ORIGINAL ARTICLE

Time course, factors related to, and prognostic impact of venoarterial extracorporeal membrane flow in cardiogenic shock

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Abstract

Aims Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is currently one of the most used devices in refractory cardiogenic shock. However, there is a lack of evidence on how to set the 'optimal' flow. We aimed to describe the evolution of VA-ECMO flows in a cardiogenic shock population and determine the risk factors of 'high-ECMO flow'.

Methods and results A 7 year database of patients supported with VA-ECMO was used. Based on the median flow during the first 48 h of the VA-ECMO run, patients were classified as 'high-flow' or 'low-flow', respectively, when median ECMO flow was ≥3.6 or <3.6 L/min. Outcomes included rates of ventilator-associated pneumonia, ECMO-related complications, days on ECMO, days on mechanical ventilation, intensive care unit and hospitalization lengths of stay, and in-hospital and 60 day mortality. Risk factors of high-ECMO flow were assessed using univariate and multivariate cox regression. The study population included 209 patients on VA-ECMO, median age was 51 (40–59) years, and 78% were males. The most frequent aetiology leading to cardiogenic shock was end-stage dilated cardiomyopathy (57%), followed by acute myocardial infarction (23%) and fulminant myocarditis (17%). Among the 209 patients, 105 (50%) were classified as 'high-flow'. This group had a higher rate of ischaemic aetiology (16% vs. 30%, $P = 0.023$) and was sicker at admission, in terms of worse Simplified Acute Physiology Score II score [40 (26–58) vs. 56 (42–74), $P < 0.001$], higher lactate [3.6 (2.2–5.8) mmol/L vs. 5.2 (3–9.7) mmol/L, $P < 0.001$], and higher aspartate aminotransferase [97 (41–375) U/L vs. 309 (85–939) U/L, $P < 0.001$], among others. The 'low-flow' group had less ventilator-associated pneumonia (40% vs. 59%, $P = 0.007$) and less days on mechanical ventilation [4 (1.5–7.5) vs. 6 (3–12) days, $P = 0.009$]. No differences were found in lengths of stay or survival according to the ECMO flow. The multivariate analysis showed that risk factors independently associated with 'high-flow' were mechanical ventilation at cannulation [odds ratio (OR) 3.9, 95% confidence interval (CI) 2.1–7.1] and pre-ECMO lactate (OR 1.1, 95% CI 1.0–1.2).

Conclusions In patients with refractory cardiogenic shock supported with VA-ECMO, sicker patients had higher support since early phases, presenting thereafter higher rates of ventilator-associated pneumonia but similar survival compared with patients with lower flows.

Introduction

Refractory cardiogenic shock (CS) represents the worst clinical scenario of acute heart failure, consisting of profound systemic hypoperfusion due to a primary cardiac dysfunction.[1,2] In such cases, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has arisen as one of the most used devices for mechanical circulatory support (MCS), given its ease of deployment and widespread availability.[3,4]

Management of VA-ECMO requires a high level of expertise and appropriate assessment of multiple elements, including ventilator parameters, sedation, anticoagulation, pharmacokinetics, and optimal VA-ECMO performance to avoid complications. In VA-ECMO-supported patients, the blood flow goes in a non-physiological, retrograde direction that increases left ventricular (LV) afterload and LV end-diastolic pressure, thus favouring the development of pulmonary oedema. The drawbacks of this 'reverse' flow have been consistently reported,[5,6] and several strategies to 'unload' the left ventricle have been proposed.[7,8] Pharmacological unloading with inotropic drugs and reduction of the VA-ECMO flow are commonly the first steps.[9] Nevertheless, these measures are often insufficient, and additional unloading with devices such as intra-aortic balloon pump (IABP) or Impella is frequently needed. The choice of the unloading strategy usually depends on the clinician's experience, centre availability, and CS aetiology. Moreover, refractory CS is a dynamic clinical condition that demands continuous assessment of the VA-ECMO performance. However, there is a lack of evidence on what the 'optimal' ECMO flow is, and how it can be assessed. Because a reasonable strategy would consist of assuring 'the minimum flow to maintain organ perfusion',[10] a sustained high flow beyond the early phases of CS could turn out to be deleterious.

In the present work, we sought to describe the evolution of VA-ECMO flow in a CS population according to the degree of support ('low-flow' vs. 'high-flow') during the first 48 h. Secondly, we analysed the unloading strategy, the factors associated with 'high-flow', and the impact on short-term outcomes.

Methods

Study population and design

This is a retrospective, single-centre study including patients in refractory CS supported with peripheral VA-ECMO admitted at La Pitié-Salpêtrière University Hospital in Paris between 1 January 2010 and 31 December 2016. The database for this study has previously been used to analyse the impact of an awake VA-ECMO strategy published elsewhere.[11]

CS was defined as sustained systolic blood pressure < 90 mmHg or requiring vasoactive drugs to maintain it ≥90 mmHg, with concomitant evidence of tissue hypoperfusion.[12,13] CS was considered refractory when acute cardiovascular failure developed despite high-dose catecholamine infusion (epinephrine ≥ 1 μg/kg/min or dobutamine ≥ 15 μg/kg/min or norepinephrine ≥ 1 μg/kg/min). Exclusion criteria were patients aged <18 or >75 years old, cannulated during cardiopulmonary resuscitation, post-cardiotomy, or patients with atypical CS aetiologies. In addition, we excluded patients in cardiac arrest that required intubation before starting ECMO, those with ECMO for ≤24 h, and patients who were transferred late to our centre without information about mechanical ventilation (MV) details of the early part of the ECMO run. Moreover, patients with no data regarding ECMO flow on Days 1 (D1) and 2 (D2) were also excluded (see Supporting Information, *Table S1* for additional information regarding basal characteristics of the latter).

The study complies with the Declaration of Helsinki and is in accordance with the ethical standards of our hospital's institutional review board and French law. Informed consent was not necessary due to the retrospective and observational design of this study. The National Commission for Informatics and Liberties approved this study (No. 1950673).

Extracorporeal membrane oxygenation management

VA-ECMO cannulas were inserted by trained cardiovascular surgeons with femoral–femoral 23F to 29F–15F to 18F cannulas as previously described.[14] An additional 7F catheter was systematically inserted into the femoral artery to prevent leg ischaemia. For highly unstable patients, our mobile ECMO team travelled to primary-care hospitals to implant the device at the bedside and to transport the patient to our centre.

The management of VA-ECMO, including ECMO flow, depended on the physician in charge. As is usual practice in our centre, most patients were initially managed with an unloading strategy that usually began with implantation of an IABP combined with ECMO in the contralateral femoral access, at the same time as VA-ECMO implantation. If despite routine unloading measures, the patient develops progressive pulmonary oedema or the aortic valve opens only sporadically, we would consider upgrading to Impella.

Data collection

At intensive care unit (ICU) admission, we collected demographic information, cardiovascular risk factors, main comorbidities, and Simplified Acute Physiology Score (SAPS) II. During the pre-ECMO period, the Sequential Organ Failure

Assessment (SOFA) score, the Survival after Veno-Arterial ECMO (SAVE) score,[15] the inotrope score, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification, the Society for Cardiovascular Angiography and Interventions (SCAI) classification of CS,[16] cannulation by the mobile ECMO team, haemodynamic parameters, blood–gas analysis, renal and liver functions, left ventricular ejection fraction (LVEF), and intubation status were noted. Because all patients had digitized medical charts, ECMO flow, intubation and MV status, and need of renal replacement therapy (RRT) were recorded daily for a maximum of 14 days on ECMO. According to the time on MV during the ECMO run, patients were categorized as 'awake' or 'non-awake' ECMO when time on invasive MV was ≤50% or >50% of the total time on VA-ECMO run, respectively, as described previously.[11]

Based on the median flow through the first 48 h of VA-ECMO run of the whole cohort, patients were classified as 'high-flow' or 'low-flow' if ECMO flow was ≥3.6 or <3.6 L/min, respectively.

Outcomes

Complications during ECMO support included rates of ventilator-associated pneumonia (VAP), stroke, leg ischaemia, bacteraemia, cannula site infection, vena cava thrombosis, and conversion to central ECMO. We also reported days on ECMO, days on MV, and ICU and hospitalization length of stay. Lastly, bridge to heart transplant (HTx), time from ECMO to HTx, and in-hospital and 60 day mortality were noted. Details about ECMO-related complications are reported in the supporting information.

Statistical analysis

Continuous variables were expressed as median [interquartile range (IQR)] and compared with Wilcoxon rank-sum tests. Categorical variables were expressed as numbers (percentage) and compared with χ^2 tests.

To identify the factors related to 'high-flow' support, a multivariate stepwise logistic regression model was constructed including the baseline variables found to be associated in the univariate analysis with a *P* value < 0.10.

Kaplan–Meier curves were used to evaluate the association between the VA-ECMO flow classification with 60 day mortality.

All statistical tests were two-sided, with a *P* value ≤ 0.05 considered significant. Statistical analysis was computed with STATA software, Version 13.1 (Stata Corp, College Station, Texas).

Results

Clinical characteristics and time course of extracorporeal membrane oxygenation flow in the study population

Two hundred and nine patients were included in the analysis (*Figure 1*). Overall, the median age was 51 (40–59), where 78% were males, and the median SAPS II was 51 (32–66) (*Table 1*). The most frequent aetiology leading to CS was end-stage dilated cardiomyopathy (DCM) (57%), followed by acute myocardial infarction (AMI) (23%) and fulminant myocarditis (17%).

One hundred and four (50%) patients were classified as 'low-flow' and 105 (50%) as 'high-flow'. In general, the median ECMO flow showed a tendency to decrease, from the initial 3.7 (3.0–4.2) L/min on Day 1 to 3.2 (2.7–3.8) L/min on Day 6. Median flows between both groups were continuously lower in 'low-flow' patients at any time point, with the 'low-flow' group maintaining VA-ECMO flows around 3.0–3.1 L/min. *Figure 2A* shows the evolution of the VA-ECMO support during the first 14 days for these groups. Compared with the 'low-flow' patients, those with 'high-flow' had similar demographic and cardiovascular risk profiles, but ischaemic aetiology was more frequent. Moreover, they had greater ICU severity scores and a lower SAVE score. In addition, MV at cannulation and cannulation by the mobile ECMO unit was more frequent in the 'high-flow' group (*Table 1*).

Factors related to high extracorporeal membrane oxygenation flows
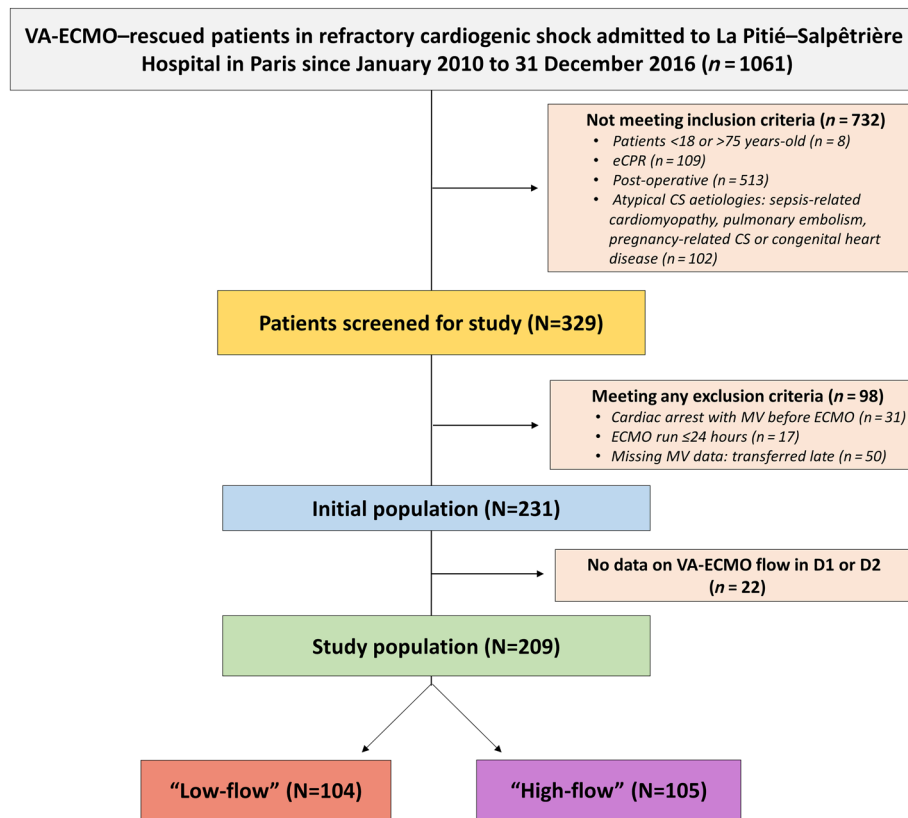
In the multivariate analysis, MV at implantation and pre-ECMO lactate were independently associated with high ECMO-flows {with respective odds ratio [OR] 3.9 [95% confidence interval (CI) 2.1–7.1], *P* < 0.001 and 1.1 [95% CI 1.0–1.2], *P* < 0.001}.

Extracorporeal membrane oxygenation management

More than 40% of all patients were managed with an awake strategy, with a higher rate in the 'low-flow' group (52% vs. 30%, *P* < 0.001). Additionally, 54% required RRT, with higher needs in the 'high-flow' group (41% vs. 66%, *P* < 0.001).

Almost 70% of the study population was managed with LV unloading with no differences between the two groups (*Table 1*). Regarding the type of LV unloading, IABP was the most employed device (94%). Baseline characteristics were similar among the non-unloaded and unloaded subgroups,

Figure 1 Flow chart of the study population. CS, cardiogenic shock; D1, Day 1; D2, Day 2; eCPR, ECMO-rescued cardiopulmonary resuscitation; MV, mechanical ventilation; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

except for the predominance of males (83% vs. 67%, $P = 0.011$) and non-myocarditis aetiology in the unloaded subgroup (Supporting Information, *Table S2*). Unloaded patients were managed with higher flows (*Figure 2B*) and higher doses of inotropic drugs from Day 3 to Day 5, and they were also more frequently managed with an awake ECMO strategy (47% vs. 29%, $P = 0.012$) (Supporting Information, *Table S3*).

Outcomes

Half of the study population presented with at least one VAP during admission, followed by cannula site infection (42%) and bacteraemia (30%). Patients with 'high-flow' had more VAP and leg ischaemia episodes than 'low-flow' patients, but fewer bacteraemia and cannula site infections.

The median length of VA-ECMO support was 9 (5–15) days, with no differences between groups. The median length of time on MV was 4 (2–10) days, with a significantly shorter time in the 'low-flow' group [4 (1.5–7.5) vs. 6 (3–12) days, $P = 0.009$, respectively]. No differences were

found in the ICU length of stay or the days of hospitalization. The 'low-flow' group was more frequently bridged to transplant during the index admission (33% vs. 18%, $P = 0.015$), with no differences in rates of bridging to left ventricular assist device (LVAD) (24% vs. 20%, $P = 0.481$) (*Table 2*).

On the other hand, non-unloaded patients were less frequently bridged to HTx (21% vs. 41%), and the waiting time from ECMO implantation to HTx was significantly shorter [5 (1–15) days vs. 13 (5–165) days, $P = 0.031$]. Outcomes according to mechanical LV unloading are reported in Supporting Information, *Table S3*.

Comparison among in-hospital survivors did not show significant differences in either MV or VA-ECMO duration nor in ICU or hospitalization length of stay. In-hospital survivors did not present significant differences in rates of transplant or LVAD (Supporting Information, *Table S4*).

Finally, in-hospital mortality of the study population was 46%, with a non-significant lower mortality rate in the 'low-flow' group (41% vs. 51%, respectively, $P = 0.144$). Mortality at 60 days was comparable in the two groups (log-rank $P = 0.222$) (*Figure 3*).

Table 1 Baseline characteristics and outcomes of the study population according to the median VA-ECMO flow in the first 48 h

Variable	Study population (n = 209)	Low-flow (n = 104; 50%)	High-flow (n = 105; 50%)	P value
Age, years	51 (40–59)	51 (37–58)	52 (42–61)	0.194
Male sex	162 (78)	80 (77)	82 (78)	0.839
Body mass index	25.2 (23.1–27.8)	25.2 (22.2–27.6)	25.3 (23.4 29.4)	0.216
Diabetes mellitus	48 (23)	24 (23)	24 (23)	0.970
Dyslipidaemia	38 (18)	15 (14)	23 (22)	0.161
Pre-ECMO data				
Aetiology				0.023
Dilated cardiomyopathy	119 (57)	69 (66)	50 (48)	
Acute myocardial infarction	48 (23)	17 (16)	31 (30)	
Fulminant myocarditis	36 (17)	14 (13)	22 (21)	
Other	6 (3)	4 (4)	2 (2)	
SAPS II	51 (32–66)	40 (26–58)	56 (42–74)	<0.001
APACHE II	23 (12–32)	15 (9–28)	29 (17–35)	<0.001
SOFA pre-implantation	10 (6–13)	8 (5–12)	12 (8–14)	<0.001
SAVE score	−3 (−8 to 1)	−1 (−5 to 1)	−6 (−10 to 0)	<0.001
INTERMACS category				0.047
I	115 (55)	49 (48)	66 (63)	
II	79 (38)	44 (43)	35 (33)	
SCAI classification				<0.000
Stage D	59 (28)	44 (42)	15 (14)	
Stage E	150 (72)	60 (58)	90 (86)	
MV at implantation	114 (55)	38 (37)	76 (73)	<0.001
Inotrope score, μg/kg/min	37 (11–102)	18 (11–72)	57 (15–128)	0.029
pH	7.41 (7.26–7.46)	7.43 (7.36–7.49)	7.35 (7.20–7.44)	<0.001
Lactate pre-ECMO, mmol/L	4.5 (2.5–7)	3.6 (2.2–5.8)	5.2 (3–9.7)	<0.001
LVEF, %	15 (10–20)	15 (10–15)	15 (10–20)	0.144
Creatinine, mmol/L	135 (100–185)	125 (98–175)	147 (105–196)	0.078
AST, U/L	158 (52–720)	97 (41–375)	309 (85–939)	<0.001
Bilirubin, mmol/L	25 (14–39)	22 (13–36)	26 (15–41)	0.249
Mobile ECMO unit	62 (30)	22 (21)	40 (38)	0.007
Management				
ECMO flow D3, L/min	3.5 (2.9–4.2)	3.1 (2.6–3.5)	4.2 (3.6–4.7)	<0.001
ECMO flow D5, L/min	3.3 (2.8–4)	3.1 (2.6–3.4)	3.7 (3.2–4.3)	<0.001
ECMO flow D7, L/min	3.3 (2.7–3.9)	3.1 (2.7–3.5)	3.7 (2.9–4.3)	0.001
ECMO flow D14, L/min	3.5 (2.8–4)	3.2 (2.7–3.8)	3.7 (2.9–4.2)	0.13
LV unloading	139 (67)	72 (69)	67 (64)	0.406
Awake status[a]				<0.001
Awake	85 (41)	54 (52)	31 (30)	
Non-awake	124 (59)	50 (48)	74 (70)	
RRT	112 (54)	43 (41)	69 (66)	<0.001

Note: Values are expressed as median (interquartile range) or *n* (%). Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation II; AST, aspartate aminotransferase; D1, Day 1; D2, Day 2; D3, Day 3; D4, Day 4; D5, Day 5; D6, Day 6; D7, Day 7; D14, Day 14; ECMO, extracorporeal membrane oxygenation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVEF, left ventricular ejection fraction; MV, mechanical ventilation; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score II; SAVE, Survival after Veno-Arterial ECMO; SOFA, Sequential Organ Failure Assessment.
[a]Definition: ≤50% of the time of ECMO support without MV or >50% of the time of ECMO support with MV.
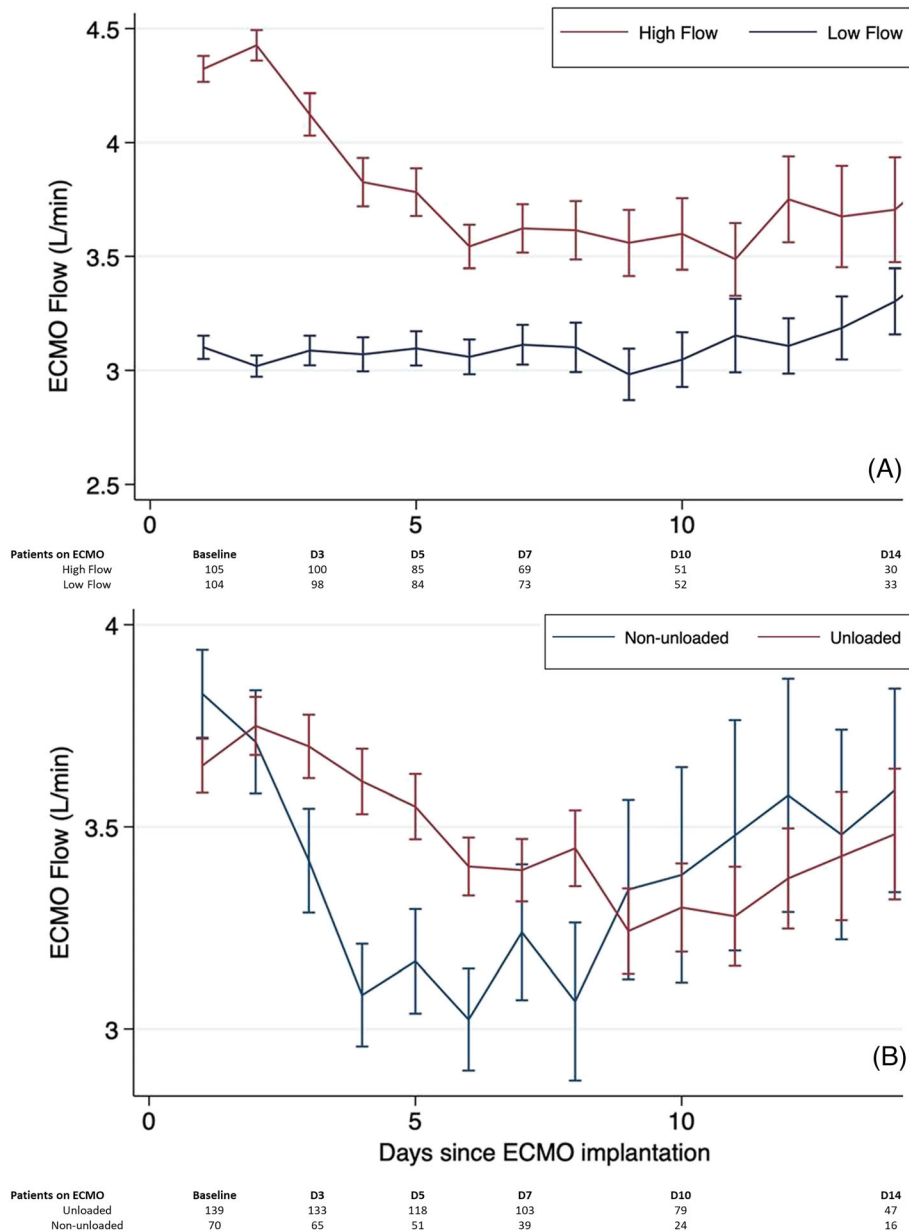
Discussion

Main findings

To the best of our knowledge, this is the largest study to report the time course, factors related to, and prognostic impact of ECMO flow on patients with VA-ECMO-supported refractory CS. In our population, sicker patients at ECMO cannulation were managed with higher flows from early stages and the divergence of ECMO flows was kept from initial assessments during the first week of support. Whereas the so-called 'high-flow' group had higher rates of VAP, the 'low-flow' had higher rates of 'awake ECMO' management and fewer days of MV but eventually did not have significantly different short-term survival when compared with

the high-flow group. The independently associated factors with higher ECMO support in the first 48 h were MV at implantation and pre-ECMO lactate. Finally, the decision of adding LV unloading was influenced by the aetiology of CS but did not affect survival in our cohort.

Nowadays, there is a lack of solid recommendations regarding the proper VA-ECMO flow throughout the different phases of CS. There is a variety of clinical practice recommendations ranging from 60–80 mL/kg[17] to 50–70 mL/kg,[18] or even 5 L/min during the first 24 h.[19] However, reported data on VA-ECMO flows in MCS literature are scarce and heterogeneous.[19–21] Theoretically, the amount of flow needed may vary widely throughout VA-ECMO support depending on the CS phase and the clinical profile of patients. Thus, patients with a more profound CS at admission are sup-

Figure 2 VA-ECMO support during the first 14 days showing the VA-ECMO flow in the 'low flow' vs. 'high flow' and unloaded vs. non-unloaded groups. (Panel A) Differences in VA-ECMO flow are overt during the first 3 days, reaching differences of 1 L/min between groups. Thereafter, differences began to shorten, mainly from D5. (Panel B) The VA-ECMO flows are not different in the early phases according to the unloading, but, thereafter, they tended to be lower in the 'non-unloaded' group. The predominance of myocarditis, the lesser bridge to transplant in the index admission, and the lesser ino-tropic support in early phases in the latter might suggest a perception of a lower severity by the treating physicians or a presumed prompt ECMO explantation because of a nearly expected heart transplant or in self-limited aetiologies like myocarditis. ECMO, extracorporeal membrane oxygenation.

posed to require a higher degree of VA-ECMO support, at least in the early phase. Similarly to our results, Truby *et al*. reported a median flow of 3.61 ± 0.84 L/min in the first 2 h in a study evaluating LV distension.[21]
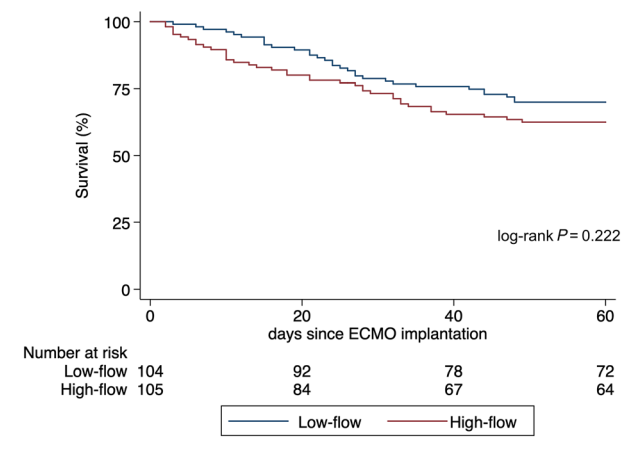
Not surprisingly, the independent factors related to early 'high-flow' were both related to clinical severity. Lactate is

the classical marker of tissular hypoperfusion. As such, the higher levels of lactate at cannulation in sicker patients may be logically associated with a higher degree of support in the early phases. Patients mechanically ventilated at VA-ECMO implantation are usually sicker, so again higher flows appear logical. Furthermore, MV at cannulation ap-

Table 2 Complications and outcomes of the study population according to the median VA-ECMO flow in the first 48 h

	Study population (n = 209)	Low-flow (n = 104; 50%)	High-flow (n = 105; 50%)	P value
Complications				
VAP	104 (50)	42 (40)	62 (59)	0.007
Stroke	35 (17)	18 (17)	17 (16)	0.829
Leg ischaemia	33 (16)	11 (11)	22 (21)	0.04
Bacteraemia	63 (30)	39 (37)	24 (23)	0.021
Cannula site infection	87 (42)	52 (50)	35 (33)	0.015
Conversion to central ECMO	17 (8)	7 (7)	10 (10)	0.460
Vena cava thrombosis	32 (15)	15 (14)	17 (16)	0.723
Outcome measures				
Days on ECMO	9 (5–15)	9.5 (5.5–17)	9 (5–15)	0.747
Days on MV, total	4 (2–10)	4 (1.5–7.5)	6 (3–12)	0.009
Days in ICU	22 (12–37)	22 (13–35)	21 (10–37)	0.515
Days of hospitalization	37 (24–66)	41 (24–70)	36 (21–62)	0.302
Bridge to transplant on ECMO admission	53 (22)	34 (33)	19 (18)	0.015
Bridge to LVAD	46 (22)	25 (24)	21 (20)	0.481
In-hospital mortality	97 (46)	43 (41)	54 (51)	0.144
Dead 60-D	70 (34)	31 (30)	39 (38)	0.239

Note: Values are expressed as median (interquartile range) or n (%). Abbreviations: 60-D, 60 days; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVAD, left ventricular assist device; MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

Figure 3 Kaplan–Meier survival curves at 60 days according to the VA-ECMO support in the first 48 h. Kaplan–Meier survival estimates for patients with 'low-flow' (blue line) and 'high-flow' (red line) showed lower mortality in the 'low-flow' group, although not reaching statistical significance. ECMO, extracorporeal membrane oxygenation.

most constant around 3.0–3.1 L/min in the 'low-flow' group. From D4 to D5, the differences began to decrease but remained constant until the end of the first week. Interestingly, despite having achieved practical normalization of levels of lactate, the 'high-flow' group kept a higher degree of VA-ECMO support after the acute phase was over, likely because of an increased perception of severity by the physicians in charge. Nevertheless, whether the worse prognosis was related to the initial greater severity or rather to the pulmonary effects of higher afterload remains uncertain and warrants future research.

In some circumstances, the severity of CS might drive to look for increasing VA-ECMO flows due to the refractoriness of multiorgan failure. However, disproportionately high VA-ECMO flows are not useful for improving microcirculation. This relates to the well-known lack of relationship between macrocirculation and microcirculation[22–24] and also corroborates the need of keeping VA-ECMO flow as low as possible to maintain the aortic valve opened, the mean arterial pressure > 65 mmHg, and normal lactate levels.

When comparing unloaded and non-unloaded patients, our findings showed a clear predominance of non-unloading in myocarditis compared with AMI or DCM. Indeed, reduced VA-ECMO flow in non-unloaded patients from D2 to D7 is accompanied by less pharmacological unloading with dobutamine. Likely, that might be explained by a perception of a lower severity by the treating physicians or a presumed prompt ECMO weaning because of an expected HTx or self-limited aetiologies like myocarditis.

The increase in afterload of VA-ECMO has potentially harmful consequences at the pulmonary level. Alveolar oedema produces local hypoxia, reduces the production of alveolar surfactant, produces local vasoconstriction, and, eventually, induces self-perpetuation of the systemic inflammatory response syndrome (SIRS).[25–28] These pulmonary effects may imply ventilator-induced lung injury and prolonged MV.[21] In our study, patients within the 'low-flow' group had a median of two fewer days of MV than the 'high-flow' patients. Although there may be clinical confounders, the previous pathophysiological effects could have contributed to prolonged MV. We believe our study is hypothesis-generating and this fact should be studied in specifically designed studies.

Clinical research on LV unloading has developed enormously in recent years. However, data on VA-ECMO flow in these studies are generally lacking and, in our opinion, are critical to understand the best time for implantation and to decide the best type of unloading device. In our experience, IABP is generally enough in most patients to unload the LV, especially if care is taken with disproportionate flows and LV distension.[21] In our study, 94% of unloaded patients were unloaded with IABP, whereas only 12 patients (9%) needed Impella. The usefulness of the IABP in reducing afterload and intraventricular pressures has been known for years, as well as its effect in reducing pulmonary oedema or days of

peared independently associated with reduced odds of 'awake ECMO' management,[11] and that might also have prognostic importance.

Median VA-ECMO flows were more than 1 L higher in the 'high-flow' group during the first 72 h of support, keeping al-

MV.[29] However, there exists up to seven different methods of unloading,[6,8,30] from which the combination of VA-ECMO and Impella (i.e. ECMELLA/ECPELLA) has recently gained strong attention.[30–34] In most of these studies, the mortality risk was reduced when unloading was added, yet the high rates of complications make its routine applicability dubious. At present, there is still a lack of a randomized controlled trial (RCT) comparing these strategies to define the time of implantation and the ideal clinical scenario.

In our study, the worse condition of the 'high-flow' group may have led to a greater number of complications. It is known that the probability of infection while on ECMO increases with the severity of illness before initiation of MCS,[35,36] so higher rates of VAP might have been likely conditioned by that. Yet, the potential impact of the pathophysiological mechanisms explained above cannot be disregarded, and therefore, our study aims to be suggestive rather than conclusive in terms of respiratory outcomes. Specifically designed RCTs evaluating different flow strategies in CS and modalities of LV unloading are now warranted to test if early high flows while on VA-ECMO do impact the length of MV, rates of VAP, or mortality.

Limitations

First, the present study has the inherent limitations of a retrospective design. However, we present the largest series of patients supported by VA-ECMO, reporting the VA-ECMO flow data throughout the first 14 days of support. Secondly, unavoidable confounding factors prevent the conclusion of any definitive association between flows and outcomes. However, even though sicker patients are managed with higher flows, it is plausible that an increased afterload may have an impact on prolonged MV duration or rates of VAP because of greater lung injury. Thirdly, VA-ECMO flows are dependent on preload, afterload, impeller revolutions, and static variables like diameter and cannula length, and we lack this information. Lastly, data on pulmonary congestion (x-ray, B-lines on pulmonary echo, or pulmonary artery catheter information)[37–39] would have enabled the comparison of flow impact and afterload on pulmonary pathophysiology but were not available for this study.

Conclusions

In patients with refractory CS supported with VA-ECMO, sicker patients were managed with higher support from early phases. Patients with high flows had higher rates of VAP and leg ischaemia, but their in-hospital and short-term survival were not significantly different compared with patients with lower flows. Independently related factors with a higher degree of VA-ECMO support were MV at cannulation and pre-ECMO lactate. Future research is now warranted to address the specific and direct impact of higher flows in lung injury or length of MV, as well as the best timing and type of unloading strategy for these patients.

Conflict of interest

CEL reports personal fees from Carmat, Merck, Biomérieux, Thermofischer Brahms, Bayer Healthcare, and Faron; AC reports personal fees from Getinge and Baxter; MS received lecture fees from Getinge, Xenios, and Dräger. The other authors declare that they have no competing interests.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the excluded population compared to the study population.
Table S2. Baseline characteristics according to the presence of mechanical left ventricular unloading during VA-ECMO support.
Table S3. Management and outcomes according to the presence of mechanical left ventricular unloading during VA-ECMO support.
Table S4. Outcomes of the in-hospital survivors according to the early ECMO flow.
Figure S1. Differences of VA-ECMO flow during the first 14 days according to in-hospital survival.

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