Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: A 5-year multi-institutional experience

Veno-Arterial Extracorporeal Membrane Oxygenation for Acute Fulminant Myocarditis in Adult Patients: a 5-Year Multi-Institutional Experience

Running title: VA-ECMO in Adult Fulminant Myocarditis

Lorusso Roberto, Centofanti Paolo^, Gelsomino Sandro*, Barili Fabio###, Di Mauro Michele°°°, Botta Luca§, Actis Dato Guglielmo^^, Casabona Riccardo^^, Casali Giuseppe^, Musumeci Francesco^, De Bonis Michele**, Zangrillo Alberto**, Alfieri Ottavio**, Pellegrini Carlo***, Mazzola Sandro***, Coletti Giuseppe, Vizzardi Enrico°, Bianco Roberto§§, Gerosa Gino§§, Massetti Massimo°°, Caldaroni Federica°°, Pilato Emanuele^^^, Pacini Davide^^^, Di Bartolomeo Roberto^^^, Marinelli Giuseppe^^^, Sponga Sandro§§§, Livi Ugolino§§§, Rinaldi Mauro^, Mariscalco Giovanni#, Beghi Cesare#, Miceli Antonio##, Glauber Mattia##, Pappalardo Federico**, and Russo Claudio Francesco§, on behalf of the GIROC Investigators.

*Cardiac Surgery Units, Spedali Civili Hospital, Brescia, ^^Mauriziano Hospital, Turin, §Niguarda Hospital, Milan, **S. Raffaele Hospital, Milan, §§University Hospital, Padua, ^^^S.Orsola Hospital, Bologna, ***S.Matteo Hospital, Pavia, §§§S.Maria Misericordia Hospital, Udine, °°Gemelli Hospital, Rome, ^Molinette Hospital, Turin, ###S.Anna Hospital, Cuneo, and Cardiology Units, °Spedali Civili Hospital, Brescia, and °°°Cardiology Institute, University of L'Aquila, *Cardiovascular Research Centre, Careggi Hospital, Florence, Italy*

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Address correspondence to:

Roberto Lorusso, MD, PhD

Cardiac Surgery Unit – Spedali Civili Hospital

Piazzale Spedali Civili, 1- 25128 Brescia – Italy

Tel. : +39 030 3995636 - Fax : +39 030 3995004 E-mail : roberto.lorussobs@gmail.com

Background. Acute fulminant myocarditis (AFM) may represent a life-threatening event characterized by rapidly progressive cardiac compromise ultimately leading to refractory cardiogenic shock or cardiac arrest. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides effective cardiocirculatory support in this circumstance, but a few clinical series are available about early and long-term results. This study reports data from a multicentre study group which analysed subjects affected by AFM and treated with VA-ECMO during a 5-year period.

Methods : From hospital databases, 57 patients with diagnosis of AFM submitted to VA-ECMO in the last 5 years were found and analysed. Mean age was 37.6±11.8 years, and 37 patients were female. At VA-ECMO implant, cardiogenic shock was present in 38 patients, cardiac arrest in 12, and severe hemodynamic instability in 7, respectively. Forty-seven patients received peripheral approach, while 10 patients had a central implantation or other access, respectively.

Results. Mean VA-ECMO support was 9.9±19 days (range 2-24 days). Major complications were recorded in 40 patients (70.1%). Cardiac recovery with ECMO weaning was achieved in 43 patients (75.5%), major complications occurred in 40 cases (70.1%), and survival to hospital discharge in 41 (71.9%), respectively. Two patients received another type of ventricular assist device during hospitalization, and 3 were transplanted. After hospital discharge (median follow-up 15 months) there were late 2 deaths. The 5-year actuarial survival was 65.2%±7.9%, with recurrent self-recovering myocarditis observed in 2 cases (at 6 and 12 months from the first AFM event, respectively), and 1 heart transplant.

Conclusions. Cardio-pulmonary support with VA-ECMO provides an invaluable tool in AFM although major complications may characterize the hospital course. Long-term outcome appears favourable with rare episodes of recurrent myocarditis or cardiac-related events.

Key words : acute myocarditis – extracorporeal membrane oxygenation – cardiac arrest – cardiogenic shock – mechanical circulatory support

Recently, the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases has defined acute fulminant myocarditis (AFM) as a clinical manifestation of cardiac inflammation with rapid onset and severe hemodynamic compromise (1). No specific histological or immunohistological diagnosis and related functional myocardial compromise have been, however, established, thereby making AFM, as mentioned, a clinical syndrome rather than an etiological disease. Infective etiology is usually the most frequent finding, followed by drug-induced myocyte compromise, or by autoimmune disease (1,2). Profound contractile dysfunction leading to quick onset of refractory cardiogenic shock or cardiac arrest may characterize the clinical scenario of AFM (1,2). Aggressive pharmacological therapy and intra-aortic balloon pump (IABP) are often insufficient, and mechanical circulatory support may therefore account for the unique mean capable to sustain the failing heart and provide time to enhance heart recovery or to more advanced therapies if adequate native cardiac function is not eventually restored (1-4). Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been shown to provide prompt and effective support in these circumstances (4-12). Published series of VA-ECMO in AFM are, however, limited in terms of patient number and late outcome (4-12). The aim of this study was, therefore, to analyse through a multicentre investigation the in-hospital and post-discharge results in patients affected by AFM requiring VA-ECMO due to severe cardio-circulatory impairment.

Material and Methods

The study was approved by the Ethical Committee (study code nr.1438, approved on date 26/06/2014) of the principal investigator (R.L.) and provided to all Ethical Committees of study centres.

All data related to AFM in adult patients submitted to VA-ECMO from January 2008 till December 2013 were obtained from institutional databases of 13 different centres. Such a time frame was purposely chosen in order to assess “modern ECMO system and management” which included advanced VA-ECMO technology and components, like polymethylpenthene membrane

oxygenation, heparin-coated tip-to-tip circuitry and cannulae, last generation of centrifugal pumps, as well as more advanced expertise achieved in adult VA-ECMO for emergent cardiovascular diseases.

AFM was clinically defined by three primary criteria: a) Sudden and refractory cardiogenic shock, cardiac arrest, or severe hemodynamic instability despite aggressive inotropic drugs with or without IABP, b) Demonstration of diffuse and severe myocardial hypokinesia with normal coronary artery anatomy at angiogram, c) Echocardiographic signs of myocardial tissue swelling and biventricular involvement. Secondary criteria were: 1) Positive blood colture tests, 2) Confirmation of ongoing autoimmune cardiac involvement at blood tests, 3) Prodromal clinical signs and symptoms of inflammatory state with fever and malaise (1,2,13).

Exclusion criteria were: a) Concomitant organic valvular or coronary artery disease, b) Any chronic form of dilated cardiomyopathy, c) Previous pharmacological therapies potentially harmful to the heart, d) mediastinal radiation, e) Treatment with other mechanical circulatory support (excluding IABP).

Fifty-seven patients fulfilled study entry criteria. Patient pre-ECMO characteristics are shown in Table 1. Cardiocirculatory support with VA-ECMO was instituted mainly during cardiogenic shock (figure 1) and the majority of patients had a peripheral approach. Endomyocardial biopsy was performed in one forth of the patients, with AFM confirmed in all cases. Viral etiology was predominant in case of pathogen-based AFM. Left ventricular venting was applied in 14 patients, and included catheter positioned in the pulmonary artery in 2 patients, in the right pulmonary vein in 4 cases, in the left ventricular apex in 4 cases, and in unreported site in 4 cases, respectively. Marked myocardial damage was detected in all patients associated to hypoxia and metabolic acidosis present despite aggressive inotropic therapy and/or partial mechanical circulatory assistance with IABP.

Statistical analysis

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data were expressed as mean ± standard deviation whereas non-normally-distributed data were presented as median and interquartile range and frequencies as proportions. Between-group differences were assessed by the unpaired t test, Mann-Whitney test, or Pearson χ^2 test. Actual survival was determined by means of Kaplan-Meier analysis.

Multivariable logistic regression analysis was performed to identify preoperative predictors of early death. Forty-nine parameters were investigated for their predictive value. To enhance the accuracy of the model, the number of variables was reduced using variable clustering. Model fit for logistic regression was assessed with the Hosmer-Lemeshow (HL) statistic and predictive accuracy was assessed by the concordance index c. Models proved to be reliable and accurate (HL, p=0.123; c=0.758). Internal validation of predictors generated by multivariable logistic regression was performed by means of bootstrapping techniques, with 1000 cycles and generation of OR and bias corrected 95% CI.

IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) and R version 3 (R Foundation for Statistical Computing, Wien, Austria) software packages were used for calculations. Significance for hypothesis testing was set at the 0.05 two-tailed level.

Results

Mean VA-ECMO support ranged from 2 to 24 days. Extubation during cardiocirculatory assistance was achieved in 22 patients (38.6%). Following quick stabilization of the hemodynamic conditions, mean time of recovery from acidotic state was achieved in slightly more than 2 days, with normalization of cardiac injury-related biomarkers from 5 to 6 days post-implant. Major complications were recorded in 40 patients (70.1%). ECMO run-related information is presented in table 2.

Mean time of ECMO implant-to-cardiac recovery was 9.0±10.6 days and observed in 43 patients (75.5%). During hospitalization, 2 patients received another type of mechanical support, and 3 patients were eventually transplanted.

Hospital mortality was observed in 16 patients (28.1%) and causes of death included multi-organ failure in 8 patients, cerebral injury in 3 (2 cases of brain death and 1 case of intra-cranial hemorrhage), 1 for left ventricular assist device rupture, 1 for sepsis, and 2 cases for unreported reasons, respectively.

At univariable analysis several factors were found significant for predicting in-hospital death (Table 3). Multivariable analysis showed that low pH prior to VA-ECMO implantation, absence or long lactate normalization time, and absence of functional cardiac recovery on ECMO, were predictive of in-hospital mortality (table 4).

At follow-up (median 15 months, IQR 6-28 months), recurrent myocarditis was observed in 2 cases only (at 6 and 12 months from the first FM event, respectively) with self-recovery, and 8 patients experienced adverse events (2 patients had venous stasis at the limb of ECMO implantation, 1 developed pancytopenia, 1 had ICD pocket infection, 1 limited cerebral bleeding, 1 had sternal and groin wounds dehiscence, and 2 patients had transient episode of ventricular tachycardia). Mean LVEF at follow-up was 51.2%±10.8%, with 11 cases with ≤40%, and only 2 patients with LVEF ≤30% (1 transplanted). There were 2 late deaths, due to complications after heart transplant in 1 case, and for unknown reason the second case, respectively. Five-year actuarial survival rate was 65.2%±7.9% (figure2).

Comment

Clinical scenario of AFM may be characterized by self-limiting form with rather rapid cardiac recovery and excellent early and mid-term prognosis (1,2,13,14). On occasion, a more malignant course, however, might also occur with severe and refractory hemodynamic compromise ultimately leading to patient death if no mechanical cardiocirculatory is promptly instituted (1-12). Available

epidemiological information indicates that acute myocarditis is a rare cardiovascular pathology, involving mostly young female patients and accounting for 10% of patients with newly developed cardiac compromise, and responsible of 8% to 12% of sudden deaths in young adults (1,2,13,14). Etiology of acute myocarditis often remains undetermined, but recent investigations have indicated that the viruses represent the most frequent agent (1,2,13,14). Endomyocardial biopsy is considered the gold-standard diagnostic tool, although this procedure remains largely underutilised and has shown low negative predictive value (1,2,13,14). In our series, one forth of the patients had endomyocardial biopsy performed, and acute myocarditis was confirmed in all cases. Pathogens, however, were found in 11 patients (19.3%) only, with predominance of viral agents. Cardiac Troponin-I levels were elevated in all cases. Elevations of cardiac Troponin I is a well-known and reliable indicator of ongoing myocardial injury. In the Myocarditis Treatment Trial, 34% of 53 patients with histological diagnosis of myocarditis had increased Troponin-I values, whereas only 5.7% of the patients had an increase of CPK-MB levels (14). Elevated levels of Troponin-I were shown to be correlated with a rapid course of heart failure (less than 1-month duration) suggesting that myocardial necrosis is an early event requiring in most of the cases a prompt diagnosis and aggressive treatment to limit such an overwhelming process (15). Our study population was characterized by AFM, and expected to have a lethal outcome if not aggressively and rapidly treated due to severe and refractory cardiocirculatory compromise requiring full mechanical circulatory support. The efficacy of VA-ECMO in critical AFM cases have been consistently proved to be highly advisable and effective based on the ease and rapidity of application, on biventricular as well as respiratory support provided, and on a more limited resource allocation, concomitantly providing a bridge to recovery or to more aggressive treatments (4-12). Published VA-ECMO weaning rates due to cardiac recovery in AFM have ranged from 66% to 93% (7,8,11,12), with a survival to hospital discharge ranging from 60% to 73.3% (7-11). Our findings showed a weaning rate of 81% and discharge rate of 72% in the overall patient population, in accordance with published series (3,4,10) and confirming that a limited quote of patients successfully weaned may still have a poor

outcome for major complications. A high complication rate is usually expected in VA-ECMO cases (16), but poorly described in AFM cases (4,5,7,8,12). Acute renal failure with need of dialysis, neurologic deficits, bleeding, hemolysis, sepsis, and lower limb-related complications occur in a substantial percentage of patients. We observed major adverse events in 70% of our patients during hospitalization, taking into account that 21% of the subjects were in cardiac arrest at VA-ECMO implant. In our series, cerebral events and acute renal failure were the most frequent complications, followed by bleeding, multi-organ failure, sepsis and renal failure requiring dialysis (table 3). We observed lower incidence of renal replacement therapy, bleeding, and sepsis than other series (7,8,9,11), whereas lower extremity ischemia and neurologic injuries were similar to the data of other investigators (7,8). Notwithstanding, almost one forth of our patients had evidence of left ventricular distension requiring ventricular venting, in accordance to the rate reported by Hsu and colleagues (8).

Regarding immunosuppressive therapy as a potential adjuvant in AFM, our series included only a minority of patients who had concomitant steroid therapy, and none received immunoglobulin or other type of such agents. The use of steroid or immunosuppressants has been previously shown to have limited or no impact of patients affected by acute myocarditis (17), and poorly applied in many clinical experiences (10), although beneficial effects have been documented (11), making this aspect also worthy of further evaluation.

Our study confirmed that patient management may indeed differ among centres in case of VA-ECMO for AFM. In our study, concomitant IABP was applied in 65% of the patients depending on centre strategy, and ranged from 20% to more than 90% in published single-centre series of AFM (7,8,10,11). The same applies for overcoming left ventricular distension during cardiac assistance, with switch from peripheral to central cannulation, or application of LV venting through different configurations as observed in our and other experiences (8,10). This variability reflects the lack of agreement or the ongoing debate about these peculiar aspects in VA-ECMO (18,19), and underlines that further investigations in this respect would be highly advisable.

Predicting the likelihood about native cardiac recovery or dismal outcome is of paramount importance, particularly for resource allocation or for planning and implementing more definitive treatments in these patients. Our data highlighted the relevance of peripheral perfusion impairment prior to and its improvement following VA-ECMO application. Indeed, less profound organ hypoperfusion and time of VA-ECMO implant-to lactate normalization were strong determinants of either cardiac recovery with successful ECMO weaning, or survival to hospital discharge. The relevance of lactate clearance in VA-ECMO patients has been recently highlighted by Li and associates who showed that mean lactate concentration prior to and lactate clearance 12 hours after VA-ECMO implantation provided prognostic guidance in post-cardiotomy ECMO patients (20). Severity of myocardial illness at ECMO implantation, as indicated by elevated creatinin-kinase cardiac isoform or Troponin-I levels (>12 μg/L), was found to be a predictor of unsuccessful weaning and death (10,16). Furthermore, rapid cardiac contractile recovery and decline of Troponin-N blood levels were also shown to reflect a better in-hospital outcome (4,7). Although use of biomarkers or speed of functional cardiac recovery as predictors of successful and sustained ECMO weaning have not been confirmed in all VA-ECMO series for AFM (21), these aspects will need further investigations in an attempt to provide reliable prognostic information with an expected beneficial impact on patient management in this setting.

McCarthy and collaborators has claimed that AFM has more favourable prognosis than other forms of acute myocarditis showing a 1-year survival and freedom from heart transplant of 93% in 15 patients (22). However, this experience was characterized by the need of LVAD in only 2 patients during initial hospitalization, being the remaining patients successfully treated with medical therapy only, suggestive of less critical conditions in these subjects as compared to our experience. Late outcome of patients affected by AFM and managed with VA-ECMO are available only in a few published experiences, showing a 1-year survival approaching 100% of discharged patients (5,9-12). In our series, survival as well as freedom from recurrent myocarditis or heart failure, were also favourable. Recurrence of acute myocarditis was a rare event, as also shown by other investigators

(5,9,11,12), and our 5-year follow-up data were consistent with this finding. Persistence of depressed myocardial contractility may, however, occur, and in our experience was limited to a few cases, with only one patients requiring heart transplant following hospital discharge, and no further patients hospitalized for chronic heart failure symptoms, as shown also by other investigators (5,9,11,12).

Limitations of the study

This is a retrospective observational multicentre study, and patient management was carried out according to individual centre strategy or protocol, with heterogeneous approaches and clinical decisions, therefore making definitive conclusions inapplicable. Comprehensive information regarding relevant issues (days from disease onset to ECMO implantation, CPR-to-ECMO implantation time) was not available for all patients. Information about the total number of acute myocarditis treated in each centre was also not available. Endomyocardial biopsy was performed in a limited number of cases again in relation to individual centre policy (routinely performed in centres performing cardiac transplantation, not performed in the centre without transplant program), thereby hampering comprehensive information in this regard. Autopsy assessment was not performed systematically, and no pathological confirmation was also available regarding cardiac tissue features of these patients.

Conclusions

The use of VA-ECMO in case of AFM with severe cardiocirculatory compromise is life-saving and provides a useful bridge to cardiac recovery in the majority of patients. Pre-implant patient conditions and early response to ECMO support may provide meaningful insights about likelihood of cardiac recovery and successful weaning. Although most of AFM patients may recover effective native cardiac contractility, major complications are nonetheless frequent and may impact successful VA-ECMO weaning. Following hospital discharge, recurrent episodes of AFM are rare,

and, in case, self-recovery might be expected. Persistent functional cardiac recovery is common, with a few cases of impaired contractility at long term. This multicentre study underlines, however, that VA-ECMO management and strategies in these patients are variable among centres utilizing such a support. Indeed, several aspects related to ECMO configuration and ancillary features, like left ventricular venting or concomitant IABP, require additional investigations to rule out which strategy for which patients should be applied.

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References

1. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636-48
2. Maisch B, Ruppert V, Pankuweit S. Management of fulminant myocarditis: a diagnosis in search of its etiology but with therapeutic options. Curr Heart Fail Rep 2014;11:166-77
3. Acker MA. Mechanical circulatory support for patients with acute fulminant myocarditis. Ann Thorac Surg 2001;71:S73-6
4. Cheng R, Hachamovitch R, Kittleson M, et al. Clinical outcome in fulminant myocarditis requiring extracorporeal membrane oxygenation: a weighted meta-analysis of 170 patients. J Card Fail 2014;1-7
5. Pages ON, Aubert S, Combes A, et al. Paracorporeal pulsatile biventricular assist device versus extracorporeal membrane oxygenation : extracorporeal life support in adult fulminant myocarditis. J Thorac Cardiovasc Surg 2009;137:194-7
6. Mody KP, Takayama H, Landes E, et al. Acute mechanical circulatory support for fulminant myocarditis complicated by cardiogenic shock. J Cardiovasc Trans Res 2014;7:156-64
7. Chen YS, Yu HS, Huang SC, et al. Experience and results of extracorporeal membrane oxygenation in treating fulminant myocarditis with shock: what mechanical support should be considered first? J Heart Lung Transplantat 2005;24:81-7
8. Hsu KH, Chi NH, Yu HY, et al. Extracorporeal membranous oxygenation support for acute fulminant myocarditis : analysis of a single center's experience. Eur J Cardio-Thorac Surg 2011;40:682-8
9. Ishida K, Wada H, Sakakura K, et al. Long-term follow-up on cardiac function following fulminant myocarditis requiring percutaneous extracorporeal cardiopulmonary support.

Heart Vessels 2013;23:86-90

10. Mirabel M, Luyt CE, Leprince P, et al. Outcomes, long-term quality of life, and psychological assessment of fulminant myocarditis patients rescued by mechanical circulatory support. Crit Care Med 2011;39:1029-35
11. Asaumi Y, Yasuda S, Morii I, et al. Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 2005;26:2185-92
12. Maejima Y, Yasu T, Kubo N, et al. Long-term prognosis of fulminant myocarditis rescued by percutaneous cardiopulmonary support device. Circ J 2004;68:829-33
13. Gupta S, Markham DW, Drazner MH, Mammen PPA. Fulminant myocarditis. Nat Clin Proc Cardiovasc Med 2008;11:693-706
14. Mason JW, O'Connel JB, Herskowitz A, et al. A clinical trial of immunosoppressive therapy for myocarditis. New Engl J Med 1995;333:269-75
15. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997;95:163-8
16. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610-6
17. Nakashima H, Umeyama Y, Minami K. Successive immunosoppressive treatment of fulminant myocarditis thaat is re fractory to mechanical circulatory support. Am J Case Rep 2013;14:116-9
18. Petroni T, Harrois A, Amour J, et al. Intra-aortic balloon pump effects on macrocirculation and microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. Crit Care Med 2014;42:2075-82
19. Hacking DF, Best D, d'Udekem Y, et al. Electove decompression of the left ventricle in pediatric patients may reduce the duration of venoarterial extracorporeal membrane

oxygenation. Artigf Organs 2014; in press.

20. Li J, Long C, Lou S, et al. The early dynamic behavior of lactate is linked to mortality in postcardiotomy patients with extracorporeal membrane oxygenation support: a retrospective observational study. J Thorac Cardiovasc Surg 2014, in press
21. Luyt CE, Landivier A, Leprince P, et al. Usefulness of cardiac biomarkers to predict recovery in patients on extracorporeal membrane oxygenation support for refractory cardiogenic shock. J Crit Care 2012;27:7-14
22. McCarthy III RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared to acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690-5

Table 1. Patient pre-ECMO characteristics (N= 57).

M/F		20 / 37 (35.1/64.9)
Age (years)		37.6±11.8
Patient Status		
	Shock	38 (66.7)
	Cardiac Arrest	12 (21.0)
	Hemodynamic Instablility	7 (12.3)
ECMO Access		
	Femoro-Femoral	47 (82.4)
	Femoro-Femoral + Central	2 (3.5)
	Central	6 (10.5)
	Femoral-Subclavian	1 (1.7)
	LV Apex-Subclavian	1 (1.7)
SBP (mmHg)		61.8±30.4
Arterial Size (French)		18.8±3.86
Venous Size (French)		23.8±6.38
Distal Perfusion of Cannulated Femoral Artery		
	No	21 (36.9)
	Yes	36 (63.1)
IABP		
	No	20 (35.2)
	Yes	37 (64.8)
LV Vent		
	No	43 (75.4)
	Yes	14 (24.6)
LV Distension		
	No	41 (71.9)
	Yes	16 (28.1)
Blood Values (at ECMO start)		
	pH	7.2±0.1
	PaO2 (mmHg)	68.8±47.5
	Lactate (mmol/L)	12.0±4.6
	Bilirubine (mg/dL)	6.0±6.2
Myocardial Biopsy		
	No	42 (73.7)
	Yes	15 (26.3)
Pathogen		
	No/Unknown	46 (80.6)
	Adenovirus	1 (1.7)
	Cytomegalovirus	2 (3.5)
	Coxackie Virus	1 (1.7)
	H1N1	5 (8.9)
	Staphylococcus Warneri	1 (1.7)
	Autoimmune	1 (1.7)

Values are shown as mean ± standard deviation for normally distributed data or number (percentage) for categorical data. **Abbreviations:** M/F: Male/Female**;** ECMO: Extra Corporeal Membrane Oxygenation; V.V.: veno-venous; LVAD: Left Ventricular Assist Device; SBP: Systolic Blood Pressure; IABP: Intra-Aortic Balloon Pump; LV: Left Ventricular.

Table 2. ECMO-related data.

ECMO Run (days)	9.9±19
Cardiac Recovery	
No	14 (24.5)
Yes	43 (75.5)
Cardiac Recovery Time (days)	9.0±10.6
Blood Values	
Tn-I peak (ng/ml)	244.7±311
Tn-I peak (days from ECMO start)	2.7±34
CK-MB peak (ng/ml)	46.8±37.3
CK-MB peak (days from ECMO start)	3.2±2.3
pH at 6 hrs from ECMO start	7.3±0.08
pH at 24h from ECMO start	7.3±0.09
PaO2 at 24hrs from ECMO start (mmHg)	21.4±77.9
Lactate at 24hrs from ECMO start (mmol/L)	64±4.0
Bilirubine peak (days from ECMO start)	4.8±3.8
Lactate normalization time (hours)	50.6±51.3
Tn-I normalization time (days from ECMO start)	4.9±6.5
CK-MB normalization time (days from ECMO start)	6.1±6.0
Min. PaCO2 on ECMO (mmHg)	27.7±3.4
Max. PaO2 on ECMO (mmHg)	292.3±86.4
Steroids Use	
No	47 (82.2)
Yes	10 (17.8)
In-Hospital Major Complications	
No	17 (29.9)
Yes	40 (70.1)
Type of In-Hospital Complications	
AKI	10 (17.5)
Neurologic Complication	10 (17.5)
Bleeding	8 (14)
MOF	6 (10.5)
Sepsis	6 (10.5)
CVVH – Dyalisis	6 (10.5)
Politransfusion (> 15 Blood Units)	5 (8.8)
Tracheostomy	5 (8.8)
Liver failure	4 (7)
Limb dysfunction & ischemia	4 (7)
Arrhythmia (VT, VF)	3 (5.2)
Vascular complications	3 (5.2)
ARDS	3 (5.2)
DIC	2 (3.5)
ECMO system or LVAD dysfunction	2 (3.5)
Bowel ischemia or bleeding	1 (1.7)

Values are shown as mean ± standard deviation for normally distributed data or number (percentage) for categorical data. Abbreviations: ECMO: Extra Corporeal Membrane Oxygen. Tn-I: Troponin I; CK-MB: Creatine Kinase Myocardial Isoenzyme; PaO2: Arterial Blood Oxygen Partial Pressure; PaCO2: Arterial Blood Carbon Dioxide Partial Pressure; AKI:acute kidney failure, MOF: multi-organi failure, CVVH: continuous veno-venous hemofiltration, DIC: disseminated intravascular coaugulopathy, ECMO: extracorporeal membrane

oxygenation, LVAD: left ventricular assist device, ARDS: acute respiratory distress syndrome, VT:ventricular tachycardia, VF: ventricular fibrillation.

Table 3. Univariable Analysis. Data are provided as mean±standard deviation

	Alive (n=40)	Dead (=17)	P
Age	35.5±11.1	42.7±12.1	0.035
Male/Female	15/25 (37.5/62.5)	5/12 (29.5/70.5)	0.763
Systolic blood pressure (mmHg)	76.2±10.1	71.1±13.0	0.185
Arterial cannula size (French)	19.2±2.2	18.4±1.8	0.226
Cardiac arrest	4 (10.0)	8 (47.0)	0.004
Unstable angina	6 (15.0)	1(5.9)	0.662
ECMO femoro-femoral	33 (82.5)	14 (82.3)	>0.9
ECMO central	3(7.5)	3 (17.6)	>0.9
ECMO femoral-central	1 (2.5)	11(5.9)	>0.9
ECMO femoral- subclavian	1 (2.5)	0 (0)	>0.9
ECMO apex-subclavian	1 (2.5)	0 (0)	>0.9
Venous cannula size (French)	24.4±3.5	24.4±3.2	>0.9
Distal femoral artery perfusion	24(60.0)	12 (70.5)	0.555
IABP	22 (55.0)	12 (70.5)	0.766
LV vent	8 (20.0)	5 (29.4)	0.738
LV distension	10 (25.0)	6 (35.3)	>0.9
Troponin-I peak (ng/ml)	154.7±180.8	375.2±357.2	0.003
Troponin-I peak (days)	2.1±1.1	4.0±6.2	0.067
CPK-MB peak (ng/ml)	372.1±274.7	689.5±488.7	0.003
CPK-MB peak (days)	2.8±1.6	4.0±3.4	0.09
pH prior ECMO	7.2±0.1	7.0±0.1	0.006
pH at 6 hours	7.3. ±0.8	7.2. ±0.7	0.001
pH at 24 hours	7.4±0.7	7.3±0.1	0.1
paO_2 before ECMO (mmHg)	72.7±54.7	59.5±21.9	0.342
paO_2 at 24 hours (mmHg)	219.4±61.5	203.4±108.7	0.481
Lactates before ECMO (mmol/L)	10.8±4.3	11.0±4.1	0.01
Lactates at 24 hours (mmol/L)	5.2±3.2	9.3±4.3	<0.001
Lactates normalization (hrs.)	44.0±39.6	82.2±85.3	<0.001
Birilubin peak (mg/dL)	4.2±4.6	10.4±7.4	<0.001
Birilubin peak time (days)	4.2±2.3	6.0±5.9	0.103
Troponin-I normalization (days)	5.1±6.9	4.8±1.4	0.342
CPK-MB normalization (days)	6.0±2.5	6.4±2.2	0.883
Lactates normalization (pts nr.)	38 (95.0)	8 (47.0)	<0.001
Troponin-I normalization (pts. nr)	34 (85.0)	5 (29.4)	<0.001
CPK-MB normalization (pts nr.)	37 (92.5)	7 (41.1)	<0.001
Min $PaCO_2$ on ECMO (mmHg)	27.2±3.2	27.1±3.9	>0.9
Max PaO_2 on ECMO (mmHg)	300.0±62.5	274.1±126.8	0.305
Myocarditis at biopsy	13 (32.5)	2 (11.7)	0.187
Cardiac recovery	38 (95.0)	5 (29.4)	<0.001
Steroids use	5 (12.5)	5 (29.4)	>0.9
In-hospital major complications	23 (57.5)	17 (100)	0.01
Brain injury	6 (15.0)	4 (23.5)	0.464
Left ventricular dysfunction	12 (30.0)	2 (11.7)	0.018
MOF	0 (0)	6 (35.2)	0.001
ECMO run (days)	9.2±3.7	9.0±5.7	0.882
Awake on ECMO	18 (45.0)	4 (23.5)	0.140
Hypotension on ECMO	30 (75.0)	8 (47.0)	0.065
Cardiac recovery time (days)	8.2±8.8	6.2±13.3	0.574

Values are shown as mean ± standard deviation for normally distributed data or number (percentage) for categorical data. Abbreviations: CPK-MB: ; ECMO: extracorporeal membrane oxygenation; MOF: multi-organ failure; IABP: intra-aortic balloon counterpulsation

Table 4. Multivariable Analysis

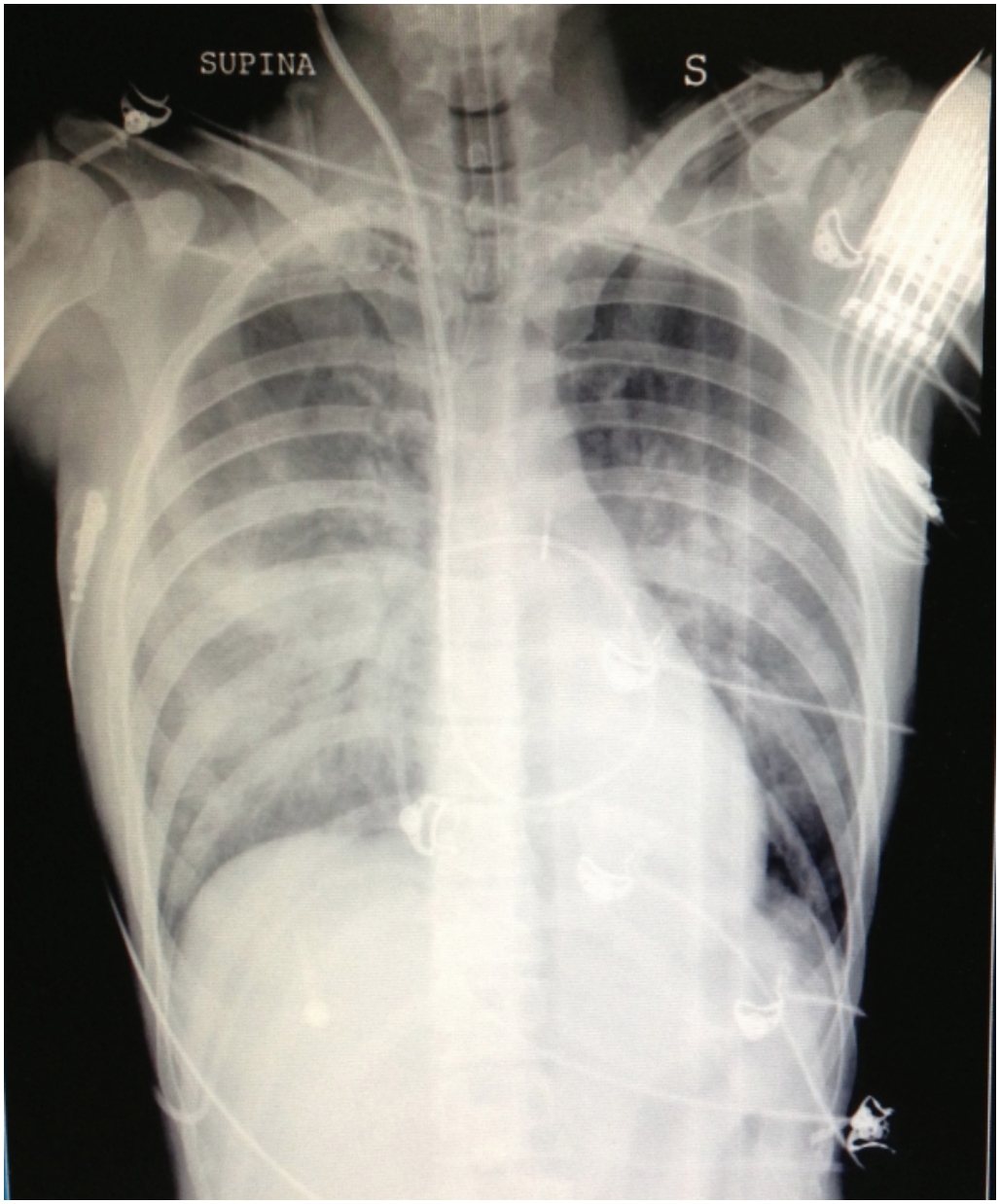
	β	S.E	Exp (β)	p
pH prior to ECMO implant	-14.251	7.148	.000	0.046
Lactate normalization (hours from ECMO implant)	0.029	0.012	1.029	0.013
Cardiac Recovery	5.288	1.769	197.930	0.003

VA-ECMO: Veno-arterial extracorporeal membrane oxygenation

Legends to the figures.

Figure 1. Chest-x ray of a representative patient affected by acute fulminant myocarditis showing signs of acute pulmonary edema and absence of cardiac dilatation.

Figure 2. Kaplan-Meyer representation of postoperative cumulative (Cum) survival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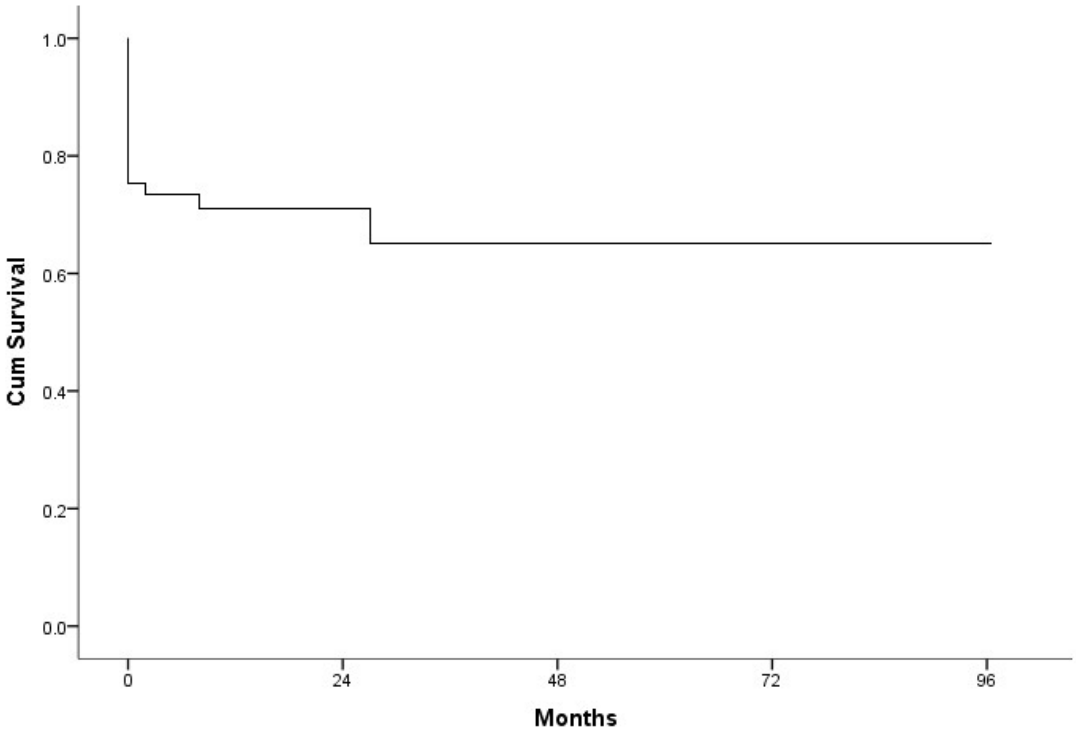

Patients at risk

Months	0	12	24	36	48
	57	30	15	9	3