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Cardiovascular & Thoracic Abstracts

Contents

Cardiopulmonary Bypass and Deep Hypothermic Circulatory Arrest in a Patient with Sickle Cell Disease

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INTRODUCTION

More than 10% of Sickle Cell Disease (SCD) patients develop Chronic Thromboembolic Pulmonary Hypertension (CTEPH). The definitive treatment of CTEPH is a Pulmonary Thromboendarterectomy (PTE) which requires cardiopulmonary bypass (CPB), and intermittent periods of Deep Hypothermic Circulatory Arrest (DHCA) at a core temperature of 20°C. These interventions are known triggers of sickling. Unfortunately, the optimal management of SCD during CPB and DHCA remains unclear. In particular, there is no consensus on the hemoglobin S (HbS)% threshold below which CPB and DHCA can safely be performed. Various groups have suggested red blood cell exchange (RCE) should be used to maintain HbS below 5% (1), less than 30% (2), or that perioperative RCE is not needed at all (3). In this case report, we present the successful intraoperative management of CPB and DHCA in an SCD patient with a simple modification performed prior to the institution of CPB.

CASE PRESENTATION

A 29-year-old male with HbSS type SCD and CTEPH presented for PTE. Complications of his SCD included a stroke, acute chest syndrome, and priapism. His SCD is managed with a routine monthly RCE.

Cardiac catheterization showed a pulmonary artery pressure of 87/28mmHg, and an echocardiogram showed mild enlargement of the right ventricle with reduced systolic function.

Three days before surgery, he underwent a 12-unit automated RCE which dropped the HbS from 55.1% to 18.5%. This corresponded to a hemoglobin of 102g/dL. Pre-induction, an intravenous, arterial line and cordis with pulmonary artery (PA) catheter were placed. The pre-induction systemic pressure was 150/80, and the PA pressure was 75/30. The induction was hemodynamically stable. With the CPB circuit primed with 2 units of packed red blood cells (PRBC), a further manual RCE was performed by draining and discarding 500ml of the patient's blood before initiating CPB. Following this, the HbS was 17.3%.

Once cooled to 20°C, three periods of circulatory arrest were performed, for a total duration of 72 minutes. After 282 minutes of CPB and a cross-clamp of 154 minutes, the patient was weaned from CPB without difficulty. To minimize the risk of sickling, tranexamic acid and autologous cell salvage were not used.

In the intensive care unit, the patient required 1 unit of PRBC on postoperative day (POD) 2 for a Hgb of 75g/dL. He was extubated on POD 4, and subsequently discharged home on

POD 15 on room air. There was no evidence of sickling complications during the hospitalization.

CONCLUSION

The feasibility of performing PTE in SCD patients with successful outcomes have been recognized worldwide. However, the parameters for safely performing PTE which necessitates the CPB with DHCA in SCD patients are not well defined. Careful planning to achieve the target HbS level with RCE perioperatively, as well as maintaining oxygenation and adequate perfusion pressure during the surgery are important to guarantee the success of the surgery. In our case, RCE to achieve an HbS of approximately 18% avoided any sickling complications throughout the patient's hospitalization. To further minimize the risk, tranexamic acid and cell saver were not used.

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Intraoperative Transesophageal Echocardiography in an Uncommon Case of Left Atrial Appendage Perforation During Minimally Invasive Cardiac Surgery

AUTHORS

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INTRODUCTION

Minimally invasive cardiac surgery (MICS) encompasses a wide range of surgical procedures with multiple potential benefits including reduced pain and hospital stay as well as increased patient satisfaction.[1] These procedures are not without challenges and require careful planning, pre-operative patient assessment and excellent intraoperative communication. Anesthetists involved in MICS need not only to be highly skilled in assessing each heart chamber and valves but need to be proficient in guiding the CPB cannula placement.

CASE PRESENTATION

A 64-years-old man presented to the emergency department with heart failure and atrial fibrillation. The patient's medical history included dyslipidemia, fatty liver, and L4-L5 spinal stenosis. The transthoracic echocardiogram revealed severe mitral regurgitation and an Ostium Secundum atrial septal defect (ASD). After medical optimization, he was scheduled for a minimally invasive mitral valve repair, ASD closure, left atrial ablation, and left atrial appendage (LAA) closure.

Intraoperative transesophageal echocardiography (TEE) confirmed the diagnosis of mitral regurgitation due to a myxomatous disease, biatrial enlargement, a large ASD (19 x 18mm) with a left to right shunt, severe right ventricular enlargement, and a flattened interventricular septum.

To perform the procedure, Right IJV was successfully cannulated and under TEE guidance, and a cannula was placed in the superior vena cava (VC). Left femoral artery was exposed, and cannulated. Right femoral vein was used for inferior VC cannulation.

We observed the wire and the cannula passing into the LA through the ASD in ME bicaval view using TEE guidance. The subsequent observation of a growing pericardial effusion in the TG mid-SAX and the following hemodynamic instability aided in diagnosing cardiac tamponade. The decision to convert the operation to a sternotomy was made while the patient was being resuscitated. On opening the pericardium, the source of bleeding was a small perforation in the LAA (a possibly a complication from the transient passage of the wire and cannula through the ASD into the left atrium).

After sternotomy, ASD closed, MV repaire
The post-cardiopulmonary bypass was uneventfull

CONCLUSION

Emergency conversion to full sternotomy occurs in 2–3% of MICS cases.[2 3] The most frequent reason is excessive bleeding, which is associated with a mortality rate upwards of 20%. Other conversion reasons include poor surgical site exposure, adhesions, and iatrogenic aortic dissection.[4] Excellent communication is fundamental during this period. In emergency conversion, extra personnel is needed to manage massive transfusions and reposition the patient simultaneously.
During the cannulation, the continuous visualization of the cannula tip is essential to avoid possible complications. Recognizing a growing pericardial effusion during its early stages and excellent communication allowed swift decision-making and prevented potentially catastrophic outcomes.

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Fig 1 ME5C Fi

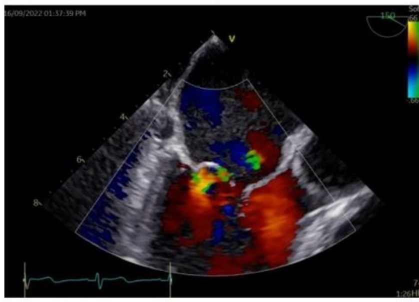
g 2 MELAX


Fig 3 TG SAX

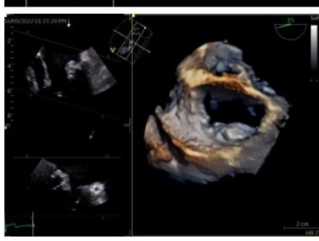
Fig 4 3D picture of MV

Pharmacokinetics of Intranasal Insulin Administration During Cardiac Surgery: Dose Escalation Study

AUTHORS

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INTRODUCTION

Approximately 50% of cardiac surgery patients suffer from perioperative neurocognitive disorder (PND), which leads prolonged cognitive impairment and dementia, and increased mortality[1]. While the prevention, prompt diagnosis and treatment are clinically important, the evidence for treating PND with pharmocologic agent is inconclusive[2].
The intranasal insulin administration (INI) bypasses the blood-brain-barrier and causes a sustained elevation of insulin concentrations in the cerebrospinal fluid[3]. The 20-160 IU INI improves memory performance in patients suffering from cognitive impairment[4] and may prevent PND. While 40 and 80IU INI did not cause hypoglycemia during cardiac surgery[5], the maximum safety dose of INI and the pharmacokinetics during cardiac surgery are unknown.

METHODS

With the approval from the local research ethics board, we recruited patients scheduled for elective cardiac surgery or major vascular surgery requiring cardiopulmonary bypass in phase 1, single center, open label clinical trial. During dose escalation, patients were enrolled in successive dose-escalation cohorts of 6 patients each. Subsequent dose escalation cohorts examined 0, 40, 80, 160, and 240 IU insulin.
Insulin was applied using a sterile metered nasal dispenser after the induction of general anesthesia and endotracheal intubation. Arterial blood samples were collected every 10 min for first 60 min and every 30 min thereafter. Blood glucose and serum insulin were measured. We also measured C-peptide, which is produced in equimolar amounts to endogenous insulin. Hypoglycemia was defined as a blood glucose level < 3.9 mmol/L. When two cases of hypoglycemia were observed in one group, recruitment of the patients was terminated. The primary outcome was incident of the hypoglycemia in each group. The secondary outcomes were serum insulin and C peptide concentrations. We used student T test to compare the concentrations. Significant difference was set at P<0.05.

RESULTS

Twenty-seven patients were enrolled in this study. No hypoglycemia was observed in 0, 40, 80 and 160 IU group (n=6 in each group). No significant changs in blood glucose were observed at any time points among the four groups (0, 40, 80 and 160 IU group). In 240 IU

group, two of three patients showed hypoglycemia.
Insulin concentration in 160IU was higher than that in control at 10 - 40 min after INI but C-peptide concentration was similar at all time point.

DISCUSSION

Our data demonstrated that INI at doses up to 160 IU did not cause clinically important hypoglycemia in cardiac surgery. Considering the results that the serum C-peptide is not elevated in any insulin group, and serum insulin level was elevated in 160 IU INI, hypoglycemia observed in 240 IU would have caused by partial spilling into systemic circulation rather than endogenous insulin secretion. Further research is needed to clarify whether INI prevent or treat PND.

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Strain Echocardiographic Parameters and Clinical Outcomes Associated with Significant Atrioventricular Regurgitation in an Adult Fontan Cohort

AUTHORS

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INTRODUCTION

As Fontan patients continue to experience longer life expectancy, the general anesthesiologist will inevitably contribute to the care of adult Fontan patients undergoing non-cardiac surgery. Significant atrioventricular valve regurgitation (AVVR) is common in adult Fontan patients and its hemodynamic and clinical significance must be evaluated in the perioperative setting. Strain echocardiography is now commonly reported in pre-operative echocardiograms. This technology of two-dimensional speckle-tracking echocardiography permits evaluation of subclinical myocardial dysfunction and offers technical benefits over traditional echocardiographic parameters. We aimed to evaluate the association of AVVR with echocardiographic parameters and adverse outcomes.

METHODS

Fontan adult patients (≥18 years) with lateral tunnel or extracardiac connection actively followed at our institution were retrospectively reviewed. Patients with AVVR on most recent transthoracic echocardiogram (≥grade 2 as per American Society of Echocardiography guidelines) were matched with Fontan controls. All routine echocardiographic parameters, including global longitudinal strain (GLS), were measured. The composite outcome of Fontan failure included Fontan conversion, protein losing enteropathy, plastic bronchitis, and New York Heart Association Class III/IV.

RESULTS

Sixteen patients (14%, mean age 28.4 ± 7.0 years) with predominantly moderate AVVR (81%) were identified. The mean duration of AVVR was 8.1 ± 5.8 months. There was no significant reduction in ejection fraction (EF) (51.2% ± 11.7% vs. 54.7% ± 10.9%, P = 0.39) or GLS (−16.0% ± 5.2% vs. −16.0% ± 3.5%, P = 0.98) associated with AVVR. Larger atrial volumes and longer deceleration time (DT) were observed in the AVVR group. Patients with AVVR and a worse GLS (≥−16%) had higher E velocity, DT, and medial E/E' ratio. The incidence of Fontan failure did not differ from controls (38% vs. 25%, P = 0.45). Patients with worse GLS (≥−16%) demonstrated a marked trend toward a higher incidence of Fontan failure (67% vs. 20%, P = 0.09).

DISCUSSION

In Fontan adults, a short duration of AVVR did not influence EF or GLS but was associated with larger atrial volumes and those with worse GLS demonstrated some differences in diastolic parameters. These findings may inform the perioperative care of adult Fontan patients. Larger multicenter studies throughout its disease course are warranted.

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Systolic Anterior Motion of the Mitral Valve Leaflet Presenting as Unstable Supraventricular Tachycardia: A Case Report

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INTRODUCTION

Systolic anterior motion (SAM) of the mitral valve leaflet can cause dynamic left ventricular outflow tract (LVOT) obstruction in patients without hypertrophic cardiomyopathy and can be a rare cause of hemodynamic instability in the perioperative period. It can present as hypotension, tachycardia or hypoxia intraoperatively and is diagnosed with transthoracic or transesophageal echocardiography.[1,2] SAM occurs with the anterior translation of one or both of the mitral valve leaflets into the LVOT during systole, which can be precipitated by decreased preload or systemic vascular resistance and increased cardiac contractility.[3,4] Here, we present a case of tachycardia and hypotension following anesthetic induction which initially was treated as supraventricular tachycardia before diagnosis of systolic anterior motion of the mitral valve leaflet with point-of-care ultrasound. Consent for case report publication was obtained from the patient.

CASE PRESENTATION

A 41-year-old otherwise healthy woman underwent transsphenoidal resection of a pituitary macroadenoma. The patient did not endorse a history of arrhythmia on pre-operative assessment. Approximately 1 minute after induction of general anesthesia, the patient became acutely tachycardic (170 bpm) and hypotensive (65/30 mmHg). Synchronized cardioversion was done for an unstable supraventricular tachycardia (SVT) and was unsuccessful. The patient became normotensive following a bolus of intravenous phenylephrine (200 mcg), and subsequent administration of adenosine did not cause conversion to sinus rhythm.

Conversion to normal sinus rhythm occurred following a further bolus of IV phenylephrine and IV fluid bolus. Two minutes after conversion to sinus rhythm, the patient again became tachycardic (160 bpm). The patient again converted to sinus rhythm following administration of IV phenylephrine bolus and crystalloid fluid bolus. After one dose of metoprolol, there were no further episodes of tachycardia.

Transthoracic echocardiography after the event demonstrated normal left ventricular size and function, however there was an elongated anterior mitral valve leaflet. Given this finding, the lack of response to treatment for SVT and response to treatment for SAM, it was hypothesized that the acute hemodynamic instability could be due to LVOT obstruction from SAM. A discussion was held between the surgeon, anesthesia team and patient's family, and the decision was made to proceed with surgery. The patient received further volume resuscitation and a phenylephrine infusion was started to target a systolic blood pressure greater than 120 mmHg. There were no further episodes of hypotension or tachycardia in the perioperative period.

CONCLUSION

The presenting signs of SAM of the mitral valve leaflet and associated LVOT obstruction can be non-specific. In this case, acute tachycardia and hypotension was initially treated as an unstable SVT. Although there was no evidence of dynamic LVOT obstruction on echocardiogram, SAM was proposed as a diagnosis after there was no response to cardioversion, but resumption of normal hemodynamics after administration of IV fluids, phenylephrine and metoprolol, the classic treatment for SAM. Intraoperative ultrasound allowed for exclusion of structural disease, and surgery was safely carried out with clear hemodynamic goals to avoid further episodes.

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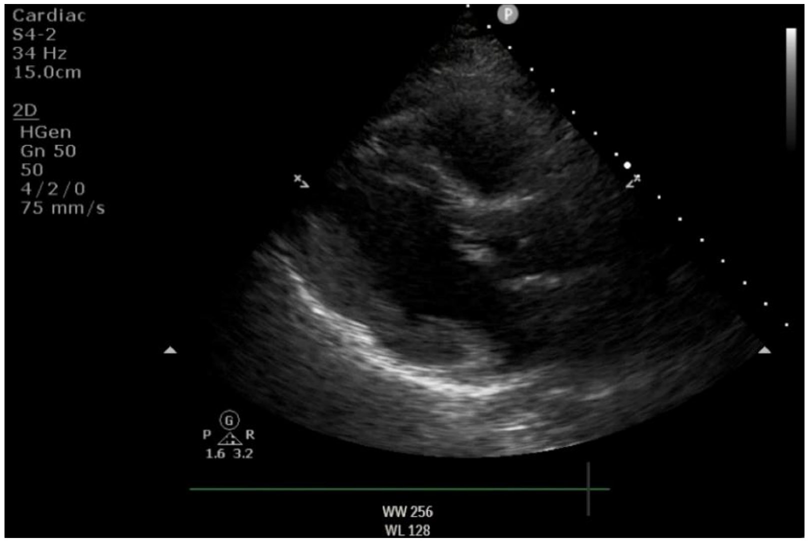
Cardiac
S4-2
34 Hz
15.0cm
2D
HGen
Gn 50
50
4/2/0
75 mm/s
P R
1.6 3.2
WW 256
WL 128

Figure 1

Temporal Change in Severity of Aortic Insufficiency After Ross Procedure

AUTHORS

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INTRODUCTION

Aortic valvular disease poses significant risk for an individual's morbidity and mortality[1]. The Ross procedure has gained wide acceptance in correcting structural heart disease[2]. There has been a growing interest in utilizing this technique in young-middle aged adults undergoing an aortic valve replacement (AVR). Over the last two decades, the literature has shown promising outcomes and potential survival benefit with the Ross operation without an increased risk of re-intervention when it is performed at a high-volume centre[3].

Echocardiography has been deemed as the "gold-standard" for intraoperative assessment for valvular functions post-AVR[4-5]. However, we have experienced some cases where the aortic insufficiency (AI) improves postoperatively despite intraoperatively-observed significant AI. Therefore, we conducted this study to compare intraoperative AI to postoperative AI in the weeks/months following the Ross procedure to investigate the change in the severity of AI with time.

METHODS

Following Research Ethics Board approval, one hundred patients who had undergone a Ross procedure between 2012 and 2020 were retrospectively analyzed. The operations were performed by two cardiac surgeons. Data collection was done via Electronic Medical Record review.

All patients had intraoperative transesophageal echocardiograms (TEE), and 93 patients had postoperative transthoracic echocardiograms (TTE) at 1 week and up to 6 months post-Ross. The intraoperative TEE was interpreted by a single anesthesiologist. The postoperative TTE was interpreted by a group of sonographers. On echocardiography images, the degree of AI was graded from none-trace (0) to severe (3). The primary outcome of the study was the change in severity of AI comparing intraoperative TEE to TTE performed postoperatively.

RESULTS

One hundred patients who had a ROSS procedure performed were analyzed. All 100 patients had intraoperative echo images. Ninety-three had postoperative echo images (no images were available in five patients and two patients died postoperatively).

Intraoperatively, 20 patients (Group A) developed greater than mild AI post-CPB while 80 patients (Group B) had mild or less AI. Of the patients in Group A, 12 patients (60%) had improved AI on postoperative TTE, 2 patients (10%) had worse AI, and 6 patients (30%) were unchanged. In Group B, of the 80 patients, 17 (21%) had improved AI, 13 (16%) had worse AI, and 43 (63%) remained the same on postoperative TTE.

Overall, 78 patients had an improvement and/or the same degree of their AI weeks/months postoperatively, while 15 patients had worse AI when comparing intraoperative TEE to postoperative TTE.

DISCUSSION

The majority of patients in our study had reduced severity of AI on postoperative TTE in the weeks/months following surgery. These findings may indicate that residual AI immediately after weaning cardiopulmonary bypass has a high probability of improvement, and thus, repair or replacement of the neo-aortic valve may not always be necessary when the AI is greater than mild and less than severe.

Although our study used different modalities to assess valvular function, most patients routinely receive TEE intraoperatively and TTE postoperatively. Therefore, an assessment with different modalities is reasonable and reflects real clinical practice.

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The Impact of Phenylephrine on Muscle and Cerebral Perfusion in an Experimental Rat Model– How can a Vasoconstrictor Improve Brain Perfusion?

AUTHORS

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INTRODUCTION

Increasing incidence of perioperative stroke is associated with hypotension1, supporting the practice of vasopressors including phenylephrine (PE) to maintain mean arterial blood pressure (MAP) and optimize vital organ perfusion, including the brain, during anesthesia. Clinical studies have demonstrated that an increase in MAP with PE is associated with a decrease in brain oxygen saturation (SaO2) measured indirectly by near infrared spectroscopy (NIRS)2. Evidence that NIRS may not accurately reflect brain tissue PO2 (PBrO2) is demonstrated through an increase in PBrO2 and a concurrent decrease in brain SaO2 with PE administration3. We explored the impact of PE on MAP, brain and muscle perfusion in a rat model utilizing direct measurements of microvascular blood flow and tissue PO2. We hypothesized that changes in MAP induced by PE would affect muscle and brain perfusion differently, possibly due to the reduced α1 receptor density in brain microvasculature4.

METHODS

Animal protocols utilized male Sprague-Dawley rats (n=6 to 9) were approved by the Animal Care and Use Committee. Data from a previously published study5, consisted of measurements of cerebral microvascular blood flow and caudate nucleus PBrO2 in isoflurane anesthetized rats (n=6) receiving a phenylephrine infusion of 2-3µg/kg/min to increase MAP progressively from 80 to 120mmHg. Tissue PBrO2 was measured using oxygen sensing microelectrode within the caudate nucleus (LICOX GMS; Harvard Apparatus), and bilateral laser Doppler flow probes (OxyFlo; Oxford Optronix, Oxford, UK) over the cerebral cortex. Additional new experiments measured skeletal muscle microvascular flow and PO2 in isoflurane anesthetized rats receiving increasing phenylephrine doses to achieve a MAP of 80 to 120mmHg (PE range of 1.2-18µg/kg/min) using microsensor G4 probes (G4 Oxyphor, Oxygen Enterprises) (n=9), and laser Doppler flow probes (OxyFlo; Oxford Optronix, Oxford, UK) (n=6) in the rectus abdominus muscle.

For each group, arterial blood gas analysis and co-oximetry were performed prior to and after the experiment. Data are presented as mean ± SEM and analysis performed by one-way ANCOVA for linear regression with $p<0.05$ as significant.

RESULTS

With each experiment, a consistent increase in MAP was associated with escalating dosage of PE administration from a baseline near 80mmHg to a target MAP of 120mmHg (Figure 1). In skeletal muscle, increasing MAP with PE resulted in a slight decrease in normalized microvascular blood flow and no change in muscle tissue PO2 (Figure 1, panel A and B respectively). By contrast, increasing MAP with PE resulted in a proportional increase in normalized cerebral microvascular blood flow ($y=0.02x -0.71$) and brain tissue pO2 ($y=0.51x - 19.40$) (Figure 1, panel C and D respectively). Lines of regression between muscle and brain for both microvascular blood flow and tissue PO2 were significantly differently (ANCOVA, $p<0.001$). Arterial blood gases and co-oximetry data, including PaO2 and blood oxygen content, remained comparable before and after PE administration.

DISCUSSION

Our data supports the hypothesis that PE impacts muscle and brain perfusion differently. Activation of α1 receptors using PE increases MAP through vasoconstriction of skeletal vasculature, shunting blood away from the muscle and towards the brain, where there is a lack of α1 receptors4, as demonstrated by the increased cerebral microvascular blood flow and cerebral PO2. The discordance between direct brain tissue PO2 and brain vascular oxygen saturation measured by NIRS may be due to the increased proportion of cerebral venous blood from central vasoconstriction—further research is required to determine the optimal means of supporting MAP and brain perfusion.

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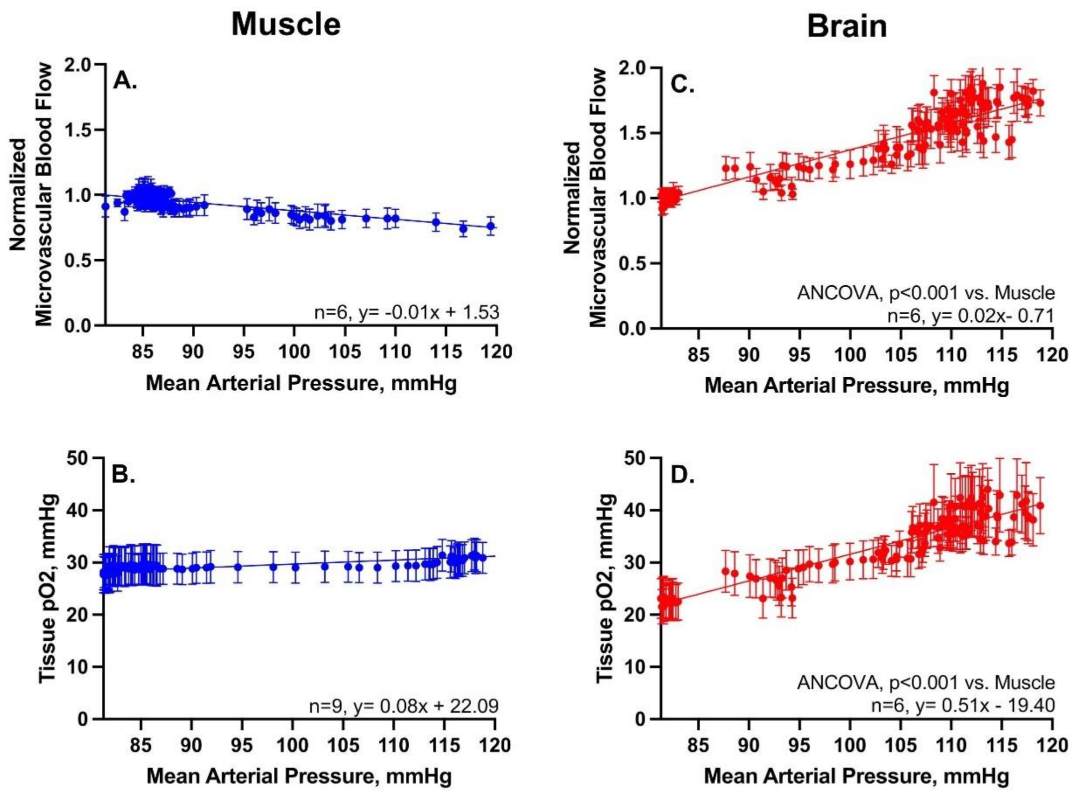

Figure 1. The impact of increasing mean arterial pressure through phenylephrine adminstration on (**A**) muscle normalized microvascular blood flow, (**B**) muscle tissue oxygen tension pO2, (**C**) cerebral normalized microvascular blood flow, and (**D**) cerebral tissue oxygen tension pO2 in experimental rat models. Significant linear increases were seen in cerebral microvascular blood flow and tissue pO2 with increasing mean arterial pressure compared to muscle.

The Intra-Aortic Balloon Pump in Action – A Systematic Review & Meta-Analysis of Hemodynamic Effects

AUTHORS

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INTRODUCTION

The intra-aortic balloon pump (IABP) is one of the most frequently used mechanical circulatory support devices in clinical practice[1]. It operates by counter-pulsation, whereby a balloon catheter placed in the proximal descending aorta deflates in systole and inflates in diastole. Thus, the functions of this device are to increase cardiac output and diastolic coronary perfusion. The IABP is deployed in cardiogenic shock from myocardial infarction, refractory heart failure, cardiac surgery, and high-risk percutaneous coronary interventions. The American Heart Association/American College of Cardiology recently assigned the IABP a Class IIa recommendation based on recent trials showing limited mortality benefit in myocardial infarction[2,3]. Nonetheless, it remains a relevant tool in clinical practice thanks to its ease of use and low complication rate compared to other mechanical circulatory support devices[1]. This systematic review and meta-analysis highlight the applied hemodynamic impacts of the IABP to guide clinicians on its effectiveness in various clinical scenarios.

METHODS

We searched MEDLINE, EMBASE, CENTRAL, Web of Science databases, Google Scholar and reference lists of resulting studies, from database inception to 27 August 2021, for observational studies and randomized controlled trials evaluating the hemodynamic effects of the intra-aortic balloon pump in adults older than 18 years of age. The primary outcome will be change in cardiac index, while secondary outcomes include changes in systolic & diastolic blood pressure, pulmonary artery occlusion pressure, central venous pressure, heart rate and systemic vascular resistance. Outcomes related to IABP use will be examined in myocardial infarction, heart failure, and cardiac surgery subgroups. Risk of bias assessment was performed by two independent reviewers using the Joanna Briggs Institute Critical Appraisal Tool. Primary and secondary outcomes are presented as mean differences with 95% confidence intervals.

RESULTS

1895 studies were identified, and 28 were included for analysis. Overall, cardiac index increased by 0.53 L/min/m2 (95% CI 0.39, 0.68). This effect was most pronounced in the cardiac surgery population, with an increase of 0.73 L/min/m2 (95% CI 0.39, 1.06). Cardiac index increased by 0.45 L/min/m2 (95% CI 0.19, 0.72) and 0.28 L/min/m2 (95% CI 0.24, 0.32) in the myocardial infarction and heart failure groups respectively. A significant increase was found in diastolic blood pressure (20.63 mmHg, 95% CI 5.68, 35.57), while systolic and mean arterial pressure as well as heart rate showed no significant changes. Central venous pressure (-1.72 mm Hg, 95% CI –2.77, -0.67), pulmonary artery occlusion pressure (-4.12 mm Hg, 95% CI -6.11, -2.14), and systemic vascular resistance (-149.81 dyn*sec/cm5, 95% CI –222.6, -77) all decreased significantly.

DISCUSSION

IABP increases cardiac output in all subgroups, while showing surrogates of increased coronary perfusion (increased diastolic pressure) and increased forward flow (reduced pulmonary artery occlusion pressure and central venous pressure). Limitations include heterogeneity in concomitant therapy (ie: inotrope use) due to the complexity of care in these populations, and in timing of hemodynamic measurements after IABP installation. Nonetheless, given a mortality rate of 40-60% in cardiogenic shock despite medical therapy[4], the results of this systematic review and meta-analysis demonstrated that the intra-aortic balloon pump remains a clinically useful tool for patients in cardiogenic shock and in cardiac surgery.

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Study or Subgroup	Mean Difference	SE	Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.2.1 Myocardial infarction						
Mueller 1971	0.47	0.11	10	4.5%	0.47 [0.25, 0.69]	1971
Dunkman 1972	0.79	0.08	34	4.7%	0.79 [0.63, 0.95]	1972
Ehrich 1977	0.4	0.05	16	4.9%	0.40 [0.30, 0.50]	1977
Taguchi 2000	−0.1	0.23	12	3.4%	−0.10 [−0.55, 0.35]	2000
Thiele 2003	0.3	0.14	23	4.2%	0.30 [0.03, 0.57]	2003
Thiele 2005	0.17	0.12	20	4.4%	0.17 [−0.07, 0.41]	2005
Li 2007	1.4	0.08	20	4.7%	1.40 [1.24, 1.56]	2007
Christoph 2008	0.2	0.05	12	4.9%	0.20 [0.10, 0.30]	2008
Seyfarth 2008	0.11	0.18	13	3.9%	0.11 [−0.24, 0.46]	2008
Prondzinsky 2010	1	0.06	19	4.8%	1.00 [0.88, 1.12]	2010
Malick 2019 (MI)	0.08	0.06	73	4.8%	0.08 [−0.04, 0.20]	2019
Subtotal (95% CI)			**252**	**49.1%**	**0.45 [0.19, 0.72]**	
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 319.26$, df = 10 ($P < 0.00001$); $I^2 = 97\%$						
Test for overall effect: $Z = 3.35$ ($P = 0.0008$)						
1.2.2 Cardiac surgery						
Christenson 1997 (1)	0.95	0.11	13	4.5%	0.95 [0.73, 1.17]	1997
Christenson 1997 (2)	1.36	0.16	19	4.0%	1.36 [1.05, 1.67]	1997
Christenson 1999	1.17	0.11	30	4.5%	1.17 [0.95, 1.39]	1999
Arafa 2000	0.72	0.08	5	4.7%	0.72 [0.56, 0.88]	2000
Christenson 2003	0.59	0.1	15	4.6%	0.59 [0.39, 0.79]	2003
Schreuder 2005	0.31	0.15	15	4.1%	0.31 [0.02, 0.60]	2005
Ferreira 2018	0.67	0.08	90	4.7%	0.67 [0.51, 0.83]	2018
Omar 2020	0.1	0.03	144	4.9%	0.10 [0.04, 0.16]	2020
Subtotal (95% CI)			**331**	**36.0%**	**0.73 [0.39, 1.06]**	
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 237.79$, df = 7 ($P < 0.00001$); $I^2 = 97\%$						
Test for overall effect: $Z = 4.24$ ($P < 0.0001$)						
1.2.3 Heart failure						
Jeevanandam 2002	0.5	0.4	5	2.0%	0.50 [−0.28, 1.28]	2002
Annamalai 2017	0.28	0.27	10	3.0%	0.28 [−0.25, 0.81]	2017
Fried 2018	0.26	0.03	132	4.9%	0.26 [0.20, 0.32]	2018
Malick 2019 (HF)	0.3	0.03	132	4.9%	0.30 [0.24, 0.36]	2019
Subtotal (95% CI)			**279**	**14.9%**	**0.28 [0.24, 0.32]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.19$, df = 3 ($P = 0.76$); $I^2 = 0\%$						
Test for overall effect: $Z = 13.29$ ($P < 0.00001$)						
Total (95% CI)			**862**	**862 100.0%**	**0.53 [0.39, 0.68]**	
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 606.24$, df = 22 ($P < 0.00001$); $I^2 = 96\%$						
Test for overall effect: $Z = 7.13$ ($P < 0.00001$)						
Test for subgroup differences: $Chi^2 = 8.15$, df = 2 ($P = 0.02$), $I^2 = 75.5\%$