Venoarterial Extracorporeal Membrane Oxygenation for Acute Fulminant Myocarditis in Adult Patients: A 5-Year Multi-Institutional Experience

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

Method. **From hospital databases, 57 patients with diagnoses of AFM treated with VA-ECMO in the past 5 years were found and analyzed. Mean age was 37.6 ± 11.8 years; 37 patients were women. At VA-ECMO implantation, cardiogenic shock was present in 38 patients, cardiac arrest in 12, and severe hemodynamic instability in 7. A peripheral approach was used with 47 patients, whereas 10 patients had a central implantation or other access.**

Results. **Mean VA-ECMO support was 9.9 ± 19 days (range, 2 to 24 days). Cardiac recovery with ECMO weaning was achieved in 43 patients (75.5%), major complications were observed in 40 patients (70.1%), and survival to hospital discharge occurred in 41 patients (71.9%). After hospital discharge (median follow-up, 15 months) there were 2 late deaths. The 5-year actual survival was 65.2% ± 7.9%, with recurrent self-recovering myocarditis observed in 2 patients (at 6 and 12 months from the first AFM event), and 1 heart transplantation.**

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

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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 histologic or immunohistologic diagnosis and related functional myocardial compromise have been, however, established, thereby making AFM, as mentioned, a clinical syndrome rather than a causative disease. Infective etiologic process is usually the most frequent finding [1, 2]. Profound contractile dysfunction that leads to quick onset

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of refractory cardiogenic shock or cardiac arrest may characterize the clinical scenario of AFM [1, 2]. Aggressive pharmacologic therapy and intraaortic balloon pump (IABP) are often insufficient, and mechanical circulatory support may therefore account for the unique means capable of sustaining the failing heart and providing time to enhance heart recovery or to more advanced therapies if adequate native cardiac function is not eventually restored [1–3]. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) has been shown to provide prompt and effective support in these circumstances [3–14]. Published series of VA-ECMO in AFM are, nonetheless, limited in terms of patient number and late outcome [3–14]. The aim of this study was, therefore, to analyze through a multicenter investigation the in-hospital and results after discharge in AFM patients who require VA-ECMO due to severe cardiocirculatory impairment.

Material and Methods

The study was approved by the ethical committee (study code no.1438, approved June 26, 2014) of the principal investigator (R.L.) and provided by all ethical committees of study centers.

All data related to AFM in adult patients treated with VA-ECMO from January 2008 to December 2013 were obtained from institutional databases of 13 different centers. Such a time frame was purposely chosen to assess modern ECMO systems and management which included advanced VA-ECMO technology and components and more advanced expertise achieved in adult VA-ECMO for emergent cardiovascular diseases.

Myocarditis diagnosis followed the International Classification of Disease, Ninth Revision in all centers, according to the national coding system. Acute myocarditis was clinically defined by the concomitant presence of the following three primary criteria: (1) sudden and refractory cardiogenic shock, cardiac arrest, or severe hemodynamic instability despite aggressive inotropic drugs with or without IABP; (2) demonstration of normal coronary artery anatomy at angiogram; and (3) echocardiographic signs of myocardial tissue swelling and biventricular involvement. Secondary criteria were (1) positive blood culture test results, (2) confirmation of ongoing autoimmune cardiac involvement at blood tests, and (3) prodromal clinical signs and symptoms of inflammatory state with fever and malaise [1–3, 15].

Exclusion criteria were (1) concomitant organic valvular or coronary artery disease, (2) any chronic form of dilated cardiomyopathy, (3) toxic myocarditis [1], (4) mediastinal radiation therapy, or (5) treatment with other mechanical circulatory support (excluding IABP).

Fifty-seven patients fulfilled study entry criteria (primary criteria were present in all 57 patients, whereas secondary criteria were as follows: 57 patients with flu-like illness and 11 patients with positive blood culture test results. Pre-ECMO patient characteristics are shown in Table 1. Cardiocirculatory support with VA-ECMO was instituted mainly during cardiogenic shock, and a peripheral approach was used in most patients.

Table 1. Patient Characteristics Before ECMO (n = 57)

Characteristic	Value
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, mm Hg	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
PaO_2, mm Hg	68.8 ± 47.5
Lactate, mmol/L	12.0 ± 4.6
Bilirubin, 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 mean ± SD for normally distributed data or n (%) for categorical data.

ECMO = extra corporeal membrane oxygenation; F = female; IABP = intraaortic balloon pump; LV = left ventricular; M = male; PaO2 = arterial blood oxygen partial pressure; SBP = systolic blood pressure.

Endomyocardial biopsy was performed in one-fourth of the patients, with AFM confirmed in all patients. Viral etiologic process was predominant in cases of pathogen-based AFM. Left ventricular (LV) venting was applied in

14 patients and included catheter positioned in the pulmonary artery in 2 patients, in the right pulmonary vein in 4 patients, in the LV apex in 4 patients, and in unreported sites in 4 patients. Marked myocardial damage, associated with hypoxia and metabolic acidosis, was detected in all patients.

Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Continuous data are expressed as mean ± standard deviation, whereas non-normally distributed data are 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.

Significant ($p < 0.05$) and borderline ($p \leq 0.1$) results at univariate analysis were put into multivariate logistic regression analysis performed to identify predictors of early death. Forty-nine variables were investigated for their predictive value. To enhance the accuracy of the model, the number of variables was reduced with variable clustering [16]. Model fit for logistic regression was assessed with the Hosmer-Lemeshow statistic, and predictive accuracy was assessed by the concordance index *c*. Models proved to be reliable and accurate (Hosmer-Lemeshow: $p = 0.123$, $c = 0.758$). Internal validation of predictors generated by multivariate logistic regression was performed by means of bootstrapping techniques, with 1,000 cycles and generation of odds ratio and bias-corrected 95% confidence interval. IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY) and R version 3 (R Foundation for Statistical Computing, Vienna, 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%). 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 after implantation. Major complications were recorded in 40 patients (70.1%). ECMO run-related information is presented in Table 2.

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

Hospital death was observed in 16 patients (28.1%); causes of death included multiorgan failure in 8 patients, cerebral injury in 3 (2 cases of brain death and 1 case of intracranial hemorrhage), 1 for LV assist device rupture, 1 for sepsis, and 2 patients for unreported reasons.

At univariate analysis several factors were significant for predicting in-hospital death (Table 3), but multivariate analysis showed that low pH before VA-ECMO implantation, absence or long lactate normalization time, and absence of functional cardiac recovery on ECMO were predictive of in-hospital death (Table 4).

Table 2. ECMO-Related Data

Variable	Value
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 hours from ECMO start	7.3 ± 0.08
pH at 24 hours from ECMO start	7.3 ± 0.09
PaO_2 at 24 hours from ECMO start, mm Hg	21.4 ± 77.9
Lactate at 24 hours from ECMO start, mmol/L	64 ± 4.0
Bilirubin 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
Minimum $PaCO_2$ on ECMO, mm Hg	27.7 ± 3.4
Maximum PaO_2 on ECMO, mm Hg	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 – dialysis	6 (10.5)
Polytransfusion (>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 mean ± SD for normally distributed data or n (%) for categorical data.

AKI = acute kidney failure; ARDS = acute respiratory distress syndrome; CK-MB = creatine kinase myocardial isoenzyme; CVVH = continuous veno-venous hemofiltration; DIC = disseminated intravascular coagulation; ECMO = extra corporeal membrane oxygen; LVAD = left ventricular assist device; MOF = multiorgan failure; PaCO2 = arterial blood carbon dioxide partial pressure; PaO2 = arterial blood oxygen partial pressure; Tn-I = troponin I; VT = ventricular tachycardia; VF = ventricular fibrillation.

Table 3. Univariate Analysis

Variable	Alive (n = 40)	Dead (n = 17)	*p* Value
Age, years	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, mm Hg	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 before 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, mm Hg	72.7 ± 54.7	59.5 ± 21.9	0.342
paO_2 at 24 hours, mm Hg	219.4 ± 61.5	203.4 ± 108.7	0.481
Lactate before ECMO, mmol/L	10.8 ± 4.3	11.0 ± 4.1	0.01
Lactate at 24 hours, mmol/L	5.2 ± 3.2	9.3 ± 4.3	<0.001
Lactate normalization, hours	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
Lactate normalization, pts no.	38 (95.0)	8 (47.0)	<0.001
Troponin-I normalization, pts no.	34 (85.0)	5 (29.4)	<0.001
CPK-MB normalization, pts no.	37 (92.5)	7 (41.1)	<0.001
Min $PaCO_2$ on ECMO, mm Hg	27.2 ± 3.2	27.1 ± 3.9	>0.9
Max PaO_2 on ECMO, mm Hg	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
Steroid 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 mean ± SD for normally distributed data or n (%) for categorical data.

CPK-MB = creatine phosphokinase myocardial isoenzyme; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon counterpulsation; LV = left ventricular; MOF = multi-organ failure; $PaCO_2$ = arterial blood carbon dioxide partial pressure; PaO_2 = arterial blood oxygen partial pressure.

Table 4. Multivariate Analysis

Variable	β	SE	Exp (β)	*p* Value
pH before ECMO implantation	−14.251	7.148	.000	0.046
Lactate normalization, hours from ECMO implantation	0.029	0.012	1.029	0.013
Cardiac recovery	5.288	1.769	197.930	0.003

ECMO = extracorporeal membrane oxygenation.

At follow-up (median, 15 months; interquartile range, 6 to 28 months), recurrent myocarditis was observed in 2 patients (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 had pancytopenia, 1 had implantable cardioverter-defibrillator pocket infection, 1 limited cerebral bleeding, 1 sternal and groin wound dehiscence, and 2 patients had transient episodes of ventricular tachycardia). Mean LV ejection fraction at follow-up was 51.2% ± 10.8%, with 11 patients with ≤40%, and only 2 patients with LV ejection fraction ≤30% (1 received transplant). There were 2 late deaths due to complications after heart transplantation in 1 patient, and for unknown reasons in the second patient. Acutal survival rates were 77.3 ± 6.2 at 1 year, 76.2 ± 6.5 at 2 years, and 65.2% ± 7.9% thereafter. A significant difference was detected in survival between patients undergoing or not undergoing cardiac transplantation ($p < 0.001$; Fig 1).

Comment

The clinical scenario of AFM may be characterized by a self-limiting form with rather rapid cardiac recovery and excellent early and mid-term prognosis [1, 2, 13, 15]. On occasion, however, a more malignant course might occur with refractory hemodynamic compromise, ultimately leading to patient death if no mechanical cardiocirculatory support is promptly instituted [1–15]. Available epidemiologic information indicates that acute myocarditis is a rare cardiovascular pathologic process, involving mostly young female patients and accounting for 10% of patients with newly developed cardiac compromise, and responsible for 8% to 12% of sudden deaths in young adults [1, 2, 15, 17]. The cause of acute myocarditis often remains undetermined, but investigations have indicated that viruses represent the most frequent agent [1–3, 14, 15]. Endomyocardial biopsy is considered the gold standard diagnostic tool, although this procedure remains largely underused and has shown low negative predictive value [1, 2, 13, 15]. In our series, one-fourth of the patients had endomyocardial biopsy performed, and acute myocarditis was confirmed in all patients. Pathogens, however, were found in 11 patients (19.3%) only, with predominance of viral agents. Cardiac troponin-I concentrations were elevated in all patients. 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 histologic diagnoses of myocarditis had increased troponin-I values, whereas only 5.7% of the patients had increased creatine phosphokinase myocardial isoenzyme concentrations [17]. Elevated troponin-I concentrations were associated with a rapid course of heart failure (less than 1-month duration), suggesting that myocardial necrosis is an early event that requires a prompt diagnosis and aggressive treatment in most patients to limit such an overwhelming process [18]. Our study population was characterized by AFM and was expected to have a lethal outcome if not aggressively and rapidly treated. The efficacy of VA-ECMO in critical AFM cases has been consistently proved to be highly advisable and effective on the basis of the ease and rapidity of application, on biventricular and respiratory support provided, and, on a more limited resource allocation, concomitantly providing a bridge to recovery or to more aggressive treatments [4–14]. Published VA-ECMO weaning rates due to cardiac recovery in AFM have ranged from 66% to 100% with a survival to hospital discharge ranging from 60% to 100% (Table 5). Our findings showed a weaning rate of 81% and discharge rate of 72% in the overall patient population, in accordance with published series [3, 7, 9, 12] and confirming that a limited number of successfully weaned patients may still have a poor outcome due to major complications (Table 5). Our in-hospital survival rate was slightly better than the one recently reported from the Extracorporeal Life Support Organization (ELSO) Registry, but it should be highlighted that our experience focused on the past 5 years, and more importantly included the most updated ECMO technology, whereas the ELSO Registry has provided results starting from 1995 [6]. This difference accounts for less performant devices and less efficient patient management used previously in this setting, with expected impact on early survival.

A high complication rate is usually expected in VA-ECMO patients [23], but poorly described in AFM

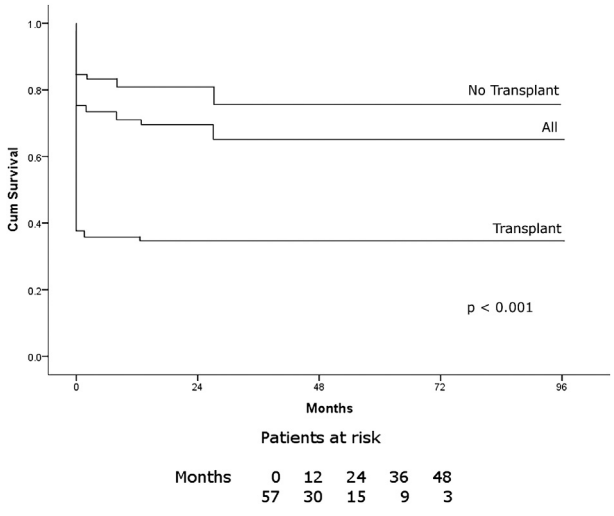

Fig 1. Kaplan-Meyer representation of postoperative cumulative (Cum) survival in overall population and by transplantation/no transplantation subgroups.

Table 5. Review of Published Studies That Included 6 or More Adults Patients Affected by Acute Fulminant Myocarditis and Supported by ECMO

Reference	Time Span	Patients, n	ECMO Weaning, n (%)	Survival to Hospital Discharge, n (%)	Postoperative Survival, % (follow-up, years)
Kawahito et al [19]	1991–1997	6	5 (80)	5 (80)	NA
Aoyama et al [5]	1989–2000	52	42 (80.7)	31 (59.6)	NA
Chen et al [9]	1994–2001	15	14 (93)	11 (73)	NA
Asaumi et al [13]	1993–2001	6	4 (67)	4 (67)	NA
Maejima et al [14]	1991–2000	8	NA	6 (75)	100 (range, 1.4–5.9)
Sezai et al [20]	1999–2006	7	7 (100)	7 (100)	NA
Pages et al [6]	2001–2006	6	5 (83)	5 (83)	80% (1)
Thiagarajan et al [21]	1992–2007	16	NA	9 (56)	NA
Hsu et al [10]	1994–2009	51	NA	31 (61)	NA
Mirabel et al [12]	2002–2009	35	NA	24 (69)	100 (1.5)
Beurtheret et al [22]	2005–2009	14	NA	9 (65)	NA
Diddle et al [6]	1995–2014	147	101 (69)	90 (61)	NA

ECMO = extracorporeal membrane oxygenation; NA = not available.

patients [4, 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 implantation, remarkably in accordance to the extracorporeal cardio-pulmonary resuscitation rate shown in the ELSO Registry report [6]. In our series, cerebral events and acute renal failure were the most frequent complications, as again shown by Diddle and associates in the ELSO Registry [6], followed by bleeding, multiorgan failure, sepsis, and renal failure that required dialysis (Table 3). We observed a lower incidence of renal replacement therapy, bleeding, and sepsis than other series [9, 10, 11, 13], whereas lower extremity ischemia and neurologic injuries were similar to the data of other investigators [9, 10]. Note that almost one-fourth of our patients had evidence of LV distension that required ventricular venting, in accordance with the rate reported by Hsu and colleagues [10].

For immunosuppressive therapy as a potential adjuvant in AFM, our series included only a few patients who had concomitant steroid therapy, and none received immunoglobulin or other types of such agents. Steroidal or immunosuppressive agents have been previously shown to have limited or no impact in acute myocarditis [17, 24] and were poorly applied in many clinical series [12] although beneficial effects have been nonetheless documented [13], making this aspect worthy of further evaluation.

Our study confirmed that current patient management may indeed differ among centers in cases of VA-ECMO for AFM. Indeed, concomitant IABP was applied in 65% of the patients, depending on center strategy, and ranged from 20% to more than 90% in published single-center series of AFM [9, 10, 12, 13]. The same applies for overcoming LV distension during cardiac assistance, by switching from peripheral to central cannulation, or application of LV venting through different configurations as observed in our and other's experiences [10, 12]. This variability reflects the lack of agreement or the ongoing debate about these peculiar aspects in VA-ECMO [25, 26] and underlines that further investigations in this respect would be highly advisable.

Predicting the likelihood of native cardiac recovery or dismal outcome is of paramount importance, particularly for resource allocation or for planning more definitive treatments in these patients. Our data highlighted the relevance of peripheral perfusion impairment before and its improvement after VA-ECMO application. Indeed, less profound organ hypoperfusion and shorter time of VA-ECMO implantation-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 [27] who showed that mean lactate concentration before and lactate clearance 12 hours after VA-ECMO implantation provided prognostic guidance in ECMO patients after cardiotomy. These findings are in accordance with the recent ELSO Registry data showing that external cardiopulmonary resuscitation before ECMO implantation and the need of higher flow in the first hours of support were independent predictors on unfavourable outcome [6].

Severity of myocardial illness at ECMO implantation, as indicated by elevated creatine kinase cardiac isoform or troponin-I concentrations (>12 μg/L), predicted unsuccessful weaning and death [12, 18]. Furthermore, rapid cardiac contractile recovery and decline of troponin-N blood concentrations were also shown to reflect a better in-hospital outcome [4, 9]. 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 [28], 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 [29] have claimed that AFM has a more favorable prognosis than other forms of

acute myocarditis, showing a 1-year survival and freedom from heart transplantation of 93% in 15 patients. However, this experience was characterized by the need of aggressive mechanical circulatory support in only 2 patients during initial hospitalization; the remaining patients were successfully treated with medical therapy only, suggestive of less critical conditions in these subjects compared with our patient cohort. Late outcome of patients affected by AFM and managed with VA-ECMO are available only in a few published studies (Table 5), with a 1-year survival ranging from 80% to 100% of discharged patients [7, 11–14]. In our series, survival and freedom from recurrent myocarditis or heart failure after hospital discharge were also favorable. Recurrence of acute myocarditis was a rare event, as also shown by other investigators [7, 11, 13, 14], 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, as also shown by other investigators [7, 11, 13, 14].

Limitations of the Study

This was a retrospective observational multicenter study, and patient management was performed according to individual center strategy or protocol, with heterogeneous approaches, therefore making definitive conclusions inapplicable. The diagnosis of AFM relied on the adjudication of clinical assessment by the attending physicians in each center to such cardiac disease, according to the mentioned primary and secondary criteria, and was not always followed by histologic confirmation. Endomyocardial biopsy was performed in a limited number of patients, again in relation to individual center policy (routinely performed in centers performing cardiac transplantation, not performed in the center without a transplantation program). Autopsy assessment was not performed systematically, and no pathologic confirmation was available about cardiac tissue features of these patients. Comprehensive information about relevant issues (days from disease onset to ECMO implantation, cardiopulmonary resuscitation-to-ECMO implantation time) was not available for all patients. Information about the total number of acute myocarditis patients treated in each center was also not available because less critical clinical conditions do not require surgical team consultations, and patients are admitted to different wards (internal medicine, general intensive care, cardiology, cardiologic intensive care), thereby making patient data more difficult to obtain.

Conclusions

The use of VA-ECMO in cases of AFM with severe cardiocirculatory compromise is life saving and provides a useful bridge to cardiac recovery in most patients. Patient conditions before implantation and early response to ECMO support may provide meaningful insights about the likelihood of cardiac recovery and successful weaning. Although most AFM patients may recover effective native cardiac contractility, major complications are nonetheless frequent and may affect in-hospital outcome. After hospital discharge, recurrent episodes of AFM are rare, and, in some situations, self-recovery might be expected. Persistent functional cardiac recovery is common, with a few cases of impaired contractility at long term. This multicenter study underlines, however, that VA-ECMO management and strategies in these patients are variable among centers that use such a cardiocirculatory support. Indeed, several aspects related to ECMO configuration and ancillary features, such as LV venting or concomitant IABP, require additional investigations to rule out which strategy for which patient should be applied.

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