

## Review Article

# Review of Venoarterial Extracorporeal Membrane Oxygenation and Development of Intracardiac Thrombosis in Adult Cardiothoracic Patients

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**Abstract:** Venoarterial extracorporeal membrane oxygenation (VA ECMO) has become an indispensable treatment option for adult cardiothoracic patients experiencing acute refractory cardiogenic shock. VA ECMO is not without inherent complications as in-hospital mortality has ranged from 45% to 65% (1–3). Intracardiac thrombosis (ICT) is a rare but life-threatening complication associated with VA ECMO. VA ECMO cases complicated by ICT were searched for using the MEDLINE (PubMed and OVID), Society of Cardiovascular Anesthesiology Headquarters, and Google Scholar databases. Twelve cases of VA ECMO-associated ICT were discovered for review. Indications for VA ECMO were postcardiotomy cardiogenic shock and

heart failure. The primary location of thrombus was the left ventricle and aortic root. Majority of the cases did not report subtherapeutic systemic anticoagulation. Two patients survived after the development of ICT. VA ECMO-associated ICT is a devastating consequence with high mortality. The majority of ICT occurred in cases with perceived adequate anticoagulation, but this may not result in complete suppression of the coagulation response. Continued exposure to procoagulant stimuli and worsening ventricular function and intracardiac stasis can shift the balance toward a hypercoagulable state and development of thrombosis. **Keywords:** venoarterial extracorporeal membrane oxygenation, thrombosis, coagulation, cardiothoracic. *J Extra Corpor Technol. 2016;48:162–7*

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The first successful use of extracorporeal membrane oxygenation (ECMO) in an adult occurred in the early 1970s, and remains a mainstay of acute peri-interventional treatment for the adult cardiothoracic patient. Heart failure, postcardiotomy cardiogenic shock, and cardiac arrest are unfortunate complications in this patient population and venoarterial ECMO (VA ECMO) has become a valuable management option to allow for recovery of cardiopulmonary function while maintaining hemodynamic stability. VA ECMO complicated by thromboembolic disease has a mortality rate of 8.7% ( $n = 108$ ) (4). Intracardiac thrombosis (ICT) associated with VA ECMO is rare but devastating event in terms of worsening mortality given the risk of cerebral, renal, and mesenteric embolization. The true

incidence of cardiac thrombotic complications with VA ECMO is not well documented in the literature, and what information is known is based off of case reports. The low incidence seen in the literature is likely secondary to underreporting, but may also be the result of underdiagnoses given that in postcardiotomy VA ECMO patients, systemic thrombosis was diagnosed in post mortem examinations in 24 of 59 cases (5). Primary disease pathology including depressed ventricular function, ongoing coagulation activation caused by continued blood exposure to a synthetic surface, and hemostatic imbalances likely contribute to a prothrombotic state and increase risk of ICT development. We therefore sought to compile all cases of VA ECMO-associated ICT in cardiac patients to delineate and summarize case characteristics, potential risk factors, and outcomes after development of ICT.

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## METHODS

A search of the literature involving VA ECMO-associated ICT in adult cardiothoracic patients was performed

using the MEDLINE (PubMed and OVID), Society of Cardiovascular Anesthesiology headquarters (SCAHQ), and Google Scholar databases. The following key words were used in the search: “veno arterial extracorporeal membrane oxygenation,” “VA ECMO,” “intracardiac thrombosis,” “intracardiac clot,” “thromboembolic,” “hypercoagulable state,” and “emboli(c).” We included all case reports of adult cardiothoracic patients on VA ECMO that developed ICT regardless of year of publication. Cases without adequate clinical information, cases not in the English language, cases with subjects <18 years old, patients with prior diagnosis of ICT before initiation of VA ECMO, adult cardiopulmonary bypass (CPB) cases without VA ECMO, ventricular assist devices without VA ECMO, and cases with suspected but unconfirmed ICT were excluded. Venovenous ECMO cases were not included given the limited possibility of arterial systemic thrombosis.

Eleven articles met inclusion criteria for a total of 12 cases of VA ECMO-associated ICT. One case report included two individual cases. Each case was analyzed for demographics, and clinical information including age, gender, weight, primary diagnosis, surgical intervention if applicable, anticoagulation management, and outcomes and survivals. Continuous variables are presented as mean values and categorical variables are presented as total number of events over total number of cases.

## RESULTS

There were 12 cases from 11 case reports between 2008 and 2015 (Table 1) with a small predominance of male patients (7/12) over females (5/12), and the mean age of patients was 46 years with a range of 19–73 years (6–17).

ICT was diagnosed with transesophageal echocardiography (TEE) in all 12 cases. The majority of cases (9/12) included left-sided thrombus, primarily of the left ventricle, but also could include the pulmonary veins, left atrium, and aorta. Three cases had isolated aortic root and ascending aorta thrombus and one case developed bilateral thrombi including the pulmonary artery and the right and left ventricles. Time to diagnosis of ICT was an average of 3 days (range 1–7 days) and TEE was prompted by a variety of clinical situations including hemodynamic instability or failure to wean from ECMO (5/12), but also as part of further follow-up, post intervention, or during chest washout.

Primary indication for institution of VA ECMO was cardiogenic shock secondary to myocardial infarction (8/12). In the remaining cases, one required VA ECMO secondary to primary graft failure following heart transplant, one developed nonischemic cardiomyopathy following a viral illness, and two cases had worsening heart failure secondary to hypertrophic obstructive cardiomyopathy (Table 2).

Eight cases explicitly reported using heparin anticoagulation during VA ECMO, three cases reported use of anticoagulation but did not provide specific details, and one declined use of anticoagulation secondary to coagulopathy. Activated partial thromboplastin (aPTT) time was followed the majority of the time (7/12), followed by activated clotting time (4/12), and anti-factor Xa levels were followed in one patient. aPTT ranged from 44 to 97.3 seconds; in one case aPTT was elevated (97.3 seconds) while antifactor Xa levels were .1 IU/mL (11).

Two patients survived within this series. The first required VA ECMO secondary to ischemia-induced cardiogenic shock, and underwent placement of HeartMate II

**Table 1.** Summary of cases: VA ECMO-associated ICT in cardiothoracic patients.

Reference No.	Age/Sex	Days on ECMO	Anticoagulation	ACT or PTT Range (Second)	TEE	Thrombi Location	Outcome
6	65/M	NR	*NR	*Therapeutic	Y	LV	Survived
7	20/F	6	*NR	PTT 44–65 ACT >160	Y	PV, LA, LV	Expired
8	35/F	7	Heparin	NR	Y	Asc Aorta	Expired
9	58/M	2	Heparin	PTT 64 ACT 434	Y	Ao root, Asc Aorta	Expired
10	37/M	3	Heparin	PTT 47	Y	PA, RV, LV, AV	Expired
11	45/M	3	Heparin	PTT 97.3	Y	LV	Expired
12	51/F	1	Heparin	PTT 85.7	Y	LA, LV	Expired
13	57/M	<1	Heparin	PTT 79.9	Y	LA, LV, Asc Aorta	Expired
14	73/M	3	Heparin	PTT 44–65		Ao Root, Asc Aorta	Expired
15	49/F	2	None	NA	Y	LV	Expired
16	54/F	2	Heparin	ACT 160–180	Y	LV	Survived
17	19/M	4	*NR	NR	Y	LV	Expired

Ao, aorta; ACT, activated clotting time; Asc, ascending; AV, aortic valve; BiV, biventricular; CHF, congestive heart failure; F, female; LA, left atrium; LV, left ventricle; M, male; MI, myocardial infarction; NA, not applicable; NR, not reported; PA, pulmonary artery; PV, pulmonary veins; PTT, partial thromboplastin time; RV, right ventricle; VSD, ventricular septal defect.

\*Authors reported “therapeutic anticoagulation” or use of anticoagulation but did not specify further details including either type of anticoagulant used or anticoagulation laboratory monitoring results.

**Table 2.** Shows description of primary patient diagnosis, description of procedures, and subsequent management following diagnosis of ICT.

Primary diagnosis	
Myocardial infarction	8
Hypertrophic obstructive cardiomyopathy	2
Primary graft failure (post heart transplant)	1
Unspecified cardiomyopathy	1
Procedure	
Coronary artery bypass graft	2
Orthotropic heart transplant	1
Ventricular assist device	1
TandemHeart (CardiacAssist, Inc., Pittsburgh, PA)	1
Ventricular assist device	1
Percutaneous coronary intervention/angiography	3
Transcatheter ablation of septal hypertrophy	1
None	3
Management following ICT diagnosis	
Thrombectomy	2
TNKase	1
Total artificial heart	1
LV assist device	1
Anticoagulation adjustment	2
Closure of proximal ascending aorta	1

(Thoratec, Pleasanton, CA) left ventricular (LV) assist device and concurrent thrombectomy (6). The second survival, after failure to improve with increasing anticoagulation, had localized injection of recombinant tissue plasminogen activator (TNKase<sup>®</sup>; Genetech USA, Inc., South San Francisco, CA) into the LV cavity via a LV vent with resolution of thrombus in 24 hours (16). The remaining patients developed neurological injury or severe multiorgan failure resulting in withdrawal of care. Two patient developed cerebral emboli (10,11) and one patient developed liver emboli and died from acute liver failure (7).

## DISCUSSION

VA ECMO has an increasing range of applications in the adult cardiothoracic population including hemodynamic support for heart failure, postcardiotomy cardiogenic shock, and as a rescue therapy following cardiac arrest. A complication of VA ECMO is the development of ICT and subsequent cerebral, renal, or mesenteric embolization and worsen patient prognosis. Due to the rarity of this complication, the actual incidence of ICT on VA ECMO is not well documented in the literature, but several case reports have made clear the significant mortality associated with this event.

### Factors Associated With a Prothrombotic State

Following endothelial tissue injury thrombin is produced, but generation increases dramatically after initiation of CPB and exposure of blood to the extracorporeal circuit as evident by significant increases in markers of thrombin

generation (18). The extracorporeal circuit is a strong pro-coagulant stimulus, and in simulated experiments, there is a modest increase in activated factor XII that drives production of thrombin and activation of factor VII (19). A combination of production of extrinsic tenase (tissue factor and FVIIa) from tissue factor exposed at surgical wound sites and contact activation on account of continued exposure to a synthetic surface maintains coagulation activation, and results in greater systemic thrombin generation over localized reactions (19).

Advances in the material design of ECMO circuits attempt to increase hemocompatibility, suppress the inflammatory and coagulation responses, and reduce thrombogenicity of the circuit (20). Newer hollow fiber and more compact oxygenators allow for reduce direct contact of blood elements with the synthetic components in attempts to attenuate the coagulation response (21).

For the same reasons, there has been a trend toward use of heparin-bonded circuits. In 2006, a survey of 220 ECMO specialists reported that 45% were exclusively using heparin-coated or biocoated circuits (22), and prior studies demonstrated reduced degree of contact pathway activation based on decrease fibrin deposition on the oxygenator (23). Prior reports evaluated the use of heparin-coated circuits without systemic anticoagulation and reported several incidences of ICT in postcardiotomy patients (24,25), including one study that found a 20% incidence of ICT ( $n = 30$ ) after recognition of thrombotic material within the mechanical pump (26). It appears that improved biocompatibility of ECMO circuitry does not negate the use of systemic anticoagulation to prevent thromboembolic disease, but rather aids in attenuating the coagulation response induced by the synthetic circuit.

Coagulation responses are traditionally suppressed with intravenous unfractionated heparin, which exerts its therapeutic effects through enhancement of antithrombin III (ATIII) activity; a primary endogenous anticoagulant that inhibits circulating unbound thrombin (FIIa) and factor Xa (FXa). In the presence of ongoing thrombin generation and accelerated bonding of ATIII and thrombin secondary to heparin, ATIII is constantly consumed resulting in deficient plasma activity and acquired deficiency (27). Increased thrombotic risk was seen with ATIII activity less than 70% ( $n = 823$ , hazard ratio = 3.48; 95% CI = 2.16–5.61), and when analyzed as a continuous variable, progressive declines in ATIII activity were associated with increasing risk of venous thromboembolism (VTE) recurrence (28). It is difficult to achieve clinical anticoagulation with heparin when ATIII falls below a certain level. Intravenous heparin was found to have a decrease dose response with declining plasma activity of ATIII, and at activity levels below 30%, heparin became undetectable as measured by anti-factor Xa assay, and recovery was dependent on ATIII and heparin supplementation (29,30).

Circuit and oxygenator replacements secondary to thrombogenic material may precede a systemic thrombotic event partly due to insufficient anticoagulation, and have been associated with lower anti-FXa activity and lower ATIII levels (31). The literature is controversial regarding the routine use of ATIII supplementation in ECMO patients given heterogeneous findings regarding clinical outcomes. A study by O'Meara et al. reported that routine ATIII supplementation in pediatric ECMO cases did not reduce the number of oxygenator/circuit changes. A difference may not have been detected as this patient population had significantly low baseline ATIII levels, and received 500 IU of Thrombate III® (Grifols Inc., Barcelona, Spain) regardless of activity level which may not have been sufficient supplementation (32). Adequate ATIII activity appears to be necessary to prevent suboptimal anticoagulation, but is likely only a piece of the mechanism behind ICT formation.

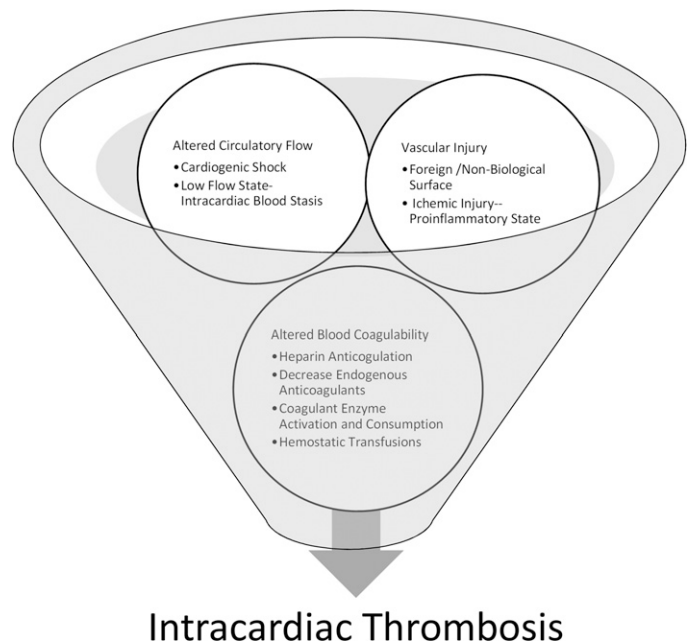
Severely depressed ejection fraction, cardiogenic shock, and hypertrophic ventricles were common findings within this population. Development of LV thrombosis secondary to akinetic or dyskinetic wall segments is present in 7–46% of patients presenting with acute myocardial infarction and ventricular dysfunction (33). Decrease contractility of the dilated ventricular cavity leads to increase potential for intracavitary blood stasis. Patients are often on inotropic support to help maintain ventricular ejection in the presence of VA ECMO. If LV ejection is negligible with inadequate decompression of the left ventricle, reduction of blood flow leads to intracardiac blood stasis and increase risk of ICT. Clinicians may consider placement of a LV vent to improve decompression. A few reports have shown promising results regarding placement of trans-aortic LV vents, simultaneous use of the Impella® system (Abiomed, Danvers, MA) or intra-aortic balloon pumps, and placement of pulmonary vein LV vents with central VA ECMO cannulation to aid in ventricular unloading (34,35). In addition, patients with known or suspected incomplete ventricular unloading (i.e., ventricular distention, spontaneous echo contrast, loss of pulsatile arterial waveform) may benefit from increase serial echocardiographic monitoring and adjustments in anticoagulation management; balancing this with possible increased bleeding risk.

The development of ICT with VA ECMO is multifactorial involving a coalition of several processes (Figure 1). The pathophysiological factors underlying VA ECMO-associated ICT are likely a combination of incomplete suppression of the coagulation response, imbalances between endogenous procoagulant and anticoagulant factors, inadequate systemic anticoagulation, and significant intracardiac and intra-aortic blood stasis promoting a prothrombotic state. Deficiencies in other endogenous anticoagulants or undiagnosed thrombophilia may also contribute to this phenomenon.

### Alternative Anticoagulation Management

Alternative anticoagulation monitoring techniques have been proposed to optimize anticoagulation and further prevent thromboembolic events in patients on VA ECMO. Anti-FXa levels are subject to less variation due to coagulation deficiencies, thrombocytopenia, and hypothermia (36). Anti-FXa assay showed less variability and outliers over the aPTT and ACT with heparin dosing (37). Target assay levels of .3–.7 IU/mL are recommended, and anti-FXa levels can provide further insight into anticoagulation, given that an elevated aPTT can occur with subtherapeutic heparinization as in the case report by Gaide-Chevronnay et al. (aPTT = 97.3 seconds and anti-FXa = .1 IU/mL) (11). Monitoring of global coagulation may also prove beneficial in providing further information in regard to actual thrombin generating potential and evaluation of bleeding or thrombotic risk in a heparinized patient (36).

Bivalirudin as an alternative to heparin therapy in VA ECMO patients confers some advantages including no dependence on ATIII to exert its therapeutic effects, and produces higher ACT and aPTT values (38). Although there has been concerns regarding increase bleeding with the use of intravenous direct thrombin inhibitors, similar bleeding rates were seen with bivalirudin when compared to heparin, and there was a small difference in the number of thrombotic events (three thrombotic events in the heparin group vs. one in the bivalirudin group) (39).



**Figure 1.** Proposed pathophysiological factors involved in formation of ICT on VA ECMO. It shows the interactions of elements involved in ICT formation on VA ECMO based on Virchow's triad of creation of a prothrombotic state.



Argatroban has had less promising results, as one small series showed significant increase in bleeding in ECMO patients, but bleeding complications decreased and therapeutic anticoagulation was still achieved, when a 10-fold lower dose than the manufacturer recommendation was used (40). Current information is based on a limited number of retrospective and prospective studies, and larger trials are still needed.

### Patient Outcomes

Management of VA ECMO-associated ICT is a unique challenge secondary to balancing risk of bleeding with treatment of thrombotic disease. Overall survival in this patient population is low and optimal management strategies remain unclear. The majority of patients (10/12) expired secondary to subsequent multiorgan failure, or care was withdrawn after critical neurological insult. Upon discovery of ICT following CPB, thrombectomy was performed in the majority of cases (41); however, this exposes the patient to additional surgical risk and further complications. In our series, in the two patients that underwent surgical thrombectomy only one survived and had received simultaneous LV assist device (6). The second patient that survived received TNKase<sup>®</sup> via an LV vent (16). In four of the reported cases, there was limited additional management options given the presence of cerebral insult or multiorgan failure (11,13,14,17), and no further steps were taken following diagnosis. Average time to diagnosis was 3 days; it is possible that with increased surveillance and earlier detection, clinicians may be able to intervene earlier and decrease morbidity of this complication.

### Limitations

The drawbacks of this review are the low incidence of VA ECMO-associated ICT in adult cardiac patients yielding limited clinical information. In addition, due to a larger body of pediatric literature, certain findings were extrapolated from the pediatric to the adult population to garner further clinical insights by using available existing data. Finally, despite the greater number of neonatal and pediatric VA ECMO patients, clinically significant arterial thrombotic events compared to adults are infrequent based on analysis of ECMO-related complications reported to the national extracorporeal life support registry, and therefore pediatric patients were not included in this review (42,43).

### CONCLUSIONS

The majority of ICT occurred in cases with severe LV dysfunction, and incomplete ventricular unloading promoting intracavitary blood stasis. Anticoagulation was perceived as adequate with each case, but with limitations of

standard coagulation test and ongoing coagulation activation and consumption of ATIII, ineffective heparin therapy may not be detected. It is still unclear based on the abovementioned factors the reason ICT occurred in these patients, but addressing these questions would require a more thorough retrospective analysis. The development of ICT is followed by a rapidly deteriorating course and is associated with high mortality.

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