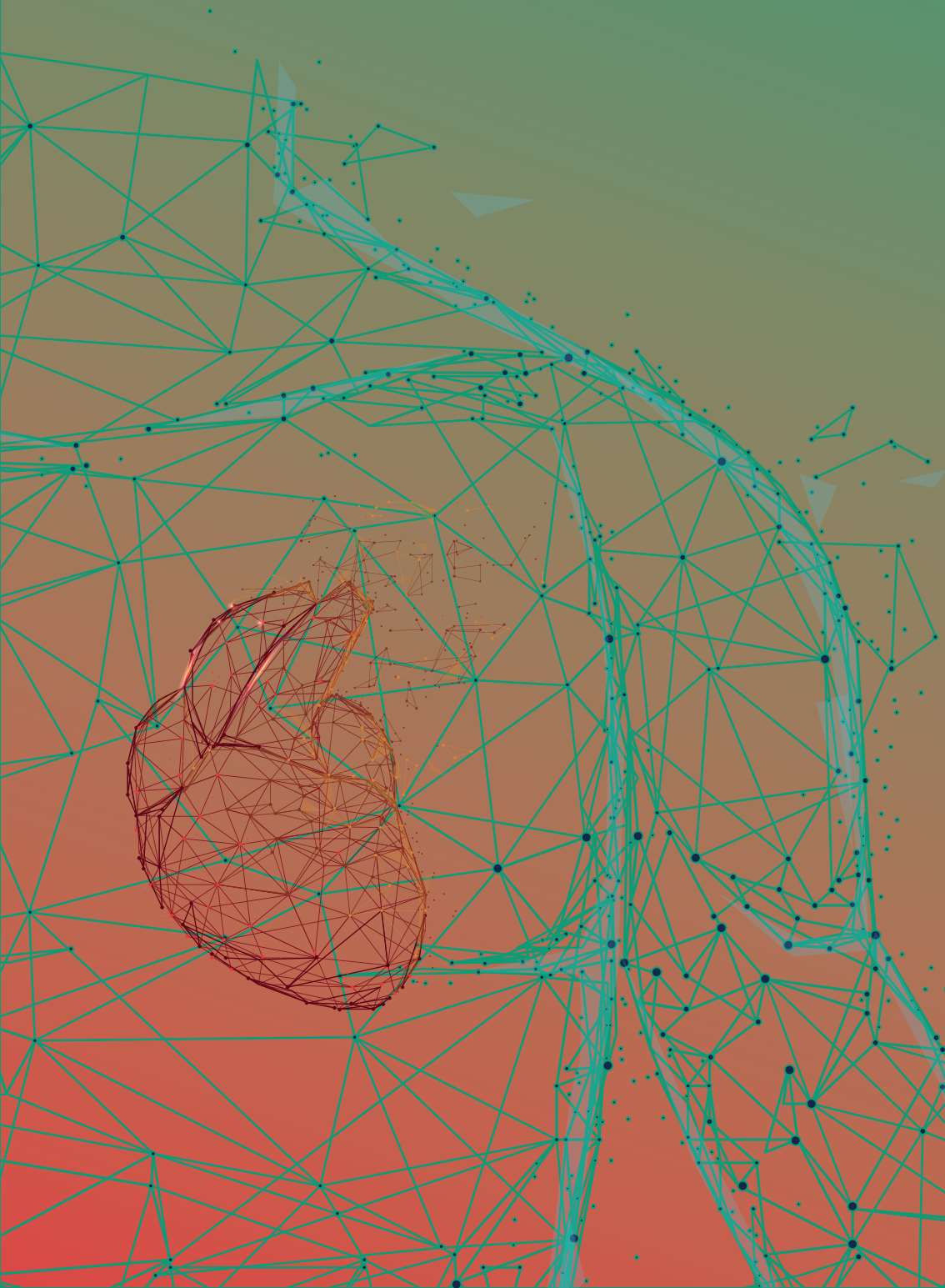
ISSUE 23

PRIME

Perfusion-Related Insights – Management and Evidence



- Specialty insights
- Basic Facts
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Editorial Letter

It is with immense pleasure that we present the 23rd 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 guidance recommendations. Starting with the first section 'Speciality Insights,' it contains a systematic review which summarizes long term outcomes of the implantation of a RVAD following LVAD.

The second section, 'Basic Facts', contains two articles. The first article is a randomized pilot trial which focuses on the importance of Human Fibrinogen Concentrate (HFC) in neonate and infant patients undergoing CPB. The second article in this section is a study which shows a correlation between the lactate peak concentration and its clearance with VA-ECLS therapy with respect to ICU mortality of Refractory cardiogenic shock patients.

The third section 'Practice Pearls' contains a case study of successful implantation of temporary RVAD after redo aortic valve surgery and LVAD implantation in a patient with end-stage HF.

The next section 'Journal Talk' contains a review article which focuses on heparin Resistance during CPB in adults and its management.

The fifth section 'Expert Opinion' contains article which discusses the importance of retrograde arterial perfusion and its outcome in robotic mitral-valve surgery.

The sixth section, 'Success Stories', contains a case series showing four cases of cardiac patients in which intravenous beta blockers were used with VA-ECMO for successful treatment of their conditions.

The seventh section of this newsletter 'News Corner' contains two articles. The first article introduces a new apheresis device, PUR-01, a hemoperfusion pump, which is used with CytoSorb as an extracorporeal circuit for the removal of antithrombotic drugs during off-pump coronary artery bypass (OPCAB) procedures. The second article consists of novel therapeutic strategies to reduce Reperfusion Injury after Acute Myocardial Infarction (AMI).

We hope this newsletter enriches your knowledge of 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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Table of Contents

OUTCOME OF RIGHT VENTRICULAR ASSIST DEVICE IMPLANTATION FOLLOWING LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION: SYSTEMATIC REVIEW AND META-ANALYSIS

Introduction

- Among the cardiac patients with right ventricular failure following left ventricular assist device (LVAD) implantation (9 - 44%), 10%–15% of patients may require subsequent implantation of a separate right ventricular assist device (RVAD).
- Right heart failure (HF) may lead to impaired LVAD flow, difficulty in weaning from cardiopulmonary bypass (CPB), decreased tissue perfusion, prolonged inotropic support, and multi-organ failure, which increases morbidity and mortality rate.
- This systematic review presented long term outcomes on the implantation of a RVAD in a LVAD through surgical intervention.

Methods

- Medline, Web of Science and EMBASE databases were used to evaluate outcomes of RVAD implantation following LVAD implantation.
- Inclusion criteria were reports on adults, on mortality or survival and on morbidity after LVAD and/or after a LVAD/RVAD procedure, minimal duration of follow-up >1 year, completeness of follow-up 90% and study size n > 10.
- The primary endpoints were in-hospital mortality, survival at 1 (short-term), 3 and 5 years (long-term) of follow-up.
- The secondary endpoints were stroke, thromboembolic event, bleeding and transplantation rate.

Results

- A total of 25 retrospective studies which include 3260 patients were reported in Figure 1.
- Pooled in-hospital mortality was reported lower in the LVAD implantation group than in the LVAD/RVAD implantation group at 30 days, one year and after a five-year follow-up. In 30 days, the mortality was 6.74% (95% CI 1.98 - 11.50) in LVAD and 31.9% (95% CI 19.78 - 44.02) p = 0.001 in the LVAD/RVAD cohort. In case of one year (short term), mortality was 19.66% (95% CI 15.73 - 23.59) in LVAD versus 45.35% (95% CI 35.31 - 55.40) p = 0.001 in the LVAD/RVAD group. In 5 years, the mortality was reported at 33.90% in LVAD and 48.23% (p = 0.686) in the LVAD/RVAD group.
- Thromboembolic event was reported in only one study, and was 40% in the LVAD/RVAD procedure.
- Incidence of a bleeding event was found lower in LVAD (one report - 7%) than in the LVAD/RVAD group (two report 8.6%) (IQR 23.8 - 33.3%).
- The proportion of patients that had a stroke was also found lower (12.2% [IQR 11.1 - 13.3%]) in LVAD than in the LVAD/RVAD group (21.4% [IQR 5.9 - 33.3%]).

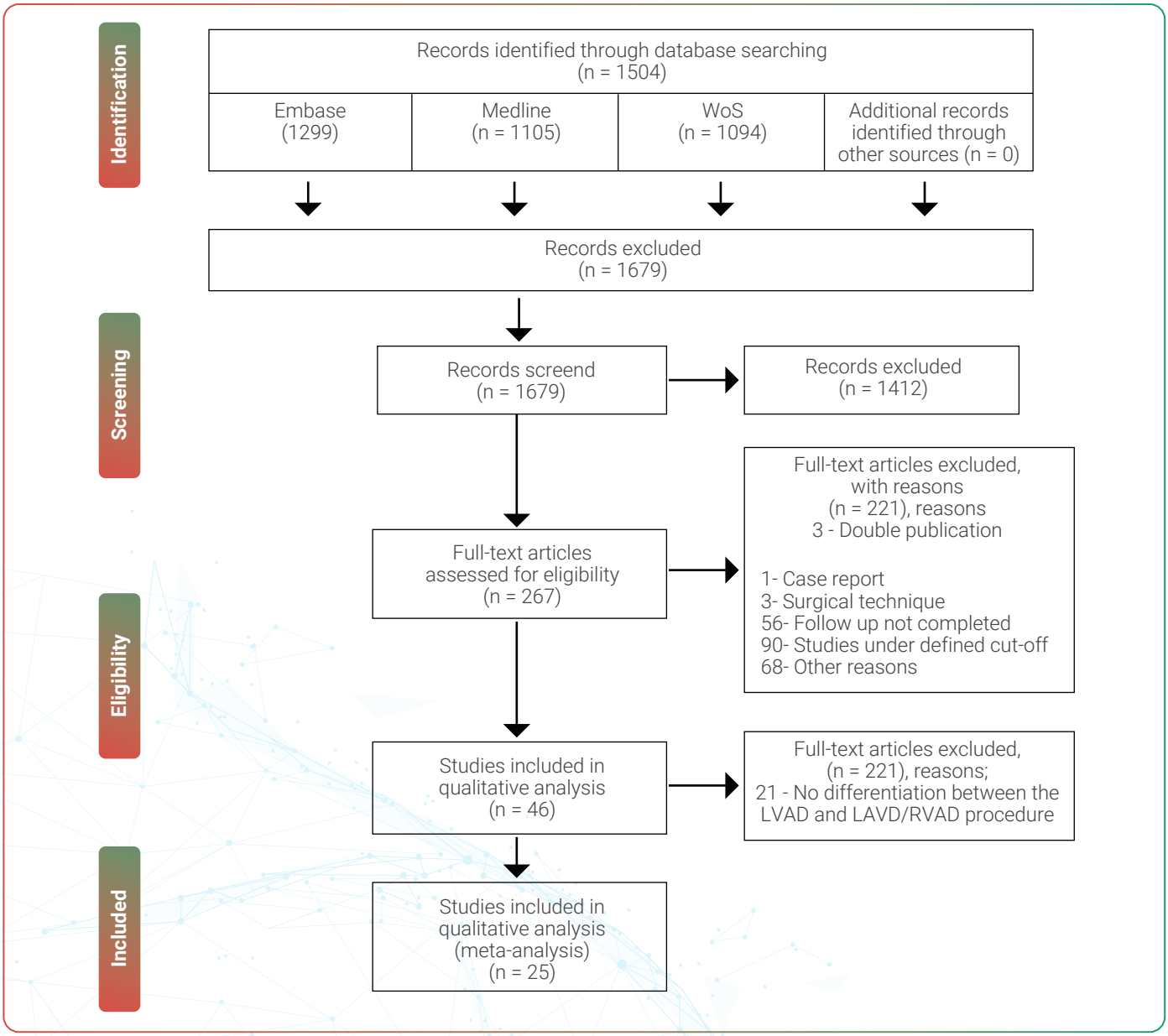


Figure 1: PRISMA flow diagram summarizing the process of study selection

Conclusion

- Temporary RVAD was associated with a worse outcome during primary hospitalization and follow-up.
- Compared to isolated LVAD support, biventricular mechanical circulatory support leads to elevated mortality and a higher incidence of adverse events such as bleeding and stroke.

Reference

Reid G, et al. Outcome of right ventricular assist device implantation following left ventricular assist device implantation: Systematic review and meta-analysis. Perfusion. 2022; 37(8): 773-84.

Basic Facts

A RANDOMIZED PILOT TRIAL ASSESSING THE ROLE OF HUMAN FIBRINOGEN CONCENTRATE IN DECREASING CRYOPRECIPITATE USE AND BLOOD LOSS IN INFANTS UNDERGOING CARDIOPULMONARY BYPASS

Introduction

- Fibrinogen replacement therapy is currently recommended for both congenital heart disease and acquired fibrinogen deficiency, in children ≤ 12 months of age, caused by various conditions, including major postoperative bleeding after cardiac surgery.
- The present study has shown that treatment with Human Fibrinogen Concentrate (HFC) decreases the need for component blood therapy and blood loss in neonate and infant patients undergoing CPB.

Methods

- This was a prospective, randomized, placebo-controlled pilot study (2017-2018, USA) (Figure 2).
- Neonates and infants (≥ 37 weeks gestational age to 12 months) cardiac surgery patients (N = 30) were randomized (1:1) to either treatment or placebo group.
- The treatment group received a prophylactic infusion of 70 mg/kg HFC after CPB and the placebo group received normal saline 0.9% (NS).
- The primary endpoint was the amount of cryoprecipitate administered.
- Secondary endpoints included estimated blood loss during the 24 h post-surgery; perioperative blood product transfusion; effects of fibrinogen infusion on global hemostasis, and adverse events (AEs).

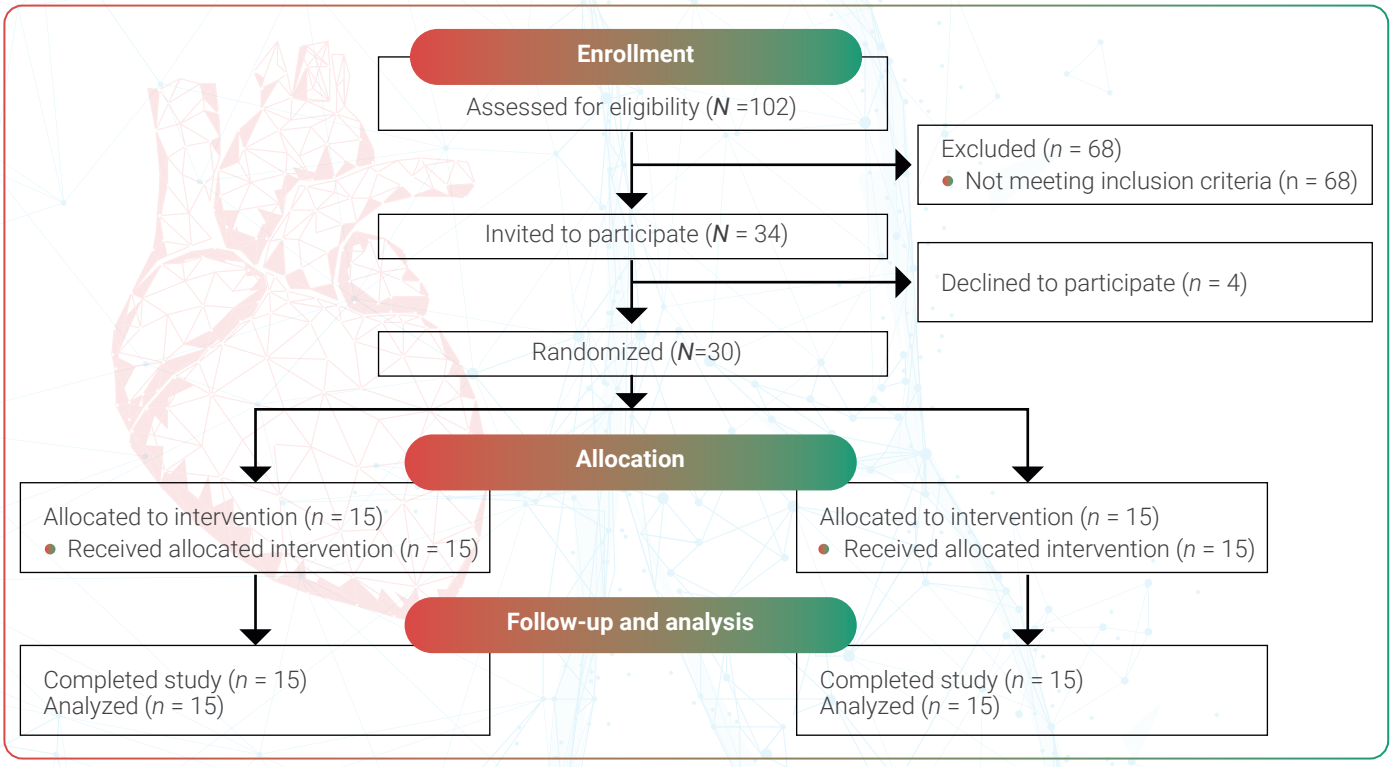


Figure 2: Study design

Results

The majority were white (76.7%) and male (56.7%). The mean age was 148 (5 - 286) days and 146 (4 - 353) days for both groups.

- Significantly less cryoprecipitate (P < 0.0001) was given in the treatment group compared to placebo (Table 1).

Parameters	Treatment		Placebo		*P* value*
	N	Median (IQR)	*N*	Median (IQR)	
ICU estimated blood loss (cc/kg)	15	35.2 (20.6 – 61.1)	15	34.4 (27.8 – 54.3)	0.62
Total Factor VII (mcg/kg)	14	0 (0 – 0.0)	15	0.0 (0.0 – 0.0)	N/A
Total packed red blood cells (cc/kg)	15	55.3 (44.7 – 77.2)	15	57.9 (44.8 – 89.2)	1
Total fresh frozen plasma (cc/kg)	15	0.0 (0.0 – 23.2)	15	13.6 (0.0 – 45.1))	0.27
Total platelets (cc/kg)	16	61.3 (50.1 – 69.3)	15	59.9 (50.9 – 73.0)	0.98
Total cryoprecipitate (cc/kg)	15	0.0 (0.0 – 0.0)	15	12.0 (8.2 – 14.3)	**< 0.0001**
Total cell saver (cc/kg)	15	27.3 (20.3 – 34.8)	15	23.7 (13.5 – 47.5)	0.51
Total blood (cc/kg)	15	142.1 (137.6 – 174.8)	15	140.9 (136.2 – 219.3)	0.87
Intubation time (h)	15	0.0 (0.0 – 28.5)	15	24.0 (0.0 – 70.0)	0.40
LOS ICU (days)**	14	8.0 (4.0 – 23.0)	15	8.0 (5.0 – 12.0)	0.89
LOS hospital (days)**	14	9.0 (6.0 – 23.0)	15	8.0 (6.0 – 12.0)	0.75

Bold value denote statistical significance at the P < 0.05 level; ICU intensive care unit, IQR interquartile range, LOS length of stay; P < 0.05 based on Exact Wilcoxon 2-sample test; **excluded a patient with LOS 99 days

Table 1. Post-HFC clinical characteristics of patients

- No difference was observed between treatment groups in blood loss, laboratory coagulation tests, use of other blood components, or incidence of AEs.
- Overall, 7 (46.6%) and 5 (33.4%) patients from treatment and placebo groups, respectively, had at least one AEs (Table 2).

Adverse events	Treatment group (*N*=15) (%)	Placebo group (*N*=15) (%)
Thrombus	4 (26.7)	2 (13.3)
Respiratory failure	3 (20.0)	3 (20.0)

Table 2. Adverse events associated with the treatment of HFC

Conclusions

- The present study has shown that administration of HFC after CPB in neonate and infant patients was efficacious and reduces the need for transfusion without increasing AEs.

Reference

Tirotta CF, et al. A Randomized Pilot Trial Assessing the Role of Human Fibrinogen Concentrate in Decreasing Cryoprecipitate Use and Blood Loss in Infants Undergoing Cardiopulmonary Bypass. Pediatr Cardiol. 2022; 43(7): 1444-54.

ELEVATED LACTATE LEVELS AND IMPAIRED LACTATE CLEARANCE DURING EXTRACORPOREAL LIFE SUPPORT (ECLS) ARE ASSOCIATED WITH POOR OUTCOME IN CARDIAC SURGERY PATIENTS

Introduction

- Refractory cardiogenic shock (RCS), a cardiac and circulatory failure, resulting in organ hypoperfusion unresponsive to conventional medical therapies, may be one cause of severe hyperlactatemia (> 10.0 mmol/L).
- Early aggressive management with initiation of veno-arterial extracorporeal life support (VA-ECLS) represents a valuable therapeutic option to stabilize patients' condition in medically RCS in ICU to reduce mortality.
- Thus, the present study has shown a correlation between the lactate peak concentration and its clearance with VA-ECLS therapy with respect to ICU mortality of RCS patients after cardiac surgery.

Method

- It was a retrospective, observational, single-centre study (2020 - 2021).
- 51 cardiac surgery ICU patients with ECLS therapy were included (23 survivors and 28 non-survivors).
- Lactate measurement was performed before, during and after ECLS therapy. ICU scores (SAPSII, SOFA and TISS-28) were also evaluated.
- Laboratory parameters such as bilirubin level, pH-Minimum, and thrombocyte counts were also measured and compared between both groups.

Results

- Compared to the non-survivors, survivors had a lower last SOFA score and a lower overall minimum SOFA score and in case of the SAPSII score, a lower last, overall minimum and maximum SAPSII score and had a lower last TISS28- score (Table 3)
- The overall minimum and last thrombocytes count remained lower in the non-survivor's group (Table 4).
- Higher level of the last bilirubin, an elevated overall minimum and maximum bilirubin level and a lower overall pH minimum in the non-survivor group (Table 4).
- In case of lactate level in survivor compared to the non-survivors, they had a lower last lactate level at VA-ECLS. Additionally, survivors had a significant lower post VA-ECLS weaning lactate level. The overall peak lactate level was elevated in the non-survivor group (Table 4).
- An optimal cut-off point to discriminate between survivors and non-survivors could be a lactate level of 11.5 mmol/L.
- Likewise, survivors presented with significant lower hours compared to non-survivors in all the pre-specified lactate intervals (20.1: 0.0 ± 0.0 vs. 4.42 ± 7.19; $p < 0.001$ for all the intervals) (Figure 3).

Score	Survivors (N=23)	Non-survivors (N=28)
SOFA-First	11.6 ± 4.8	12.5 ± 5.7
SOFA-Last	7.5 ± 2.9	18.1 ± 4.5*
SOFA-Minimum	5.2 ± 2.1	11.8 ± 5.4#
SOFA-Maximum	13.8 ± 4.6	18.3 ± 4.6
SAPS II-First	69.2 ± 17.3	65.4 ± 17.7
SAPS II-Last	53.0 ± 23.0	86.2 ± 12.4*
SAPS II-Minimum	40.3 ± 18.5	52.2 ± 19.0#
SAPS II-Maximum	84.5 ± 10.4	94.3 ± 8.6*
TISS 28-First	44.1 ± 10.7	39.6 ± 12.2
TISS 28-Last	32.8 ± 9.0	48.8 ± 8.4*
TISS 28-Minimum	27.3 ± 6.6	32.0 ± 10.5
TISS 28-Maximum	53.6 ± 6.9	55.4 ± 6.0

Table 3. ICU scores among survivors and non-survivors

Parameters	Survivors (N=23)	Non-survivors (N=28)
Bilirubin-first [mg/dl]	1.3 ± 1.1	2.0 ± 1.6
Bilirubin-last [mg/dl]	3.4 ± 6.8	21.1 ± 19.9*
Bilirubin-minimum [mg/dl]	0.8 ± 1.0	1.6 ± 1.2*
Bilirubin-maximum [mg/dl]	6.5 ± 7.6	27.2 ± 20.6*
Thrombocytes-first [mcL]	217 ± 106	173 ± 87
Thrombocytes-last [mcL]	176 ± 80	84 ± 47
Thrombocytes-minimum [mcL]	67 ± 42	47 ± 29
Thrombocytes-maximum [mcL]	245 ± 104	216 ± 85
pH-Minimum	7.19 ± 0.09	7.08 ± 0.15
Lactate pre VA-ECLS [mmol/L]	8.63 ± 4.72	10.34 ± 6.13
First lactate at VA-ECLS [mmol/L]	8.59 ± 4.71	11.28 ± 6.11
Last lactate at VA-ECLS [mmol/L]	1.56 ± 0.66	13.71 ± 8.96*
Lactate Post VA-ECLS [mmol/L]	1.49 ± 0.71	11.4 ± 8.03*
Lactate maximum [mmol/L]	12.41 ± 12.71	19.70 ± 6.64*
Lactate minimum [mmol/L]	1.32 ± 1.31	2.61 ± 2.61

*p < 0.001; # p < 0.05

Table 4. Bilirubin, thrombocyte, PH-Minimum, and lactate evaluation among survivors and non-survivors

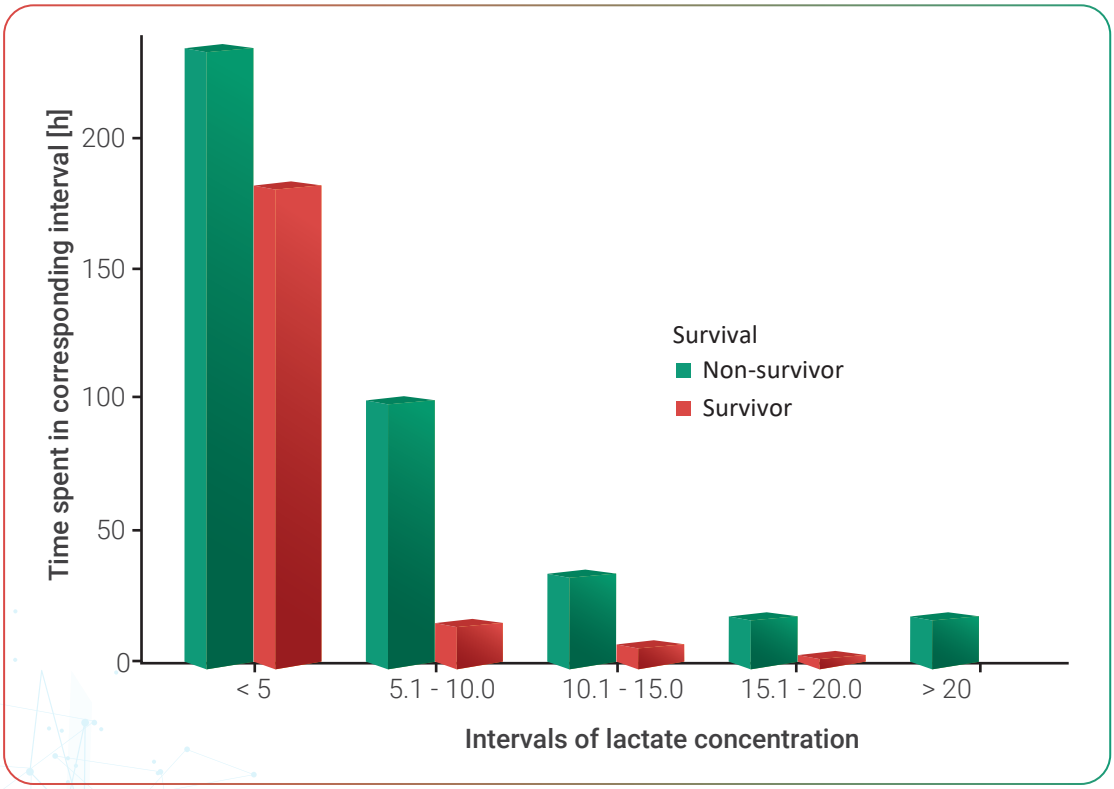


Figure 3. Temporal distribution of lactate levels

Conclusion

- ECLS support is an option for life-threatening conditions such as RCS after cardiac surgery.
- The temporal distribution of elevated serum lactate levels (> 5.0 mmol/L) is associated with higher mortality on VA-ECLS therapy.
- The lactate peak concentration was increased in the non-survivor group and could be a factor to distinguish between survival and non-survival.

Reference

Rissel R, et al. Elevated lactate levels and impaired lactate clearance during extracorporeal life support (ECLS) are associated with poor outcome in cardiac surgery patients. PLoS One. 2022; 17(11): e0278139.

Practice Pearls

TEMPORARY RIGHT VENTRICULAR ASSIST DEVICE AFTER REDO AORTIC VALVE REPLACEMENT AND HEARTMATE 3TM IMPLANTATION – A CASE REPORT

Introduction

- The implantation of the LVAD, HeartMate 3TM, is used as a bridge to or as an alternative to heart transplantation for the management of end-stage HF.
- In case of CPB weaning failure, temporary RVAD might be required after LVAD implantation, due to right ventricle dysfunction despite inotropic support.
- The HeartMate 3TM implantation (9 - 44%) might be associated with early or late right ventricular dysfunction and among them, 10-15% of patents might require temporary right ventricular support (RVAD).
- The present case illustrates the successful implantation of temporary RVAD after redo aortic valve surgery and LVAD implantation in a patient with end-stage HF.

Case study

- A 38-years-old male (80 Kg/178cm) was admitted to the hospital with decompensated HF.
- He had a history of mechanical aortic valve re-placement, cardiac resynchronization therapy with defibrillation (CRT-D) implantation, atrial tachycardia and multiple admissions for acute pulmonary edema episodes. Also, he had type-II diabetes, hypercholesterolemia, obstructive sleep apnea and latent tuberculosis.
- He was treated with furosemide, amiodarone and non-invasive ventilation for the management of the condition. However, it failed to improve clinical conditions despite three infusions of levosimendan and the patient developed stage II acute kidney injury.
- The clinician decided to implant a HM3 device (LVAD) as a bridge to heart transplantation.
- Pre-operative evaluation of the right ventricle demonstrated that the patient was classified as INTERMACS-2 and EuroSCORE-II with 69% preoperative mortality risk estimation. Other preoperative laboratory values are reported in Table 5.

Preoperative analysis of laboratory parameters	Admissions	iImmediate Post-operative value	Postoperative day 8 (post-temporary RVAD removal)
Leukocytes (G/L)	12.9	11.3	16.4
Platelets (G/L)	262	149	301
aPTT (s)	76	49	61
Fibrinogen (g/l)	4.6	2.7	–
Urea (mmol/l)	16	13.5	–
Creatinine (umol/l)	183	187	61

Preoperative analysis of laboratory parameters	Admissions	iImmediate Post-operative value	Postoperative day 8 (post-temporary RVAD removal)
eGFR (ml/min/1,73m2)	36	35	> 60
CRP (mg/l)	22	20	143
NT-proBNP (ng/l)	49'995	–	–
CK (U/L)	45	428	41
ASAT (U/L)	165	716	36
ALAT (U/L)	137	357	53
HM3 (LVAD) settings			
RPM	–	5600	6200
Flow (l/min)	–	5	5.5
PI	–	3.7	3.6
Power (watts)	–	4.1	5
Centrimag (RVAD) settings			
RPM	–	3800	–
Flow (l/min)	–	4.95	–

Table 5. Pre and post-operative laboratory parameters value

- After induction of general anaesthesia, the left ventricular dysfunction (ejection fraction [EF] 15%) was observed with dilated left heart cavities, severe mitral regurgitation, moderate tricuspid regurgitation and pulmonary hypertension (systolic pulmonary artery pressure 60 mmHg).
- CPB was instituted using double venous cannulation (superior vena cava and right femoral vein) and arterial cannulation in ascending aorta.
- In the first operative stage, the mechanical aortic valve was replaced with a pericardial valve. Then, following aorta clamp release, the HM3 device was implanted in the apex of the left ventricle. The ejection cannula was implanted in the right anterolateral face of the ascending aorta after lateral clamping of the ascending aorta.
- A temporary RVAD with Centrimag® system was inserted through a pulmonary arteriotomy.
- This prosthesis was then cannulated and connected to the infusion line of the Centrimag system, reinforced with several tie bands.
- For venous drainage, cannulation placed in the right femoral vein was used and connected to the drainage line of the Centrimag system (Figure 4). After this double implantation, the CPB could be weaned, and the patient was transferred to ICU with the implanted LVAD and temporary RVAD (Total CPB duration 152 min, aortic cross-clamping 65 min).

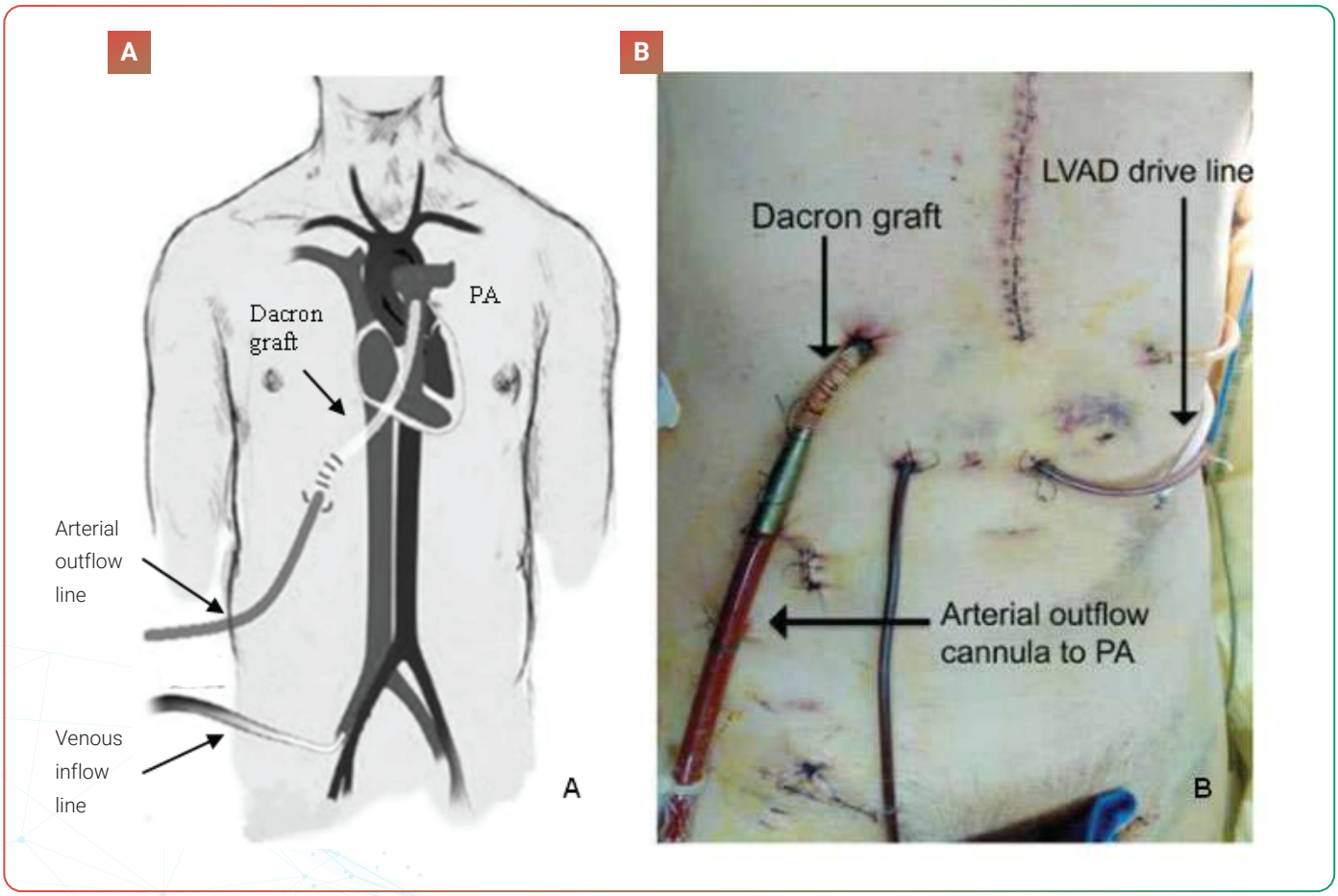


Figure 4. A- Illustration of the temporary RVAD system with cannulation by dacron graft between the right femoral vein and the pulmonary artery. B- Front view with dacron graft tunneled under the right costal margin and LVAD drive line; PA- pulmonary artery.

The patient was extubated on post-operative day 2. Finally, the temporary RVAD was removed on day 8. The patient was discharged from the ICU on day 16 and from the hospital on day 21. After 25 months, follow-up has shown that after HM3 implantation, heart transplantation was successfully performed (Figure 5).

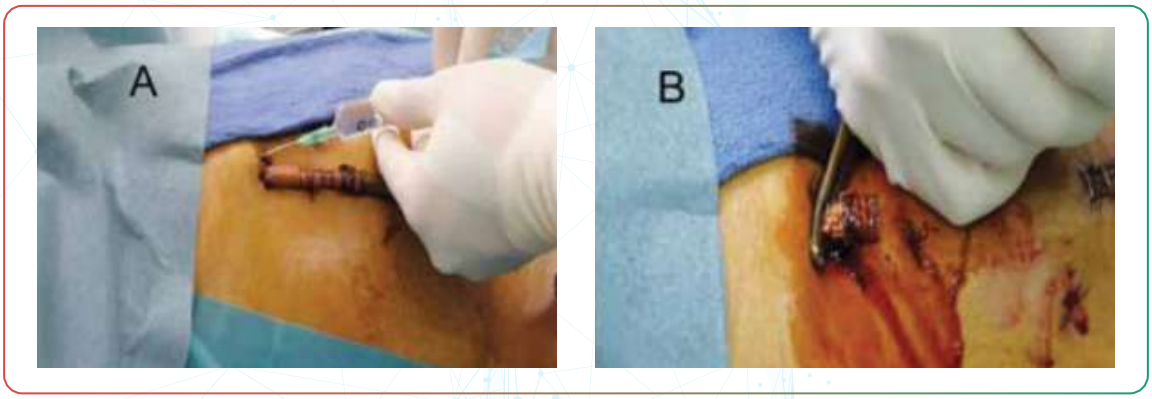


Figure 5. A- Retrieval of the device under local anesthesia; B- Retraction of the dacron graft into the mediastinum

Conclusion

The successful implantation of temporary RVAD was performed after redo aortic valve surgery and LVAD implantation in a patient with end-stage HF.

Reference

Mendes V, et al. Temporary Right Ventricular Assist Device After Redo Aortic Valve Replacement And Heartmate 3tm Implantation - A Case Report. Port J Card Thorac Vasc Surg. 2022; 29(3): 51-4.

HEPARIN RESISTANCE DURING CARDIOPULMONARY BYPASS IN ADULT CARDIAC SURGERY

Introduction

- The technical challenge of preventing thrombosis within the extracorporeal circuit (ECC) was overcome with the use of heparin and its effective antidote, protamine, in CPB procedures. The adequacy of heparin anticoagulation during CPB is commonly monitored using the activated clotting time (ACT), which is considered as a gold standard for monitoring of coagulation.
- Heparin resistance, sometimes referred to as diminished responsiveness to heparin, can occur in some cardiac patients during CPB and causes sub-therapeutic ACT levels.
- Inadequate anticoagulation takes place due to activation of the coagulation cascade, which causes complications such as consumptive coagulopathy, excessive postoperative bleeding, and thromboembolic phenomena.
- Thrombin is also necessary for activating platelets, factors V, VIII, and XI, and preventing the spread of clots by activating protein C and releasing tissue plasminogen activator and tissue factor pathway inhibitor.
- In clinical practice, a wide variation of ACT targets, ranging usually from 400-500 seconds for initiation and maintenance of CPB.
- This review article focuses on heparin resistance and its current therapy.

Heparin Resistance

- Heparin resistance develops because heparin is routinely used as an anticoagulant during CPB.
- When a sufficient dose of heparin shows inability to produce an acceptable ACT or shows a reduced slope on the Heparin Drug response (HDR) curve, characterized by heparin resistance. Additionally, heparin resistance can also be determined by using a heparin sensitivity index (< 1 s/U/kg), obtained by using the slope values from the HDR curve to quantify heparin responsiveness.

Mechanisms of Heparin Resistance

- There are the following mechanisms (Figure 6) for heparin resistance-

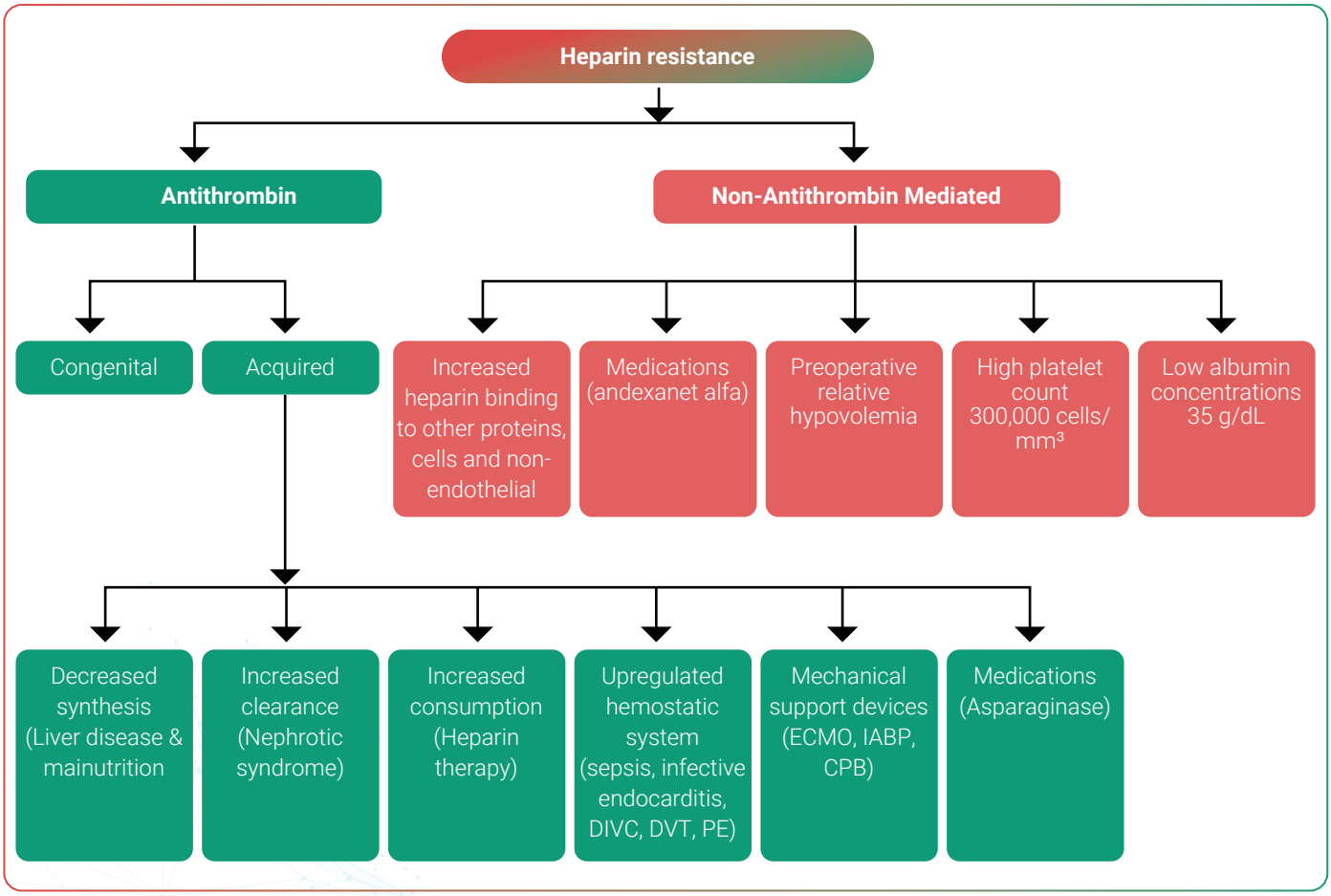


Figure 6. Mechanisms of Heparin Resistance

Mamagement of Heparin Resistance

- There are four main approaches for management of heparin resistance during CPB.
  - Provide more heparin to get the required ACT (usually 300 - 500 U/kg).
  - Give fresh frozen plasma (FFP) to supply more anti-thrombin (~ 500 mL FFP for 500 IU of anti-thrombin).
  - To supplement anti-thrombin with anti-thrombin concentrate (~ 500 - 1000 IU).
  - To accept the sub therapeutic ACT (~ 250 seconds or more) and begin CPB without providing any other medications.
- Alternatives for Anticoagulation
  - Direct thrombin inhibitors (DTI)
    Bivalirudin and argatroban are used as substitutes for heparin in patients of CPB. However, it requires a skilled anesthesiologist-perfusion-surgical team because use of bivalirudin requires avoidance of the stagnation of blood in the CPB circuit to avoid thrombosis and also they have no specific reversal agents.
  - Nafamostat mesilate, a short-acting synthetic protease inhibitor, prolongs ACT by directly inhibiting thrombin and other activated coagulation factors. It successfully overcomes heparin resistance during the conduct of CPB without increasing the risk of perioperative ischemic stroke or death.
- Treatment Algorithm

A stepwise approach toward treatment instead of administering drugs and products without understanding their mechanism. The easy algorithm (Figure 7) adopted from Finley and Greenberg's 2013 is -

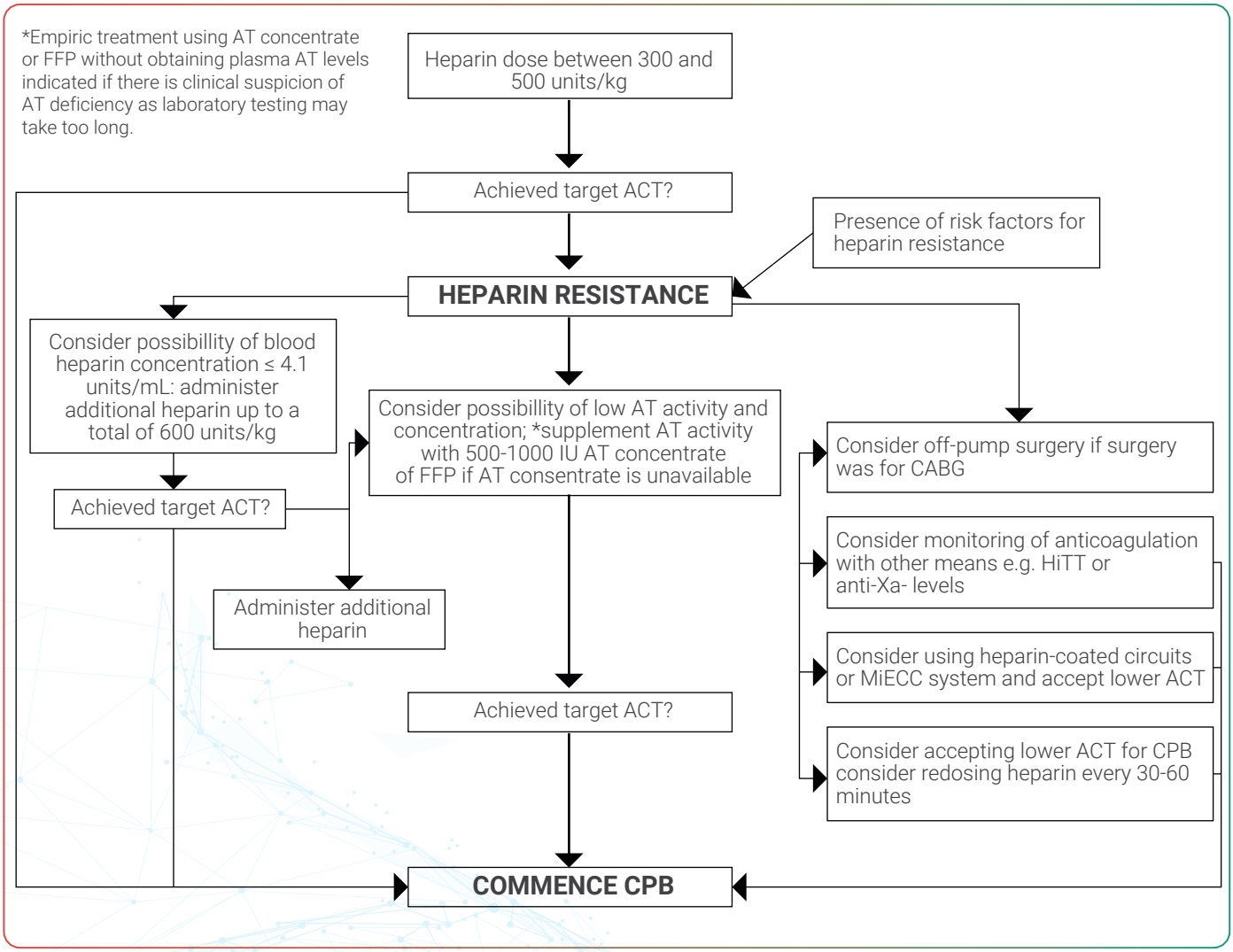


Figure 7. Algorithm for treatment of heparin resistance. Flow chart adapted from Finley and Greenberg

Conclusion

- Heparin resistance is a multifaceted, intricate problem that causes complications in CPB procedures.
- Before starting CPB, clinicians should consider the patient's medical history, especially ACT limitations and pharmacology of heparin.
- They should also be aware of the limitations of ACT in assessing the appropriateness of anticoagulation for CPB.
- For the management of heparin resistance, more amount of heparin, alternatives for heparin or algorithm management can be used.

Reference

Chen Y, et al. Heparin Resistance during Cardiopulmonary Bypass in Adult Cardiac Surgery. J Cardiothorac Vasc Anesth. 2022; 36(11): 4150-60.

Expert Opinion

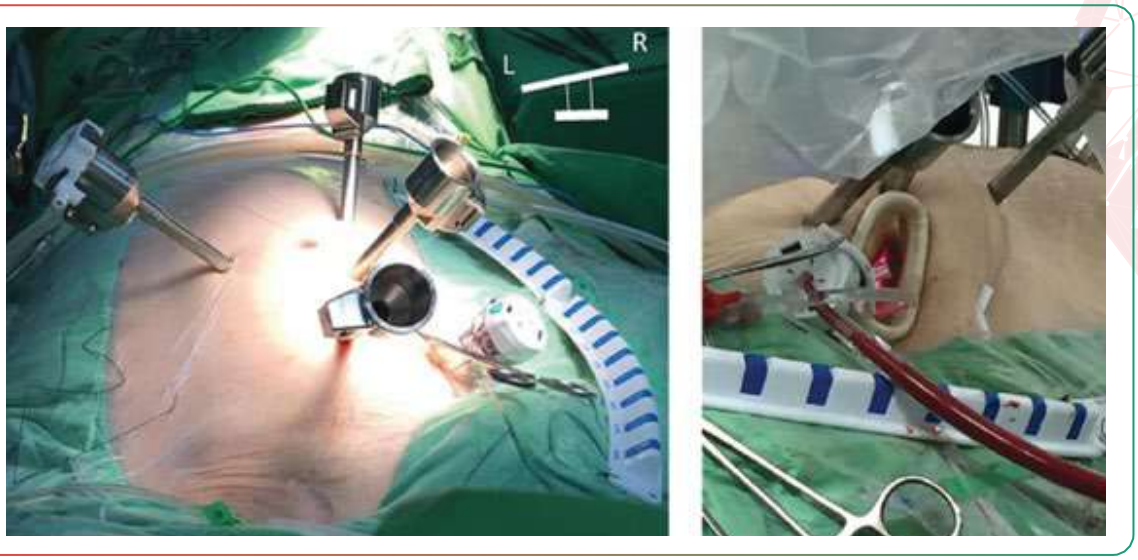
RETROGRADE ARTERIAL PERFUSION AND ITS OUTCOME IN ROBOTIC MITRAL-VALVE SURGERY

Introduction

- Retrograde arterial perfusion is mostly used in minimally invasive cardiac surgery.
- The safe limits of pump flow rate and mean arterial pressure (MAP) during CPB are important for the success of cardiac surgery using retrograde arterial perfusion.
- There is also no standard flow rate regarding optimal pump flow during CPB. Mostly, a flow rate of 2.2 - 2.5 L/min/m² is reported in normo-thermic anesthetized patients with a normal haematocrit level.
- This prospective observational cohort study has investigated the safety of retrograde arterial perfusion and the influence of MAP and pump flow during CPB on clinical outcomes in elective robotic mitral valve surgery.

Introduction

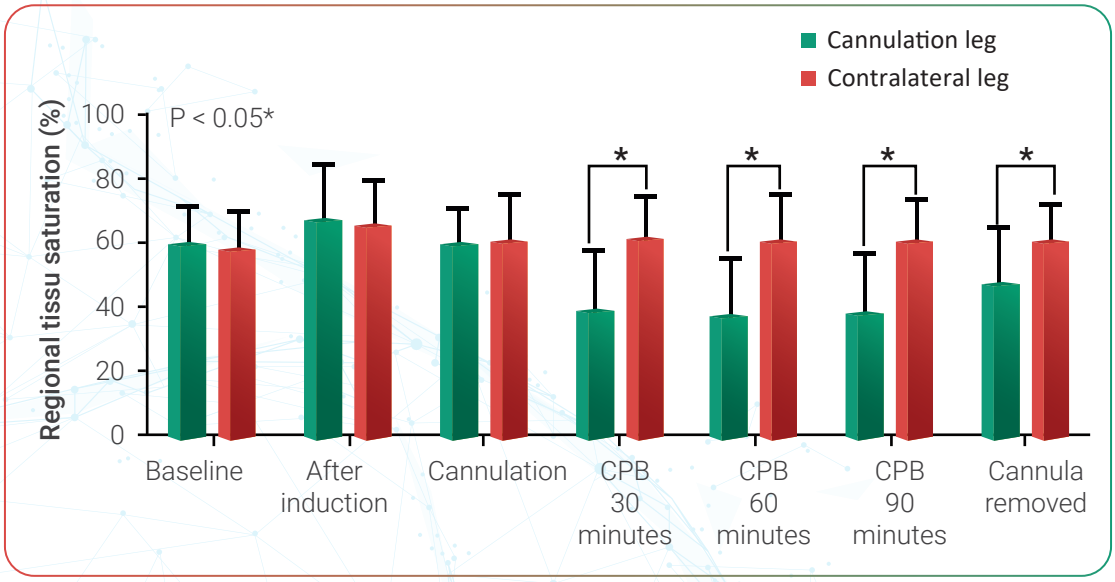
- A prospective observational cohort study recruited 117 adult patients who had successful mitral valve repair or replacement (27.3%) by robotic mitral surgery (2016 to 2018).
- The right side femoral artery and femoral vein are used for the bypass route.
- Set CPB flow to 2.5 - 3.0 L/min/m², and pump flow rate was adjusted to achieve adequate cerebral oxygenation. The upper limit of arterial cannula pressure was 250 mmHg.
- Patients were divided into four groups (High flow High mean blood pressure [MBP]; High flow Low MBP; Low flow High MBP; and Low flow Low MBP) by average pump flow of 2.2 L/min/m² and average MAP of 45 mmHg.
- Outcomes such as surgical mortality, hospital stay, ventilator use, neurological outcomes, acute kidney injury, distal limb saturation, and post-operative clinical complications were monitored for analysis.
- Patients who had previous cardiac surgery or neurological deficits which impaired their daily activities were not included in this study.



Figue 8. Port setting in robotic mitral valve surgery

Results

- All patients with rheumatic heart disease received mitral valve replacement, whereas 27.3% of the infective endocarditis patients and 5.1% of patients with chordae rupture received mitral valve replacement (Figure 8).
- Mortalities (02) - one died due to a pulmonary hypertension crisis and the other due to cardiac rupture.
- Hemorrhagic stroke (02) after the surgery - Had systemic lupus erythematosus and infective endocarditis.
- Fifteen patients had an elevated right side diaphragm by image, but their weaning process was not delayed compared to other patients.
- Vascular injury (02) - At superior vena cava and right atrium junction (repaired with pledget suture during robotic surgery).
- Femoral artery repair needed (02) - After artery cannulation removal.
- Femoral cannulation and its effect on distal limb perfusion were measured by near-infrared spectroscopy (NIRS) and depicted in Figure 9.



Figue 9. Lower limb regional tissue saturation at different time points during robotic surgery

- Oxygenation in cannulation limb decreased even more after CPB started. The difference between cannulation limb and contralateral limb was significant 30 minutes after CPB started, and persisted through the surgery. ($p < 0.001$)
- After de-cannulation, 80% of the patients had their cannulation side distal limb oxygenation recover in 10 minutes, and all recovered before going to ICU. During follow-up period, no distal limb complication was noted.
- The characteristics and clinical outcomes of patients of four groups were shown in Table 6.

	High flow High MBP	High flow Low MBP	Low flow High MBP	Low flow Low MBP	p-value	Post hoc
N	47	20	26	24		
Age (year)	57.4 (13.8)	52.0 (19.4)	56.7 (14.9)	56.2 (14.1)	0.61	
Sex (male %)	38.3	30	65.4	83.3	< 0.001	C,E
Body height (cm)	159.5 (7.4)	162.9 (10.5)	165.4 (9.6)	163.5 (20.7)	0.22	
Body weight (kg)	59.1 (10.3)	53.9 (10.6)	67.5 (16.1)	69.4 (15.2)	< 0.001	C,D,E
BMI (kg/m^2)	23.2 (3.6)	20.3 (3.2)	24.5 (4.7)	29.7 (4.9)	0.06	

	High flow High MBP	High flow Low MBP	Low flow High MBP	Low flow Low MBP	p-value	Post hoc
EuroScoreII (%)	1.3 (0.9)	1.5 (0.8)	1.9 (1.5)	0.8 (0.3)	0.17	
LVEF (%)	65.1 (9.4)	69.2 (7.7)	65.2 (11.6)	68.3 (5.5)	0.24	
CPB setting						
Baseline MBP	75.5 (12.5)	68.9 (11.0)	74.3 (13.2)	68.9 (12.0)	0.12	
CPB MBP	53.2 (7.0)	39.0 (4.1)	52.8 (6.7)	39.2 (3.8)	< 0.001	A,C,D,F
CPB flow	3.9 (0.4)	3.8 (0.3)	3.5 (0.4)	3.5 (0.4)	< 0.001	B,C,D,E
Femoral artery diameter(mm)	7.9 (1.2)	7.9 (1.0)	9.6 (2.2)	8.4 (1.1)	0.04	B
CPB duration (min)	132.3 (24.0)	128.1 (24.5)	134.0 (25.1)	127.9 (17.3)	0.72	
Cross-clamp duration (min)	73.6 (15.6)	68.1 (15.3)	75.4 (22.1)	68.3 (14.9)	0.34	
Cannulation duration (min)	151.2 (29.6)	132.8 (13.8)	160.4 (47.8)	151.2 (17.5)	0.23	
Hb during CPB	9.5 (1.4)	9.3 (1.6)	9.4 (1.5)	9.4 (1.5)	0.99	
Temperature during CPB	33.8 (2.3)	34.1 (2.5)	34.3 (1.2)	34.4 (1.9)	0.71	
Outcomes						
Survival	97.9%	95%	100%	100%	0.49	
ICU stay	4.2 (9.7)	5.3 (13.4)	2.9 (1.8)	2.6 (1.9)	0.40	
Hospital stay	17.8 (17)	24.4 (42.6)	16.3 (15.9)	11.4 (5.0)	0.17	
Serum lactate	3.3 (2.0)	3.9 (2.8)	4.2 (3.1)	3.4 (1.8)	0.49	

Table 6. Characteristics of patients with different CPB flow and perfusion pressure

- There were no ischemic stroke events in patients.
- Serum creatinine level was significantly higher in patients with the low pump flow group on post-operative day 1 (Figure 10) ($p < 0.006$) and non-significant on post-operative day 3 ($p = 0.66$).
- Correlation of urine output was positively significant with MBP during CPB ($p = 0.019$), but it was not significant on post-operative day 1.
- Acute kidney injury was defined by AKIN classification, and there was a trend for higher AKIN stage in patients with low pump flow (AKIN > 0 16.4% in high CPB flow group and 30% in low CPB flow group; $p = 0.08$).

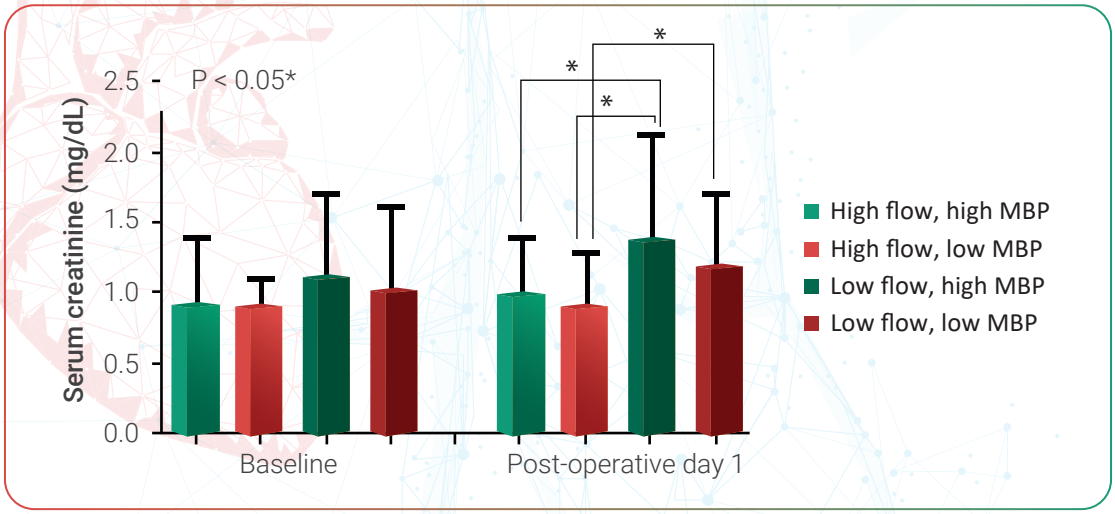


Figure 10. Serum creatinine change before and one day after surgery in different CPB settings

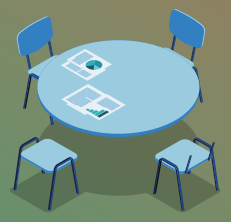
Conclusions

- This study shows that retrograde arterial perfusion is a safe method for minimally invasive cardiac surgery for less than 3.5 hours under mild hypothermic status.
- It has also shown that there is a higher chance of acute kidney injury with low CPB flow.
- NIRS is a useful method to monitor limb perfusion during retrograde arterial perfusion, and its recovery predicts limb complications in this study.

Reference

Wang YC, et al. Retrograde arterial perfusion and its outcome in robotic mitral-valve surgery. Asian J Surg. 2022; 45(10):1849-54.

Success Stories



SUCCESSFUL USE OF INTRAVENOUS B-BLOCKER THERAPY IN CARDIOGENIC SHOCK SUPPORTED WITH VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION: A CASE SERIES

Introduction

- Cardiogenic shock is a life threatening condition in which the heart is suddenly unable to pump enough blood to the meet body's requirements and leads to spontaneous tachycardia.
- Tachycardia in cardiogenic shock (CS) might reduce the cardiac output (CO) by decreasing the ventricular filling time.
- Beta blockers (Esmolol, dopamine, and dobutamine) are used to regulate heart rate (HR) by preventing the effects of adrenaline that causes the heart to beat more slowly.
- In order to fast and safe recovery of cardiogenic shock patients, VA-ECMO (Venoarterial Extracorporeal Membrane Oxygenation), a temporary mechanical circulatory support combined with extracorporeal gas exchange, used with intra-venous beta blockers to control severe tachycardia in CS patients.
- This article presented four cases of cardiac patients in which intravenous beta blockers were used with VA-ECMO for successful treatment of their conditions.

Case 1: Asian male smoker (31 years of age)

- He was presented with an inferior wall myocardial infarction (IWMI).
- Percutaneous coronary intervention (PCI) was performed and during PCI, he developed 22 multiple episodes of ventricular fibrillation (22 minutes duration) which required direct current shocks in addition to the insertion of an intra-aortic balloon pump (IABP).
- He was hemodynamically unstable. Hence, VA-ECMO support (2.5 - 3 L/min) and IABP 1:1, dobutamine and noradrenaline support was given to him to improve hemodynamic parameters.
- Next day, ECG showed severe reduction in left ventricular function (EF 23%) and developed tachycardia with 134 bpm HR. The MAP was 62 - 52 mmHg while he was on dobutamine (5 mcg/kg/min) and noradrenaline (0.2 mcg/kg/min) with an ECMO pump flow of 3.3 L/min.
- To control tachycardia, esmolol infusion at a rate of 10 mcg/kg/min began. His HR dropped to 118 bpm after an hour. After that, he was kept on esmolol and dobutamine for a total of five days while having the infusion rate adjusted in accordance with his HR and lactate levels.
- On the eighth day post ECMO insertion, when the ECMO pump flow was 2 L/min, he was successfully decannulated from ECMO with 31% EF, and 1 week later, his EF improved to 35%.

Case 2: Asian male (31 years of age)

- He was admitted with no history of illness after cardiac arrest. He recovered after one cycle of cardiopulmonary resuscitation (CPR).

- His EF upon admission was 33%, but he was diagnosed with anterolateral ST-elevation MI (STEMI) with hypotension and respiratory distress.
- Thrombus aspiration was performed, but a huge burden of thrombus persisted, and the patient developed ventricular fibrillation.
- One direct current shock after thrombus aspiration failed to remove the heavy burden of thrombus and IABP inserted. The patient transferred to OT for CABG. After two attempts, CPB was unsuccessful.
- Therefore, VA-ECMO was inserted with IABP 1:1 along with milrinone (0.4 mcg/kg/min), noradrenaline (0.1 mcg/kg/min), and vasopressin (1.5 units/h).
- Next day during EMCO insertion, the patient developed tachycardia and treated within 24 hours with esmolol.
- Tachycardia again developed on the sixth day of ECMO insertion while receiving noradrenaline and dopamine support. Esmolol (20 mcg/Kg/min) was given again.
- Esmolol was stopped on the 9th day and dopamine switched to dobutamine.
- On the 14th day, tachycardia developed again and hence, esmolol was repeated.
- On the 15th day, ECMO was removed successfully when the patient was stabilized and had improved 33% EF, 3 days post ECMO removal.

Case 3: middle Eastern male (63 years of age)

- He was admitted to the hospital with non-ST elevated MI (NSTEMI), planned for CABG.
- On that day, he had epigastric discomfort with hypotension and pulseless electrical activity (PEA) arrest. Until the return of spontaneous circulation, they provide CPR for 10 minutes.
- VA-ECMO was intubated, but he was again arrested with PEA with EF dropping from 53% to 20%. The patient was transferred to OT for an emergency CABG with ECMO support.
- He had EF < 20% and LVOT VTI of 5 cm on the same day after CABG.
- On the fourth day, post ECMO, supraventricular tachycardia was developed while on noradrenaline (0.15 mcg/Kg/min) and dopamine (5 mcg/Kg/min).
- Dopamine stopped, esmolol infusion started (20 mcg/Kg/min). When the HR was improved, esmolol infusion was reduced to 10 mcg/kg/min. But tachycardia again developed, 40 mcg/kg/min esmolol had started again to control HR.
- Esmolol was continued with ECMO support for a total of 4 days to control HR and lactate levels. On the 9th day, ECMO was successfully decannulated with EF 29%, LVOT VTI of 17.7 cm.

Case 4: Middle Eastern male (59 years of age)

- He was admitted to the hospital due to chest pain and palpitations for 4 hours.
- The ECG showed atrial fibrillation and he was given metoprolol (5 mg intravenous). Shortly after that, the HR was 80s, EF was 44% and 485 ng/L troponin T readings and he was diagnosed with NSTEMI.
- The patient developed sudden flash pulmonary edema and cardiac arrest with an initial rhythm of PEA. He required three direct current shocks and a lidocaine infusion in ventricular fibrillation and CPR for 43 minutes.
- PCI was done with VA ECMO support.
- The next day, patients developed tachycardia while on noradrenaline (0.2 mcg/Kg/min) and dopamine (5 mcg/Kg/min). Hence, withdrawal of dopamine was done and esmolol (20 mcg/Kg/min) was initiated to control HR.
- Esmolol was adjusted to 10- 100 mcg/Kg/min for the management of HR.
- One hour later, he was successfully decannulated from ECMO with an EF of 44%, a LVOT VTI of 20 cm, and a pulse pressure of 55 mmHg.

Conclusion

- Improvement in survival of CS patients can be possible with the help of revascularization of the infarcted vessels through fibrinolytic medications or PCI.
- VA-ECMO support has been used in CS patients to make them hemodynamically stable and also restore perfusion.
- In this case series, four cases of AMI complicated with CS used VA-ECMO support along with short acting beta blockers intravenously to control the HR successfully in all patients.
- In conclusion, intravenous short acting B-blockers (esmolol) supported with VA-ECMO could be used for the treatment of severe and complex tachycardia.

Reference

Rahhal A, Omar AS, Aljundi A, Kasem M, Mahfouz A, Alyafei S. Successful Use of Intravenous B-blocker Therapy in Cardiogenic Shock Supported With Venoarterial Extracorporeal Membrane Oxygenation: A Case Series. Curr Probl Cardiol. 2022; 47(11): 101071.

News Corner

A NEW APHERESIS DEVICE FOR ANTITHROMBOTIC DRUG REMOVAL DURING OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Introduction

- Dual antiplatelet therapy (DAPT) like aspirin and $P2Y_{12}$ inhibitor (ticagrelor) requires for a patients who undergo CABG to reduce adverse effects such as high perioperative bleeding.
- The current guidelines allow for aspirin to be continued through CABG, but require at least 3 - 7 days of $P2Y_{12}$ inhibitor discontinuation prior to elective surgery of any type, which may not be feasible in urgent or emergency procedures.
- The hemoadsorption device CytoSorb® used in cardiac surgery to remove efficiently ticagrelor from whole blood in-vitro and early clinical experiences with the integration of this device on the CPB circuit has shown meaningful reductions in adverse events in on-pump cases.
- This case report describes a novel approach, PUR-01 (Nikkisio Co., Ltd., Tokyo, Japan), a hemoperfusion pump, which can be used as an ECC for the removal of ticagrelor during off-pump coronary artery bypass (OPCAB) procedures with CytoSorb® (Figure 11).
- The CytoSorb® adsorber consists of a 300 mL cartridge containing biocompatible porous polymer beads (surface area covered > 40, 000 square meters) that are able to bind hydrophobic substances of a molecular size of up to 60 kDa from whole blood by pore capture and their irreversible surface adsorption properties.
- The circuit is equipped with protective systems and features like pressure sensors, air, blood, and blood tubing line detectors (Figure 12).
- Anticoagulation is possible either continuously with a heparin pump or with a single injection of heparin (5000 IU) to achieve a recommended clotting time of > 180 s. The blood flow rate during treatment can be set from 0 to 200 mL/min.

Figure 11. PUR-01 loaded with a venous blood tubing line and a hemoadsorption device.

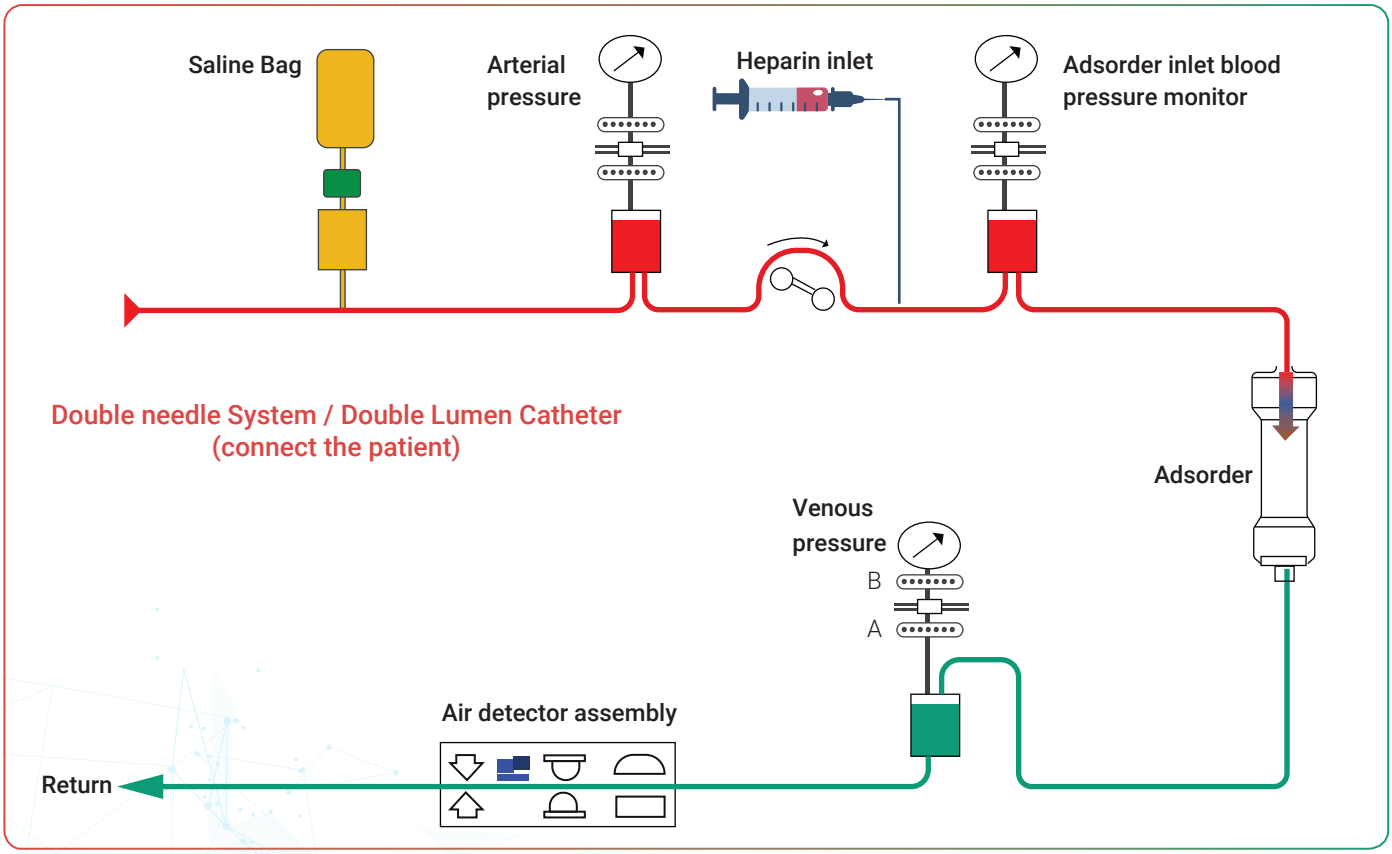


Figure 12. Schematic drawing of the extracorporeal circuit equipped with protective systems and features to help ensure patient safety and correct operation. BP: blood pump.

Case report

- A 74-year-old male patient was admitted for urgent CABG for severe three-vessel disease.
- The medical history included hypothyroidism, moderate diverticulitis, hypercholesterolemia, and hypertension. The patient was treated with DAPT (Ticagrelor 2 × 90 mg/day + Aspirin 100 mg/day) for acute coronary syndrome and NSTEMI and also on medication with rosuvastatin, bisoprolol and L-thyroxin.
- Ticagrelor was stopped the day before surgery.
- After the initiation of standard anesthetic care, PUR-01 was connected to the right cervical vein of the patient for treatment with the CytoSorb®.
- Adsorption was initiated with a skin incision and was continued for 221 min to eliminate ticagrelor. With the start of PUR-01, a 5000 I.E. single injection of heparin was given (Blood flow rate -150 and 200 mL/h [mean: 176.7 mL/min]).
- Following the sternotomy, left internal thoracic artery (LITA) harvesting was performed. Prior to the bypass anastomosis, another 10,000 units of heparin were administered (ACT > 300s). Myocardial revascularization was performed with the OPCAB technique.
- Protamine was given to reverse the heparin action after the completion of the bypass anastomosis. The transit-time flow measurement revealed good flow rates of the grafts. The procedure was then finished using standard techniques.
- The circulated blood volume through the CytoSorb® was 39.04 L in total over a treatment duration of 221 min.
- The chest tubes were removed on the second postoperative day and two units of red blood cells were infused due to dropped Hemoglobin (Hb) from 13.1 g/dL preoperatively to 9.3 g/dL postoperatively.
- On discharge, the Hb (12.4 g/dL), maximum creatine kinase level (232 U/L), and the creatine kinase MB (CKMB) isoenzyme (6.5 µg/L) were under the normal limits.

- A good recovery was achieved with no uneventful postoperative course. In the 6 weeks follow-up, the patient had a normal left ventricular function and sinus rhythm, without any cardiac symptoms.

Application of CytoSorb® with PUR-01 apheresis device to remove ticagrelor in OPCAB procedures

- Four male patients (61.6 ± 9.4 years of age) with chronic heart disease, on DAPT medication, have been operated on with OPCAB (bypass grafts: 2.5 ± 0.3 received the LITA) using a CytoSorb® hemoadsorbtion cartridge integrated into the PUR-01 apheresis device to remove ticagrelor throughout the operation.
- The blood volume circulating through the CytoSorb® was 28.5 ± 9.0 L over 170 ± 36 min of treatment.
- Three patients received two units of red blood cells each. However, one patient needed five units of red blood cells, three units of fresh frozen plasma, and two units of thrombocyte concentrates as he was presented with preoperative anemia, multiple sclerosis, insulin-dependent diabetes, NSTEMI, and a suspected coagulopathy in his medical history.
- There was no enhanced bleeding during intraoperative surgical procedures and no patients had a re-operation. The postoperative course was uneventful and no device-related adverse events occurred.
- The patients were discharged with a renewed prescription for DAPT for the next 6 months. The follow-up time was 9.3 ± 4.8 months.

Conclusion

- The combination of the PUR-01 apheresis pump and hemoadsorption with the CytoSorb® column used during OPCAB procedures, appears to be safe and effective to eliminate ticagrelor.

Reference

Mair H, et al. A New Apheresis Device for Antithrombotic Drug Removal during Off-Pump Coronary Artery Bypass Surgery. Medicina (Kaunas). 2022; 58(10): 1427.

NOVEL THERAPEUTIC STRATEGIES TO REDUCE REPERFUSION INJURY AFTER ACUTE MYOCARDIAL INFARCTION

Introduction

- Reduction of ischaemic injury by shortening the time for revascularization in STEMI patients is the main focus of interventional cardiology.
- When revascularization became faster and primary PCI (pPCI) was successfully performed within 60 - 90 minutes, the interest in a potential additive effect of targeting reperfusion injury vanished.
- Reperfusion injury causes almost 50% of myocardial scars.
- The rate of survival in STEMI patients is increasing by focusing on the reduction of HF hospitalization after STEMI.
- Thus, by limiting reperfusion injury, it prevents microvascular obstruction and reduces final infarct size, thereby may be lowering the HF events and improving quality of life in AMI survivors.

- Several approaches have tried to reduce HF events by targeting final infract size (FIS) and microvascular obstruction in STEMI patients.
- Only the AMIHOT I & II clinical trial provided a significant positive result for FIS reduction (from 25.0% to 18.5% [P = 0.02]) in patients with anterior STEMI by using super-saturated oxygen therapy (additive procedure starts after successful completion of pPCI).

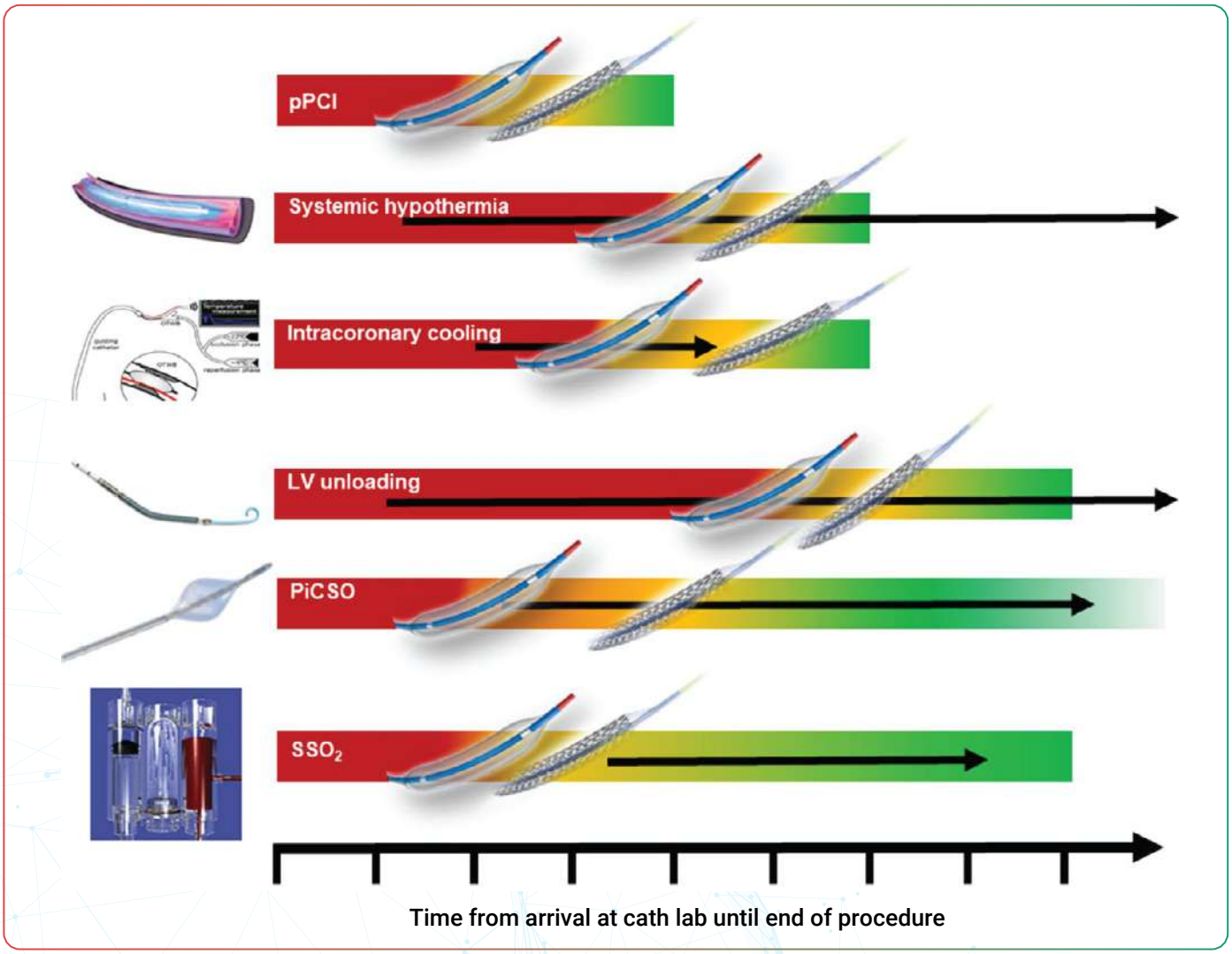


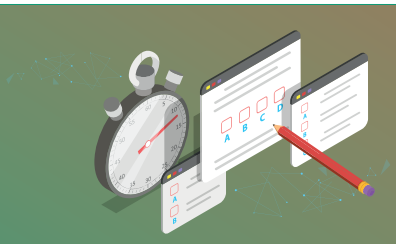
Figure 13. The influence of different procedures aiming to lower reperfusion injury and to reduce final infarct size in patients undergoing pPCI for treatment of acute STEMI; the downward ticks on the arrow below represent 15 minute intervals. Red colour indicates prolonged ischaemic time, orange colour indicates the PCI procedure, and green colour indicates the PCI procedure occurs once; the total time span of the additive procedure is indicated by the black arrows.

Conclusion

In conclusion, by improving post AMI outcomes such as pPCI procedure before balloon dilatation, between balloon dilatation and final stenting, and after final stenting before moving the patient to the cath lab, and also systemic hypothermia, intracoronary cooling, left-ventricular (LV) unloading, pressure-controlled intermittent coronary sinus occlusion (PiCSO), and intracoronary super-saturated oxygen (SSO2) therapy may reduce the risk of reperfusion injury after AMI and hence, decreases the risk of HF (Figure 13).

Reference

Schafer A, Konig T, Bauersachs J, Akin M. Novel Therapeutic Strategies to Reduce Reperfusion Injury After Acute Myocardial Infarction. Curr Probl Cardiol. 2022; 47(12): 101398.



Multiple choice questions (MCQs)

1. The chances of HF in STEMI patients can be reduced by

a) Shortening the time for revascularization
b) By reducing the risk of reperfusion injury
c) Both a and b
d) None

2. Intracoronary super-saturated oxygen (SSO2) therapy is used ……..

a) For FIS reduction
b) In STEM patients
c) Reduces HF burden
d) All of the above

3. Cases of acute myocardial infarction complicated with cardiogenic shock can be treated with

a) Intravenous short acting beta blockers
b) ACE inhibitors
c) VA-ECMO support
d) Both a and c

4. . Retrograde arterial perfusion is safe and effective method for minimally invasive cardiac surgery-

a) For less than 3.5 hours under mild hypothermic status
b) For more than 5.3 hours under mild hypothermic status
c) For less than 3.5 hours under mild hyper thermic status
d) less than 5.3 hours under mild hyper thermic status

5. Heparin resistance can be managed by-

a) Use of more amount of heparin
c) Use of alternatives for heparin such as bivalirudin, argatroban and nafamostat mesilate
c) Give fresh frozen plasma
d) All of the above

6. Elevated lactate levels and impaired lactate clearance during extracorporeal life support (ECLS) are associated with

a) Better outcomes in cardiac surgery patients
b) Poor outcomes in cardiac surgery patients
c) None
d) Both a and b

7. Administration of Human Fibrinogen Concentrate after CPB in neonate and infant patients

a) Decreases use of cryoprecipitate
b) Increases use of cryoprecipitate
c) Increases adverse events
d) None

8. The mechanisms of heparin resistance are-

a) Antithrombin deficiency
b) Non- antithrombin deficiency
c) Both a and b
d) None

9. For the prevention of high perioperative bleeding in patients who undergo Coronary Artery Bypass Grafting requires

a) Aspirin only
b) Ticagrelor only
c) Dual antiplatelet therapy (Aspirin and ticagrelor)
d) None

Both a and b	All of the above	Both a and c	For less than 3.5 hours under mild hypothermic status	All of the above	Poor outcomes in cardiac surgery patients	Decreases use of cryoprecipitate	Both a and b	Dual antiplatelet therapy (Aspirin and ticagrelor)

Abbreviations

A	High flow high MBP vs high flow low MBP is significant
ALAT	Alanine transaminase
aPTT	Activated Partial Thromboplastin Time
ASAT	Aspartate aminotransferase
B	High flow high MBP vs Low flow high MBP is significant
BMI	Body mass index
C	High flow high MBP vs Low flow low MBP is significant
CABG	Coronary bypass graft surgery
CK	Creatine Kinase
CPB	Cardiopulmonary bypass
CRP	C-Reactive Protein
D	High flow low MBP vs low flow high MBP is significant
DIVC	Disseminated intravascular coagulopathy
DVT	Deep vein thrombosis
E	High flow low MBP vs low flow low MBP is significant
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated Glomerular Filtration Rate
F	Low flow high MBP vs low flow low MBP is significant
FFP	Fresh frozen plasma
Hb	Hemoglobin
HiTT	High-dose thrombin time
HM3	HeartMate 3TM
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LVADleft	Ventricular assist device
LVEF	Left ventricular ejection fraction
MBP	Mean blood pressure
MiECC	Minimally invasive extracorporeal circulation
NT-proBNP	N-Terminal pro hormone B-type natriuretic peptide
PE	Pulmonary embolism
PF4	platelet factor 4
PI	pulsatility index
RPM	Pump speed in revolutions per minute
RVAD	Right ventricular support