myocardial function. Serious consideration should be given to the potential for myocardial recovery for females who present with cardiogenic shock secondary to myocarditis. But, given the limited sample size, this finding should be further investigated.

Additionally, even with the presentation of myocarditis with incessant ventricular tachycardia, patients can recover myocardial function and a normal sinus rhythm following a short period of haemodynamic support [22]. As we have confirmed, patients who manifest successful recovery of myocardial function following myocarditis demonstrate the long-term maintenance of ventricular systolic function [4]. This further supports the need for aggressive early mechanical support of the haemodynamic function, as this patient population often regains excellent long-term cardiovascular function [3]. All patients should be given a trial of weaning from mechanical support, though it appears that patients who do not have a rapid onset of symptoms will have a lower likelihood of myocardial recovery.

Patients who present with giant cell myocarditis are known to have an exceedingly low rate of myocardial recovery, as such, this patient population should be listed for heart transplantation as soon as a pathological diagnosis is available [23]. Moreover, as we have demonstrated, patients with a rapid progression from the onset of symptoms to acute fulminant myocarditis should be given the opportunity to recover myocardial function. Given the long-term sustainability of this function, recovery of the myocardial function and subsequent VAD explant are far superior to heart transplant. The complications associated with immunosuppression, the limited availability of organs and the limited long-term survival of patients following OHT should not be taken lightly. But, the subset of patients who present with a slowly progressive indolent course with subsequent myocardial deterioration should be considered for early listing for heart transplant as the chance for myocardial recovery is much lower. Moreover, based upon this study, it appears that female gender may favour myocardial recovery. Despite this, we recognize that, given the limited size of the study, it is difficult to make gender conclusions regarding myocardial recovery.

In conclusion, acute rapid progression of myocarditis is associated with rapid recovery of myocardial function and successful VAD explants. Patients with a recovery of myocardial function demonstrate a near-normal ventricular function that is sustained in the long-term. The absence of a rapid recovery of ventricular haemodynamics should prompt the heart failure team to list the patient for subsequent OHT.

Conflict of interest: none declared.

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