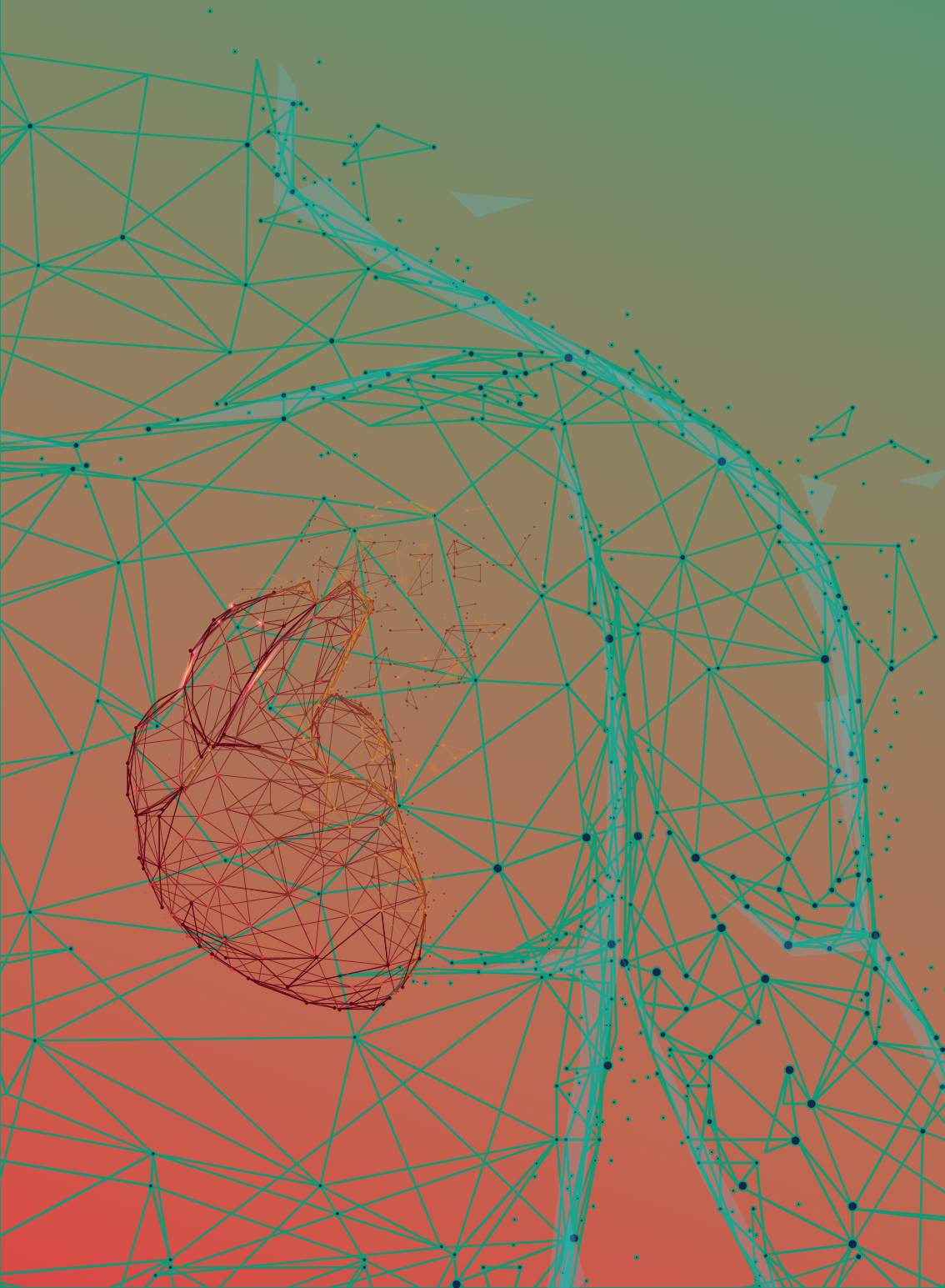
ISSUE 22

PRIME

Perfusion-Related Insights – Management and Evidence



- Specialty insights
- Basic Facts
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TERUMO

Editorial Letter

It is with immense pleasure that we present the 22nd issue of PRIME Newsletter — "Perfusion-Related Insights–Management and Evidence" — a quarterly scientific newsletter that includes review articles, case reports, randomized control trials, expert opinions, and practice pearls on cardiopulmonary bypass (CPB) and perfusion strategies.

The current issue brings you interesting articles and guideline recommendations, starting with the first section 'Speciality Insights' which is comprised of three articles. The first article is a systematic review and meta-analysis which summarizes the use of direct thrombin inhibitors (DTIs) over heparin in patients during ECMO support. The second article under this section highlights the risk of development of postoperative stroke due to perioperative bleeding and blood transfusions after surgical (SAVR) and transcatheter aortic valve replacement (TAVR). The third article of this section investigates a possible significant correlation between perioperative COVID-19 infection and hemorrhagic complications in COVID-19 positive patients who underwent CPB surgery.

The second section, 'Basic Facts', contains two articles. The first article is a review which presents the efficacy and safety of A-II (Angiotensi II) in the management of post-CPB vasoplegia. The second article in this section spread awareness among clinicians regarding the significant risk of VA-ECMO-related aortic stasis.

The third section 'Practice Pearls' contains a case study of two cardiac patients with mesenteric artery embolism associated complications and their treatment with ECMO support for improvement in prognosis.

The next section 'Journal Talk' exhibits the monitoring of heparin and protamine with the help of the standard ACT+ test in two cases of CPB with severe FXII deficiency.

The fifth section 'Expert Opinion' contains three articles. The first article describes management of anticoagulation during ECMO in children. The second article of this section highlights the association between long-term beta-blocker therapy and major adverse cardiovascular events (MACEs) in CABG patients. The third article describes the main indications for therapeutic plasma exchange in ICU.

The sixth section, 'Success Stories', contains two articles. The first article is a case study showing successful use of Cytosorb® hemoadsorption column during prolonged CPB in complex cardiac surgery. The second article is also a case report on successful treatment of a child with COVID-19 reinfection-induced fulminant myocarditis by Cytokine-adsorbing oxiris® hemofilter continuous with VA-ECMO.

The seventh section of this newsletter 'News Corner' contains therapeutic advances in guideline-directed medical therapy for heart failure.

We hope this newsletter enriches your knowledge with the current practices and research updates in the field of CPB and perfusion.

Kindly let us know your comments and suggestions to help us improvise from the next edition.

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PRIME Newsletter invites new authors for their contribution to the perfusion community. If you are interested in volunteering your time writing an article or a topic of your expertise and willingness to share your knowledge with our readers, we certainly encourage you to do so. We invite everyone interested in joining our team, and you can contact us at the email given below. Any amount of time that you can volunteer in adding to our quality of publication will be greatly appreciated. Thank you for your interest in PRIME Newsletter. What are you waiting for?

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EVALUATION OF CLINICAL OUTCOMES IN PATIENTS TREATED WITH HEPARIN OR DIRECT THROMBIN INHIBITORS DURING EXTRACORPOREAL MEMBRANE OXYGENATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Introduction

- The number of patients treated with ECMO devices has continuously increased
- Heparin is a standard therapy for anticoagulation in ECMO patients to prevent coagulation
- However, heparin induced thrombocytopenia and heparin resistance are the major problems which require the use of alternative anticoagulants such as direct thrombin inhibitors (DTIs) like bivalirudin and argatroban
- The current study evaluated clinical outcomes in patients treated with DTIs compared to heparin during ECMO

Methods

- Systematic research was performed in electronic medical databases from inception to January 2022 to screen relevant articles including argatroban or bivalirudin (DTIs) and heparin in ECMO patients (included full-text)
- The primary endpoint was in-hospital mortality
- Secondary endpoints were bleeding events, thrombotic events, hours of ECMO support, days of hospital stay, percentage of time within therapeutic range and time to therapeutic range

Results

- 18 relevant articles were included in the final data synthesis
- A total of 1942 patients with EMCO were included in the study, of which 1097 patients received heparin, 703 patients received bivalirudin and 89 patients received argatroban
- In-hospital mortality was significantly lower for DTIs as compared to heparin [p = 0.001] (Table 1)
- Adult (P=0.0009) and pediatric patients (P = 0.04) both showed lower incidence of mortality with DTIs as compared to heparin
- Major bleeding was lower in the DTIs group as compared to the heparin group (P= 0.006)
- Overall, no significant differences in minor bleeding events were detected between DTIs and Heparin (P = 0.20)
- Subgroup analysis has shown:
  - Significant reduction of in-hospital mortality for bivalirudin but not for argatroban as compared to heparin
  - Significant reduction in major bleeding events in bivalirudin (P=0.01) but not for argatroban (P=0.20) in pediatric patients (P < 0.0001) but not in adult patients (P=0.36) with DTIs
- Pump-related thrombosis occurred less frequently in the DTIs group as compared to the heparin group (P = 0.0003)
- Overall length of ECMO therapy showed no difference between DTIs and Heparin (P= 0.11)
- Patients with DTIs during ECMO had a higher percentage of time within the therapeutic range (P= 0.008)

S. No	Outcomes	Assumed risk unfractionated heparin	Corresponding risk Direct thrombin inhibitors	Relative effect (95% CI)	No of Participants (studies)
1	Mortality	474 per 1000	393 per 1000 (346 to 450)	RR 0.83 (0.73 to 0.95)	1777 (17)
	Major bleeding events	501 per 1000	336 per 1000 (251 to 456)	RR 0.67 (0.5 to 0.91)	1355 (16)
2	Minor bleeding events	287 per 1000	247 per 1000 (195 to 316)	RR 0.86 (0.68 to 1.10)	632 (8)
3	Pump-related thrombosis	233 per 1000	163 per 1000 (121 to 217)	RR 0.7 (0.52 to 0.93)	1361 (13)
4	Patient-related thrombosis	200 per 1000	162 per 1000 (118 to 220)	RR 0.81 (0.59 to 1.10)	1447 (15)
5	Length of ECMO therapy (Hours and days)	No difference between DTI and Heparin	The SMD in length of ECMO therapy in the intervention groups was 0.12 higher (-0.03 lower to 0.27 higher)	—	1274 (12)
6	Length of hospital stays (days)	5 to 47 days	in the intervention groups was 0.19 higher (-0.30 lower to 0.69 higher)	—	467 (4)
7	Time to anticoagulation goal (hours)	9 to 32 h	The SMD in time to anticoagulation goal in the intervention groups was 0.2 lower (-0.73 lower to 0.34 higher)	—	324 (4)
8	Percentage of time within therapeutic range (%)	11 to 31 percent	The SMD of percentage of time within therapeutic range in the intervention groups was 0.54 higher (0.14 to 0.94 higher)	—	491 (5)

*Pooled analysis evaluation

Table 1. Summary of DTIs compared with heparin for ECMO therapy

Conclusion

Use of DTIs for anticoagulation in patients undergoing ECMO reduced in-hospital mortality and also reduced the incidence of major bleeding and thrombotic events

Reference

M'Pembele R, et al. Evaluation of clinical outcomes in patients treated with heparin or direct thrombin inhibitors during extracorporeal membrane oxygenation: a systematic review and meta-analysis. Thromb J. 2022; 20(1): 42.

PERIOPERATIVE BLEEDING REQUIRING BLOOD TRANSFUSIONS IS ASSOCIATED WITH INCREASED RISK OF STROKE AFTER TRANSCATHETER AND SURGICAL AORTIC VALVE REPLACEMENT

Introduction

- Postoperative stroke is a severe complication of cardiovascular interventions
- The risk factors for post-procedural stroke during CPB include, preoperative anemia, prior stroke, intraoperative hypotension, and low hemoglobin/hematocrit levels
- The current study was aimed to investigate the effects of perioperative bleeding and blood transfusions on the development of postoperative stroke after surgical (SAVR) and transcatheter aortic valve replacement (TAVR)

Methods

- It was a retrospective, nationwide observational study
- Data was collected from five Finnish university hospitals that participated in the registry
- A total of 6,463 patients included those who underwent SAVR (n = 4,333) or TAVR (n = 2,130)

Results

- The incidence of postoperative stroke after SAVR was 3.8% and TAVR was 2.5%
- Transfused RBC units were one of the independent predictors of postoperative stroke in both SAVR and TAVR (Table 2)
- The incidence of stroke increased, with the severity of perioperative bleeding, according to the European Coronary Artery Bypass Grafting (E-CABG) bleeding grades (Table 2)
- Logistic regression identified prior cardiac surgery, preoperative use of direct oral anticoagulants, cardiopulmonary bypass time, and the number of transfused RBC units as independent predictors of postoperative stroke after SAVR (Table 2)

Predictors of Stroke in Multivariate Analysis	SAVR Cohort	TAVR Cohort
Age	1.028, 0.997-1.059	–
Female	–	0.493, 0.274-0.889
NOACs	5.386, 1.994-14.548	–
Prior TIA or stroke	1.578, 0.978-2.547	–
Prior cardiac surgery	2.499, 1.113-5.387	–
Aortic valve max gradient	0.993, 0.985-1.001	–
Cardiopulmonary bypass time	1.005, 1.002-1.009	–
RBC transfused units	1.098, 1.064-1.133	–
Nadir hemoglobin	–	–
Adjusted analysis		
E-CABG bleeding grades		
Grade 0	–	–

Predictors of Stroke in Multivariate Analysis	SAVR Cohort	TAVR Cohort
Grade 1	1.841, 1.105-3.066	1.270, 0.532-3.035
Grade 2	3.282, 1.948-5.529	2.898, 1.101-7.627
Grade 3	7.103, 3.612-13.966	10.706, 2.389-47.987
E-CABG bleeding grade 2 to 3 (it excludes peripheral vascular bleeding)	2.137, 1.414-3.228	2.949, 1.093-7.957

Table 2. Independent predictors of post-procedural stroke in the surgical and transcatheter aortic valve replacement cohorts

Conclusion

- Perioperative bleeding measured by RBC transfusions is associated with an increased risk of post-procedural stroke after both SAVR and TAVR
- Blood management and meticulous pre-procedural planning and operative techniques aiming to avoid significant perioperative bleeding may reduce the risk of cerebrovascular complications
- New oral anticoagulants, prior cardiac surgery, and prolonged cardiopulmonary bypass duration are known to increase the risk of perioperative bleeding

Reference

Tauriainen T, et al. Perioperative bleeding requiring blood transfusions is associated with increased risk of stroke after transcatheter and surgical aortic valve replacement. J Cardiothorac Vasc Anesth. 2022; 36(8 Pt B):3057-64.

BLEEDING COMPLICATIONS IN PATIENTS WITH PERIOPERATIVE COVID-19 INFECTION UNDERGOING CARDIAC SURGERY: A SINGLE-CENTER MATCHED CASE-CONTROL STUDY

Introduction

- Patients with COVID-19 are associated with complications such as interstitial pneumonia with respiratory failure and acute respiratory distress syndrome (ARDS), acute renal failure, and thromboembolic events
- Previous studies reported a poor outcome in COVID-19 patients who underwent cardiac surgery
- The current study was performed to investigate a possible significant correlation between perioperative COVID-19 infection and hemorrhagic complications compared to non-COVID-19 patients of CPB surgery

Methods

- The present study was a retrospective, matched (1:2), case-control analysis. Data was acquired from an electronic database of 87 cardiac surgery studies in which patients were undergoing for CPB (February 2019 - March 2020)
- Study categorized patients of open-heart cardiac surgery between study group (COVID-19 patients [n=23]) and control group (without COVID-19 infection [n=46])

Results

- A total of 826 patients underwent cardiac surgery, of which 773 patients required CPB
- 19 patients (age 68.7 ± 8.3 years) with COVID-19 were men (83%)
- There was mortality of 2 patients (9%) in the ICU from ARDS, shock, and multiple organ failure in the study group (Table 3)
- Also, patients have shown a significantly higher incidence of bleeding complications (48% v 2%, p = 0.0001), cases of surgical re-exploration for bleeding (35% v 2%, p = 0.0001), severe postoperative thrombocytopenia (39% v 6%, p = 0.0007), and a higher need of blood transfusions (74% v 30%, p = 0.0006). Chest tubes blood loss and surgical hemostasis time were markedly prolonged (p = 0.02 and p = 0.003, respectively) in study group
- CBP time in the study group was 152 ± 79 minutes (p = 0.08), and aortic cross-clamp time was 106 ± 36 minutes (p = 0.07). Surgical hemostasis time (SHT) was significantly prolonged in the study group (p = 0.0003) due to bleeding

Postoperative Results	Study group (COVID-19 positive) n = 23	Control group (Non-COVID-19) n = 46	*P* Value
Mortality, n (%)	2 (9)	0 (0)	–
Severe respiratory failure, n (%)	6 (26)	2 (4)	*0.008
Hemorrhagic complications, n (%)	11 (48)	1 (2)	*0.00001
Surgical re-exploration for bleeding (patients), n (%)	8 (35)	1 (2)	*0.0001
Cardiac tamponade, n (%)	4 (17)	0 (0)	–
Multiple surgical re-explorations (patients), n (%)	4 (17)	0 (0)	–
Intracranial hemorrhage, n (%)	1 (4)	0 (0)	–
Pleural effusion requiring drainage, n (%)	2 (9)	0 (0)	–
Fluid loss from drains, (mean ± SD) mL	1,535 ± 1.915	463 ± 164	*0.02
Rehospitalization, n (%)	2 (9)	2 (4)	0.4
Severe thrombocytopenia, n (%)	9 (39)	3 (6)	*0.0007
Platelet count, *109/L, median (25th-75th)	112(82-157)	176 (139-207)	*0.01
Fibrinogen, mg/dL, median (25th-75th)	457 (331-675)	467 (362-653)	0.9
APTT, s, median (25th-75th)	42 (36-49)	35 (31-37)	*0.01
Patients transfused, n (%)	17 (74)	14 (30)	*0.0006
Procoagulant drugs, n (%) †	17 (74)	9 (19)	*0.00001
Sternal dehiscence, n (%)	3 (13)	1 (2)	0.06
Total intubation time, (mean ± SD) h	13 ± 6	10 ± 2	*0.01
Acute renal failure, n (%)	2 (9)	0 (0)	
Hemodialysis, n (%)	1 (4)	0 (0)	
Hospital stay, (mean ± SD) d	17 ± 2.5	9.2 ± 4.7	*0.01

Table 3. Summary of postoperative results comparing study group with control group

Conclusions

- All patients undergoing CPB, bleeding were the most frequently encountered complication
- This study observed an increased hemorrhagic risk in patients with active COVID-19 at the time of surgery or early postoperatively
- Patients with perioperative COVID-19 undergoing cardiac surgery experienced a poor outcome, with a high rate of complications, including early and late postoperative bleeding

Reference

Chiariello GA, et al. Bleeding complications in patients with perioperative covid-19 infection undergoing cardiac surgery: a single-center matched case-control study. J Cardiothorac Vasc Anesth. 2022; 36(7):1919-26.

Basic Facts

THE USE OF ANGIOTENSIN II FOR THE TREATMENT OF POST-CARDIOPULMONARY BYPASS VASOPLEGIA

Introduction

- Vasoplegia is a post-CPB complication (in 5–25% of patients) associated with high peri-operative morbidity and mortality due to persistent hypotension which leads to end-organ dysfunction
- Despite its poor prognosis and it is a very common complication in CPB patients, there is still lack of consensus about guided treatment strategy for the management of vasoplegia
- Basically, it can be treated with fluid resuscitation and catecholamine infusions. In December 2017, angiotensin II (A-II) was approved by the FDA for the treatment of vasoplegia
- In addition to the ATHOS-3 trial, mainly case reports are published about the use of A-II in vasoplegic patients that underwent cardiac surgery on CPB
- Thus, this review presents the efficacy and safety of A-II in the management of post-CPB vasoplegia in cardiac patients

Methods

- A systematic search was performed by two independent reviewers in PubMed, Embase, Web of Science, and Cochrane library with the help of relevant MeSH terms (Angiotensin II, Vasoplegia, Cardiopulmonary Bypass, cardiac Surgical Procedures) for study selection
- A total of 1504 articles were obtained. After removing duplicates following proper screening by applying exclusion and inclusion criteria, 9 studies were included for qualitative synthesis of A-II (Figure 1)
- Among 9 studies, 2 were randomized clinical trials (RCTs), 6 were case reports, and one was a retrospective cohort study (Table 4)

Results

- Giapreza® is the FDA approved A-II intended for continuous intravenous administration (20 ng/kg) diluted in 0.9% sodium chloride solution prior to use. The initial dose can be titrated to affect every 5 min and the maximum infusion should not exceed 80 ng/kg during the first 3 h. The A-II is metabolized and forms A-III which is responsible for 40% of the total A-II vasoconstriction effect

Efficacy and Safety

- Studies of A-II demonstrated that it is effective and safe. It is helpful in raising blood pressure in vasoplegic condition of patients and no major significant adverse events have been reported (Table 4)

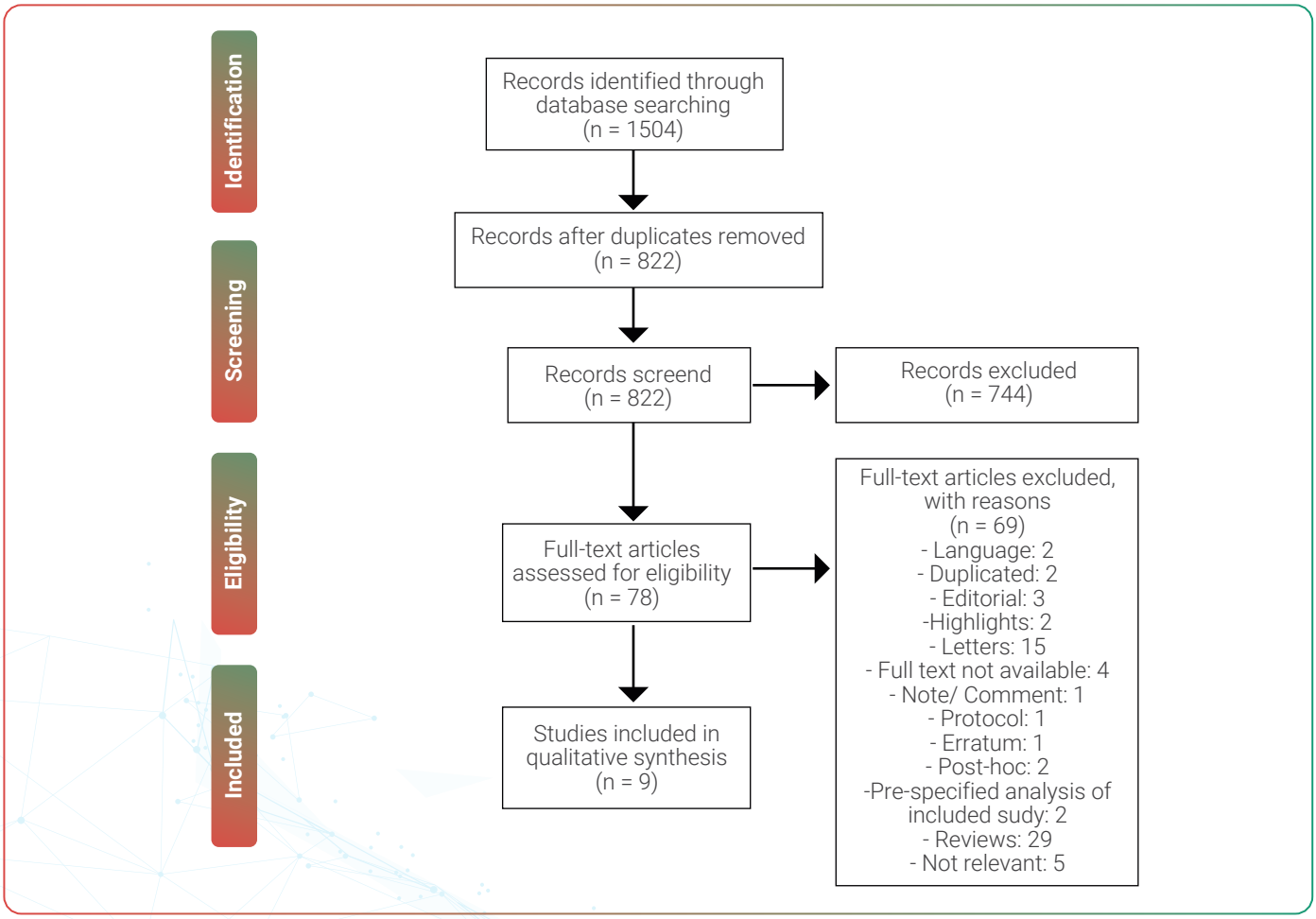


Figure 1. Flowchart of the systematic literature search and study selection procedure for A-II

Studies	Population	A-II dose	Other vasopressor used	Findings
CR1	1	6 µg/min	PE; NE	MAP =70-75 mmHg during
CR2	2	6-7 µg/min	PE; NE; Epi	post-CPB
CR3	1	I - 20 ng/kg/min; T- 40 ng/kg/min	NE; AVP; MB; Hydroxocobalamine	Increase PP Increase MAP & SVR rapidly; Lower NE dose
CR4	4	I – 10-20 ng/kg/min; T- 30 ng/kg/min	AVP; Epi; Ascorbic acid; NE; MB; Hydorxocobalamine	Lower NE dose; Increase MAP; Improved oliguria
CR5	1	I - 20 ng/kg/min	NE; AVP; Midodrine	Lower NE dose; Increase MAP ≥ 65 mmHg
CR6	4	I – 2.5-10 ng/kg/min; T- 30-80 ng/kg/min	NE; AVP; MB; Epi; Hydroxocobalamin	Reduce dose/ discontinuation of mentioned vasopressors
Retrospective study	28vasoplegia/ 270	I-20 ± 12 ng/kg/min; T- 52 ± 24 ng/kg/min	NE; Epi; PE; AVP; Dopamine	Increased MAP & decreased NED Responders exhibited a higher chance of 30-day survival

Studies	Population	A-II dose	Other vasopressor used	Findings
RCT	10 A-II vs 10 PE	10 2.5 mg /50 ml NS	PE	A-II had better response than PE (1 patient) Pre-operative HF chances with higher need of vasoconstrictors
RCT	163 A-II vs 158 placebo (vasoplegia- 19) 10 A-II vs 9 placebo)	I - 20 ng/kg/min Between 3 h 15'– 48 h -1.25–40 ng/kg/min	PE	Increased MAP (P < 0.001) Tolerated greater decreases in AII doses and background vasopressors Great improvement in cardio-vascular SOFA (P=0.01) Non- significant adverse events- Deep vein thrombosis; Tachycardia; Ventricular fibrillation

CR- Case Report; AVP-Arginine vasopressin; Epi-Epinephrine; PE-Phenylephrine; MB - Methylene blue, NE-norepinephrine; MAP- Mean arterial pressure; PP – partial pressure; SVR - Low systemic vascular resistance; RCT – Randomized clinical trial; HF – Heart failure; SOFA - Sequential Organ Failure Assessment

Table 4. Summary of efficacy and safety of use of A-II in post CPB vasoplegia

Conclusions

- The existing studies and case reports provide a positive impression of use and safety of A-II
- Administration of A-II seems to favor survival in severely ill patients who are on RRT

Reference

Papazisi O, et al 2022. The use of angiotensin II for the treatment of post-cardiopulmonary bypass vasoplegia. Cardiovasc Drugs Ther. 2022; 36(4):739-48.

USE OF EXTRACORPOREAL MEMBRANE OXYGENATION AND IMPELLA AS BRIDGE TO SURGERY THROUGH IMAGING FOR CARDIOGENIC SHOCK

Introduction

- Left ventricular (LV) myocardial infarction complicated by papillary muscle rupture and resultant cardiogenic shock is associated with significant morbidity and mortality
- Papillary muscle rupture is a lethal complication of STEMI and associated with a 65% risk of cardiogenic shock and often requires mechanical circulatory support devices for hemodynamic support

- The goal of hemodynamic support is to reduce afterload and improve systemic blood pressure and blood flow to critical organs
- The present case illustrates the use of ECMO and Impella Abiomed as a bridge to surgery through transesophageal echocardiographic (TEE) imaging for cardiogenic shock due to acute severe mitral regurgitation (MR)

Case study

- A 75-year-old man had an inferior ST elevation myocardial infarction (STEMI) complicated by cardiac arrest and cardiogenic shock
- Ultrasound revealed LV inferior wall akinesis and mitral regurgitation (MR) with suspected papillary muscle rupture (Figure 2 & 3)
- In angiography, significant three-vessel coronary artery disease was confirmed
- The TEE confirmed -
  - Ruptured posteromedial papillary muscle with severe MR
  - Effective regurgitant orifice area of 1.4 cm^2
  - Regurgitant volume of 72 mL
  - LV dilation (diameter = 4.5 cm) with LV ejection fraction = 45%
  - Mild right ventricular dilatation with systolic dysfunction
  - Mild left atrial dilatation

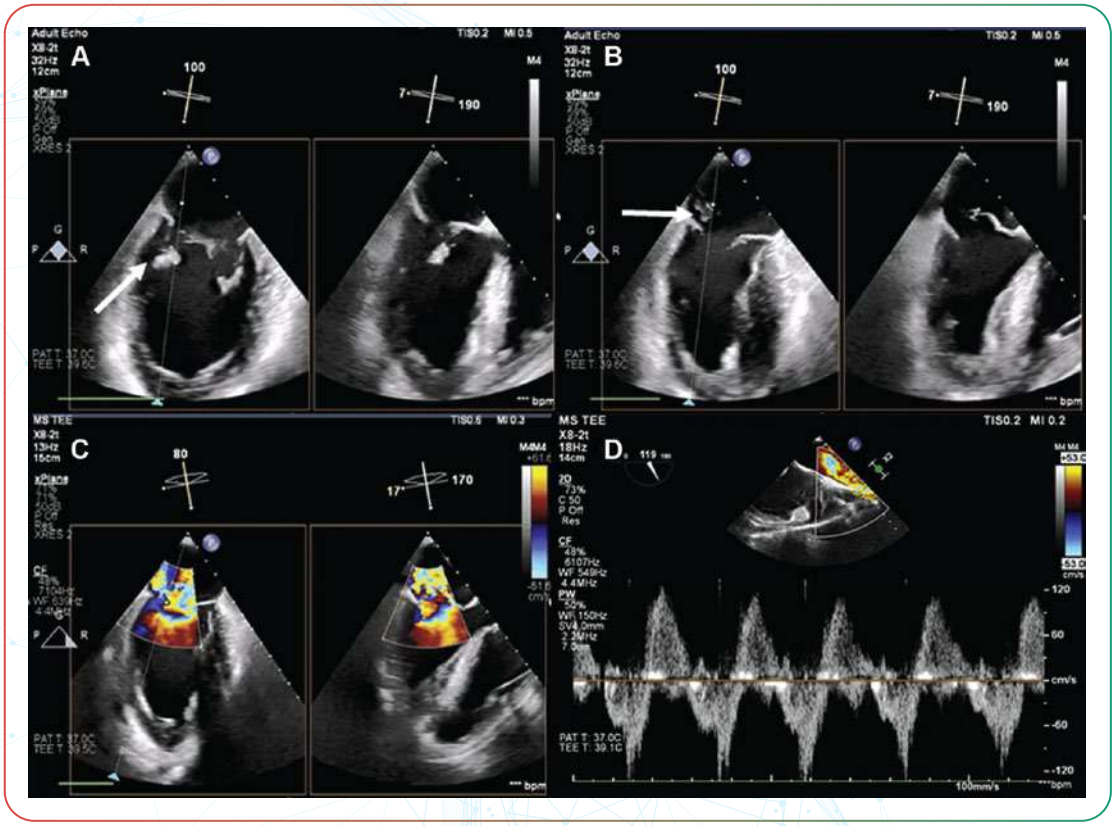


Figure 2. Two-dimensional TEE mitral commissural view with biplane imaging showing the mitral valve, left ventricle, and left atrium in - diastole (A) and systole (B). With color Doppler (C) and pulsed-wave Doppler analysis of the systolic flow reversal in the pulmonary veins (D), severe MR

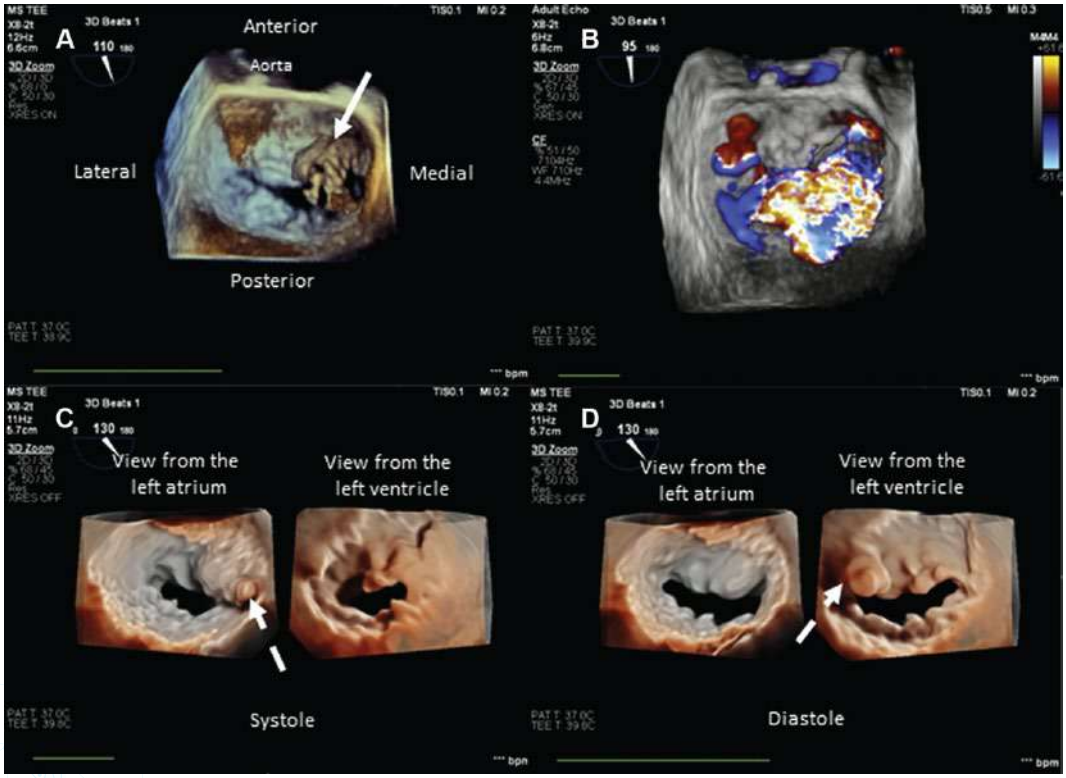


Figure 3. Three-dimensional TEE for view of the mitral valve. (A) The left atrial demonstrates a flail A3 segment with a ruptured posteromedial papillary muscle (arrow) (B) Three-dimensional color Doppler demonstrates severe MR. C& D- Three-dimensional transillumination; left atrial (left) and LV (right) perspective demonstrated.

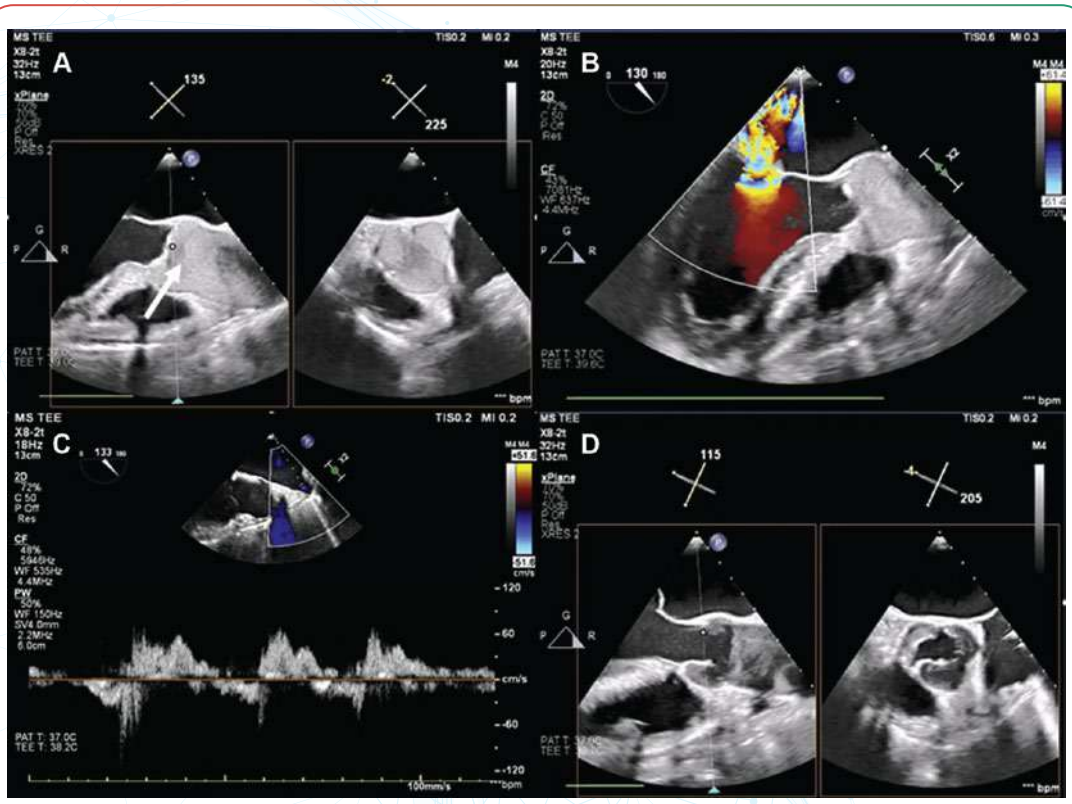


Figure 4. Two-dimensional TEE midesophageal long-axis view with biplane imaging. A & D following commencement of VA-ECMO, demonstrating minimal aortic valve opening and significant stasis of blood flow in the aortic root and ascending aorta (arrow). B- Two-dimensional color Doppler demonstrates significant but reduced MR. (C) Pulsed-wave Doppler demonstrates systolic flow reversal in the left upper pulmonary vein (D) Temporary reduction in ECMO flow, and thus LV loading, resulted in improved aortic valve opening and reduction in stasis at the aortic root/ascending aorta.

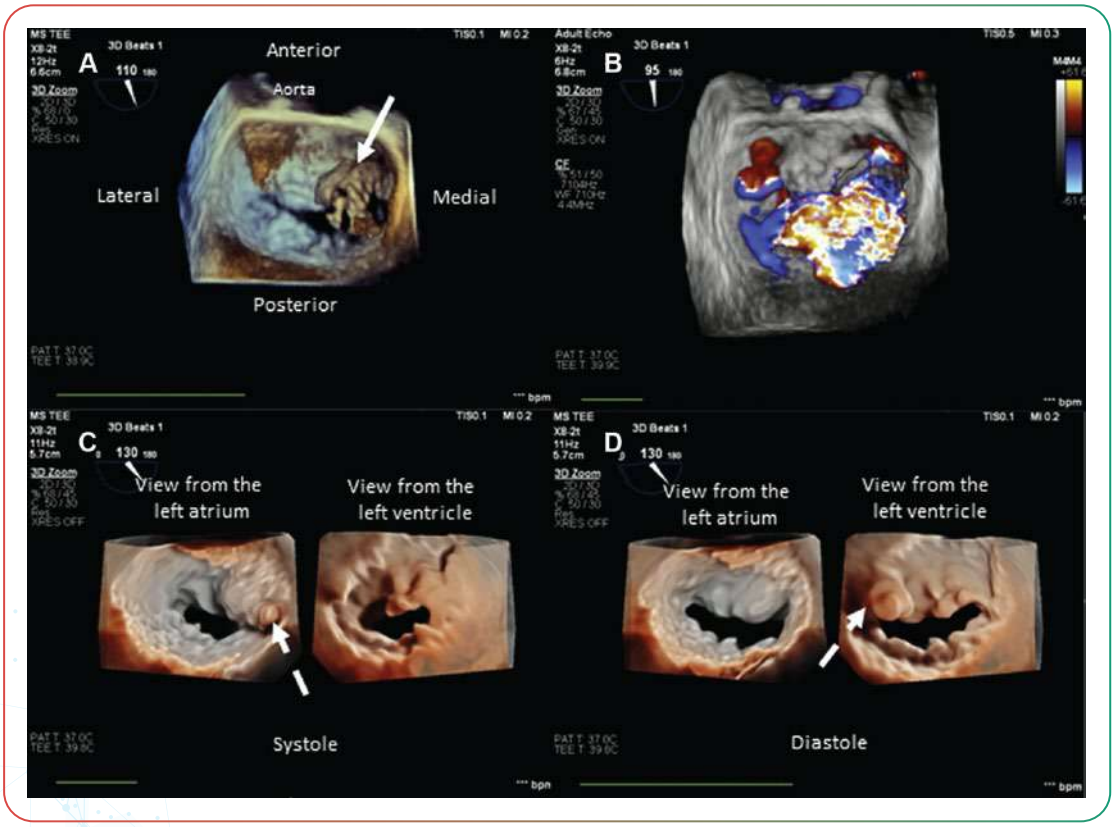


Figure 5. Two-dimensional TEE midesophageal long-axis view with biplane imaging. A&C-placement of an Impella device (arrow). A - with no interaction of the ventricular component of the device with the mitral valve or subvalvular apparatus. B - systole. C - diastole. D -Two-dimensional color Doppler demonstrates further reduction in MR

- Staged surgical intervention was the chosen strategy over emergent surgery due to uncertain neurological status
- Hemodynamic support with peripheral (femoral) veno-arterial ECMO (VA-ECMO) which was act as a bridge to surgery was commenced within hours in the hospital
- VA-ECMO was initially chosen over empella to avoid right ventricular systolic dysfunction
- While increasing ECMO flow, LV stasis developed within 15 minutes of initiating VA-ECMO. TEE demonstrated minimal aortic valve leaflet opening and significant stasis at the aortic root and ascending aorta, despite of systemic anticoagulation administration (Figure 4)
- Hence, transient reduction in ECMO flow was done to overcome these problems (Figure 5). However, this was associated with hypotension and systemic hypo-perfusion. For the resolution of the aortic stasis, an Impella device was placed which enabled LV unloading and antegrade flow support, and aortic root washing.
- Finally, the patient had stabilized hemodynamic status, stable LV end-diastolic dimensions and no elevation in right ventricular systolic pressures. Therefore, after 48 hours, he subsequently underwent for surgery

Conclusion

This case study spread awareness among the clinicians regarding the significant risk of VA-ECMO-related aortic stasis. ECG can be used to identify a strategy of LV unloading which is able to reduce afterload and provide more effective hemodynamic support in this condition

Reference

Anastasius M et al. Use of Extracorporeal Membrane Oxygenation and Impella as Bridge to Surgery Through Imaging for Cardiogenic Shock. CASE (Phila). 2022; 6(5):223-27.

Practice Pearls

TWO CASES OF INTESTINAL PERFORATION DUE TO MESENTERIC ARTERY EMBOLISM DURING EXTRACORPOREAL MEMBRANE OXYGENATION AND INTRA-AORTIC BALLOON PUMPING

Introduction

- The ECMO support in cardiac or pulmonary failure acts as a life support therapy for cardiac patients
- To stabilize patients with hypoxemic or hypercapnic pulmonary failure during the COVID- 19 pandemic, the application of ECMO can be implemented. However, many complications are associated with the use of ECMO that seriously affect prognosis
- Mesenteric artery embolism refers to a series of complications caused by thrombi or emboli leading to intestinal ischemia
- This study presents the details of two consecutive cases of mesenteric artery embolism using ECMO support

Case 1

- A man (age -50 years) was presented to the hospital with chest pain and syncope for 3 hours
- The patient had a history of fatty liver disease and hypertension for 5 years, consumed 30 cigarettes/day, 250–500 mL of white wine per day and previously underwent appendectomy

Clinical examination

- ECG revealed acute myocardial infarction (AMI) with elevated troponin I (TNI). Dobutamine was administered due to the appearance of cardiogenic shock
- A veno-arterial VA-ECMO was performed after 2 hours. After 67 minutes of cardiopulmonary resuscitation, circulatory support was established, and coronary angiography was performed

Management

- The patient was transferred to the ICU after implantation of intra-aortic balloon pumping (IABP)
- To maintain circulatory assistance with ECMO and treat AMI, postoperative systemic heparin anticoagulation, aspirin (100 mg q.d) and ticagrelor (90 mg b.i.d) were administered. Abdominal dilation was observed. Coffee-like fluid was drained from the gastric tube, and proton pump inhibitor therapy was given
- The patient was transferred to veno-arterial-venous (VAV)-ECMO
- On the ninth day of ECMO, abdominal computed tomography revealed significant intestinal canal dilatation with multiple air–fluid levels and multiple small gas shadows (Figure 6)
- To reduce gastrointestinal pressure, gastroscopy was performed but due to persistent abdominal pressure, surgical exploration was done which suggested ileal necrosis. The necrotic ileum was resected, and an ileostomy fistula was performed

- Due to poor postoperative cardiac recovery and difficulty with ECMO evacuation, heart transplantation of the patient was decided. However, the patient declined further treatment and hence, discharged on day 16 of ECMO support

Case 2

- An old man (age – 58 years) was admitted to hospital with abdominal pain lasting for 3 days, which was worse by irritability for half a day
- Sudden ventricular tachycardia and failure to palpate the aorta were noted and preformed ECG
- ECG showed ST-segment elevation. Angiography showed sub-total occlusion of the LMCA opening and approximately 50% stenosis

Clinical examination

- IABP was performed and drug stents were placed in the LAD and gyral branches to open the vessel. After surgery, a VA-ECMO was performed due to cardiogenic shock.
- Systemic heparin anticoagulation, aspirin (100 mg qd) and ticagrelor (90 mg b.i.d) were administered
- Cardiac function of patients was gradually improved and circulation was stable with small doses of norepinephrine, and the haemoglobin was maintained
- His blood pressure dropped significantly and was maintained with high-dose norepinephrine (0.8 μg/kg/minute)
- Arterial blood gas analysis showed that haemoglobin was 5.2 g/dL (lower than before) and lactate was 9.2 mmol/L. Intra-abdominal pressure was elevated and ultrasonography revealed the abdominal cavity had dark fluid

Management

- A diagnostic puncture was performed and an abdominal CT revealed fluid accumulation with haematoma formation
- A dissection was also performed and it was found that the bleeding in the abdominal cavity (around 4,000 mL), the presence of free faecal fluid, and part of the small intestine was covered with faecal moss, and the dark color of the caecum and part of the ileum. Around 1.5 m of the ileocaecal portion with part of the necrotic small intestine was removed (Figure 7)
- The patient was successfully withdrawn from ECMO assistance on day 11. However, after ECMO withdrawal, he developed short bowel syndrome

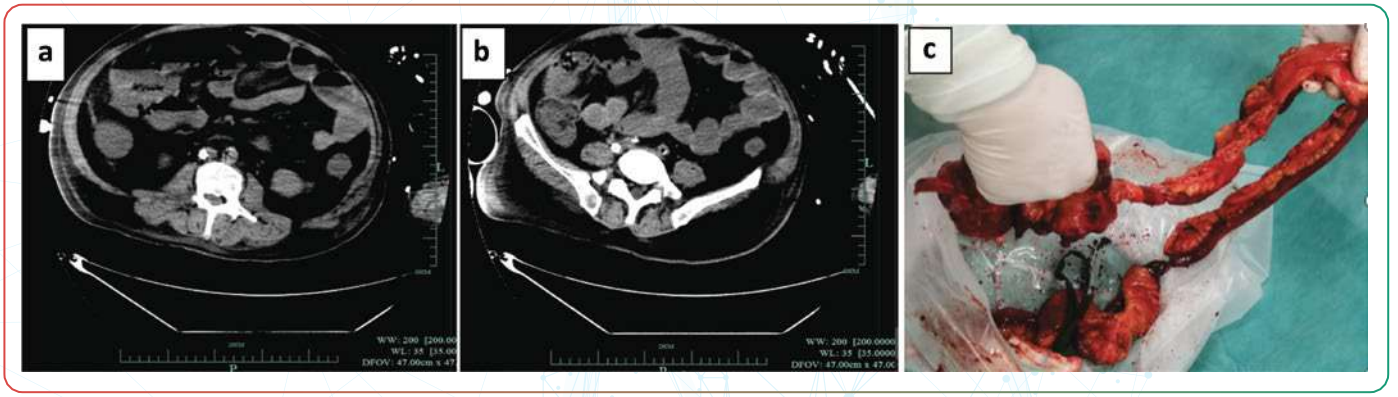


Figure 6. a and b) Preoperative abdominal computed tomography (CT). a) CT showing intestinal obstruction. b) CT showing an increased density in the intestinal wall. c) Postoperative intestinal perforation and necrosis.

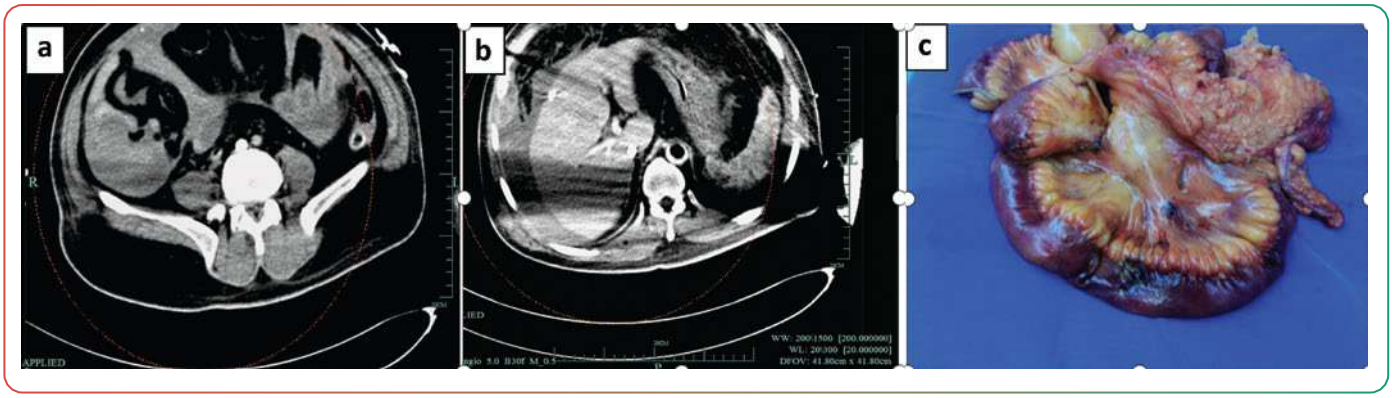


Figure 7. a and b) Preoperative abdominal computed tomography. a) CT showing ileocaecal effusion. b) CT showing perihepatic effusion. c) Postoperative intestinal perforation and necrosis.

Conclusion

- These cases alert the clinicians to the possibility of mesenteric artery embolism associated complications and their treatment with ECMO support improves prognosis

Reference

Wang S, et al. Two cases of intestinal perforation due to mesenteric artery embolism during extracorporeal membrane oxygenation and intra-aortic balloon pumping. Clin Med (Lond). 2022; 22(4): 360-63.

THE STANDARD POINT-OF-CARE HEMOCHRON JR. ACT+ TEST IN MONITORING HEPARIN ADMINISTRATION FOR CARDIOPULMONARY BYPASS IN SEVERE FACTOR XII DEFICIENCY

Introduction

- Coagulation factor XII (FXII) belongs to the contact activation complex responsible for initiating the intrinsic coagulation pathway and, due to severe deficiency of FXII, this pathway is impaired by prolonged activated partial thromboplastin time (aPPT- 120 S) and activated clotting time (ACT- > 500 S)
- Therefore, for screening of the intrinsic coagulation pathway, the aPTT and ACT are used
- FXII deficiency poses a real challenge in patients undergoing CPB surgery and hence, as the point of- care ACT measurements remain the cornerstone in monitoring the adequacy of intraoperative heparin administration
- In this study, two case reports of CPB with severe FXII deficiency in which the standard ACT+ test was used to monitor both heparin and protamine administration were presented. ACT+ test calibrated to be used during full heparinization for CPB

Case 1

- A 72-year-old man who had coronary artery disease and diabetes was scheduled for elective bioprosthetic aortic valve replacement due to severe aortic stenosis (mean pressure gradient - 63 mmHg)
- Previously, he had undergone PCI of the left anterior descending and circumflex coronary arteries, and recent coronary angiography revealed no in-stent
- He was on aspirin, normal renal function, and routine coagulation parameters (platelet count & prothrombin time) and preoperative aPTT was found 89 S

Monitoring of ACT during CPB surgery

- After anesthesia, an infusion of 2.5 g of tranexamic acid was initiated
- Baseline ACT-LR measurements were found repeatedly out of range (>400 celite-based seconds, S)
- The kaolin and heparinase tests showed reaction times (R) of 45-48 minutes which were much higher than the normal range (4-8 minutes)
- Based on prolonged ACT and aPTT, normal INR values, and the lack of evidence of heparin effect in thromboelastography (TEG), there was a chance of risk of coagulation disorder. Hence, ACT+ test monitoring was considered to monitor the effect of heparin administration
- An ACT+ test gave a normal result of 123 S
- After full heparinization of 30,000 IU, ACT+ increased to 707 S.
- It was decided to guide heparin administration with ACT+ test to maintain a higher-than-normal ACT
- Duration of 114 minutes of CPB, ACT+ ranged between 621 and 707 S (Patient received three extra boluses of heparin 5,000 IU each and 7,500 IU in the CPB prime)

- After weaning from CPB, the patient received-
  - An infusion of 300 mg of protamine
  - Simultaneously, 4 units of solvent or detergent plasma to enable the measurement of ACT with the ACT-LR test.

Post CPB monitoring

- The ACT+ test was at the preoperative level, ACT-LR (208 S), normal TEG R value range (<8 minutes)
- Total intraoperative blood loss was 700 mL and chest tube drainage was 520 mL in ICU, and no further protamine dosing was required

A full coagulation factor analysis was performed on the 5th postoperative day and FXII activity was found at 3.7% (normal range, 52-142%). Lupus anticoagulant was positive

The patient was discharged from the hospital after an uneventful recovery on the 6th postoperative day

Importantly, baseline ACT+ values were low, while at heparin concentration of 4 IU/mL, which is considered relevant for CPB, they ranged from 458 to 520 S

Case 2

- 69-year-old woman was scheduled for elective surgery for severe aortic stenosis bioprosthetic aortic valve replacement and closure of the left atrial appendage, and a small atrial septal defect (mean pressure gradient of 65 mmHg)
- Previously, she had normal renal function with no significant comorbidities. However, she was diagnosed with paroxysmal atrial fibrillation just before the surgery
- She was not on anticoagulant due to type 1 von Willebrand disease which was diagnosed based on family history and suspected bleeding diathesis in 2004
- Preoperatively, von Willebrand factor activity was in normal range. While, severe FXII deficiency was confirmed due to > 180 S aPTT and <2% FXII activity
- Based on the previous experience, monitoring of anticoagulation using ACT+ was decided

Monitoring of ACT during CPB surgery

- After the induction of anesthesia, an infusion of 2.5 g of tranexamic acid was started
- Baseline ACT-LR expectedly out of range while ACT+ remained at 109 S
- In addition, thromboelastometry was performed, with a normal CT (63 S) in the ExTEM test but markedly prolonged CT in both the InTEM (1355 S) and the HepTEM (1234 S) tests
- Following the initial dose of 28,000 IU of heparin, ACT+ was elevated to 567 S
- During the 178-minute CPB, the patient received three additional boluses of heparin, totaling 12,500 IU, plus 7,500 in the CPB prime, and ACT+ ranged between 517 and >999 S
- Because of heparinization, RoTEM CT was prolonged to 135 seconds in the ExTEM test and over the measurement range in InTEM and HepTEM tests
- After weaning from CPB and administration of 200 mg of protamine, ACT+ decreased to 109 S. In addition, RoTEM CT returned to its preoperative level in all three tests. Based on the history of previously suspected von Willebrand disease, 24 mg of desmopressin was infused

- The total intraoperative blood loss was 550 mL, and one unit of packed red blood cells was transfused, while no other blood products were needed. In the ICU, chest tube drainage was 430 mL, and no extra protamine was given

After an uneventful recovery, the patient was discharged from home on the 6th postoperative day. Importantly, baseline ACT+ values were low, while at heparin concentration of 4 IU/mL, which is considered relevant for CPB, they ranged from 458 to 520 S

Reference

Erkinaro T et al. The Standard Point-of-Care Hemochron Jr. ACT+ Test in Monitoring Heparin Administration for Cardiopulmonary Bypass in Severe Factor XII Deficiency. J Cardiothorac Vasc Anesth. 2022; 36(7):2031-34.

Expert
Opinion

MANAGEMENT OF ANTICOAGULATION DURING EXTRACORPOREAL MEMBRANE OXYGENATION IN CHILDREN

Introduction

- Extracorporeal Membrane Oxygenation (ECMO) is often used in critically ill children with severe cardiopulmonary failure
- Thrombosis and bleeding are the significant complications during ECMO which require close anticoagulation monitoring
- The hemodilution effect is much higher in children who are on ECMO and resulting significant decrease in platelet count and coagulation factors

Heparin Anticoagulation Monitoring (Table 5 & 6)

ELSO guideline for ACT level

- The current ELSO guidelines do not specify a number. The suggested ACT range during the ECMO support is 180-220 S (Table 5)

ELSO guideline for aPTT level

- The usual aPTT range during ECMO is 60–80 S. The aPTT poorly correlates with anti-factor Xa levels in children more than adults
- The aPTT is frequently prolonged in children during ECMO due to developmental differences in hemostasis (Table 5)

Anti-factor Xa assay

- The anti-factor Xa assay poorly correlated with the ACT assay in children and adults undergoing CPB for cardiac surgery and measured only the heparin effect on AT
- The anti-factor Xa assay estimates UFH activity and does not measure UFH concentration
- Recommended anti-factor Xa levels are 0.3–0.7 IU/mL and correlate to a heparin level of 0.2–0.4 U/mL

Laboratory Tests	Frequency	Target range
ACT	Every 1 h for first six hours of ECMO, then every 2 h if stable	Range 180–220 second
PT/aPTT/INR	Q 6–12 h	PT 10–13 second PTT 1.5–2.5 times normal (60–80 second) PT/INR normal or close to normal <1.5
Fibrinogen/FDP	Q 12–24 h	Fibrinogen > 150 mg/dL (bleeding patient) >100 mg/dL (nonbleeding patient) FDP 10–40
Platelet Count	Q 6 h first 48 h, then Q 12 h	50,000–100,000 × 109/L unless VHA indicates need to give >100,000 × 109/L if bleeding

Table 5. ELSO guideline level for heparin anticoagulant therapy

Parameter	Goal	Guideline
PRBC's	Hemoglobin 70–90 gm/L	PRBC's 10 mL/kg (maximum 2 units)
Platelets	>80,000 >100,000 × 109/L (in bleeding patients)	Platelets 10 mL/kg (maximum 2 units)
FFP	INR < 1.5 (bleeding patient) INR < 3 (non-bleeding patient)	FFP 10 mL/kg (maximum 2 units)
Cryoprecipitate	Fibrinogen > 1.5 gm/L (bleeding patient) >1 gm/L(non-bleeding patient)	Number of units = [(200-fibrinogen) (kg)] ÷ 200 1 unit/5 kg (maximum 6 units)

Table 6. Blood product transfusion guidelines during ECMO.

Conclusions

- Children are at higher risk of bleeding than adults because of age-related developmental hemostatic changes
- Advancement in ECMO circuit designs, monitoring with effective assays, and more experience with newer anticoagulants may decrease the bleeding, thrombosis risk and improve outcomes in children

Reference

Chegondi M, et al. Management of Anticoagulation during Extracorporeal Membrane Oxygenation in Children. Pediatr Rep. 2022; 14(3): 320-32.

BETA BLOCKERS AND LONG-TERM OUTCOME AFTER CORONARY ARTERY BYPASS GRAFTING: A NATIONWIDE OBSERVATIONAL STUDY

Introduction

- Myocardial revascularization by coronary artery bypass grafting (CABG) is still the most common open cardiac surgical procedure
- Beta blockers improve reduced left ventricular function and previous MI in patients
- European and North American guidelines also recommend lifelong medication with beta blockers after CABG for patients with reduced LVEF and MI
- The current study was aimed to investigate the association between long-term beta-blocker therapy and major adverse cardiovascular events (MACEs) of CABG patients

Methods

- It was a nationwide observational study
- Patient's data were collected from four Swedish registries (2006 to 2017), who underwent open heart surgery and followed for at least 6 months

Results

- At baseline, 33 159 (94.2%) patients were dispensed beta blockers, 30 563 (92.2%) of which were cardio-selective beta blockers
- After 10 years, the dispensing of cardio-selective beta blockers had declined to 73.7%
- Cardio-selective beta blockers were associated with a slight reduction in MACEs (Table 7)
- The risk of MI was largely reduced and consistent in all groups
- There was no significant reduction in all-cause mortality and stroke

Parameters	Observations
MACEs	HR – 0.93; 95% CI (P=0.0063)
Risk of MI reduction	HR – 0.83; 95% CI (P=0.0003)

Table 7. Hazard ratio of parameters observed

Conclusion

- Cardio-selective beta blockers after CABG was associated with reduced risk of MACEs and MI while non-cardioselective were not associated with MACEs

Reference

Lindgren M, et al. Beta blockers and long-term outcome after coronary artery bypass grafting: a nationwide observational study. Eur Heart J Cardiovasc Pharmacother. 2022; 8(5):529-36.

PLASMA EXCHANGE IN THE INTENSIVE CARE UNIT: A NARRATIVE REVIEW

Introduction

- Therapeutic plasma exchange (TPE) are used as a bridge during the transplant of liver in acute liver failure along with multiple organ failure. TPE serves to remove pathogenic substances or to administer deficient substances present in plasma of healthy donors. This article was described the main indications for TPE
- TPE is a potentially lifesaving but also invasive procedure with risk of adverse events and complications and requires close monitoring by experienced teams

In the ICU, the indications for TPE can be divided into

- **Absolute,** well-established, and evidence-based, for which TPE is recognized as first-line therapy
- **Relative,** for which TPE is a recognized second-line treatment alone or combined with other interventions
- **Rescue therapy,** where TPE is used with limited evidence of benefits but a plausible theoretical rationale
- TPE has two mechanisms of action (Figure 8):
  - Removal of a pathogenic substances from the plasma
  - Delivery of large amounts of deficient plasma components

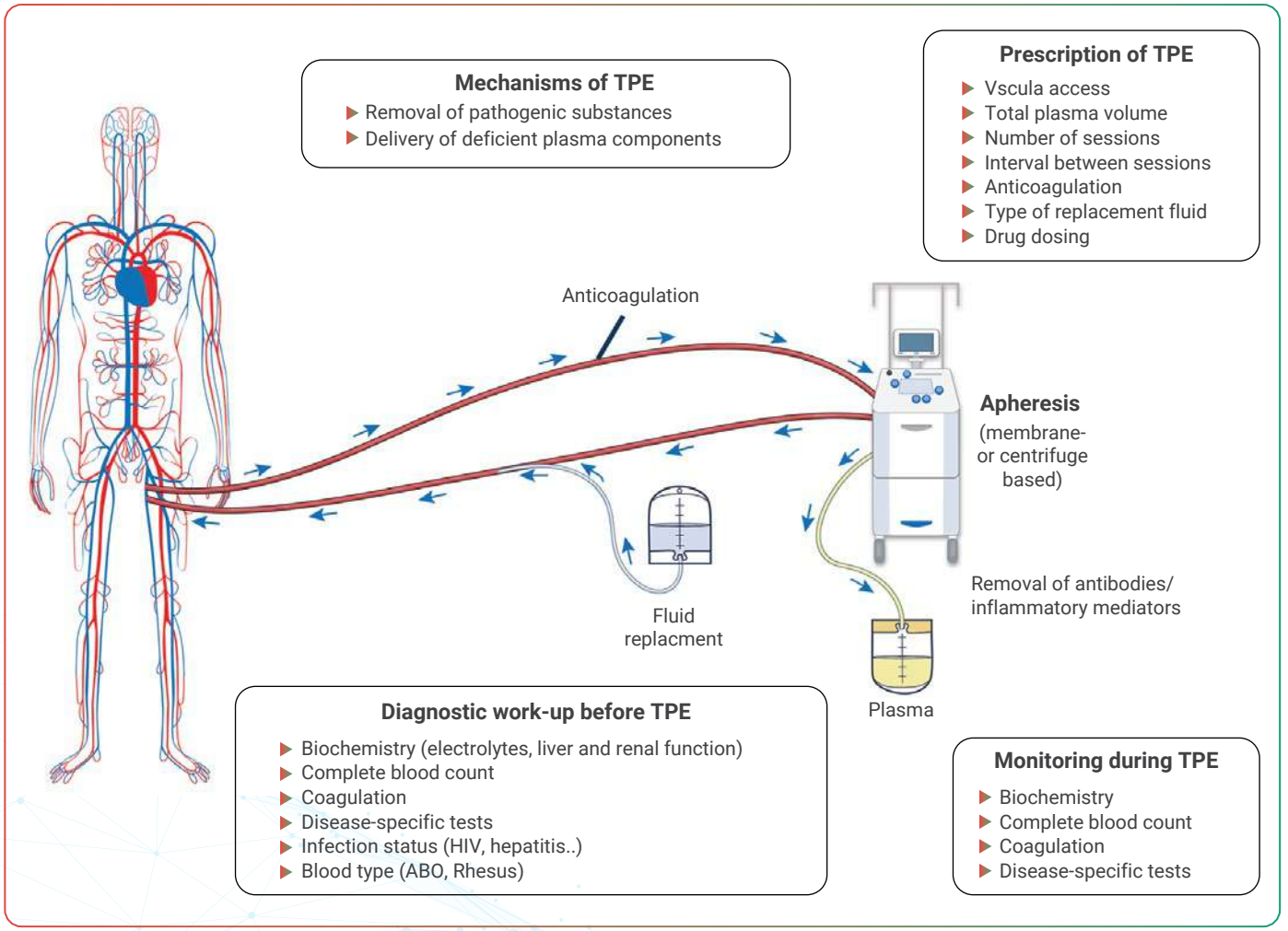


Figure 8. Therapeutic plasma exchange overview

Discussion points
In TTP, the aim is to raise the platelet count >150,000/μL and by reversing hemolysis by removing anti-ADAMTS13 inhibitory antibodies, removing ultra large von Willebrand factors multimers and replacing ADAMTS13 enzyme (Table 8)
During TPE, close monitoring is essential to prevent adverse events
In most nephrology departments and ICUs, the preferred devices are membrane-based (mTPE), including multifunctional renal replacement therapy (RRT) machines
To reduce costs and donor exposures, up to 30% of the replacement fluid may be a suitable crystalloid. The choice of vascular access for TPE depends primarily on the method used: cTPE typically requires lower blood flow rates (Qb) (50–120 mL/min) than mTPE (150–200 mL/min)
A lower Qb enables the use of narrower catheters such as peripheral devices (e.g., 18-Gauge needle) or standard triple-lumen central venous catheters (e.g., 7 Fr)
With a peripheral vein, single-needle access is feasible when using cTPE but might increase the treatment time
Peripherally inserted central catheters should not be used, as their narrow catheter gauge will collapse with the negative pressures exerted for TPE procedures
With mTPE devices, 3-4 times more plasma volume must be processed to remove similar plasma volume as with cTPE devices
Anticoagulation for TPE aims to achieve balance between preventing circuit failure with preventing bleeding
Albumin or plasma can be used as replacement fluid, alone or in combination, and with or without the addition of a crystalloid such as saline

However, replacing plasma with crystalloid carries a risk of hypotension if the proportion of replacement with crystalloid exceeds 30%

TPE is a relatively safe procedure and usually well tolerated. Complications include catheter-related and procedure-related events

The incidence of adverse events has declined over time and now ranges from 5 to 36% depending on vascular access used, type of replacement fluid, and anticoagulation

Therapeutic goal of TPE (Table 8)

Waldenstrom macroglobulinemia - Decrease the IgM level to reduce plasma viscosity and eliminate symptoms of hypoperfusion

TTP - Raise the platelet count above 150,000/μL and reversing hemolysis by removing anti-ADAMTS13 inhibitory antibodies, ultra large von Willebrand factors multimers and replacing ADAMTS13 enzyme

Myasthenia gravis - Achieve rapid clinical stabilization by removing acetylcholine receptor antibodies, especially in case of myasthenic crisis

GBS - Improve muscle strength and to reduce the need for mechanical ventilation and hasten recovery

Precautions

During TPE, close monitoring is essential to prevent adverse events and to ensure efficacy and safety

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategya and Endpoints	Parameters to monitor
Acute inflammatory demyelinating polyradiculon-europathy (Guillain-Barré syndrome)	Removal of antibodies	Albumin or plasma	IVIG	1–1.5 TPV, 5–6 sessions over 10–14 days until clinical improvement	Clinical response
Anti-glomerular basement membrane disease (Goodpasture syndrome)	Removal of pathogenic autoantibodies (including anti-GBM antibodies)	Albumin; plasma if bleeding	Corticosteroids, cyclophosphamide, rituximab	1–1.5 TPV daily or on alternate days over 10–20 days until disease control	Renal function Clinical response
Hyper-viscosity syndrome (in hyper-gammagl-obulinemia, especially Waldenström macroglobulin-emia)	Removal of paraproteins, thereby reducing the plasma viscosity	Albumin or Albumin/ saline	Systemic chemotherapy or immunotherapy	1–1.5 TPV daily until symptoms subside, most often 1–3 procedures	Clinical response M component (mainly IgM levels)
Catastrophic antiphospholipid syndrome	Removal of antibodies (including antiphospholi-pid antibodies), cytokines, and complement factors; administration of coagulation factors	Plasma (± albumin)	Anticoagulation, corticosteroids, IVIG, rituximab or eculizumab	1–1.5 TPV daily or alternate days; until clinical response	Clinical response

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategya and Endpoints	Parameters to monitor
Myasthenia gravis	Removal of autoantibodies (including antiacetylcholine receptor antibodies) and immunomodulation	Albumin	Cholinesterase inhibitors, corticosteroids, immunosuppression, IVIG, thymectomy, eculizumab	1–1.5 TPV; 3–6 sessions over 10–14 days, until disease control	Clinical response
N-Methyl-d-aspartate receptor antibody encephalitis	Removal of antibodies (including anti-neuronal autoantibodies)	Albumin	High dose corticosteroids, IVIG, occasionally rituximab or cyclophosphamide Tumor resection (when tumor is present)	1–1.5 TPV; 5–12 sessions over 1–3 weeks until clinical response	Clinical response
Thrombotic thrombocytop-enic purpura	Administration of ADAMTS13 protease and removal of anti- ADAMTS13 autoantibodies	Plasma	Corticosteroids, rituximab, Caplacizumab (recombinant ADAMTS13?)	Daily until platelet count > 150 × 10.9/L, LDH approaching normal and resolution of non-fixed neurologic symptoms then Continue for 2 more sessions then stop	Platelet count, LDH, ADAMTS13 activity
Acute liver failurea	Removal of albumin-bound and water-soluble toxins Replacement of plasma proteins including clotting factors Immunomodul-ation Reduction of proinflamm-atory response	Plasma	Multiorgan support	High-volume TPE if possible (target 8–12 L); otherwise, 1–1.5 TPV daily until clinical improvement or transplantation	Clinical response Supportive care as a bridge to liver transplantation
Thyroid storm (refractory)	Removal of autoantibodies, catecholamines, and cytokines	Plasma, albumin	Propylthiouracil, corticosteroids, ß-blockers, cholestyramine, organ support	Daily to every 3 days, until control of systemic response	Clinical response
ANCA-associated vasculitis with diffuse alveolar hemorrhage	Removal of autoantibodies and inflammatory mediators	Plasma	Corticosteroids, rituximab, cyclophosphamide	1–1.5 TPV daily or every other day until disease control	Clinical response (resolution of pulmonary hemorrhage)
Acute disseminated encephalomye-litis	Removal of presumedly pathogenic autoantibodies	Albumin	Corticosteroids, IVIG	1–1.5 TPV every other day until disease control	Clinical response

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategya and Endpoints	Parameters to monitor
Thrombotic microangiopathy-complement-mediated (formerly known as atypical hemolytic syndrome (aHUS))	Recommended while investigations for TTP and other forms of TMA are in progress or if eculizumab is not available	Plasma	Eculizumab	1–1.5 TPV daily until TTP ruled out	Platelet count
Autoimmune hemolytic anemia	Removal of pathogenic immune complexes, autoantibodies and complement components	Albumin	Corticosteroids, rituximab, IVIG, immunosuppression, monoclonal antibody therapy, splenectomy	TPV 1–1.5 daily until disease control	Clinical response
Chronic acquired demyelinating polyneuropathies (IgA- and IgG-associated polyneuropathy	Removal of autoantibodies	Albumin	IVIG and rituximab	5–6 treatments over 10–14 days until improvement or stabilization of neurological response	Clinical response Nerve conduction studies; IgG and IgM titers
Lambert–Eaton myasthenic syndrome	Removal of autoantibodies	Aminopyridines, possibly cholinesterase inhibitors; immunosuppression if symptomatic treatment is insufficient	1–1.5 TPV daily or on alternate days until clinical response	5–6 treatments over 10–14 days until improvement or stabilization of neurological response	Clinical response
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's encephalopathy	Removal of autoantibodies	Albumin	Corticosteroids, IVIG, azathioprine, cyclophosphamide, potentially monoclonal antibody therapy	1–1.5 TPV daily or on alternate days; 3–9 procedures until Clinical response	Clinical response
HIT with progressive thrombosis	Removal of platelet-activating HIT antibodies	Albumin, Plasma	Non-heparin anticoagulation	1–1.5 TPV daily or on alternate days until clinical response	Clinical response; HIT antibody levels
Cryoglobulinemia vasculitis	Removal of cryoglobulins	Albumin	Corticosteroids, cyclophosphamide, rituximab	1–1.5 TPV every 1–3 days; 3–8 sessions until disease control	Clinical response
Pancreatitis with severe hypertriglyceridemia	Decrease of triglyceride levels, removal of inflammatory cytokines, and potential replacement of deficient lipoprotein lipase	Albumin, Plasma	Dietary restriction, lipid-lowering drugs, insulin, heparin	TPV 1–1.5 daily for 1–3 days until clinical response and triglyceride levels	Clinical response; triglyceride levels

Disease	Rationale	Replacement fluid	Adjunct therapeutic options	Strategya and Endpoints	Parameters to monitor
Paraneoplastic neurological syndromes	Removal of autoantibodies	Albumin	Antitumor therapy, immunosuppression (corticosteroids, IVIG)	1–1.5 TPV daily or on alternate days; 5–6 procedures up to 2 weeks until clinical response	Clinical response
Specific types of poisoning	Removal of toxic substances with high protein-binding capacity and low distribution volume	Albumin, plasma	Gastric lavage, activated charcoal (depending on toxic substance); multiorgan support	1–2 TPV daily until clinical response	Clinical response
Systemic lupus erythematosus with severe vasculitic complications including lupus cerebritis and pneumonitis	Removal of autoantibodies	Albumin, plasma	Immunosuppression	1–1.5 TPV daily or every other day, 3–6 sessions until clinical response	Clinical response

Table 8. Indications for TPE in the ICU: absolute, relative, and rescue therapy

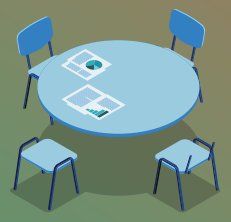
Conclusions

- TPE is considered as first- or second-line therapy in many disorders but has significant knowledge gaps, especially with regard to the exact triggers and cut-offs for initiation, optimal markers for monitoring and triggers for discontinuation
- Furthermore, the interpretation of routine laboratory blood tests and drug dosing are challenging during TPE

Reference

Bauer PR, et al. Plasma exchange in the intensive care unit: a narrative review. Intensive Care Med. 2022; 48(10):1382-96.

Success Stories



USE OF CYTOSORB® HEMOADSORPTION COLUMN DURING PROLONGED CARDIOPULMONARY BYPASS IN COMPLEX CARDIAC SURGERY PATIENT

Introduction

- A novel hemoadsorption therapy, called CytoSorb® is a safe and effective method that has recently shown to reduce bleeding and inflammatory mediators associated complications in ECMO therapy supported patients
- This case report presented the use of CytoSorb® adjunct therapy in a patient who had complex cardiac disease and multiple comorbidities

Case study

- A 61-year-old man was assessed by cardiac surgery for consideration for mitral valve surgery following a congestive heart failure presentation. The right and left ventricles had mild dysfunctions with an ejection fraction of 46%
- The patient's history includes renal disease (on hemodialysis), autoimmune cytopenia with preoperative steroids, class III heart failure, hypertension, chronic obstructive pulmonary disease, severe untreated sleep apnea, previous Grave's disease diagnosis and atrial fibrillation. The patients' preoperative levels: platelet count (74 × 109/L), hemoglobin (91 g/L), hematocrit level (29%), creatinine level (598 umol/L), and glomerular filtration rate (8 mL/min/1.73 m²) (Table 9)
- A decision was made to integrate the CytoSorb® cartridge into the CPB circuit. The device was inserted between the recirculation line (high-pressure line) and the venous reservoir of the CPB circuit. The cartridge was primed and flushed with one liter of Ringer's Lactate
- Blood flow rates through the CytoSorb® were estimated to be between 200 and 230 mL/min. Anticoagulation was achieved using heparin with target ACT greater than 400 s, monitored every 20 to 30 min. Roughly 10 min into the bypass run, the patient required further vasoactive support and the norepinephrine infusion was increased to 5 mcg/min (Table 10)
- Mean arterial blood pressures were sustained around 45–50 mmHg with 5 mcg/min of norepinephrine for the first half hour of the bypass run. At the 40 min mark, MAP increased to a mean of 65–70 mmHg and the norepinephrine dose was reduced to 2 mcg/min. After one hour on the bypass, MAP increased to 70–75 mmHg and norepinephrine was discontinued
- Zero balance ultrafiltration was performed during bypass, with a total of 2.2 L of PrismaSol '0' dialysate solution administered and 5.2 L of fluid removed via the hemoconcentrator. A total of 12.7 L of microplegia was delivered to ensure adequate myocardial protection
- CytoSorb®, was processed in a cell salvage device to be later transfused. The total bypass time was 154 min, with a cross-clamp time of 115 min
- The patient required dobutamine 5 mcg/kg/min, norepinephrine 4 mcg/min, epinephrine 5 mcg/min and vasopressin 0.04 units/min for support 10 min post-bypass
- A total of 3 units of packed red blood cells (pRBC), 2 units of platelets and 1 unit of prothrombin complex concentrate were administered to treat perioperative anemia and coagulopathy. The patient was transferred to the cardiac intensive care unit on 5mcg/kg/min of dobutamine, 6 mcg/min of norepinephrine, 5mcg/min of epinephrine and 0.04 units/min of vasopressin

- No adverse events or any device-related side effects were documented during or after CytoSorb® treatment
- The patient was extubated 48 hours post-surgery. Hemodialysis treatments were resumed on the third postoperative day
- The patient was transferred to the ward on the 6th postoperative day and discharged on the 11th postoperative day

Parameters	Pre-CPB	Post-surgery	6 h post-surgery	24 h post-surgery	48 h post-surgery	72 h post-surgery
Creatinine (umol/L)	598	389	412	464	357	470
GFR (mL/min/1.73 m2)	8	13	13	11	15	11
PLT × 109/L	74	100	127	83	54	69
Hgb (g/L)	91	102	74	77	85	90
Hct (%)	29	31	23	23	25	27
Lactate (mmol/L)	0.6	1.3	3.4	1.1	–	–

Table 9. Postoperative blood work

Medications	Pre-CPB Post Anesthesia	During CPB	At CPB Wean	Leaving OR	6 h post surgery	24 h post surgery	48 h post surgery	72 h post surgery
Norepinephrine (mcg/min)	2	5	0	0	6	2	0	0
Epinephrine (mcg/min)	0	0	5	5	5	4	2	0
Vasopressin (units/min)	0	0	0	0.04	0.04	0	0	0
Dobutamine (mcg/kg/min)	0	0	7.5	7.5	0	0	0	0

Table 10. Required vasoactive support

Conclusion

- CytoSorb® use during CPB is a safe and feasible and may contributed to improved postoperative outcomes in patient

Reference

Alarie, M., et al. Use of CytoSorb® hemoadsorption column during prolonged cardiopulmonary bypass in complex cardiac surgery patient. J Cardiothorac Surg 2022. 17; 172.

CASE REPORT: SUCCESSFUL TREATMENT OF A CHILD WITH COVID-19 REINFECTION-INDUCED FULMINANT MYOCARDITIS BY CYTOKINE-ADSORBING OXIRIS® HEMOFILTER CONTINUOUS VENO-VENOUS HEMOFILTRATION AND EXTRACORPOREAL MEMBRANE OXYGENATION

Introduction

- The COVID-19-induced fulminant myocarditis occurs due to indirect cardiomyocyte damage-related hyper-inflammatory symptoms
- Use of cytokines absorption hemofiltration along with instituting VA-ECMO support, which is novel modalities for cardiac compromise, has been clinically reported

Case study

- A 9-year-old boy with recurrent COVID-19 infection-causing fulminant myocarditis was admitted to the hospital
- He was treated successfully by using novel modalities of oXiris® hemofilter continuous venovenous hemofiltration (CVVH) and VA-ECMO
- The patient made a full recovery without any complication or events

Conclusion

- This novel highly-absorptive hemofilter CVVH and VA-ECMO may be effective treatment modalities in managing SARS-CoV-2-induced fulminant myocarditis

Reference

Phan PH et al. Case Report: Successful Treatment of a Child With COVID-19 Reinfection-Induced Fulminant Myocarditis by Cytokine-Adsorbing oXiris® Hemofilter Continuous Veno-Venous Hemofiltration and Extracorporeal Membrane Oxygenation. Front Pediatr. 2022;10: 946547

THERAPEUTIC ADVANCES IN GUIDELINE-DIRECTED MEDICAL THERAPY FOR HEART FAILURE: THE IDEALISTIC VERSUS THE PRAGMATIC TRUTH FOR VULNERABLE PATIENTS

Introduction

- Along with increasing costs, the treatment of one patient's complexity is increasing with increasing number of medications recommended for a patient to take, increasing number of side effects and monitoring for each medication that is now required
- This editorial aimed to focus on the changing landscape of HF treatment and discuss obstacles solutions
- Systematic review addressing medical costs of HF in the USA between 2014 and 2020
- The total number of studies included in analysis were 87 studies, 41 of which allowed comparison of cost estimates across studies
- The annual median total medical costs for HF care were estimated at $24,383 per patient, with HF-specific hospitalizations driving up costs and accounting for approximately $15,879 per patient
- It stated that HF is a very expensive diagnosis for both patients and the healthcare system. It includes hospital fees and medications (15.6% of direct costs). Hence, special consideration has been taken to remove uninsured or underserved medical assistance
- Therefore, current treatment guidelines for patients with systolic HF with reduced ejection fraction (LVEF ≤ 40%) as recommended by the American College of Cardiology (ACC) include medications listed in Table 11

Indication during HF treatment	Medication Class	Estimated Manufacturers AWP (30-day supply±)
Symptomatic HFrEF (LVEF≥40%)	ARNIACEIARB	ARNI: $750 ACEI: $1-$5 ARB: $5-$10
	"Beta-Blocker"	$10
	"Loop Diuretic"	$15-30
	"SGLT2i"	$650-$685
	"Aldosterone Antagonist"	$40
Addition of these medications if symptoms persists after above medications	Vasodilator	Hydralazine: $10Isosorbide Dinitrate: $40-$600 (depending on dose and frequency)
Addition of these drugs if resting HR ≥70 bpm in sinus rhythm on maximum tolerated beta-blocker dose	HCN Channel Blocker	$624

Table 11. ACC medication recommendations based on indication.

- Use of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium glucose cotransporter 2 inhibitors (SGLT2) medications are expensive in reducing acute HF exacerbations and overall improvement of cardiovascular outcomes in HF patients

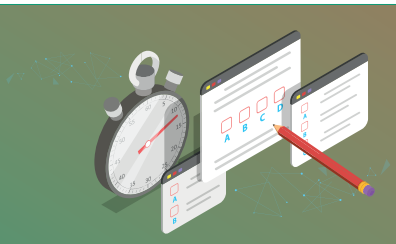
- The Affordable Care Act (ACA) came into force on 23rd March 2010 to reduce the cost of HF treatment. Significant rate was dropped 46.5 million (2010), 26.7 million (2016) and 8.5% (2018)
- Data with regard to HF medication (ACE inhibitors, angiotensin receptor blockers, and ARNI) use at discharge, at least for Hispanics, exploded by 146% after ACA expansion compared with before
- Since this study was conducted in 2018, data adjustments for costs that would have otherwise not included SGLT2i's are lacking. It should be also pointed out that less than 0.5% of these HF patients were using an ARNI or Ivabradine. This estimation was included costs of chronic comorbidities seen in elderly population such as diabetes mellitus
- There is an urgent need for transparency between pharmacy-benefit managers and drug manufacturers to reduce the costing of HF medications and could be benefited directly patients

Reference

Shannon Jones et al 2022 Therapeutic advances in guideline-directed medical therapy for heart failure: the idealistic versus the pragmatic truth for vulnerable patients. Postgraduate Medicine, 134:7, 641-43.

Abbreviations

ACEI	-	Angiotensin Converting Enzyme Inhibitor
ANCA	-	Antineutrophil cytoplasmic antibody
aPTT	-	Activated partial thromboplastin time
ARB	-	Angiotensin II receptor blocker
ARNI	-	Angiotensin receptor neprilysin inhibitor
AWP	-	Average Wholesale Price
CPB	-	Cardiopulmonary bypass
E-CABG	-	European coronary artery bypass grafting
ECMO	-	Extracorporeal membrane oxygenation
GBM	-	Glomerular basement membrane
GFR	-	Glomerular filtration rate
Hb	-	Hemoglobin
HCN	-	Hyperpolarization-activated cyclic nucleotide-gated
Hct	-	Hematocrit
HFrEF	-	Heart failure with reduced ejection fraction
HIT	-	Heparin-induced thrombocytopenia
HR	-	Heart rate
ICU	-	Intensive care unit
IVIG	-	Intravenous immunoglobulins,
NOAC	-	Novel oral anticoagulant
OR	-	Operating room
PLT	-	Platelets
RBC	-	Red blood cell
SAVR	-	Surgical aortic valve replacement
SD	-	Standard deviation
SGLT2i	-	Sodium-glucose transport protein 2 inhibitor
TAVR	-	Ttranscatheter aortic valve replacement
TIA	-	Transient ischemic attack
TMA	-	Thrombotic microangiopathy
TPE	-	Therapeutic plasma exchange
TPV	-	Total plasma volume
TTP	-	Thrombotic thrombocytopenic purpura
VA-ECMO	-	Veno arterial Extracorporeal membrane oxygenation



Perfusion Quiz (Multiple Choice Questions)

1. The example of direct thrombin inhibitors (DTIs) which are used to manage coagulation complication with ECMO

a) Bivalirudin b) Heparin c) Argatroban d) Both a and c

2. This is the independent predictor for post-operative stroke complications in TVAR and SAVR

a) Hypertension b) High hematocrit level c) Perioperative bleeding d) Vasoplegia

3. The post CPB vasoplegia can be treated by

a) Heparin b) Beta-blockers c) Angiotensin II d) None

4. Fulminant myocarditis occurs due to

a) Bleeding complications b) COVID-19 c) Heart failure d) Chronic kidney disease (CKD)

5. Use of …….. is safe and feasible to improve perioperative outcomes in CPB patients-

a) Cytokines absorption hemofiltration b) CytoSorb c) ECMO support d) Both b and c

6. Cardio-selective beta blockers are used to reduce CABG associated complication like

a) MACEs b) Perioperative bleeding c) None d) Both a and b

7. Heparin anticoagulation monitoring in ECMO support can be performed by

a) ACT level b) aPTT level c) Xa level d) All

8. The range of ACT as per ELSO guideline is

a) 60-80 second b) 180-200 second c) > 400 seconds d) None

9. The impaired contact activation complex which is responsible for initiation of intrinsic coagulation pathway occurs due to

a) Factor VII deficiency b) Factor XII deficiency c) Factor VIII deficiency d) None

10. The brand name of FDA approved angiotensin II in 2017 is -

a) Glantreza b) Giapreza c) Giapril d) None

Giapreza	Factor XII deficiency	180-200 second	All	MACEs	Both b and c	COVID-19	Angiotensin II	Perioperative bleeding	Both a and c