Original Article

Management of cardiac standstill on veno-arterial extracorporeal membrane oxygenation using a high flow strategy

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Background: Cardiac standstill may be observed during veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Management strategies to decompress the heart include left-sided vent (LSV) insertion or high flows without LSV. However, evidence that either method reduces mortality or neurological injury is unknown. In this study, we reviewed the outcomes of patients treated for cardiac standstill during ECMO with high flows instead of LSV placement.

Methods: Among 189 patients who underwent VA ECMO from 2010 to 2016, a total of 188 patients continued VA ECMO without LVS while on ECMO. Retrospective chart reviews were performed focusing on cardiac standstill while on ECMO. Cardiac standstill was defined as non-pulsatile arterial line tracing 6–8 hours after corrections of metabolic abnormalities. Patients who developed cardiac standstill were studied for the duration of cardiac standstill and their clinical outcomes.

Results: Twenty-two patients (12%) developed cardiac standstill during VA-ECMO. Nine (41%) survived ECMO therapy and 6 (27%) survived to discharge with full neurological recovery. Of the ECMO survivors, cardiac standstill was observed over 7 (range, 3–10) days and ECMO flow was increased by an average of 32%. Causes of death for non-ECMO survivors were anoxic brain injury (3, 23%), ischemic stroke (4, 31%), hemorrhagic stroke (2, 15%), sepsis (1, 7.7%), bleeding/disseminated intravascular coagulation (2, 15%) and malignant arrhythmias (1, 7.7%). Cardiac standstill persisted until death in all non-survivors. Intraventricular thrombi developed during standstill in 6 patients (27%) and resolved in 3 patients after 5.7±3.5 days. Causes of death were related to pre-existing conditions and anticoagulation regimen, not thrombus formation. Survival of patients with and without thrombi were similar (33% *vs.* 44%, P=0.999).

Conclusions: High ECMO flow adjustments can be an effective alternative to LSV as a method of decompressing the heart, without increasing neurological complications. With this strategy, patients diagnosed with cardiac arrest during ECMO have reasonable survival outcomes (40%).

Keywords: Extracorporeal membrane oxygenation (ECMO); cardiac arrest; ventricular distension; left-sided vent (LSV)

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Introduction

Complete cardiac standstill may be observed during veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for severe cardiogenic shock. Currently, there is no standard management strategy in the event of cardiac arrest during VA-ECMO. During cardiac standstill, intraventricular thrombus (IT) formation and potential neurological sequelae are concerns due to correlations with cerebrovascular occlusion (1). Left-sided vent (LSV)

insertion or left ventricular decompression devices, such as placement of Impella or trans-septal drainage catheter, are effective methods of decompressing the heart during ECMO, especially with left ventricular dysfunction and left heart dilatation (2). These procedures incur higher costs and more risk of complications as they require surgical intervention. Increasing ECMO flow, which drains the heart by increasing negative pressure on the venous system, can be an alternative to these invasive strategies. An ECMO circuit adjusted to provide high flows would decompress the heart and maintain perfusion of end organs during cardiac standstill. This study addresses whether a high ECMO flow strategy provides reasonable cardiac recovery without increasing the incidence of embolic event and other neurological complications for patients who develop cardiac arrest on VA-ECMO.

Methods

From 2010 to 2016, a total of 189 adult patients underwent VA-ECMO at our institution for cardiac support and were entered into an IRB approved database (IRB approval #11D.185). Both central and peripheral cannulation strategies were included in this study. Peripheral VA-ECMO involved percutaneous femoral artery and vein cannulation in addition to a distal limb perfusion cannula (3). Central VA-ECMO was started if the patient already had an open chest or if peripheral access was not feasible at the time. Central cannulation involved a sternotomy and surgical cannulation of the right atrium and ascending aorta (4).

Patients who had cardiac standstill for longer than 6–8 hours after correction of metabolic issues and temperature while on ECMO were included in this study. Patients who underwent LSV placement (1 patient) during VA-ECMO and patients on veno-venous ECMO (VV-ECMO) were excluded. Cardiac standstill was determined by non-pulsatile arterial line tracing and confirmed by visualization of a closed aortic valve using transesophageal (TEE) or transthoracic (TTE) echocardiography. The presence of spontaneous echo contrast (SEC) and IT formation were also recorded using echocardiography. Patient management involved increasing ECMO flow from a baseline calculation of body surface area ×2.2 L/mm. High ECMO flows were achieved by increasing the revolutions per minute (RPM) of the ECMO circuit (5). The higher flow rate was maintained until pulsatility returned or the patient was weaned off ECMO treatment for maximum decompression of the heart. Patient management for clot formation involved an anticoagulation regimen using heparin with a PTT goal of 50–65 seconds. Total time of cardiac standstill was calculated using arterial line pulsatility measurements obtained from electronic medical records.

Recovery of cardiac function was defined by pulsatility via arterial line tracing and confirmed qualitatively by ventricular activity with echocardiography. ECMO therapy was continued until full cardiac recovery or used as a bridge to a ventricular assist device (VAD) unless care was withdrawn. Weaning off of ECMO therapy was achieved by gradual decrease in ECMO flow as described before (6). ECMO survival, survival to discharge, neurologic complications, IT formation and cardiac recovery were retrospectively studied by reviewing patient medical records. Death was defined as the unsuccessful weaning off an ECMO circuit or withdrawal of care and termination of ECMO.

Results were expressed as a number with percentage, mean ± standard deviation, or median [quantile 1 – quantile 3] as appropriate. Statistical comparisons were performed using the Fisher's tests for categorical variables and the Student's *t*-test or non-parametric Mann-Whitney U-test for continuous variables using statistical software from R studio (R Studio, Boston, MA).

Results

Among the 188 VA-ECMO patients who had no LSV, 22 patients (12%) developed cardiac standstill while on VA-ECMO. Their demographics are displayed in *Table 1*. Cardiac standstill was diagnosed in these patients 1 day (0–1 day) after ECMO initiation and ECMO flow was increased by an average of 23%±15% from baseline. Nine patients (41%) survived ECMO therapy and 13 patients (59%) died. ECMO was continued for 8.9±6.6 days until cardiac recovery (8, 36%), VAD placement (1, 5%), or death (13, 59%). No patient developed aortic insufficiency on echocardiography during the therapy and there was no clinical significance of valvular abnormalities.

The demographics were compared between ECMO survivors and non-survivors after cardiac standstill was observed (*Table 2*). ECMO flow was able to be increased more in the ECMO survivors than in the non-survivors. There was no significant difference between arterial or venous cannula sizes used in ECMO survivors and non-survivors. The causes of death of ECMO non-survivors were neurological events (9/13, 69%), sepsis (1/13, 8%), bleeding/disseminated intravascular coagulation (DIC) (2/13, 15%) and non-recoverable cardiac function due

Table 1 Demographics of studied patients

Demographics	Patients studied (n=22)
Age (y)	50±17
Male gender	14 (64%)
Body surface area (cm^2)	1.87±0.27
pH	7.17±0.16
Lactate (mmol/L)	8.2±4.99
Reasons for ECMO placement	
Acute myocardial infarction	7 (32%)
Post-cardiotomy failure	6 (27%)
Acute on chronic heart failure	3 (14%)
Myocarditis	3 (14%)
Malignant arrhythmias	3 (14%)
Total days of ECMO	7 [4.5–11]
Central ECMO	4 (18%)
Peripheral ECMO	18 (82%)
E-CPR	3 (14%)

Data is expressed with number (percentage), mean ± standard deviation, or median [quantile 1 – quantile 3]. ECMO, extracorporeal membrane oxygenation; SEC-IT, spontaneous echo contrast and intraventricular thrombus.

to persistent ventricular tachycardia (1/13, 8%). Fatal neurological complications included anoxic brain injury (3/9, 33%), ischemic stroke (4/9, 44%), and hemorrhagic stroke (2/9, 22%). Cardiac standstill persisted among all non-survivors until death. One patient was bridged to a biventricular assist device, but eventually died from ischemic stroke after mechanical failure of the BiVAD.

Spontaneous echo contrast and intraventricular thrombus (SEC-IT) were observed in 6 (27%) of the patients who had cardiac standstill on ECMO. Comparisons between patients with and without SEC-IT are shown in *Table 3*. Three (50%) patients had resolution of their thrombi after 5.7±3.5 days, 2 (33%) of those patients survived to discharge and one patient subsequently died from a remote intracranial bleed. The survival rate and total cardiac standstill time between ECMO survivors observed with and without SEC-IT were both similar as shown in *Table 3*. The causes of death of patients who developed thrombi were listed in *Table 3*; deaths were related to the presence of intracardiac thrombus and not cardiac dysfunction.

After discontinuation of VA-ECMO, 6 patients (27%) survived to hospital discharge. The causes of death of the 3 patients who later died after being weaned off ECMO were sepsis (2 patients) and mechanical failure of the patient's VAD (1 patient).

Discussion

A major concern with extended cardiac standstill is ventricular distension due to the lack of ejection and persistent closure of the aortic valve (7). If decompression is not adequately provided, recovery of cardiac function can be significantly limited. In addition, afterload from retrograde VA-ECMO flow may further contribute to the over-distension and ischemic damage of the heart (8). Left-sided dilatation during cardiac standstill also increases the risk of blood stasis and thrombus formation, which could lead into cerebrovascular accidents. As a result, management of ventricular distension and neurological complications are critical aspects of care for patients who experience cardiac standstill on VA-ECMO.

Conventional methods of cardiac decompression involve LSV, a practice based on open- heart surgery and cardiopulmonary bypass. While LSV placement can be effective at reducing cardiac distension, it frequently requires operative interventions. Decompression and drainage from the left sided heart is also not always guaranteed when compared to a cardiopulmonary bypass circuit, which can measure vent flow using a separate roller pump. ECMO is a closed circuit and drainage depends on the size of the cannula. LSV drainage can be minimal as it represents only a portion of the total ECMO flow.

Left-sided venting can be achieved in a number of ways. A surgeon can directly cannulate the left ventricle or the left atrium, though this technique may be more relevant for patients with an open chest or a central ECMO circuit as it requires a sternotomy. A disadvantage of central cannulation is the increased risk of mediastinal bleeding from surgical intervention (9). Combination use of Impella with ECMO is another strategy that are shown to reasonably decompress the left. However, precise placement is required and there is a significant risk of intravascular hemolysis because of presence of two pumps (Impella and ECMO) (10-12).

Creation of trans-septal shunt between the left and right atria and placement of additional venous drainage cannula in the left atrium and draining blood to the venous side of the ECMO circuit could be alternative option of ventricular decompression (13). This strategy requires a catheterization laboratory setting for placement and may

Table 2 Demographics of studied patients

Demographics	ECMO		P value
	Survivors (N=9)	Non-survivors (N=13)	
Age (y)	53±18	49±16	0.598
Male gender	5 (56%)	9 (69%)	0.512
Body surface area (cm^2)	1.79±0.33	1.87±0.27	0.555
pH	7.23±0.11	7.14±0.15	0.121
Lactate (mmol/L)	5.8±3.9	10.4±5.7	0.036
Arterial cannula size (Fr)	19±1	20±2	0.518
Venous cannula size (Fr)	20±3	22±2	0.105
Reasons for ECMO placement			
Acute myocardial infarction	2 (22%)	5 (38%)	0.421
Post-cardiotomy failure	3 (33%)	3 (23%)	0.595
Acute on chronic heart failure	2 (22%)	1 (8%)	0.329
Myocarditis	2 (22%)	1 (8%)	0.329
Malignant arrhythmias	0 (0%)	3 (23%)	0.121
Total days of ECMO	7 [6–16]	7 [3–10]	0.120
Peripheral ECMO	8 (89%)	10 (77%)	0.474
E-CPR	0 (0%)	3 (23%)	0.121
Days of ECMO before cardiac standstill	1 [0–3]	1 [0–1]	0.295
Days of cardiac standstill	7 [3–9]	7 [3–10]*	1.000
ECMO flow increase (%)	32±9	16±17	0.010
SEC-IT (%)	2 (22%)	4 (31%)	0.658

Data is expressed as a number (percentage), mean ± standard deviation, or median [quantile 1 – quantile 3]. *, patients died before the end of ECMO treatment. E-CPR, ECMO assisted cardiopulmonary resuscitation; SEC-IT, spontaneous echo contrast and/or intraventricular thrombi.

require intervention of the atrial septum once the draining cannula is removed.

In our patients, thrombus development is defined by the presence of SEC-IT, which is associated with blood stasis in a compromised left ventricle that is not adequately drained (14,15). SEC-IT is clinically important because it can lead to ischemic stroke and anoxic brain injury (16). However, there is no consensus on a treatment protocol and the frequency of clot development in VA-ECMO patients is not known. Adjustments to anticoagulation regimen, the current standard of therapy, may cause bleeding complications and massive thrombus development has been shown to occur even with adequate anticoagulation (17). Preventing blood stasis in the cardiac chambers may be key to minimizing cerebrovascular accidents from thromboembolism. Thus, decompressing and draining the LV by placing LVS could minimize the blood stasis and risk of thromboembolism.

This study suggests that high flows without venting is an alternative method of ventricular decompression in VA-ECMO patients experiencing cardiac standstill. We acknowledge that maximum flow is limited in part by the size and location of the cannulas used (18). However, our high flow strategy does not require additional interventions, it reduces the risk of introducing further iatrogenic complications such as post-surgical bleeds and infection. In addition, high flows do not pose the same risk of intravascular hemolysis that Impella devices inherently have. Before ECMO initiation, all patients had biventricular failure. Our

Table 3 Comparison of outcomes in patients with intracardiac thrombus and without intracardiac thrombus

Outcomes	With SEC-IT (N=6)	Without SEC-IT (N=16)	P value
ECMO survivors	2 (33%)	7 (44%)	0.658
Days of cardiac standstill	6.0±4.2	6.7±4.5	0.736
Number of patients with resolution of thrombus	2	N/A	N/A
Days to resolve thrombus	5.7±3.5	N/A	N/A
Hospital (30-day) survivors	2 (33%)	4 (25%)	0.696
30-day mortality (including death while and after ECMO)	4 (67%)	12 (75%)	0.696
Causes of death during and after ECMO			
Anoxic brain injury	0	3 (19%)	0.254
Ischemic stroke	1* (17%)	3 (19%)	0.910
Hemorrhagic stroke	2 (33%)	0	0.015
Bleed/DIC	0	2 (13%)	0.364
Sepsis	0	3 (19%)	0.254
Cardiac function/VAD failure	1** (17%)	1*** (6.3%)	1.000

Data is expressed with number (percentage) or mean ± standard deviation. *, patient was in a hypercoagulable state prior to ECMO cannulation; **, patient had refractory ventricular tachycardia prior to ECMO cannulation; ***, patient died after VAD placement due to mechanical VAD failure. DIC, disseminated intravascular coagulopathy; SEC-IT, spontaneous echo contrast and/or intraventricular thrombi; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; N/A, not applicable.

data shows that increasing ECMO flow sufficiently reverses both right and left ventricular distension without causing aortic insufficiency and cardiac recovery is not affected by pre-existing valvular abnormalities. Sufficient ventricular decompression is qualitatively determined by echo, which does not provide a numerical representation of this end-point. All patients that survived to discharge have reasonable cardiac recovery and no patient died on ECMO therapy due to the development of irreversible cardiac complications. The patient who died from non-recoverable cardiac function had uncontrollable ventricular arrhythmias prior to ECMO therapy and remained in refractory ventricular tachycardia until death. In patients with thrombus development, high ECMO flow prevents progression to thromboembolic events. 50% of our patients have full SEC-IT resolution by 7.5±2.1 days and all VA-ECMO survivors with thrombus do not develop neurological complications.

A recognized possible side effect of increasing ECMO flow is an increase in cardiac afterload. Effects of increased afterload can include further distension of the left ventricle, increase in myocardial oxygen demand and precipitation of myocardial ischemia (19,20). Many of the techniques described above, including Impella devices and intra-aortic balloon pumps (IABP), have been recommended to avoid overloading the heart during ECMO therapy. Recent reports on IABPs suggest evidence is not clear that these strategies improve survival and reduce multi-organ failure (21). In this study, we use the increase in afterload from high flows to guarantee end-organ perfusion. We find that despite the increase in perfusion pressure and afterload, patients who are successfully weaned to discharge have full cardiac recovery. While it is prudent to closely monitor the afterload stress on the heart, this strategy preserves our clinical outcomes of interest.

The majority of patients (9/13, 69%) who did not survive ECMO treatment suffered from neurological injury unlikely related to embolization from SEC-IT. The patient with thrombus development who died from ischemic stroke was in a hypercoagulable state prior to ECMO cannulation leading up to his cerebrovascular accident. However, adjustments to the anticoagulation regimen of 2 patients may have played a role in the development of their fatal brain bleeds. While high ECMO flows alone is effective, a combination therapy with LSV insertion may further improve patient outcomes and decrease mortality. Of note, the increase in ECMO flow is significantly lower in those who died compared to the survivors (16% *vs.* 32%), even though there is no significant difference between

arterial and venous cannula sizes, respectively. While all non-survivors could not comparatively tolerate high flows, they all died from neurological complications. The inability to increase flow may therefore be attributed to poor pre-ECMO conditions, including having insufficient intravascular volume due to third spacing or surgical hemorrhage. For these patients who were not able to optimize ECMO flow, a LV drain insertion, such as an Impella device, or trans-septal drainage cannula may provide additional relief in unloading the left ventricle.

Limitations

A small patient population and retrospective design limit this study. Ideally, we would be able to perform a comparative analysis between patients with LSV and patients treated with high ECMO flows. The lack of ECMO patients with LSVs due to institutional management protocols restricts the scope of our study.

Conclusions

Maintaining high ECMO flow provides sufficient end-organ perfusion until recovery of ventricular function, even if the patient experiences cardiac standstill for a significant amount of time. If catastrophic neurological damage can be avoided at the onset of cardiac arrest, these patients have reasonable survival outcomes and a relatively clear road to recovery with preservation of end-organ function. Given its non-invasive and simple treatment modality, high flows should be strongly considered for cases where vent insertion may incur serious complications.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.11.03). This paper was presented at ASAIO 2018 in Washington DC, 06/14/2018. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the IRB of Thomas Jefferson University (IRB approval #11D.185). Informed consent was waived due to the retrospective nature of the study.

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