Effects, management and optimization of extracorporeal techniques and technologies in contemporary cardiac surgery

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DISSERTATION

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“Measure what can be measured and make measurable what cannot be measured.”

Galileo Galilei, Physicist (Pisa 1564- Arcetri 1642)

Chapter 1

General Introduction

The role of inflammation in relation to extracorporeal perfusion techniques (1,2), the reduction of air-blood contact, and the improvement of biocompatibility (3,4) are important aspect of extracorporeal circulation (ECC) and have been the target of many investigations, either to enhance the mechanism understanding, but also as a target of technological advancement. From an analysis of perfusion techniques in the literature, emerged that there are different approaches for optimizing the circuit which involve the selection of materials and components (5,6,7), from the use of the compact circuit to the use of minimally invasive extracorporeal circulation (MiECC) (9,10,11).

During cardiac surgery with cardiopulmonary bypass (CPB) in adult patients, hyperlactatemia (HL) is detectable at a considerable rate (10%-20%) (and is associated with postoperative morbidity and mortality (12,13). At present, the nature of HL during and after cardiac operations is not totally clear, but the majority of authors tend to attribute this finding to tissue hypoxia (type A HL), even if type B HL (without tissue hypoxia) has been advocated in some cases (13). The management and prevention of hyperlactatemia during the management of extracorporeal circulation is a complex topic (14,15),

Differences in management between CPB and ECMO have been described (18,19). In CPB the role of GDP is crucial together with the use of devices for the metabolic monitoring, however the management of Veno-Arterial (V-A) ECMO remains a macro-circulatory approach. As for CPB, predictive target parameters have been found and consolidated (24), particularly in terms of acute renal injury and the prevention of anaerobic metabolism, while for ECMO management, a blurred path remains (20).

The incidence of post-cardiotomy cardiogenic shock is low in cardiac surgery however it is a complication that greatly impacts mortality (21,22). Over the years, particularly in the last decade, there has been an important diffusion of minimally invasive cardiac surgery on the mitral valve (23,24). The most used extracorporeal supports in the treatment of refractory post-cardiotomy cardiogenic shock are ECMO and the Intra-aortic Balloon Pump (IABP) (25).

In the management of ECMO procedures, due to the complexity of the pathology, the duration of treatment on patients often exceeds the certified

duration (26,27), in particular of the circuit device and the oxygenator (28,29). A difficult to quantify parameter that could broaden the horizons of oxygenation performance is the production of condensation in the oxygenator outlet (31,32). In the Chapter 7 we presented the role of condensation in oxygenating performance in relation to the design of the various oxygenator models. A prospective data collection was presented on different models of polypropylene and polymethylpentene fiber oxygenators in relation to temperature management (33), condensate production and oxygenation performance (34,35).

The use of CO_2 in cardiac surgery in structural and valvular surgery is quite widespread and consolidated in the literature, however there are various methodologies on the management of CO_2 administration in particular in minimally invasive cardiac surgery of the mitral valve (36,37). In the Chapter 8, we presented a retrospective study on the use of continuous field flooding versus final one-shot CO_2 insufflation in minimally invasive mitral valve repair, comparing the effectiveness and efficiency between the two techniques on the time to eliminate gas micro-embolic activity from the cardiac chambers (38,39,40).

The gas micro-embolic activity in cardiopulmonary bypass exposes the patient to a series of complications of local alteration of the perfusion of the microcirculation with tissue ischemia (41,42). Although the latest generation devices for extracorporeal circulation (venous reservoirs, oxygenators and arterial filters) have designs and projects aimed at maximum elimination of gas micro-emboli (GME), there are no studies that demonstrate what the unexpected predisposing factors are for the GMEs (43,44,45). In the Chapter 9 we presented a study on Clinical Evaluation of Micro-Embolic Activity with Unexpected Predisposing Factors and Performance of Horizon AF PLUS during Cardiopulmonary Bypass.

There is limited evidence as to the pharmacokinetic changes expected in adults with extracorporeal technologies (46,47). In particular, cardiopulmonary bypass (CPB) is associated with significant changes in the pharmacokinetics and pharmacodynamics of anesthetic drugs. Drugs may be taken up by various components of the CPB circuit itself (48,49). Issues include the increased volume of the circuit leading to hemodilution; the sequestration of lipophilic drugs within the

circuit tubing; and the absorption of proteins, especially albumin, onto the circuit, which can result in increased free drug (50). In the Chapter 10 we compared Propofol dosages during CABG procedures on the use of conventional CPB and minimally invasive extracorporeal circulation (MiECC) for the bi-spectral index in relation to hemodilution, contact surface and albumin content.

The optimal management of GDP for the prevention of acute kidney injury (AKI) and anaerobic metabolism can be attributed to the pre-operative characteristics of the patient and the type of extracorporeal techniques used in relation to hemodilution, presence of hemolysis and air-blood contact (51,52). In this context, in Chapter 11 we present a study on 60 end-stage coronary artery disease patients undergoing myocardial revascularization (53,54), treated with minimally invasive extracorporeal circulation (MiECC) and conventional CPB. Both techniques had GDP management, and the incidence of peri-operative lactates and the incidence of post-operative acute renal failure were compared between the two groups MiECC vs conventional CPB (55).

The hemolysis and plasma free hemoglobin release during extracorporeal circulation can occur from a number of patient-related and technical factors and might be worse with high flows and/or excess negative pressures within the circuit and blood transfusions (56,57,58). Elevated plasma free hemoglobin is associated with multi-organ injury, including severe acute kidney injury (59,60). In the Chapter 12, we present a pilot study on two different pump technologies, a magnetic levitation pump vs a constrained vortex pump, comparing 40 patients undergoing isolated coronary artery bypass grafting (CABG) using a minimally invasive extracorporeal circulation (MiECC) type IV system, which enables volume management.

The Chapter 13 presented a letter to editor on Magnetic levitation pumps for cell-free hemoglobin prevention during VV ECMO. Graw et al. identified a cohort of 1044 ARDS patients with CFH and haptoglobin measurements before initiation of ECMO therapy. They concluded that in critically ill patients with ARDS requiring therapy with VV ECMO, increased plasma concentration of CFH were an independent risk factor for AKI. Among patients with increased CFH concentrations, higher plasma haptoglobin concentrations might protect from

CFH-associated AKI (61). In this context we reported our experience about the effect of Magnetic levitation pump versus Constrained vortex pump on the hemolysis effect during extracorporeal technologies for short time. We reported a pilot study focused on plasma free hemoglobin levels in 40 patients undergoing isolated coronary artery bypass grafting (CABG).

Aim and outline of the research project

Based on the above-mentioned peculiar and relevant aspects related to ECC and ECMO, and also in the setting of minimally invasive cardiac surgery procedures, several investigations were planned to study these aspects in several clinical scenarios. The purpose of this thesis was to analyze the impact in terms of management and optimization on extracorporeal techniques and technologies in contemporary cardiac surgery in end-organ protection. Contemporary extracorporeal perfusion technologies and techniques were compared in terms of biocompatibility and inflammation containment for Minimally Invasive Extracorporeal Circulation (MiECC), Conventional and Optimized Extracorporeal circulation (ECC) techniques in a literature review. In particular, the studies were focused on end-organ protection: on the preservation of aerobic metabolism during cardiopulmonary bypass through the monitoring of oxygen delivery (DO_2) and on the most appropriate research of the nadirs in relation to indexed oxygen extraction (ERI O_2) in terms of superiority, specificity and sensitivity compared to cardiac index (C.I.). These aspects of metabolic management on cardiopulmonary bypass for goal directed perfusion (GDP) were compared and related to the management of Veno-Arterial (VA) Extracorporeal Membrane Oxygenation (ECMO) through a literature review. We investigated the incidence of ECMO and intra-aortic balloon pump (IABP) in post cardiotomy cardiogenic shock in mitral valve surgery in conventional full sternotomy (FS) and minimally invasive approach in terms of survival and mortality. The efficacy parameters efficiency and durability of the oxygenator in ECMO procedures were studied in relation to the management of anticoagulant therapy for the short, medium and long term, in Veno Venous (VV) ECMO and in Veno Arterial (VA) ECMO Post Cardiotomy (PC).

The performance of the oxygenating modules was correlated to the production of condensate in relation to the management and the type of models and designs of the oxygenator. The elimination and reduction of the production of Gaseosus Micro-emboli (GME) during extracorporeal techniques has a crucial role in preserving the microcirculation and tissues from ischemia by promoting a correct metabolic supply. The management of gas microembolic activity (GME) in the surgical field on minimally invasive mitral valve surgery in relation to continuous or non-continuous CO2 was studied and the activity of GME in relation to the selection and management of bypass components were studied on cardiopulmonary bypass for unexpected and predisposing factors for GME. The role of MiECC compared to conventional systems was investigated on the pharmacodynamics and pharmacokinetics of propofol, on the benefit of magnetic levitation pumps compared to constrained vortex on the reduction of hemolysis and the potential protective role during ECMO, on the organ protection of MiECC compared to conventional systems in end-stage patients undergoing myocardial revascularization.

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Chapter 2

Air, inflammation and biocompatibility of the extracorporeal circuits

Condello I, Santarpino G, Nasso G, Fiore F, Moscarelli M, Mastroroberto P, Speziale G.

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Abstract

The inflammatory response in cardiac surgery using extracorporeal circulation (ECC) has been widely discussed in the literature with analysis on cytokines released in humans; demonstrating manifold trigger causes. To mitigate this response mainly linked to the contact and recognition by the blood of a “non-self” surface many efforts have been made to make the circuits of the extra-corporeal circulation “biomimetics”; trying to emulate the cardio-vascular system. In other words, biomedical companies have developed many biocompatible products in order to reduce the invasiveness of the ECC. One of the techniques used to reduce the contact of blood with “non-self” surfaces is the “coating” of the internal surfaces of the ECC. This can be done with phospholipidic, electrically neutral, and heparin derivates with anticoagulant activity. The coating can be divided into two categories: the “passive coating” with Phosphorylcholine by biomedical companies and the administration of albumin added to the “priming” during the filling of the circuit by the perfusionist. Alternatively, we have the “active” coating: treatment of the internal surfaces in contact with the blood with neutral proteins and heparin. The latter are different according to the production company, but the aim is always to maintain high levels of systemic and local anticoagulation, inactivating the “contact” coagulation between the blood and the surfaces. A recent study demonstrates that the use of an “active coating” is associated with better preservation of the endothelial glycocalyx compared with “passive coating” circuits.

Introduction

The inflammatory response in cardiac surgery using extracorporeal circulation (ECC) has been widely discussed in the literature with analysis on cytokines released in humans; demonstrating manifold trigger causes. To mitigate this response—mainly linked to the contact and recognition by the blood of a “non-self surface many efforts have been made to make the circuits of the extra-corporeal circulation “bio-mimetics; trying to emulate the cardio-vascular system. In other words, biomedical companies have developed many biocompatible products in order to reduce the invasiveness of the ECC.

One of the techniques used to reduce the contact of blood with “non-self” surfaces is the “coating” of the internal surfaces of the ECC. This can be done with phospholipidic, electrically neutral, and heparin derivates with anticoagulant activity. The coating can be divided into two categories and each of these coatings do have advantagesand disadvantages. First, “the most common biopassive coatings” attenuating the protein adsorption and it is considered more “platelet friendly”(2,3). Alternatively, we have the “active” coating: treatment of the internal surfaces in contact with the blood with neutral proteins and heparin that also attenuate the complement activation. The latter are different according to the production company, but the aim is always to maintain high levels of systemic and local anticoagulation, inactivating the “contact” coagulation between the blood and the surfaces. A recent study demonstrates that the use of an “active coating” is associated with better preservation of the endothelial glycocalyx compared with “passive coating” circuits (4). However, probably the biggest challenge for ECC, in order to improve biocompatibility, is the elimination of air-blood contact. This is very intuitive, given that in nature blood does not come into contact with air but circulates in a closed system. A blood-air interface (BAI) in the ECC circuit causes activation and inflammation of the blood elements; systemic inflammatory response syndrome (SIRS) (5). In an animal study conducted by Carr DB et al. (5), ten healthy pigs underwent ECC for 2 h through the cervical vessels and monitored for 96 h after surgery. Five pigs had minimal air exposure in the circuit, while five presented a BAI due to the presence of a reservoir. There were no significant differences in cardiopulmonary bypass flow or hemodynamics between groups. In the “BAI” group, there was an increase in hemolysis after ECC. This was demonstrated through a significantly higher value of free hemoglobin in the blood in the BAI group (5.27 vs 0.94 mg/dL), platelet consumption (28% vs 83%), and signs of activation of the inflammatory system such as the consumption of leukocytes (71% vs 107%) and increased expression of CD11b of the granulocytes (409% vs 106%). These data suggest that the inflammatory model responsible for the ECC-SIRS phenomenon may be due precisely to blood air contact (5). As already mentioned, our cardiovascular system is a system closed to air; in particular nitrogen is potentially at high embolism risk due to its low solubility. Our cardio-pulmonary system, to make the diffusion of

gas at the alveolus-capillary level a phenomenon without pathophysiological impact, has efficient mechanical and immune barrier systems. Furthermore, it promotes the molecular diffusion performance of oxygen from the alveolus to the red blood cell through the phospholipoproteic surfactant complex (i.e. composed of lipids and, to a lesser extent, proteins), secreted by alveolar cells (pneumocytes of class II). The proteins and lipids that make up the surfactant have a hydrophilic component and a hydrophobic component. The main lipid component of the surfactant is dipalmitoyl phosphatidylcholine (DPPC), a molecule capable of reducing the surface tension by placing itself at the alveolar air-water interface, with the hydrophilic head component facing the water and the hydrophobic part of the tail facing the air (6). The microporous hollow fiber oxygenating membranes in polypropylene (PPL) and polymethylpentene (PMP), have emulated the natural lung, sliding the mixture of gas inside and the blood outside of the polymer fiber lumen. They carried out a molecular diffusion exchange by functionally reversing the alveolus and the capillary. In fact, the oxygenating fiber contains the gas flow inside the capillary and the blood flows outside the capillary (7). However, with the PPL membranes is possible to introduce through the fiber gaseous micro-emboli in the blood stream, due to the micropores present in the fiber wall. In fact, at the oxygenator level there is no BAI but the system is closed, so the problem of air-blood contact in extracorporeal techniques is not at this level but occurs in systems equipped with a venous reservoir and with the aspirator management through ECC. The “standard” extracorporeal circulation (conventional ECC or CECC, (**Figure 1**),

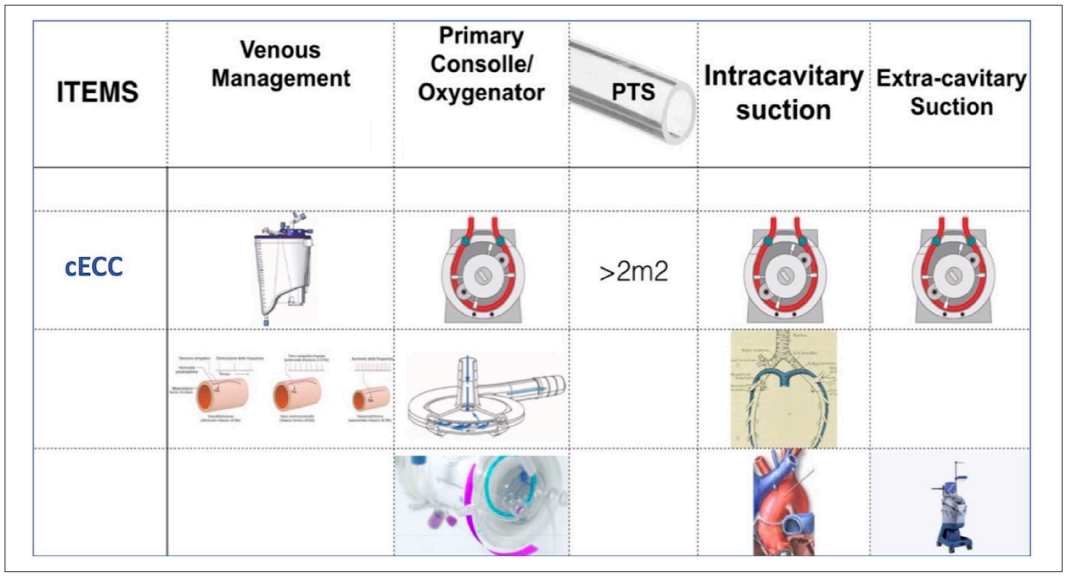

Figure 1. Conventional ECC; schema of the characteristics.

uses a venous reserve (reservoir), which is represented by a container where there is a direct interface between the surface of the blood and the air inside the container. Since this is the most represented gas in the air that is concentrated in the limited space of the reservoir, it can be deduced that the inflammation of the blood from "BAI" is mainly conditioned by the high concentration of nitrogen which interfaces with the blood surface. To reduce the nitrogen content, in order to prevent gas embolism, the administration of CO_2 in the operative field during "open chamber" cardiac surgery is a widespread clinical practice due to the higher molecular weight of the CO_2 and consequently it reduces the nitrogen percentage in the heart chambers (8). There are mini-invasive extra-corporeal circuits (MiECC, **Figure 2**)

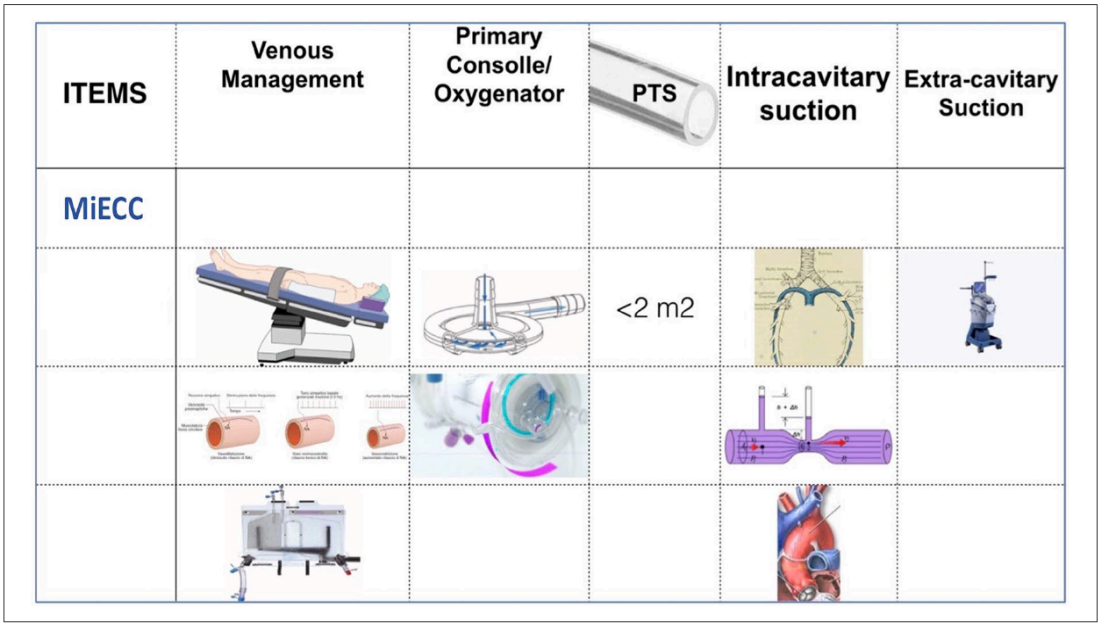

Figure 2. Minimally invasive ECC; schema of the characteristics.

that do not have a venous reservoir and use a closed bag for volume management. This strategy is the “conventional” ECC in some European regions, but in our paper we’ll use the denomination conventional/standard for the “open reservoir” approach. These circuits do not have spaces with an air-blood interface, as they are not equipped with roller pumps and use a passive suction (negative pressure of the centrifugal pump on the venous line). However, with the MiECC the aspiration of the cardiac chambers opens to the air (e.g. during valve surgery) remains difficult to perform, as well as the embolic risk in the circuit and the activation of the inflammatory cascade are unclear. On the other hand, in “closed chamber” coronary surgery, the MiECC is giving very encouraging results—also on the inflammatory level—compared to the conventional ECC with venous reserve and active aspirators (9). However, we have to highlight that there is a distinction between “minimal invasive” and “hemocompatibility”; although many minimally invasive systems have become nowadays more haemocompatible because of lower priming volume, use of coatings and separated suction techniques. There is a third methodology that subjects the air-blood interface of the venous reserve to negative pressure(–35/40 mmHg) (10).The aim of the negative pressure is based on the perfect gas laws of Boyle, Gay-Lussac and Charles which says that the “quantity” of a gas is directly proportional to the barometric pressure—to zero or at least reduce the concentration of Nitrogen in the air at BAI. This technique, called “Fibonacci” **(Figure 3),**

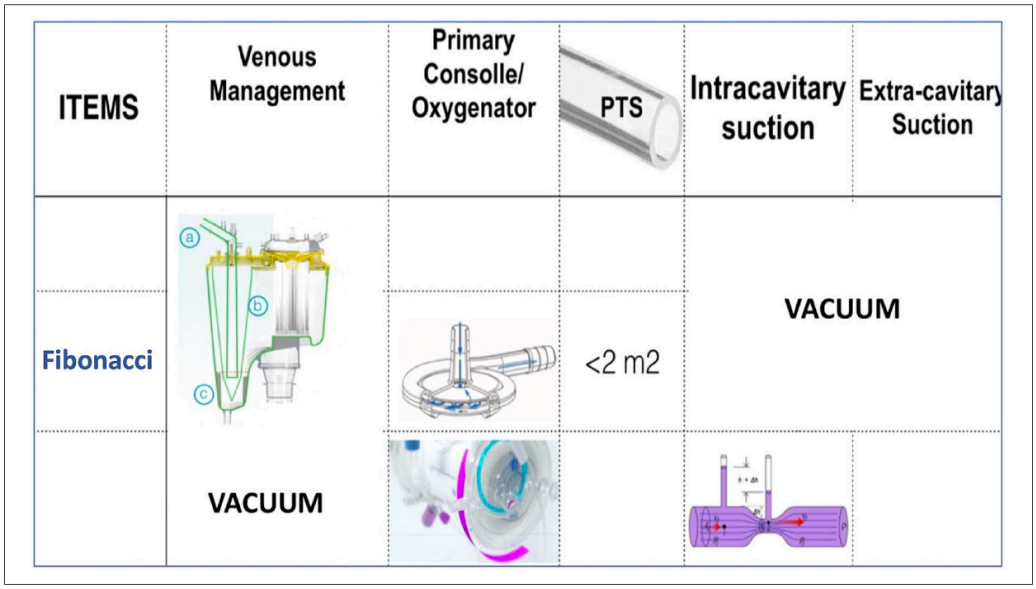

Figure 3. "Fibonacci" ECC; schema of the characteristics.

and described in our recently published study (11), eliminates the use of roller pumps, using a negative pressure of the vacuum assisted venous drainage (VAVD) of –40 mmHg for suction in the venous reserve. These technical devices allow to visualize an empty space in the venous reservoir; free of gas and in particular with a reduction of the molecular concentration of nitrogen. In particular, this reduction is speculative and not published but the reduction of gaseous micro emboli in the blood compared to “open” circuits is well demonstrated (11). The advantages obtainable with this technique are demonstrated by our study conducted on 70 patients who underwent surgery of the aortic valve and the ascending aorta. We recorded lower postoperative LDH and PCR values, as well as better postoperative coagulation compared to the patients underwent conventional “open” circuits (11). The Table 1 summarizes pro and cons of the three cardiopulmonary bypass strategies. The versatility of this technique also makes it suitable for open chamber cardiac surgery and we believe that these encouraging preliminary results deserve the development of new studies with a greater number of patients in order to confirm the data recorded so far.

Table 1. Cardiopulmonary bypass strategies.

	Pro	Cons
Conventional ECC	For all procedures usable	Hemodiluition, roller pump use, presence of BAI, risk of hemolysis
Minimal invasive ECC	No BAI, reduced contact surface, reduced hemodiluiton, no roller pumps, reduced hemolysis	Difficult to keep the goals (e.g. no BAI, absence of/reduced hemolysis) due to the use of suction/aspirators with BAI
"Fibonacci" ECC	No roller pumps, reduced hemolysis, for all procedures usable	Presence of BAI

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Chapter 3

Associations between oxygen delivery and cardiac index with hyperlactatemia during cardiopulmonary bypass

Condello I, Santarpino G, Nasso G, Moscarelli M, Fiore F, Speziale G.

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Abstract

Objective: Metabolism management plays an essential role during cardiopulmonary bypass (CPB). There are different metabolic management devices integrated to heart–lung machines; the most commonly used and accepted metabolic target is indexed oxygen delivery (DO_{2i}) (280 mL/min/m^2) and cardiac index (CI) (2.4 L/min/ m^2), which can be managed independently or according to other metabolic parameters. Our objective was to compare lactate production during CPB procedures using different metabolic management: DO_{2i} in relation to indexed oxygen extraction ratio (O_2ER_i) and CI in relation to mixed venous oxygen saturation (SvO_2).

Methods: Data on 500 CPB procedures were retrospectively collected in a special- ized regional tertiary cardiac surgery center in Italy between September and 2012 and November 2019. In group A, the DO_{2i} with 280 mL/min/m^2 target in relation to O_2ER_i 25% was used; in group B, CI with 2.4 L/min/m^2 target in relation to SvO_2 75% was used. During CPB, serial arterial blood gas analyses with blood lactate and glucose determinations were obtained. Hyperlactatemia (HL) was defined as a peak arterial blood lactate concentration>3 mmol/L. The postoperative outcome of patients with or without HL was compared.

Results: Eight pre- and intraoperative factors were found to be significantly asso- ciated with peak blood lactate level during CPB at univariate analysis. HL (>3 mmol/ L) was detected in 15 (6%) patients of group A and in 42 (16.8%) patients of group B (P 1⁄4 .022); hyperglycemia (>160 mg/dL) was found in 23 (9.2%) patients of group A and in 53 (21.2%) patients of group B (P 1⁄4 .038). Patients with HL during CPB had a significant increase in serum creatinine value, higher rate of prolonged mechanical ventilation time and intensive care unit stay. A cutoff of DO_{2i} <270 mL/min/m^2 in relation to O_2ER_i >35% in group A and a cutoff of CI <2.4 L/min/m^2 in relation to SvO_2 <65% in group B were found to have a positive predictive value of 80% and 75% for HL, respectively. A cutoff of DO_{2i} >290 mL/min/m^2 in relation to O_2ER_i 24% in group

A and a cutoff of CI >2.4 L/min/m^2 in relation to SvO_2 >75% in group B were found to have a negative predictive value of 78% and 62% for HL, respectively.

Conclusions: This retrospective observational analysis showed that management of DO_{2i} in relation to O_2ER_i was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. Group A reported a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and intensive care unit stay, compared with group B.

Introduction

During cardiac surgery with cardiopulmonary bypass (CPB) in adult patients, hyperlactatemia (HL) is detectable at a considerable rate (10%-20%) (1,2) and is associated with postoperative morbidity and mortality. At present, the nature of HL during and after cardiac operations is not totally clear, but the majority of authors (3,4,5,6) tend to attribute this finding to tissue hypoxia (type A HL) even if type B HL (without tissue hypoxia) has been advocated in some cases (7,8,9). The main factors leading to a possible organ dysoxia during CPB are the hemodilution degree and a low peripheral oxygen delivery (1,2,4,5,6,10,11,12). In the state of perfusion, there are different metabolic management devices integrated to the heart–lung machine (eg, Quantum Spectrum [Spectrum Medical, Cheltenham, England], Connect Livanova [London, England], CDI Terumo Medical, Vaughan, Ontario, Canada], Landing Eurosets [Medolla, Italy]), with multiple measured and calculated parameters; the most commonly used and accepted metabolic target for the scientific community is the value of indexed oxygen delivery (DO_{2i}) (280 mL/min/m^2) and the cardiac index (CI) (2.4 L/min/m^2). These parameters can be managed independently or according to other metabolic parameters (eg, hemoglobin [Hb], vascular resistance, temperature, and diuresis), resulting in wide variability in CPB management of each center. This study has the objective to compare lactate production during CPB procedures using different metabolic management: DO_{2i} in relation to indexed oxygen extraction ratio (O_2ER_i) (group A), and CI in relation to mixed venous oxygen saturation (SvO_2) (group B).

Materials and Methods

Population and Study Design

This study presents a comparative retrospective analysis that has been carried out between 2 historical times: the first historical period (2012-2015) used conventional extracorporeal circulation with blood gas test for metabolic management during CPB; the second historical period (2016-2019) used conventional extracorporeal circulation with blood gas test and the integration with metabolic parameter monitoring system. Between September 2012 and November 2019, 500 adults aged >28 to 80 years were collected for elective cardiac surgery procedures, without chronic kidney failure and with calculated European System for Cardiac Operative Risk Evaluation II score (mean value, 4.1%-4.5%) at our institution (Department of Cardiothoracic Surgery, Anthea Hospital, Bari, Italy). The study protocol was approved by the local ethics committee and all patients provided written consent to scientific treatment of their data. Patients were divided into 2 groups for CPB metabolic management: in group A (study group, n = 250), the DO_{2i} target with a target of 280 mL/min/m^2 was used in relation to O_2ER_i; in group B (control group, n = 250), the CI target with a target of 2.4 L/min/m^2 was used in relation to SvO_2.

Data Collection

Patients were selected according to the following criteria:

- Elective, primary cardiac surgery: complete CPB and cardioplegic arrest had to be foreseen with an expected CPB duration>90 minutes.
- Patients were excluded if they presented abnormal plasma lactate levels (>2 mmol/L) before entering CPB, renal or liver failure, obesity, uncom- pensated diabetes, autoimmune disease, active infection, any immuno- suppressant therapy, or coagulation disorder. Patients undergoing surgery with circulatory arrest or having preoperative hematocrit (Hct)
- <27% were also excluded.

The cardiac surgery procedures that were analyzed for this study are coronary artery bypass graft (n° 200), isolated aortic valve replacement (n°100) and mitral valve repair with minimally invasive approach (n°200).

Preoperative data included patient demographic characteristics, base- line serum creatinine levels, ventricular ejection fraction, comorbidities (eg, chronic obstructive pulmonary disease or previous cerebrovascular ac- cident), baseline Hb, logistic European System for Cardiac Operative Risk Evaluation II score and New York Heart Association functional class.

Perioperative data included type of operation, CPB duration, nadir body temperature during CPB, nadir Hct and Hb values (measured at the start of the CPB operation and every 20 minutes thereafter), nadir DO_2i, nadir DO_2i/O_2ER_i ratio during CPB, nadir CI, nadir CI/SvO_2, peak serum lactate, and glucose during CPB. Postoperative data included peak serum creatinine, mechanical ventilation time, and days spent in the intensive care unit (ICU). The primary end points were specificity and sensitivity, positive and negative predictive value for HL between target DO_2i in relation to O_2ER_i during CPB compared with the control group in terms of intraoperative lactate and glycemia trends. Secondary end points were peak postoperative serum creatinine level, mechanical ventilation time (13-14), and length of ICU stay.

Anesthetics and Surgical Procedures

Patients were monitored with 5-lead electrocardiography, a left radial artery catheter, capnography, pulse oximetry, and rectal/urine bladder temperature sensors. Transesophageal echocardiography was performed in all patients. Anticoagulant therapy consisted of heparin sodium before CPB at 300 IU/kg to give an activated clotting time of>480 seconds (ACT PLUS; Medtronic, Minneapolis, Minn); for antagonization of heparin, 0.5 to 0.75 mg protamine was applied for every 100 U heparin. Anesthesia was induced with intravenous sufentanil (0.5-1 mg/kg) and midazolam (0.08- 0.2 mg/kg), and tracheal intubation was facilitated with intravenous rocuro- nium (0.6-1 mg/kg). Anesthesia was maintained with propofol (2-5 mg/kg) and sufentanil (0.5-2.0 mg/kg), and the depth of anesthesia was monitored using bispectral index values (BIS XP; Aspect Medical System, Newton, Mass). The dose of propofol was titrated to maintain bispectral index values between 40 and 60. Aortic valve replacement and coronary artery bypass graft procedures were performed in median sternotomy with central cannulation, MVR in right minithoracotomy approach with peripheral can- nulation, and surgical procedures were performed as routine by 2 surgeons. Concentrated red blood cells were transfused whenever Hb concentrations fell below 6 g/dL during surgery or below 8 g/dL during ICU stay.

CPB Setting

Both open (Admiral; Remo-well Eurosets; EOS Dideco; Mirandola, Italy; Inspire 6F; LivaNova) and closed circuits (Closed Eurosets) were used for CPB. Pericardial blood was collected separately and could be processed or reinjected, if needed. The hard shell and soft shell reservoir, oxygenating module and circuits were treated with phosphorylcho- line (Agile Eurosets; P.hisio. LivaNova). All patients were treated with mild hypothermic CPB (34 C-36 C); a volume of 1250 mL crystalloid Ringer acetate solution was used for priming. The surgical procedures selected for this study do not justify the use of moderate hypothermia by falling below 34 C. For this reason, in the event of an initial increase in anaerobic metabolism, the first compensation approach was not to lower the temperature but possibly liquids or red blood cells were integrated.

The hardware consisted of a Stockert S5 heart-lung machine and a Stockert Heater Cooler System 3T (LivaNova) and the same cannulae were employed in both groups. For the administration of myocardial protection, a closed circuit for cardioplegia with heat exchanger, with an infusion syringe pump in series and Saint Thomas solution with procaine were used and repeated every 30 minutes. Group A used the Landing moni- toring system (Eurosets) for DO_2 management during CPB. In both groups, blood gas analyses were performed using alpha-stat management with a blood-gas analyzer (GEM Premier 3000 IQM; Instrumentation Laboratory, Werfen Group IVD company, Munich, Germany) set to measure at 37 C. On the basis of arterial blood data, we assessed the lowest Hct (percentage) on CPB; every 20 minutes, an arterial blood gas analysis, including blood glucose and lactate determination, was obtained. An Hb value < 6 to 7 g/dL during CPB was considered the trigger point for red blood cell transfusion. All patients received tranexamic acid according to the routine protocol. Mean arterial pressure during CPB procedures was managed for values between 55 and 70 mmHg.

Metabolic Management During CPB in Group A

In group A, DO_{2i} with a target of 280 mL/min/m^2 was managed in relation to O_2ER_i (the cutoff for increase in DO_{2i} was >25% O_2ER_i, the cutoff for decrease in DO_{2i} was <25% O_2ER_i). DO_{2i} and O_2ER_i-related measurements were performed using a Landing system provided by Eurosets. Data were collected every 5 seconds during CPB. Data required to calculate DO_{2i} and O_2ER_i were arterial Hb; measured parameters included arterial saturation, SvO_2, blood pump flow, Hb, arterial and venous temperature, mean arterial pressure, body surface area, and CI.

DO_{2i} was calculated using the following equation:

$$DO2_i(mL/min/m_2) = 10 \times pump\ flow(L/min/m2) \times arterial\ O_2\ content\ (mL/100mL),$$

where arterial O_2 content was calculated as follows: (CaO_2) arterial O_2 content (mL/100 mL) =

$$Hb\ (mg/dL) \times 1.34 \times Hb\ saturation\ (\%) + 0.003 \times O^2\ tension\ (mm\ Hg).$$

$O_2ER_{i\,(\%)}$ was calculated using the following equation (2,15):

$$O2ERi = VO_{2i}/DO_{2i} = (CaO_2 - CvO_2) / CaO_2$$

Metabolic Management During CPB in Group B

In group B, CI with a target of 2.4 L/min/m^2 was managed in relation to SvO_2 (the cutoff for increase in CI was<75% SvO_2, the cutoff for decrease in CI was >75% SvO_2). Related measurements were performed using a Flowmeter probe in arterial line to measure the real flow of the roller pump and the blood gas analyzer (GEM Premier 3000 IQM; Instrumentation Laboratory, Werfen Group IVD company) set to measure at 37 C° for measurement of SvO_2 during CPB. Data were collected every 20 minutes during CPB.

CI was calculated using the following formula:

CI (L/min/m^2) = (Q)pump flow (L/min)/ body surface area (m^2)

where pump flow (L/min) =body surface area (m^2) X CI (L/min/m^2). SvO_2, in the clinical and intensivist practice, was a true reflection of the global balance between oxygen delivery and consumption because it is measured through the venous drainage line during CPB where venous blood returning to the right heart from the superior vena cava, inferior vena cava, and the coronary sinus have mixed. SvO_2 has been extensively studied and used clinically to monitor the global balance between DO_2 and oxygen consumption. In the literature, for patients with multiple injuries, normal SvO_2 values between 65% and 70% and increasing DO_2 are more relevant for survival.

Statistical Analysis

All data are expressed as mean ` standard error of the mean or as ab- solute numbers and percentage, as appropriate. Statistical analysis was performed using SPSS version 11.0 software (SPSS Inc, Chicago, Ill). Univariate association with peak blood lactate was tested with a correla- tion matrix. Factors significantly (P < .05) associated with peak blood lactate at this preliminary step were entered into a stepwise forward multivariable linear regression analysis, with adequate corrections to avoid multicollinearity within the model. The multivariable approach was applied to assess the independent association between the variables tested and peak blood lactate. Subsequently, the population was explored in terms of HL (>3 mmol/L) incidence.

Normally distributed continuous variables are expressed as means ` standard deviation, and categorical variables as frequencies and percentages. DO_{2i} in relation to target O_2ER_i vs CI in relation to SvO_2 during CPB were tested for association with peak lactate and peak glucose blood. Intraoperative variables were tested for predictive ability of HL by using a receiver operating charac- teristic analysis. Postoperative outcome was firstly analyzed in the popu- lation with or without HL during CPB using a univariate approach (Student t test for unpaired data or relative risk analysis) and was subsequently corrected for other covariates.

Results

Demographic, preoperative, and operative details of the patient population are shown in **Tables 1 and 2**. Eight pre- and intraoperative factors were found to be significantly associated with peak blood lactate level during CPB at uni- variate analysis (**Table 3**): age, isolated coronary operation, lowest pump flow, lowest temperature, Hct, and DO_{2i} were negatively correlated with peak blood lactate value during CPB, whereas CPB duration and peak blood glucose were positively correlated with peak blood lactate value during CPB. The same intraoperative factors were tested for predictivity of HL with receiver operating characteristic analysis (**Figure 1**). The area under the curve was significantfor all factors. We therefore decided to explore the adequate cutoff values for target DO2i in relation to O2 ERi versus CI in relation to SvO2 ratio during CPB as possible predictors of HL. A cutoff of DO2i < 270 mL/min/m^2 in relation to O2 ERi > 35% during CPB in group A (**Table 4 and Figure 2**) and a cutoff of CI< 2.4 L/min/m^2 in relation to SvO2< 65% in group B (**Table 5 and Figure 3**) were found to have a positive predictive value of 80% (sensitivity 73% ,specificity 76%) and 75% (sensitivity 68% , specificity

67%), respectively (**Figure 4**). A cutoff of 155 mg/dL for peak blood on CPB showed a positive predictive value of 85% (sensitivity 84% , specificity 83%) (**Table 6**). A cutoff of DO2i> 290 mL/min/m^2 in relation to O2 ERi 24% during CPB in group A (**Figure 2**) and a cutoff of CI> 2.4 L/min/m2 in relation to SvO2> 75% during CPB in group B (Figure 3)were found to have a negative predictive value of 78% (sensitivity 69% , specificity 75%) and 62% (sensitivity 49% , specificity 59%), respectively (**Figure 4**). A cutoff of 128 mg/dL for peak blood glucose on CPB showed a negative predictive value of 74% (sensitivity 79% , specificity 80%) (**Table 7**). HL (> 3 mmol/L) was detected in 15 (6%) patients of group A and in 42 (16.8%) patients of group B (P . .001); hyperglycemia (> 160 mg/dL) was found in 23 (9.2%) patients of group A and in 53 (21.2%) patients of group B (P . .001) (**Table 8**). Patients without HL or hyperglycemia had significantly lower values of peak blood lactate; patients with both HL and hyperglycemia had significantly higher peak blood lactate values than patients with only HL or hyperglycemia. Only patients with associated HL and hyperglycemia had significantly lower values of DO2i with higher value of O2 ERi for group A and

lower CI with low SvO2 for group B on CPB. Group A patients with higher values of DO2i and O2 ERi showed a lower incidence of HL and hyperglycemia, which was 14.4% less than in group B patients for CI and SvO2 target. Patients with HL during CPB had a significant increase in serum creatinine value,13 higher rate of prolonged mechanical ventilation time and ICU stay (**Table 9 and Figure 5**).

Patients with hyperglycemia not associated with HL were separately investigated for the outcome variables. No significant differences in terms of morbidity or mortality were detected in association with this isolated condition.

TABLE 1. Preoperative profile and operative data

Characteristic	Group A (n = 250)	Group B (n = 250)
Mean age (y)	69.6	71.3
Male sex	110 (44)	121 (48)
Mean body surface area (m^2)	1.75	1.79
Mean left ventricular ejection fraction (%)	46	48
Median NYHA functional class	2	2
EuroSCORE II (mean)	4.1	4.7
Pre-CPB hematocrit (%)	32.4 ± 1.2	32.6 ± 1.9
Pre-CPB Hb (g/dL)	10.4 ± 1.1	10.8 ± 1.2
No. of chronic obstructive pulmonary disease cases (mean)	23	24
Creatinine (mg/dL)	1.09 ± 0.6	1.06 ± 0.9
Obstructive coronary artery disease (%)	23	24

Values are presented as n (%), or mean ± standard deviation. *NYHA*, New York Heart Association; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *CPB*, cardiopulmonary bypass; *Hb*, hemoglobin.

TABLE 2. Operative data

Parameter	Group A (n = 250)	Group B (n = 250)	*P* value
CPB time (min)	125 ± 13.2	120 ± 8.37	.92
Aortic crossclamp time (min)	61 ± 4	68 ± 7	.75
Nadir temperature (°C) during CPB	34.9 ± 1.1	34.7 ± 2.1	.75
Nadir hemoglobin value (mg/dL) during CPB	8.73 ± 1.53	8.89 ± 1.25	.88
Nadir hematocrit (%) during CPB	25.6 ± 3.8	25.9 ± 3.1	.89
Nadir DO_{2i} (mL/min/m^2) during CPB	290 ± 29	278 ± 14	.039
O_2ER_i (%) during CPB	24 ± 1	29 ± 5	.0029
Nadir CI (L/min/m^2) during CPB	2.6 ± 0.2	2.4 ± 0.1	.0032
Nadir SvO_2 (%)	81 ± 2	70 ± 5	.0029

Values are presented as mean ± standard deviation. *CPB*, Cardiopulmonary bypass; *DO_{2i}*, indexed oxygen delivery; *O_2ER_i*, indexed oxygen extraction ratio; *CI*, cardiac index; *SvO_2*, mixed venous oxygen saturation.

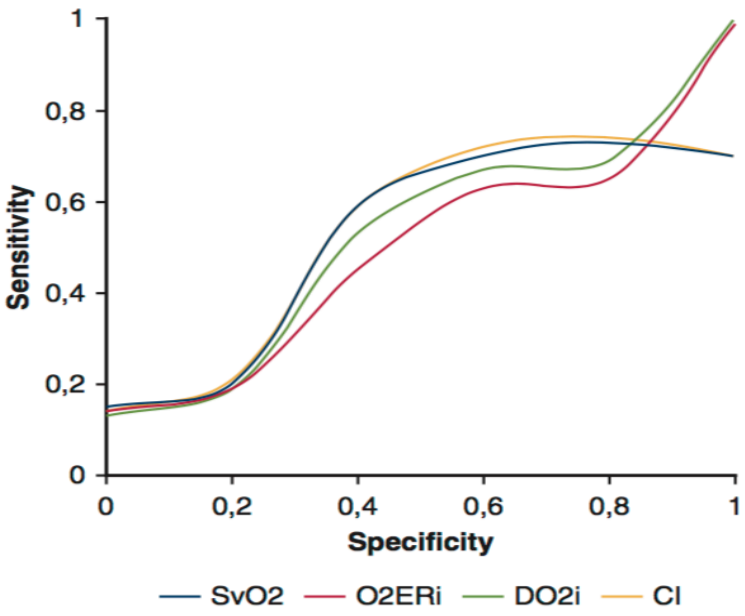

Figure 1. Receiver operating characteristic curves for lactate peak prediction based on target indexed oxygen delivery (DO2i), indexed oxygen extraction ratio (O2ERi), cardiac index (CI), and mixed venous oxygen saturation (SvO2).

TABLE 3. Univariate analysis (correlation matrix)

Factor	Correlation coefficient	*P* value
Age (y)	−0.079	.029
Isolated coronary operation	−0.075	.039
Lowest temperature on CPB	−0.219	.001
Lowest hematocrit on CPB	−0.149	.001
CPB duration	0.049	.001
Lowest pump flow	−0.239	.001
CPB lowest DO_{2i}	−0.254	.001
CPB peak blood glucose	0.497	.001

CPB, Cardiopulmonary bypass; *DO_{2i}*, indexed oxygen delivery.

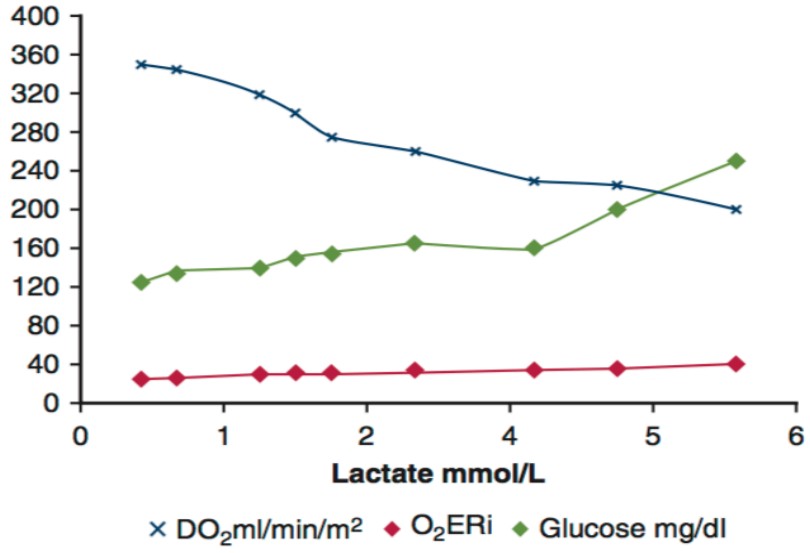

Figure 2. Lactate and glucose trend according to the distribution of target indexed oxygen delivery (DO2i) level and indexed oxygen extraction ratio (O2ERi) during cardiopulmonary bypass.

TABLE 4. Subgroup analysis for peak blood lactate and lowest indexed oxygen delivery (DO_{2i}) in relation to indexed oxygen extraction ratio (O_2ER_i) on cardiopulmonary bypass for group A (n = 250)

Variable	No HL or HG	HL alone	HG alone	HL and HG
No. of patients	223	4	12	11
Peak blood lactate (mmol/L)	1.28 ± 0.45	3.68 ± 0.35	1.82 ± 0.65	4.91 ± 3.21
Lowest DO_{2i} (mL/min/m^2)	304 ± 21	287 ± 13	289 ± 21	195 ± 40
Highest O_2ER_i (%)	20 ± 3	25 ± 2	25 ± 3	38 ± 4

Values are presented as mean ± standard deviation. *HL*, Hyperlactatemia; *HG*, hyperglycemia; *DO_{2i}*, indexed oxygen delivery; *O_2ER_i*, indexed oxygen extraction ratio.

TABLE 5. Subgroup analysis for peak blood lactate and lowest cardiac index (CI) in relation to mixed venous oxygen saturation (SvO_2) on cardiopulmonary bypass for group B (n = 250)

Variable	No HL or HG	HL alone	HG alone	HL and HG
No. of patients	187	10	21	32
Peak blood lactate (mmol/L)	1.39 ± 0.69	3.48 ± 0.38	1.79 ± 0.55	5.31 ± 3.83
Lowest CI (L/min/m^2)	2.4 ± 0.2	2.4 ± 0.1	2.4 ± 0.1	1.8 ± 0.4
Lowest SvO_2 (%)	80 ± 3	73 ± 1	72 ± 1	55 ± 12

Values are presented as mean ± standard deviation. *HL*, Hyperlactatemia; *HG*, hyperglycemia; *CI*, cardiac index; *SvO_2*, mixed venous oxygen saturation.

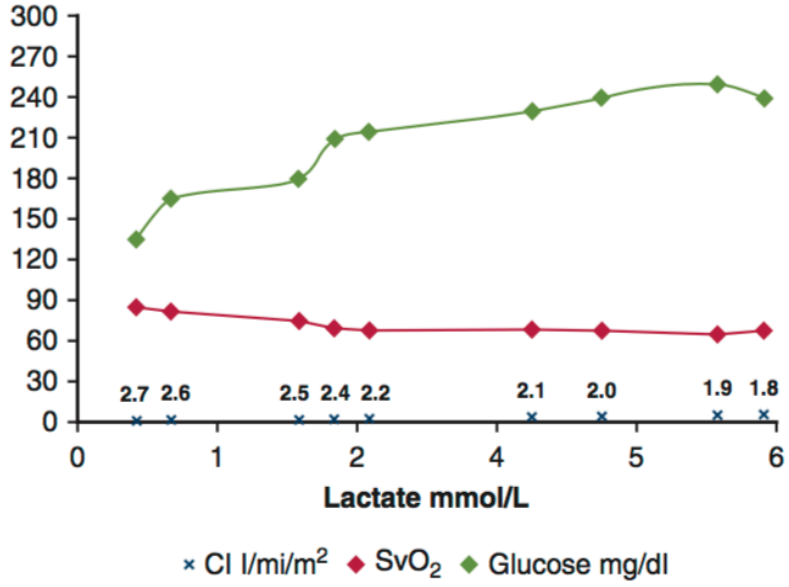

Figure 3. Lactate and glucose trend according to the distribution of cardiac index (CI) level and mixed venous oxygen saturation (SvO2) during cardiopulmonary bypass.

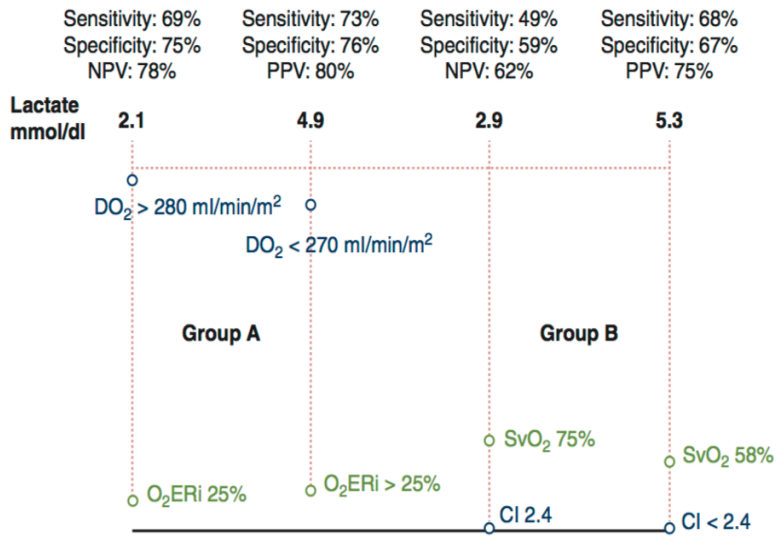

Figure 4. Negative predictive value (NPV) and positive predictive value (PPV) of hyperlactatemia.

TABLE 6. Receiver operating characteristic analysis for the 5 intraoperative positive predictive value (PPV) of hyperlactatemia

Factor	AUC	95% confidence interval	*P* value	Cutoff value	Sensitivity, %	Specificity, %	PPV, %
Lowest DO_{2i} on CPB	0.71	0.58-0.81	.001	180 mL/min/m^2	73	74	75
High O_2ER_i on CPB	0.77	0.73-0.85	.001	40%	73	76	78
Peak blood glucose on CPB	0.92	0.82-0.97	.001	160 mg/dL	81	80	85
Low CI on CPB	0.67	0.62-0.80	.009	1.8 L/min/m^2	65	69	74
Low SvO_2 on CPB	0.65	0.60-0.78	.007	55%	68	67	77

AUC, Area under the curve; *PPV*, positive predictive value; DO_{2i}, indexed oxygen delivery; *CPB*, cardiopulmonary bypass; O_2ER_i, indexed oxygen extraction ratio; *CI*, cardiac index; SvO_2, mixed venous oxygen saturation.

TABLE 7. Receiver operating characteristic analysis for the 5 intraoperative negative predictive value (NPV) of hyperlactatemia

Factor	AUC	95% confidence interval	*P* value	Cutoff value	Sensitivity, %	Specificity, %	NPV, %
High DO_{2i} on CPB	0.75	0.70-0.83	.001	299 mL/min/m^2	73	74	77
Low O_2ER_i on CPB	0.79	0.73-0.85	.001	24%	73	76	79
Low blood glucose on CPB	0.89	0.82-0.93	.001	128 mg/dL	79	80	74
High CI on CPB	0.68	0.65-0.79	.039	2.4 L/min/m^2	64	69	63
High SvO_2 on CPB	0.63	0.60-0.78	.035	85%	62	67	62

AUC, Area under the curve; *NPV*, negative predictive value; DO_{2i}, indexed oxygen delivery; *CPB*, cardiopulmonary bypass; O_2ER_i, indexed oxygen extraction ratio; *CI*, cardiac index; SvO_2, mixed venous oxygen saturation.

Discussion

In this analysis we tried to analyze the correlation of lactatesand glycemia with the target managed in relation to the oxygen consumption variables, in a different way than in theprevious studies, strengthening their conclusions (1,3,9,10). Our analysis demonstrates that the management of DO_{2i} in relation to O_2ERi was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. The group managed with DO_2 and O_2ERi reported a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and ICU stay, compared with group managed with CI and SvO2. The link between HL and hyperglycemia through the mechanism explained above was confirmed by Revelly and colleagues (16) in an elegant study dealing with cardiogenic or septic shock. The role of adrenergic agonists in this setting is well defined: in cardiogenic shock, they are both endogenous or administered for cardiovascular therapy; in our model, they are endogenous in the majority of patients. None received epinephrine during CPB, and few received norepinephrine; however, unlike epinephrine, norepinephrine usually does not increase glucose productionor induce an increase in plasma lactate concentration (6,17). The 2 mechanisms leading to HL in various clinical conditions are therefore anaerobic metabolism due to a poor DO2 and excess lactate production due to glucose failing to enter the oxidative pathway and being degraded to lactate by the glycolytic pathway (17). These mechanisms, if independently considered, lead to different acid–base balance conditions, the former being accompanied
by metabolic acidosis and the latter not necessarily so. However, in the clinical conditions of this observational study, the acid-base balance is constantly maintained at a normal pH value by bicarbonate corrections applied by the perfusionist whenever the base excess starts decreasing. Therefore, we are unable to identify differences in HL related to different values of peak blood lactate. However, the evidence that only 4 patients demonstrated HL without hyperglycemia and that only patients with an HL hyperglycemia syndrome had a significantly lower value of DO_2 seems to confirm that, in our specific clinical environment, HL and hyperglycemia are linked by the causative factor of a poor DO_2, leading on 1 hand to lactate production through the anaerobic

pathway and on the other hand to a vicious cycle of lactate production due to poor ability to use glucose through the aerobic pathway (2,5,10). Reduced oxygen content in cases of acute anemia is usually compensated by reduced blood viscosity with increased blood flow in the microcirculation and by a compensatory increase in cardiac output (12). This last mechanism may be impaired during CPB, where pump flow is usually adjusted on the basis of the patient's body surface area and temperature, not the Hb value. On the basis of our data, the main rationale for explaining HL during CPB is a DO_2 inadequate to guarantee the needed oxygen consumption of the patient.

In the present study, we investigated the role of potentially modifiable factors related to CPB surgery in determining postoperative HL and hyperglycemia. Our results demonstrate, in a relatively large series of patients treated at different sites, that a DO_{2i} <270 mL/min/m^2 with O_2ER_i >35% and low CI (<2.4 L/min/m^2) with SvO_2 <65% during CPB are associated with HL and hyperglycemia and DO_{2i} >290 mL/min/m^2 with O_2ER_i <25% and CI >2.4 L/min/m^2 with SvO_2 >75% during CPB are associated with a low incidence of HL and hyperglycemia (11). Various preoperative factors or comorbidities may create the right environment for HL during CPB. Age, female sex, congestive heart failure, low left ventricular ejection fraction, hypertension, atherosclerosis, diabetes, preoperative Hb value, redo or complex surgery, and emergency procedures were found to be risk factors for HL by Demers and colleagues, who reported an HL incidence of 18%. Some of these factors were confirmed in our study, and other new factors were identified; however, our study population had a significantly shorter CPB duration and a lower degree of hemodilution during CPB. Given that both these factors seem to favor the onset of HL, the lower HL rate in our population is reasonably explained. The role of CPB duration in the determination of HL during CPB has been highlighted by other authors (1). Some study limitations should be acknowledged. First, the design of this analysis compares 2 different extracorporeal circulation management methods. In relation to the available literature, the values taken of 75% for SvO_2 and 25% for O_2ER_i are not directly comparable because the roller pump used in group B does not correlate the calculated heart rate with the measured heart rate. Second, several patients had peripheral cannulation for CPB, which does not allow us to make a comparison between

peripheral versus central cannulation. Moreover, during conventional management; we believed it appropriate not to use hypothermia because the calculated data that we were monitoring corresponded to the set objectives of 2.4 L/min flow; this non-modification of management is intrinsically part of the retrospective nature of the study. Finally, the study focused on CPB with the use of a roller pump and does not consider the centrifuge, but it is also necessary to consider that, with its limitations, the roller pump is predominant in the daily use of cardiac surgery centers (18). The pump flow is delivered with a roller pump, often the flow management is calculated and not measured with an ultrasonic flowmeter (19), this often involves an overestimation (eg, due to occlusion of the rotor, technique with which the occlusion is made, vacuum-assisted venous drainage use, hypothermia, viscosity, positioning of the cannula, or material of the pump). Our center used a roller pump with a half silicone tube, and an occlusion of 1 cm^2/min on a three-eighths meter high column. For reasons described above, a 0.3 ± 0.2 index discrepancy occurred with ultrasound monitoring that allowed us to evaluate lower cardiac indexes that we could not have evaluated without this gap.

Conclusions

This retrospective observational study showed that management of DO_{2i} in relation to $O_2ER_i$was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. Group A patients showed a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time, and ICU stay, compared with group B patients.

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Chapter 4

Goal-directed extracorporeal circulation: transferring the knowledge and experience from daily cardiac surgery to extracorporeal membrane oxygenation

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Abstract

Metabolism management plays an essential role in extracorporeal technologies. There are different metabolic management devices integrated to extracorporeal devices; the most commonly used and accepted metabolic target in adult patients is indexed oxygen delivery (280 mL/min/m2) and cardiac index (2.4 L/min/m2), which can be managed independently or according to other metabolic parameters. Extracorporeal membrane oxygenation (ECMO) is a temporary form of life support providing a prolonged biventricular circulatory and pulmonary support for patients experiencing both pulmonary and cardiac failure unresponsive to conventional therapy. The goal-directed perfusion initiative during cardiopulmonary bypass (CPB) reduced the incidence of acute kidney injury after cardiac surgery. On the basis of the available literature, the identified goals to achieve during CPB include maintenance of oxygen delivery > 300 mL O2/min/m2 and reduction in vasopressor use. ECMO and CPB are conceptually similar but differ in many aspects and finality; in particular, they differ in the scientific evidence for metabolic management nadirs. As for CPB, predictive target parameters have been found and consolidated, particularly in terms of acute renal injury and the prevention of anaerobic metabolism, while for ECMO management, a blurred path remains. In this context, we review the strategies for optimal goal-directed therapy during CPB and ECMO, trying to transfer the knowledge and experience from daily cardiac surgery to veno-arterial ECMO.

Introduction

Goal-directed therapy (GDT) is a patient care strategy that has been implemented to improve patient outcomes. This strategy, which includes aggressive patient management and monitoring during a period of critical care, has been adapted to perfusion and has been designated goal-directed perfusion (GDP). Since this is a new concept in perfusion, the purpose of this study is to review GDT research in other areas of critical care management and compare that process to improving patient outcomes following cardiopulmonary bypass (CPB). Various areas of the GDT literature were reviewed, including fluid administration, neurologic injury, tissue perfusion, oxygenation, and inflammatory response. Data from these studies were compiled to document improvements in patient outcomes. GDT has been demonstrated to improve patient outcomes when performed within the optimal time frame, resulting in lower complication rates, shorter hospital stay, and a decrease in morbidity (1). Based on the success in other critical care areas, GDP during CPB would be expected to improve outcomes following cardiac surgery. Metabolism management plays an essential role in extracorporeal technologies. There are different metabolic management devices integrated to extracorporeal devices, which can be managed independently or according to other metabolic parameters (2). Extracorporeal membrane oxygenation (ECMO) is a temporary form of life support providing a prolonged biventricular circulatory and pulmonary support for patients experiencing both pulmonary and cardiac failure, unresponsive to conventional therapy (3,4). The GDP initiative during CPB reduced the incidence of acute kidney injury (AKI) after cardiac surgery. On the basis of the available literature, the identified goals to achieve during CPB include maintenance of oxygen delivery (DO2) > 280mL/min/m2 and reduction in vasopressor use (5). ECMO and CPB are conceptually similar but differ in many aspects and finality; in particular, they differ in the scientific evidence for metabolic management nadirs. As for CPB, predictive target parameters have been found and consolidated, particularly in terms of AKI and the prevention of anaerobic metabolism, while for ECMO management, a blurred path remains (3). In this context, we focus on one element of GDT, that is, GDP, and review the strategies for optimal

GDP during CPB and ECMO, trying to transfer the knowledge and experience from daily cardiac surgery to veno-arterial (VA) ECMO.

Literature search

PubMed was used to search for publications on GDP. The initial search term was 'goal-directed perfusion CPB' which yielded 14 articles (6,18). No articles regarding GDP following ECMO or minimally invasive extracorporeal circulation were included, but only those conducted using a conventional CPB strategy were retrieved. The characteristics of these papers are described
in **Table 1**.

Goal-directed perfusion

GDP has been practiced for nearly 30 years, but it still remains to be determined if there is a significant role for GDP in whole body perfusion, especially in renal protection strategies. The role of the perfusionist in providing cardiopulmonary support has been historically outlined in broad terms but is continually being redefined as evidence-based patient care is updated (1). AKI is a serious complication of cardiac surgery, affecting a considerable

proportion of patients and increasing postoperative morbidity and mortality. Various factors, including age, preoperative renal function, haemodynamic state, and duration and complexity of surgery, have been associated with postoperative AKI. Studies of AKI following coronary artery bypass graft surgery using the Acute Kidney Injury Network (AKIN) classification have shown that small increases in the serum creatinine level (AKIN class1) increase the risk of end-stage renal disease by 3-fold (relative risk [RR], 2.92; 95% confidence interval [CI],1.87–4.55) and that of mortality by nearly 1.5-fold (RR,1.34; 95% CI, 1.23–1.45). An association between the nadir haematocrit value during CPB and postoperative AKI was first reported in 1994 (19). Numerous retrospective studies subsequently confirmed this finding, and some authors have hypothesized that insufficient DO_2 may be the mechanism underlying the link between severe haemodilution on CPB and poor renal outcomes. Subsequent retrospective studies have confirmed the association between nadir DO2 on CPB and postoperative AKI, with the identification of a 'critical DO_2 in the range of 260–272 mL/min/m^2 for patients undergoing moderately hypothermic (> 32°C) CPB. Based on these observations, the concept of GDP, aimed at maintaining DO_2 on CPB above the critical value, was introduced. The current guidelines of the American Society of Extracorporeal Technology include measurement of DO_2 within the standard measurements for assessing arterial pump flow rate. Historically, the primary strategy for meeting oxygen and metabolic requirements during adult CPB was based on CI, typically in the range of 1.8–2.4 L/min/m^2. However, the concept that arterial pump flow should be adjusted based on DO_2 rather than simply on body surface area and temperature is still based on retrospective studies on large patient populations. To date, high-level evidence demonstrating that a GDP strategy intended to avoid a nadir

DO_2 below the critical value will reduce the rate of postoperative AKI is lacking. The Goal-Directed Perfusion Trial (GIFT) by Ranucci et al. reported that the GDP approach to avoid a DO_2 nadir < 280 mL/min/m^2 will reduce the rate of postoperative AKI in patients undergoing moderately hypothermic CPB, already detectable at stage 1 of renal insufficiency (**Figure 1**) (5). In contrast, a study evaluating the association between lactic acid and CPB by Condello et al. (2) reported that patients with hyperlactatemia (HL) during CPB had a significant increase in serum creatinine value, higher rate of prolonged mechanical ventilation time and intensive care unit stay (2). A cutoff of DO2i < 270 mL/min/m^2 in relation to indexed

Table 1. Retrieved articles after PubMed search for 'goal-directed perfusion CPB'.

	Type of study	No. Of patients	Strategy	Take-home message
Ranucci et al.[5]	Multicenter randomized trial	350	GDP during conventional CPB	GDP strategy is effective in reducing acute kidney injury
Zhang et al.[6]	Single-centre randomized trial	166 (paediatric)	GDP during conventional CPB	Ongoing
Stammers et al.[7]	Single-centre randomized trial	60	GDP during conventional CPB	Using GDP with 3 different oxygenators; there is no difference between the different generations of oxy-devices
Magruder et al.[8]	Retrospective propensity matching	176	GDP during conventional CPB	GDP strategy is effective in reducing acute kidney injury
Rubino et al.[9]	Retrospective propensity matching	210	GDP during conventional CPB	GDP associated with sutureless bioprosthesis results in better perfusion quality and clinical outcome
Overdevest et al.[10]	Retrospective	91	GDP during conventional CPB	CO2 production during CPB depends on many variables
de Somer et al.[11]	Retrospective	359	GDP during conventional CPB	GDP strategy is effective in reducing acute kidney injury
de Somer et al.[12]	Review	n/a	n/a	n/a
Bousnina et al.[13]	Retrospective	50	GDP during conventional CPB	GDP strategy confers outcome advantages
Anastasiadis et al.[14]	Retrospective	120	GDP during conventional CPB	GDP strategy allows more physiologic cardiac surgery
Machovec et al.[15]	Retrospective	50 (paediatric)	GDP during MiECC CPB	GDP strategy reduces the need for transfusions
Ranucci et al.[16]	Retrospective	16,790	GDP during conventional CPB	GDP strategy is effective in reducing acute kidney injury
Rubino et al.[17]	Retrospective	187	GDP during conventional CPB	QualyP score can help better perfusion within a GDP strategy
Magruder et al.[18]	Single-centre prospective observational	116 (paediatric)	GDP during conventional CPB	—

Abbreviations: CPB: cardiopulmonary bypass; GDP: goal-directed perfusion.

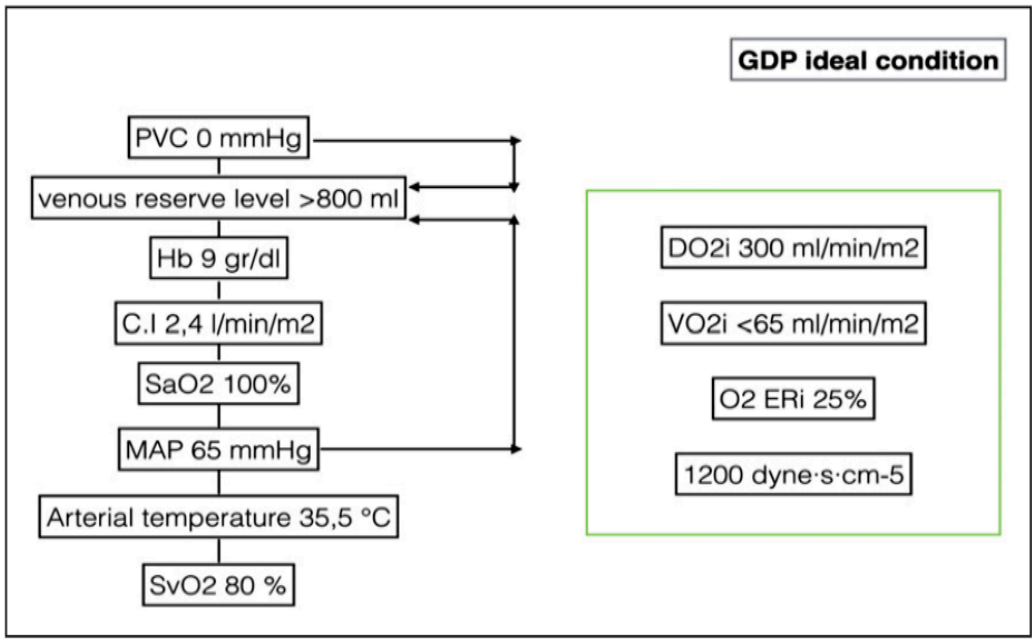

Figure 1. Ideal condition of goal-directed perfusion (GDP) during cardiopulmonary bypass (CPB).

oxygen extraction ratio (O_2ERi) > 35%in group A and a cutoff of CI < 2.4 L/min/m^2 in relation to mixed venous oxygen saturation (SvO2) < 65% in group B were found to have a positive predictive value of 80% and 75% for HL, respectively. A cutoff of DO2i > 290 mL/min/m^2 in

relation to O2ERi 24% in group A and a cutoff of CI > 2.4 L/min/m^2 in relation to SvO_2 > 75% in group B were found to have a negative predictive value of 78% and 62% for HL, respectively. These authors concluded that DO_{2i} in relation to O_2ERi was 16% more specific in terms of negative predictive value for HL during CPB compared with the use of CI in relation to SvO_2. Group A reported a significant reduction in the incidence of intraoperative lactate peak, correlated with postoperative reduction of serum creatinine value, mechanical ventilation time and intensive care unit stay, compared with group B (2).

Goal-directed perfusion during minimally invasive extracorporeal circulation and conventional cardiopulmonary bypass

The factors related to the process of CPB that contribute most significantly to 'optimal perfusion' remain an important topic of debate. Randomized data on best practice in managing hemodilution, perfusion pressure, hematocrit and pump flow are extremely limited, but in an extensive review of the literature (20,21), Bennett et al. conclude that DO_2 remains 'one of the most important determinants of optimal perfusion'. Organ dysfunction after cardiac surgery has been linked to a decrease in DO_2 during CPB (22,23). Conventional CPB requires an initial crystalloid prime of 1500–2000 mL, resulting in dilutional anemia at the onset of bypass. Autologous priming of the circuit after cannulation reduces the prime, but is incomplete, and hemodilution still occurs. Acute hemodilution during cardiac surgery is associated with an increased risk of renal failure (24,25), stroke (26) and mortality (27). A recent development, minimally invasive extracorporeal circulation, has appeared to offer theoretical advantages. These include the absence of a venous reservoir, considerably lowering the priming volume to 200–500 mL after the circuit is retrogradely primed, resulting in minimal hemodilution. This should increase DO_2 during bypass (28,30). In this respect, Anastasiadis and colleagues (14) suggested a strategy based on continuous monitoring of CI, SvO_2, DO_{2i},DO_{2i}/VCO_{2i} and regional oxygen saturation followed by action when needed. They could establish an optimal perfusion perioperatively or in other words, a 'more physiologic' cardiac surgery.

Goal-directed therapy and perfusion during ECMO

DO_2 is the amount of oxygen delivered to the peripheral tissues per minute or the product of arterial oxygen content times the cardiac output. Oxygen is present in the blood as oxygen dissolved in the plasma and bound to hemoglobin present in red blood cells. The mathematical formulas to calculate DO_2 in a patient on ECMO are the following.DO_2 (mL/min) = cardiac output (L/min) x arterial CO_2 (mL/dL) x 10 arterial O_2 content (mL/dL) =hemoglobin-bound O2 + dissolved O2 = (hemoglobin [g/dL] x saturation [%] x 1.36 mL/g) + (pO_2 [mmHg] x 0.0031 mL/mmHg/dL)DO_2 during VA-ECMO = native cardiac output x arterial O_2 content + ECMO flow x arterial O_2 content (2). If we take a closer look at the formula, DO_2 is controlled by cardiac output, hemoglobin concentration, hemoglobin saturation and dissolved oxygen, in that order. Therefore, if DO_2 is insufficient, it is necessary to calibrate it in the above order to efficiently increase DO_2.Oxygen consumption (VO_2) is controlled by tissue metabolism. The normal DO2:VO_2 ratio is 4:1. SvO_2 results from this ratio. If systemic DO_2 is moderately decreased, and there is no change in VO_2; the amount of oxygen extracted from each decilitre of arterial blood is greater. This results in decreased SvO_2. If DO_2 is severely decreased, there is insufficient oxygen to meet metabolic demands; anaerobic metabolism occurs, and finally, lactic acidosis and shock occur. In practice, this situation occurs when the DO_2:VO_2 ratio is less than 2:1. Therefore, the overall goal of management is to keep DO_2 at least twice the VO_2 and preferably 5 times the VO_2. Since SvO_2 reflects this ratio accurately, it is one of the most important considerations when monitoring and managing critically ill patients. ECMO is indicated when other treatment modalities cannot sustain the DO_2:VO_2 ratio. If the DO_2:VO_2 ratio decreases due to decreased DO_2 in cardiogenic shock, ECMO can increase systemic blood flow to replace the reduced cardiac output. Cardiogenic and obstructive shock reduces not only cardiac output but also oxygen content in the blood due to ventilation-perfusion mismatch. ECMO can correct both the decreased cardiac output and arterial oxygen content. In septic shock, the DO_2:VO_2 ratio decreases due to the increase in VO_2. Moreover, if septic shock is combined with decreased cardiac contractility, DO_2 is decreased, further reducing the DO_2:VO_2 ratio; hence, ECMO may be considered. To summarize, VA-ECMO can be an option for the treatment of various types of shock because it can increase oxygen content and

systemic blood flow and eventually increase DO_2. Hence, the goal of VA-ECMO is to restore organ blood flow and adequate tissue oxygenation while awaiting recovery, without damaging the lungs or circulation (**Figure 2**) (30).

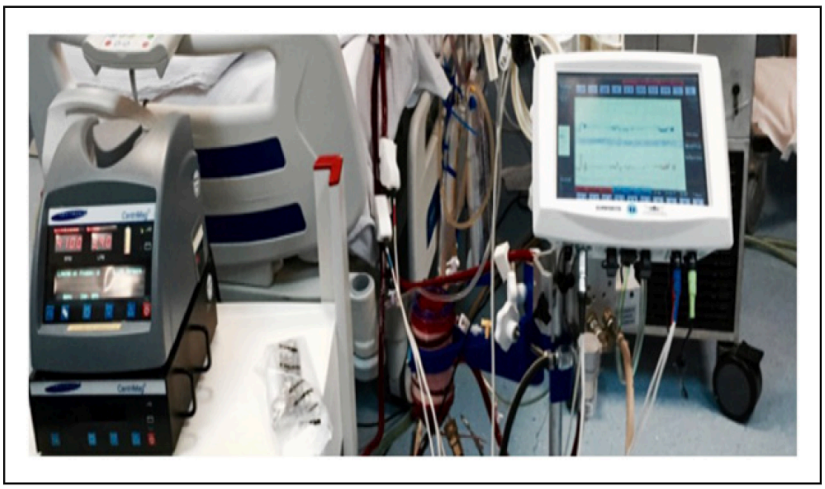

Figure 2. Goal-directed perfusion (GDP) monitoring during veno-arterial (VA) extracorporeal membrane oxygenation(ECMO).

Conclusion

In the literature, no target parameters were found for GDP; only target parameters for GDT during ECMO in the article by Su et al. (31) for AKI and HL prevention and organ protection were found. We think in a future perspective that data collection, particularly during VAECMO, for the parameters inherent to GDP and the creation of dedicated monitoring tools for ECMO GDP can allow to study and identify target parameters, which could be integrated into haemodynamic monitoring, that are extremely limited for end-organ protection and AKI and HL prevention.

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Chapter 5

Perioperative incidence of ECMO and IABP on 5901 mitral valve surgery procedures

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Abstract

Background: Report the incidence and results of peri-operative extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) of patients undergoing mitral valve surgery (MVS) through right mini-thoracotomy (RT) and conventional full sternotomy (FS) for a period of 6 years from eleven tertiary Cardiac Surgery Institutes of GVM Care & Research Italia.

Methods: From January 2016 to November 2021, a total of 5901 consecutive patients underwent MVS through RT and FS. The primary outcome of the study was the mortality and incidence of low cardiac output syndrome (LCOS) treated with intra-aortic balloon pump (IABP) with or without inotropic support and the incidence of Postcardiotomy Cardiogenic Shock (PCS) treated with Veno-arterial (VA) Extracorporeal Membrane Oxygenation (ECMO) on patients undergoing mitral valve surgery (MVS) through right mini-thoracotomy (RT) versus conventional full sternotomy (FS).

Results: The mean age was 66 +/- 15 years, 3389 patients underwent in RT approach 2512 in FS, 3081 (52%) patients were male and 2.3% had previous cardiac operations. Cardiopulmonary bypass time was 93 min for RT and 81 min for FS and cross clamp time 75 min for RT and 63 min for FS for mitral valve repair. Incidence of perioperative IABP for the treatment of low cardiac output was reported on 99 patients (1.6%), 51 for RT (1.5%), 35% used inotropic support (adrenaline and milrinone) and 48 in FS (1.9), 28% use inotropic support, 21 patients died after IABP (3 RT and 18 FS).Incidence of perioperative VA-ECMO for the PCS treatment was 13 and 4 with IABP, 9 RT (0.2%) and 4 FS approach (0.15%), 12 patients died after VA-ECMO.

Conclusion: Minimally invasive mitral valve surgery is a safe and reproducible approach associated with low mortality and morbidity. ECMO and IABP incidence for the treatment of PCS was 0.2% and for Low cardiac output syndrome (LCOS) was 1.6% in elective mitral valve surgery is very low. The patients that use the perioperative IABP in minimally invasive mitral valve surgery (MIMVS) trough RT reported a reduced mortality compared to FS in relation to the operative risk and surgical technique. Low incidence of VA-ECMO was found in RT and

FS approach, only one patient survived after VA-ECMO after minimally invasive mitral valve surgery.

Background

Mitral valve surgery using conventional full sternotomy (FS) is the conventional approach for the treatment of the mitral valve disease. Despite this procedure has shown excellent postoperative outcomes, in the last two decades minimally invasive mitral valve surgery (MIMVS) has gained consensus among surgeons as it has provided greater patients satisfaction, maintaining the same quality and safety of the standard mitral valve surgery approach (1,2). Intra-aortic balloon pump (IABP) is the most usable tool of temporary mechanical circulatory support for cardiac surgical patients suffered from low cardiac output in the early postoperative phase. Its beneficial action is attributed to a concomitant reduction in afterload of left ventricle with a substantial increase on coronary perfusion pressure due to an increase of aortic diastolic pressure. The main indication of IABP use in cardiac surgical patients is peri and post-operatively in the treatment of a low cardiac output state refractory to the usual inotropic support. In literature the 30-day mortality for the patients necessitating IABP is high because of the cardiac problems that led to the need for this pump, ranged from 26 to 50% (3). Cardiogenic shock, cardiac arrest, acute respiratory failure, or a combination of such events, are all potential complications after cardiac surgery which lead to high mortality (4). Use of extracorporeal temporary cardio-circulatory and respiratory support for progressive clinical deterioration can facilitate bridging the patient to recovery or to more durable support. Over the last decade, extracorporeal membrane oxygenation (ECMO) has emerged as the preferred temporary artificial support system in such circumstances (5). Aim of this study was to analyze the incidence and results of perioperative extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) of patients undergoing mitral valve surgery (MVS) through right minithoracotomy (RT) and conventional full sternotomy (FS) for a period of 6 years of eleven Cardiac Surgery Institutes of GVM Care & Research Italia.

Methods

Patient and data collection

A retrospective, observational study was undertaken of prospectively collected data in 5901 consecutive patients undergoing mitral valve surgery, of which 3389 underwent MIMVS through RT between January 2016 to November 2021 for a period of 6 years from 11 Cardiac Surgery Institutes of GVM Care & Research Italia. Two five hundred twelve procedures were performed in sternotomy. The main reason for performing a sternotomy approach was the selection patient for the learning curve, and in case of very poor left ventricular ejection fraction, strong pleural adhesions, severe chronic obstructive pulmonary disease and active endocarditis with abscess involving the mitro-aortic continuity. All patients signed an informed consent form to allow clinical and administrativedata storage and utilization for scientific purposes according to the General Data Protection Regulation. Because of the retrospective nature of this study, the local ethics committees waived the need for patient consent. The primary outcome of the study was the mortality and incidence of low cardiac output treated with intra-aortic balloon pump (IABP) with or without inotropic support and the incidence of Postcardiotomy Cardiogenic Shock (PCS) treated with Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) on patients undergoing mitral valve surgery (MVS) through right mini-thoracotomy (RT) vs conventional full sternotomy (FS). Low cardiac output was defined as the need for postoperative inotropic support for more than 48 h in the intensive care unit and/or from an intra-aortic balloon pump.

Surgical technique

The standardized surgical approach for MIMVS has been reported elsewhere. Briefly, MIMVS by a way of right anterior thoracotomy was performed through a 5–7 cm skin incision placed at 3th or 4th intercostal space. Two trocars are inserted in the thorax to allow positioning of a ventricular vent, CO_2 insufflator, camera device and pericardial stay sutures. Whereas at the beginning of our experience the approach involved retrograde arterial perfusion and balloon endoclamping, the procedure has evolved to a technique with ascending aorta cannulation, long femoral venous cannula drainage, and direct transthoracic aortic clamping. Specifically, direct aortic cannulation was performed using Easyflow (Sorin, Salluggia,Italy) or Straightshot (Edwards Lifesciences, Irvine, Calif)cannulas. Biomedicus single stage (Medtronic, Minneapolis,Minn) or RAP single 2 stage cannulas (Estech) were inserted through the femoral vein into the right atrium and the correct position was achieved with the Seldinger technique under transesophageal echocardiographic guidance. In case of mitral and tricuspid valve surgery, asingle 2 stage cannula (RAP, Estech) was used as it allows to drain simultaneously the superior and inferior venaecavae. After vacuum-assisted cardiopulmonary bypass (− 40 to − 60 mmHg) was established, the patients were cooled to 34 °C. the ascending aorta was clamped with the Cygnet crossclamp (ovare surgical System, Cupertino,Calif) or with the aortic clamp (Cardiomedical GmbH, Langenhagen, Germany; distributed by sorin, Salluggia,Italy) and antegrade cold crystalloid or warm blood cardioplegia is delivered directly into the ascending aorta by a needle vent catheter. For conventional approach on mitral valve surgery was performed in median sternotomy with central cannulation (6). The mitral valve is approached with a traditional left paraseptal atriotomy and exposed using a specially designed atrial retractor held by a mechanical harm inserted through a right parasternal port. Mitral valve procedures were performed under a combination of direct vision and thoracoscopic assistance. All patients received an accurate intraoperative transoesophageal echocardiogram before and after weaning from cardiopulmonary bypass machine. In patients who had an attempt to repair, our policy is to replace the mitral valve if (a) at the hydrostatic saline test after several attempts, there is still some degrees of mitral regurgitation, (b) the surface of coaptation is not enough to guarantee a long durability, (c) at intraoperative echo, there is more than mild mitral

regurgitation. Twelve surgeons contributed to this series, with 2 of them (GS, GN) performing 45.2%of the operations.

IABP indication and management

The indications for initiating treatment with IABP in this patients was the following: (a) IABP support for persistent preoperative ischemia despite maximum medical treatment (b) patients not able to be discontinued from CPB although forced inotropic support, (c) patients in low-cardiac output status just after a "difficult" discontinuation of CPB, supported by high-doses of inotropes,(d) patients with "difficult" discontinuation from CPB and spontaneous appearance of arrhythmia (premature ventricular beats or VT) not amenable in antiarrhythmic continuous infusion and (e) post cardiotomylow cardiac output syndrome. Prophylactic initiation of IABP treatment was not advocated in any of the cases [7 , 8]. A Datascope system (Datascope Corp, Paramus,NJ) was utilised. The IABP was introduced percutaneously through the common femoral artery in 95 patients and through an open access of the femoral artery in the remaining 4 patients [9]. Correct placement of the device was routinely confirmed with Chest X Ray in ICU. Oncemediastinal drainage was minimum (< 50 ml/h), patientswere anticoagulated with Heparin infusion, keeping the
ACT > 180–200 s [10 , 11].

ECMO indication and management

ECMO was initiated intraoperatively in the operating room for circulatory instability during or immediately after weaning from the cardiopulmonary bypass (CPB) in the primary cardiac procedure. The capability to institute ECMO secondarily in the ICU, for delayed PCS or cardiac arrest, was available. The clinical criteria for PCS included the following: left atrial pressure > 15 mmHg; central venous pressure > 12 mmHg; metabolic acidosis (i.e. pH < 7.3 with serum lactate > 3.0 mmol/L);end-organ hypoperfusion (urine output < 30 mL/h); cardiac index < 2.2 L/min/m2 ; and systolic blood pressure < 80 mmHg despite adequate filling volumes, use of multiple adrenergic agents (epinephrine > 0.1 μg/kg/min or dobutamine > 10 μg/kg/min, norepinephrine > 0.1 μg/
kg/min), or an intra-aortic balloon pump (IABP). VAECMO support was initiated via peripheral cannulation through the femoral route with the semi-open method, and an additional 6 Fr catheter was systematically inserted distally into the femoral artery to

prevent leg ischemia [12]. ECMO blood flow was adjusted on based on clinical assessments (e.g. pre-oxygenator venous oxygen saturation, evidence of hypoperfusion, resolution of hyperlactatemia, normalization of mean arterial pressure). Intravenous unfractionated heparin was given to maintain an activated clotting time of 180–210 s, or an activated partial thromboplastin time of 1.5–2 times normal.

ECMO-related complications were carefully monitored. ECMO weaning was performed in patients who fulfilled our published institutional weaning criteria and passed an ECMO weaning trial consisting in decreasing and clamping ECMO flow. In general, the patient should have a pulsatile arterial waveform for at least 24 h; be hemodynamically stable, with baseline mean arterial pressure greater than 60 mmHg with no or lowdoses of catecholamines; should have left ventricular ejection fraction (LVEF) of 35%, and an aortic velocity time integral (VTI) of ≥ 12 cm; and have recovered from major metabolic disturbances [13]. Weaning was considered unsuccessful if ECMO re-cannulation was required within 2 days of decannulation.

Statistical analysis

Continuous data were expressed as mean +/- standard deviation or median with the interquartile range and categorical data as percentages. All statistical analyses were performed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

The mean age was 66 +/- 15 years, 3389 patients underwent in RT approach 2512 in FS, 3081 (52%) patients were male and 2.3 had previous cardiac operations, thepatient characteristics were reported in (**Table 1**). Cardiopulmonary bypass time was, 93 min for RT vs 81 min for FS and cross clamp time, 75 min for RT vs 63 min for FS for mitral valve repair (**Table 2**). The most predominant pathology was degenerative disease, followed by functional mitral valve regurgitation rheumatic disease, endocarditis and prosthetic dysfunction (**Tables 3, 4**). Mitral valve repair was performed in 3207 patients 78% in RT and 2694 had mitral valve replacement 58% in RT. Direct aortic cannulation was achieved in 825 patients. Repair techniques included annuloplasty, leafleat resection, neochordae implantation and sliding plasty (11%). Concomitant procedures included tricuspid valve repair (14.6%), atrial fibrillation ablation (9.5%) and atrial septal defect closure (3.2%). Overall in-hospital mortality was 1.1%. 78 had conversion to sternotomy. Incidence of perioperative IABP for the treatment of LCOS was reported on 99 patients (1.6%), 51 (1.5%) for RT, 35% used inotropic support (adrenaline and milrinone) and 48 in FS (1.9%), 28% use inotropic support, 21 patients died after IABP (3 RT vs 18 FS) (**Tables 5, 6**). Incidence of perioperative VA-ECMO for the PCS treatment was 13 (0.2%) and 4 with IABP, (9 RT vs 4 FS approach), 12 patients died after VA-ECMO (**Table 7**).

	All n=5901	MIMVS n=3389	FS n=2512	P value
Male gender	52.5%	45.9%	39.9%	<0.001
Age (years)	66 (62–76)	65 (62–78)	69 (67–79)	<0.001
Body mass index (kg/m^2)	25.8 (22.2–28.8)	26.8 (23.4–29.0)	24.3 (21.7–28.4)	0.191
Arterial hypertension	36.2%	35.3%	36.1%	0.789
Diabetes mellitus				
Oral antidiabetic drugs	8.9%	7.2%	5.5%	0.006
Insulin	2.3%	2.8%	2.6%	0.530
Hypercholesterolaemia	41.2%	42.1%	44.3%	0.009
Renal dysfuntion	1.4%	2.3%	2.1%	0.254
Respiratory or lung disease	2.1%	2.3%	1.9%	0.187
Previous disabling stroke	1.5%	1.5%	1.3%	0.687
History of cancer	1.4%	1.9%	2.5%	0.030
Atrial fibrillation	9.4%	8.3%	11.2%	<0.001
Peripheral vascular disease	4.8%	4.3%	4.9%	0.556
Coronary artery disease	9.3%	10.2%	8.4%	<0.001
Left ventricular ejection fraction				0.347
LVEF > 50%	93.3%	92.4%	91.4%	
LVEF 30–50%	6.0%	7.1%	7.3%	
LVEF < 30%	0.7%	0.5%	1.3%	
Previous surgery	2.3%	1.7%	1.9%	0.211
EuroSCORE II (%)	1.2 (1.1–2.8)	1.4(1.1–2.7)	1.9 (1.3–3.1)	0.387
Urgent procedure	2.6%	2.8%	3.1%	0.338

Table 1. Characteristics of patients for MIMVS and FS. Median (interquartile range) or percentage. Renal dysfunction: dialysis or creatinine > 2 mg/dl LVEF, left ventricular ejection fraction; MIMVS, minimally invasive mitral valve surgery; FS, full sternotomy.

Surgical approach	RT n=491	FS n=513
Valve replacement n. tot = 1004		
Cardiopulmonary bypass time (min)	82 (79–98)	84 (80–99)
Cross-clamp time (min)	59 (43–69)	62 (45–71)
	n=2898	n=1999
Valve repair n. tot = 4897		
Cardiopulmonary bypass time (min)	93 (62–99)	81 (54–89)
Cross-clamp time (min)	75 (37–76)	63 (36–73)

Table 2. Intraoperative data for surgical techniques and procedures. RT, right thoracotomy; FS, full sternotomy.

Mitral valve pathology	Right-thoracotomy	Repair	Replacement
	N=3389	*N*=2898	*N*=491
Degenerative	2739 (80.8%)	2540 (87.6%)	199 (40.5%)
Functional	328 (9.6%)	231 (7.9%)	97 (19.7%)
Reumathic	247 (7.2%)	97 (3.3%)	150 (30.5%)
Endocarditis	28 (0.8%)	3 (1.0%)	25 (5.0%)
Prosthesis dysfunction	19 (0.5%)	1 (0.03%)	18 (3.6%)
Miscellaneous	28 (0.9%)	26 (0.9%)	2 (0.4%)

Table 3. Mitral valve pathology for minimally invasive mitral valve surgery.

Mitral valve pathology	Full Sternotomy	Repair	Replacement
	N=2512	*N*=1999	*N*=513
Degenerative	1781 (70.8%)	1639 (81.9%)	142 (27.6%)
Functional	367 (14.6%)	179 (8.9%)	188 (36.6%)
Reumathic	289 (11.5%)	143 (6.6%)	146 (28.4%)
Endocarditis	29 (1.15%)	7 (0.3%)	22 (4.2%)
Prosthesis dysfunction	17 (0.67%)	10 (0.5%)	7 (1.36%)
Miscellaneous	29 (1.15%)	21 (1.0%)	8 (1.5%)

Table 4. Mitral valve pathology for full sternotomy mitral valve surgery.

IABP	FS *N*=48	Repair *N*=26	Replacement *N*=22	Inotropic support 28%	Death 30 days 18
Degenerative		15	1		
Functional			11		4 Repair and 5 Replacement
Reumathic			4		1 Replacement
Endocarditis		5	3		3 Repair
Prosthesis dysfunction		6	3		2 Replacement and 3 Repair
Miscellaneous					

Table 5. Perioperative incidence of IABP for Mitral valve pathology in Full Sternotomy (FS). IABP, intra-aortic balloon pump; FS: full sternotomy.

IABP	RT *N*=51	Repair *N*=22	Replacement *N*=29	Inotropic support 35%	Death 30 days 3
Degenerative					
Functional		13	18		
Reumathic			1		1 Replacement
Endocarditis		4	1		
Prosthesis dysfunction		5	9		2 Replacement
Miscellaneous					

Table 6. Perioperative incidence of IABP for mitral valve pathology in MIMVS. IABP, intra-aortic balloon pump; MIMVS, minimally invasive mitral valve surgery; RT, right thoracotomy.

	VA-ECMO	IABP	Inotropic support	Survival
FS	4	1		
RT	9	3		1
Tot	13	4	53%	

Table 7. Perioperative incidence and mortality of ECMO in FS and RT approach. IABP, intra-aortic balloon pump; RT, right thoracotomy; FS, full sternotomy VA-ECMO, Veno-arterial extracorporeal membrane oxygenation.

Discussion

Despite this study reports a good result for mitral valve surgery both in FS and MIMVS, the perioperative LCOS the most serious complication and is associated with increased morbidity, short- and long-term mortality, and healthcare resource utilization. The presented analysis represents a pilot of our experience. Due to these preliminary results we are going to prepare a statistical analysis with a comparison between two comparable groups and multivariate. This syndrome is characterized by decreased heart pump function, leading to reduced oxygen delivery (DO^2) and subsequent tissue hypoxia. The most common definition of LCOS also includes decreases in the cardiac index (CI) to < 2.0 L/min/m^2 and a systolic blood pressure of < 90 mmHg,in conjunction with signs of tissue hypoperfusion (cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolemia. The use of inotropic agents or mechanical circulatory support always is required to improve patient hemodynamics. Although studies have reported that the occurrence of LCOS may be related to preoperative cardiac function, intraoperative operations and CPB, there are still no exact indicators to reflect the risk of its occurrence. At present, domestic and foreign studies on the risk factors of LCOS are inconsistent [14]. It is believed that the occurrence of LCOS is caused by multiple factors, including impaired systolic and diastolic function of the heart, changes in cardiac load, and activation of inflammatory transmitters [15]. The patients that use the perioperative IABP in minimally invasive mitral valve surgery (MIMVS) trough RT report a reduced mortality compared to FS in relation to the operative risk and surgical technique, this could be related to the

elimination of sternotomy, which reduces the time of mechanical ventilation and the postoperative recovery time [6]. Postcardiotomy cardiogenic shock (PCS), defined as low cardiac output syndrome with evidence of tissue hypoperfusion and end-organ dysfunction despite adequate preload, affects 0.2% to 6% of patients who undergo cardiothoracic surgery [15]. PCS is a life-threatening complication with mortality rates between 50 and 80% and includes the inability to wean from cardiopulmonary bypass (CPB) in the operating room or deterioration of myocardial function during the first postoperative days. Between 70 and 90% of the patients who cannot be easily separated from CPB because of PCS can be weaned from CPB by support of inotropes, vasopressors, and intra-aortic balloon pumps, and an estimated two thirds of these patients will recover hemodynamically without the need for other mechanical circulatory support. In comparison, PCS refractory to intravascular volume loading, pharmacologic, and intra-aortic balloon pump support occurs postoperatively in 0.5–1.5% of patients and will inexorably lead to death unless more efficient circulatory support is initiated [16]. The main limitation of this study is its retrospective nature; however our database is prospectively compiled. Although we reported the incidence of LOCS and PCS results, echocardiographic data were not available for all patients. No information has been recorded regarding the etiology of perioperative myocardial infarction as well as no information has been reported regarding the cause of late mortality. Nevertheless a well-designed study with appropriate sample size is required to validate this results.

Conclusion

ECMO and IABP incidence for the treatment of PCS was 0.2% and for Low cardiac output syndrome (LCOS) was 1.6% in elective mitral valve surgery is very low in right mini-thoracotomy (RT) and conventional full sternotomy (FS). The patients that use the perioperative IABP in minimally invasive mitral valve surgery (MIMVS) trough RT reported a reduced mortality compared to FS in relation to the operative risk and surgical technique. Only one patient survived after VAECMO after minimally invasive.

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Chapter 6

Long-term ECMO, efficiency and performance of EUROSETS adult A.L.ONE ECMO oxygenator

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Abstract

Background. The management of the oxygenator can be prolonged in the long-term procedures especially during extracorporeal membrane oxygenation (ECMO) for bridge to transplant or bridge to recovery. Long-term use often involves an overrun of the time of use with respect to certification of the oxygenating module of 14 days, for the maintenance of performance and efficiency of the oxygenator. The evaluation of the long-term oxygenator efficiency is complex and depends on the: patient pathology, ECMO configuration, the management of coagulation and anticoagulation,materials selection and circuit components, the structure, design and performance of the oxygenator. In this context we investgated the long-term performance of the A.L.ONE Eurosets ECMO oxygenator in relation to the parameters prodromal to replacement.

Methods. We retrospectively collected eight years data from Anthea Hospital GVM Care & Research, Bari, Italy on the long-term use exceeding 14 days of Eurosets A.L.ONE ECMO Adult oxygenator in Polymetylpentene fiber, for ECMO procedures, including the procedures: Veno Arterial (VA) ECMO post-cardiotomy or not, veno-venous (VV) ECMO. The primary end points were the evaluation of Gas Transfer: oxygen partial pressure (PO2) post oxygenator, Carbon dioxidepartial pressure (PCO2) post oxygenator, the oxygen transfer across the oxygenator membrane V'O2, differential CO2content across oxygenator; Pressure monitoring: oxygenator pressure Drop in relation to Blood flow rate (BFR) (ΔP); Hematologic values: Hemoglobin, Fibrinogen, Platelets, aPTT, D-Dimer, LDH.

Results. Nine VA ECMO patients who used the oxygenator for 18.5 days and two VV ECMO patients who used the oxygenators for 17.2 days on the seventeenth days reported average values PaO2(267 ± 29 mmHg); PaCO2(34 ± 4 mmHg) with gas blender values set to 3.8 ± 0.6 L/min of air and a FiO2 of 78 ± 5%; the transfer across the oxygenator membrane V'O2 was 189 ± 43 (ml/min/m2). The mean peak of partial pressure of carbon dioxide from the gas exhaust of oxygenator (PECO2) was 38 ± 4 mmHg; differential CO2 across the oxygenator "pre-oxygenator PCO2– post-oxygenator PCO2 (18 ± 6 mmHg); the mean blood flow rate (BFR) 4.5 ± 0.6 (L/minute); the pump revolution per minutes mean maximum rate was 4254 ± 345 (RPM); the mean pressure drop (ΔP) was 76 ± 12 mmHg; the mean peak of d-dimers (DDs) was 23.6 ± 0.8 mg / dL; the mean peak of LDH was 230 ± 55 (mg/dl); fibrinogen mean peak 223 ± 40 (mg/dl).

Conclusions. The performance of the Eurosets A.L.ONE ECMO Adult polymethylpentene fiber oxygenator in our experience has proven efficiency in terms of O2uptake and CO2 removal, blood fluid dynamics, metabolic compensation and heat exchange in the long-term treatment. The device was safe without iatrogenic problems over a period of 14 days in the patients undergoing ECMO VA and in all patients undergoing VV ECMO with continuous administration of anticoagulation therapy.

Introduction

With improvements in circuit technology and expanding supportive evidence, extracorporeal membrane oxygenation (ECMO) use has grown rapidly over the past decade. The management of the oxygenator can be prolonged in the long-term procedures especially during extracorporeal membrane oxygenation (ECMO) for bridge to transplant or bridge to recovery. In this study, we present a classification of the short, medium, long term use of the oxygenating module in relation to its certification and validation (1). Long-term use often involves an overrun of the time use respect to certification with only one oxygenating module. The evaluation of the longterm

oxygenator efficiency is complex and depends on the type of: patient pathology, ECMO configuration, the management of coagulation or anticoagulation, materials selection; circuit components and design, the structure, design and performance of the oxygenator (2). In this study we present a retrospective analysis about Eurosets A.L.ONE ECMO Adult Polymethylpentene fiber oxygenator a medical device validated and certified by the manufacturer (Eurosets SPA, Medolla, Italy) for ECMO procedures up to 14 days. In this context we wanted to investigate the long-term performance of the A.L.ONE Eurosets ECMO oxygenator in relation to the parameters prodromal to replacement: Hematologic profiles (Coagulopathy, Hemolysis) (1–3); Pressure monitoring (Blood Flow, Pressure Drop); Gas Transfer (O2 uptake and CO2 removal) (4, 5).

Materials and methods

Extracorporeal membrane oxygenation settings

The ECMO circuit consists exclusively of commercially available components. By default, a Thoratec Centrimag centrifugal magnetic levitation pumps (Abbott) (**Fig. 1**) and ECMOLIFE centrifugal magnetic levitation pumps (Eurosets SPA, Medolla, Italy) (**Fig. 2**) were used, in synergy with Landing system for pressure monitoring (Blood Flow, Pressure Drop); Gas Transfer (O2 uptake and CO2 removal), (Eurosets SPA, Medolla, Italy). As a standard, the Eurosets A.L.ONE ECMO Adult oxygenator was used (**Fig. 3**). The tubing and the oxygenator were treated with phosphorylcholine-coated surface (Eurosets SPA, Medolla, Italy). The system has a priming volume of 500 ml and features connectors for other emergency extracorporeal devices, such as renal replacement devices or rapid infusion systems for advanced in-center intensive care treatment during further courses of therapy. The main determinants of cannula sizing in peripheral VA ECMO are anatomical considerations and the targeted flow rate. Generally, cannulas are chosen to support a flow equivalent to a cardiac index of 2.2–2.5 L/m^2/min, which is considered full flow. Femoral Arterial cannulas that we used were 17–25 Fr and Femoral venous cannulas were usually 19–25 Fr Biomedicus (Medtronic, Minneapolis, USA). For Central VA ECMO Aortic Arterial cannulas were 20–24 Fr EOPA (Medtronic, Minneapolis,USA) and Atrial venous cannulas were 32/40–36/46 Fr (Medtronic, Minneapolis, USA). For Peripheral VV ECMO for Femoral venous cannulas were 19–25 Fr forreinfusion in jugular vein cannulas were 17–21 Fr Biomedicus (Medtronic, Minneapolis, USA) (**Fig. 4**).

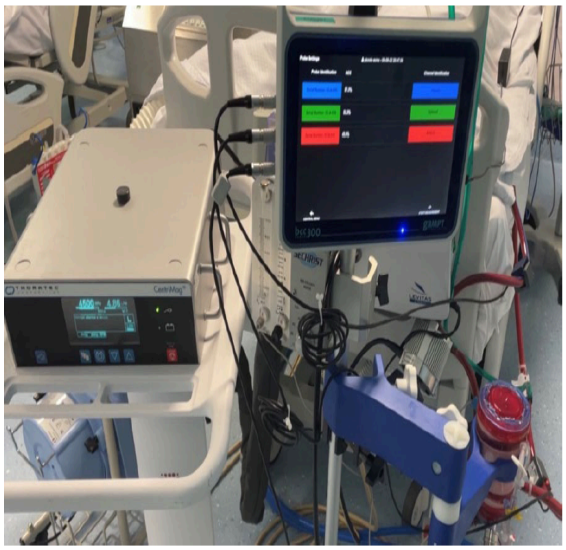

Fig. 1. Adult A.L.ONE ECMO Oxygenator (Eurosets SPA, Medolla, Italy) configuration with Thoratec Centrimag, centrifugal magnetic levitation pumps (Abbott) during VA ECMO.

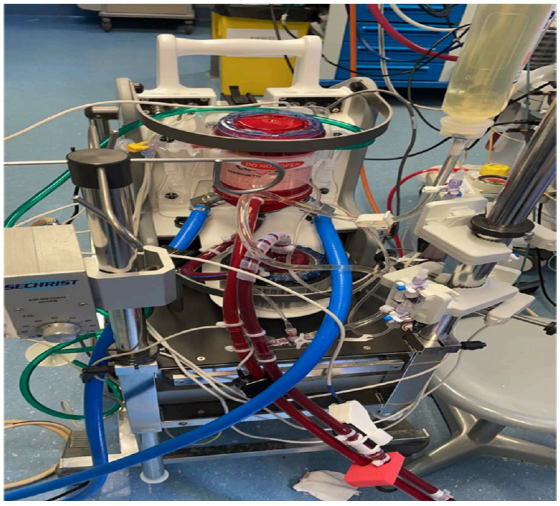

Fig. 2. Adult A.L.ONE ECMO Oxygenator configuration with ECMOLIFE, centrifugal magnetic levitation pump (Eurosets SPA,Medolla, Italy) during VA ECMO.

Fig. 3. Adult A.L.ONE ECMO Oxygenator (Eurosets SPA, Medolla, Italy).

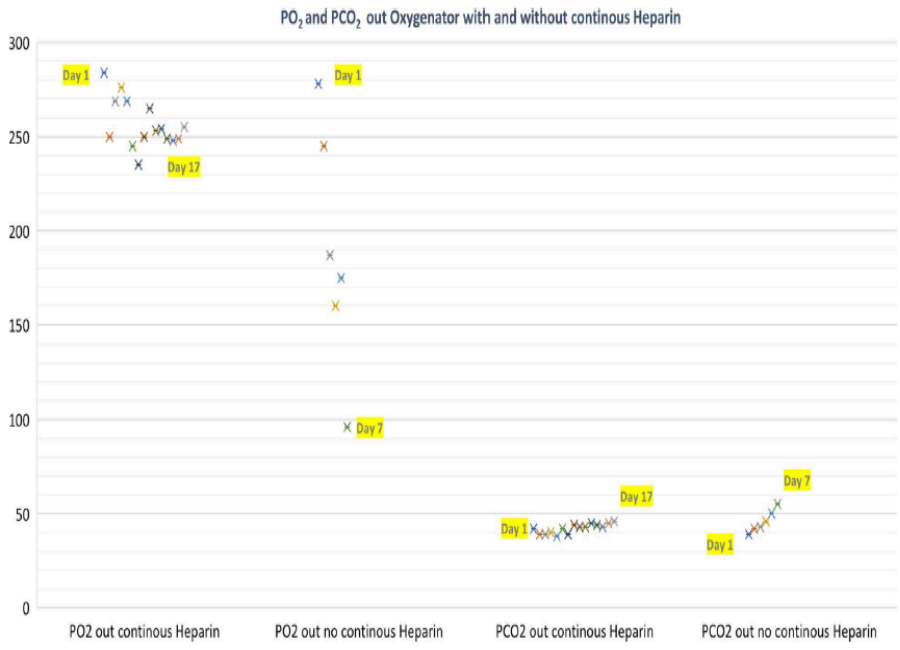

Fig. 4. Trend of PO2and PCO2 out Oxygenator with and without continuous Heparin.

Anticoagulation and blood product management

The ECMO patients are i our center are anticoagulated with a heparin infusion, with a goal activated partial thromboplastic time (aPTT) of 50–65 s unless the clinical setting (e.g., active bleeding) dictates otherwise. The heparin infusion is titrated with a nurse-managed nomogram, whereby the initial infusion dose is based on the patient's weight. Six hours after the infusion begins, an aPTT is again drawn, and the rate of infusion is increased if subtherapeutic (< 50 s), decreased if supratherapeutic (> 65 s), or kept constant if within goal (50–65 s). Another aPTT is drawn in 6 h until the second consecutive aPTT is within target range, at which point the aPTT is checked daily. In our institution the usual practice is to transfuse platelets when counts fall below 80,000/µL, although several experienced centers use a more conservative approach and transfuse platelets only when they fall below 40,000–50,000/µL, or even as low as 20,000 in non- bleeding patients. The strategies in RBC transfusion depending on Hb level—restrictive when transfusion is performed at a Hb level of 7–9 g/dL, and liberal with a Hb level between 10 and 12 g/dl, in relation to Blood Flow (BF), Cardiac Output (CO) and Oxygen Delivery (DO_2) [6].

Veno-arterial (VA) ECMO indication

ECMO was initiated for circulatory instability during or immediately after weaning from the cardiopulmonary bypass (CPB) in the primary cardiac procedure or for hemodynamic support for high risk interventional cardiology procedures. The clinical criteria for hemodynamic support included the following: left atrial pressure > 15 mmHg; central venous pressure > 12 mmHg; metabolic acidosis (i.e. pH < 7.3 with serum lactate > 3.0 mmol/L); end-organ hypoperfusion (urine output < 30 mL/h); cardiac index < 2.2 L/min/m2; and systolic blood pressure < 80 mmHg despite adequate filling volumes, use of multiple adrenergic agents (epinephrine > 0.1 µg/kg/min or dobutamine > 10 µg/kg/min, norepinephrine > 0.1 µg/kg/min), or an intra-aortic balloon pump (IABP). VA-ECMO support was initiated via peripheral cannulation through the femoral route with the semi-open method, and an additional 6 Fr catheter was systematically inserted distally into the femoral artery to prevent leg ischemia ECMO blood flow was adjusted on based on clinical assessments (e.g. pre-oxygenator venous oxygen saturation, evidence of hypoperfusion, resolution of hyperlactatemia, normalization of mean arterial pressure). ECMO-related complications were carefully monitored. ECMO weaning was performed in patients who fulfilled our

published institutional weaning criteria and passed an ECMO weaning trial consisting in decreasing and clamping ECMO flow. In general, the patient should have a pulsatile arterial waveform for at least 24 h; be hemodynamically stable, with baseline mean arterial pressure greater than 60 mmHg with no or low doses of catecholamines; should have left ventricular ejection fraction (LVEF) of 35%, and an aortic velocity time integral (VTI) of ≥ 12 cm; and have recovered from major metabolic disturbances. Weaning was considered unsuccessful if ECMO re-cannulation was required within 2 days of decannulation (2–7).

Veno-venous (VV) ECMO indication

The indication for VV-ECMO is typically severely hypoxemic and/or hypercapnic and unresponsive to optimal medical management, including protective ventilation with low-tidal volumes and plateau pressure less than 28–30 cmH_2O, high levels of PEEP, prone positioning, neuromuscular blockers and/or other adjunctive therapies, including nitrous oxide or almitrine. The recent literature suggests that a PaO2/ FIO2 ratio of 70–80 mmHg, Murray score > 3, and pH < 7.2 provide a reasonable threshold for considering VV-ECMO in adults with ARDS. It is crucial to determine the acute nature of the pulmonary failure, exclude cardiac and/or other organ failure and verify that the respiratory failure cannot be improved with optimal ventilator management (8). Indication and cut-off parameters used for oxygenator or circuit replacement. The polymethylpentene fiber oxygenator is responsible for oxygen uptake and carbon dioxide removal. The non-biologic surface of the oxygenator activates inflammatory and coagulation pathways with thrombus formation, fibrinolysis, and leukocyte activation leading to fiber dysfunction. Activation of coagulation and fibrinolysis can precipitate systemic coagulopathy or hemolysis, while clot deposition can obstruct blood flow. Additionally, moisture buildup in the gas phase and protein and cellular debris accumulation in the blood phase may contribute to shunt and dead-space physiology, respectively, impairing gas exchange. These three categories— hematologic abnormalities, mechanical obstruction, and inadequate gas exchange—prompt the majority of oxygenator exchanges. Principal Cut-off parameters for replacement the oxygenator or the circuit, Gas Transfer: Arterial oxygen partial pressure (PO2) post oxygenator (< 200 mmHg), Carbon dioxide partial pressure PCO2 (> 40 mmHg) post oxygenator, the oxygen transfer across the oxygenator membrane V'O2 (< 100–150 $ml/min/m^2$),

$$V' O2 = BFR (CPostO_2 - CPreO_2)$$

where $V' O_2 = O_2$ transfer across the oxygenator (mL/min), BFR = blood flow rate (L/min), $Cx O_2 = O_2$ content of(pre-/post-oxygenator) blood (mL/L) for

$$CxO_2 = 13.4 \cdot Hb \cdot SxO_2 + 0.03 \cdot PxO_2$$

where Hb = hemoglobin (g/dL), $Sx O_2 = O_2$ saturation of (pre-/post-ML) blood, $Px O_2 = O_2$ partial pressure of (pre-/post-oxygenator) blood (mmHg). Measurement of $V' O_2$ provides an objective measure of oxygen transfer and can confirm oxygenator dysfunction, when clinically indicated. Differential CO_2 Across the oxygenator "pre oxygenator PCO_2 – post oxygenator PCO_2 " (< 10 mmHg); Pressure monitoring: pressure Drop across the oxygenator "Pressure Pre oxygenator–Pressure Post oxygenator" (> 80 mmHg) in relation to Blood flow rate (BFR) (ΔP); Hematologic profiles: Fibrinogen(< 200 mg/dl), Platelets (< 80,000 109 /L), aPTT (> 65 s),D-Dimer (> 25–30 ng/ml), LDH (> 250 mg/dl) (1).

Patients and data collection

We recruited retrospectively from January 2014 to May 2022 at Institution of Anthea Hospital GVM Care & Research, Bari, Italy, long-term ECMO procedures (exceeding 14 days) that use the Eurosets A.L.ONE ECMO Adult oxygenator. The procedures analyzed including: Veno-arterial (VA) ECMO post-cardiotomy or not, veno-venous (VV) ECMO. ECMO characteristics are described and presented as means with sd or medians with interquartile range. The primary end point was the substitution of oxygenator incidence in relation to the oxygenator performance were Gas Transfer: O2 uptake and CO2 removal were collected in relation tothe blood flow rate (BFR), maximum rate per minute of pump (RPM), hemoglobin value (Hb), ventilation indices FiO_2 (%)/ Air (L/min), PO_2 post oxygenator (mmHg),PCO_2 post oxygenator, the transfer across the oxygenator membrane $V' O_2$ (ml/min/m2), Indexed Oxygen Delivery (i DO_2) (ml/min/m^2) only for VA ECMO patient, the partial pressure of carbon dioxide from the gas exhaust of oxygenator ($PE CO_2$) (mmHg), differential CO_2 across the oxygenator (mmHg); Hematologic profiles: Fibrinogen (mg/dl), Platelets (109 /L), aPTT (sec), D-Dimer (ng/ml), LDH (mg/dl), and incidence of Heparin- induced thrombocytopenia

(HIT) I, II, Temperature in arterial and venous line (°C) and Pressure monitoring: pressure Drop (ΔP) (mmHg).

Statistical analysis

Continuous data were expressed as mean ± standard deviation or a median with the interquartile range and categorical data as percentages. Cumulative survival was evaluated with the Kaplan–Meier method. All reported p -values were two-sided, and p -values of < 0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

From January 2014 to May 2022 twenty-two ECMO procedures with Eurosets A.L.ONE ECMO Adult Polymethylpentene fiber oxygenator were retrospectively collected from the tertiary institution Anthea Hospital GVM Care & Research, Bari, Italy. Eight peripheral VA ECMOs were used as short-term hemodynamic support for interventional cardiology procedures, the medium time of use was less than 3 h. Twelve VA ECMOs were used as cardiocirculatory assistance, nine post cardiotomy of which: two with central cannulation, seven with peripheral cannulation and one peripheral after angioplasty. In nine oxygenators with continuous endo venous heparin treatment the average use time was 18.5 days. Only three oxygenators on post-cardiotomy VA ECMO procedures without continuous endo venous heparin treatment for patient bleeding were replaced on three patients between the sixth/seventh day of use for the performance decrease for previously mentioned cut-off (Table 1). in particular, the failure of the oxygenator was mainly caused by oxygenation (PO_2 out the oxygenator < 120 mmHg with 100% FIO2 set to 10 L of gas flow), decapneization (PCO2 out the oxygenator > 45 mmHg with 10 L of gas flow and 100% FiO2) (Fig. 3), by the pressure drop (> 350 mmHg), by the reduction of the pump flow rate (< 2.4 l/min/m^2) and by the visible formation of clots in the part corresponding to the purging of the oxygenator because an area with low vorticity which could have facilitated the halving of the platelet

count (< 100,000 109/ L). None of the patients reported incidence of HIT I and II. The use of a Phosphorylcholine-treated ECMO circuit versus a heparin circuit likely reduces heparin exposure by reducing the incidence of HIT [9]. Two oxygenators were used on Veno-Venous (VV) ECMO with continuous endo venous heparin treatment for the treatment of Acute Respiratory Distress Syndrome (ARDS) the average use time was 17.2 days. The 9 VA ECMO patients who used the oxygenator for 18.5 days and the two VV ECMO patients who used the oxygenators for 17.2 days on the seventeenth days reported average values of mean hemoglobin 8.9 ± 0.8; PO2 post oxygenator (267 ± 29 mmHg);PCO_2 post oxygenator (34 ± 4 mmHg) with average values of gas blender set to Air 3.8 ± 0.6 L/min and a FiO2 of 78 ± 5%; the oxygen transfer across the oxygenator membrane V'O2 was 189 ± 43 (ml/min/m2); the mean peak of indexed oxygen delivery (iDO2) for only nine VA ECMO at seventeenth days was 340 ± 37 ml/min/m2. The mean peak of partial pressure of carbon dioxide from the gas exhaust of oxygenator ($PECO_2$) was 20 ± 4 mmHg; differential CO2 across the oxygenator "pre-oxygenator PCO2–post-oxygenator PCO2" was 18 ± 6 (mmHg); the mean blood flow rate (BFR) was 4.5 ± 0.6 (L/minute); the pump revolution per minutes mean maximum rate was 4254 ± 345 (RPM); the mean pressure drop (ΔP) was 76 ± 12 mmHg; the mean arterial blood temperature was 36.5 ± 0.3 ÅãC and in the venous line was 36.4 ± 0.2 ÅãC;the mean peak of D-dimers (DDs) was 23.6 ± 0.8 mg/dL; the mean peak of LDH was 230 ± 55 (mg/dl); fibrinogen mean peak 223 ± 40 (mg/dl); PLT 150,000 ± 987 (109/L); aPTT 53 ± 4 (sec), the other hematologic values data prodromal to oxygenator replacement are presented in the **Table 1**.

Procedures nr = 14	Long term VA (Nr = 9) and VV ECMO (Nr = 2)	Medium term VA ECMO(Nr = 3)	*p-value*
	Parameters at seventeenth day	Parameters at sixth day	
Period (days)	17.8	6.8	0.003
Hemoglobin (gr/dl)	8.9 ± 0.8	7.3 ± 0.8	0.022
PO_2 post oxygenator (mmHg)	267 ± 29	170 ± 23	0.002
PCO_2 post oxygenator (mmHg)	34 ± 4	42 ± 8	0.034
Air (L/min) /FiO_2 (%)	3.8 ± 0.6/78 ± 5	5.3 ± 0.9/100 ± 9	0.019
V'O2 (ml/min/m^2)	189 ± 43	105 ± 28	0.017
$_iDO_2$ (ml/min/m^2)	340 ± 37	245 ± 48	0.025
$P_ECO_{2\,(mmHg)}$	20 ± 4	10 ± 6	0.031
Differential CO_2 (mmHg)	18 ± 6	8 ± 3	0.021
BFR (L/min)	4.5 ± 0.6	3.9 ± 0.9	0.041
Pump revolution (RPM)	4254 ± 345	5000 ± 445	0.023
Pressure drop (ΔP)	76 ± 12	246 ± 22	0.011
Arterial blood temperature (°C)	36.5 ± 0.3	36.2 ± 0.8	0.89
Venous blood temperature (°C)	36.4 ± 0.2	36.1 ± 0.5	0.91
Continuous anticoagulation Use	Yes	No	
DDs (mg/dL)	23.6 ± 0.8	42 ± 13	0.005
LDH (mg/dL)	230 ± 55	424 ± 38	0.004
Fibrinogen (mg/dL)	223 ± 40	176 ± 40	0.003
PLT (10^9/L)	150,000 ± 987	39,000 ± 778	0.033
aPTT (sec)	53 ± 4	69 ± 23	0.018
Oxygenator replacement (nr)	0	3	0.002
Total oxygenator used (nr)	11	6	0.033
Red blood cells (units for patients)	2 ± 1	2 ± 1	0.027
Platelets (units for patients)	3 ± 1	2 ± 1	0.027

Table 1. Operative data, during long term versus medium term on Adult A.L.ONE ECMO Oxygenator.

Values are presented as n (%) or mean ± standard deviation.VA, Veno-Arterial; VV, Veno-venous; ECMO, extracorporeal membrane oxygenation; PO2, partial pressure of oxygen; PCO2, partial pressure of carbon dioxide; V'O2, the oxygen transfer across the oxygenator membrane; iDO2, indexed oxygen delivery; PECO2, partial pressure of carbon dioxide from the gas exhaust of oxygenator; BFR,blood flow rate; DDs, D-Dimers; LDH, lactate dehydrogenase; PLT, Platelets; aPTT, partial thromboplastin time.

Discussion

The main limitation of this study is the fact that it is a single center retrospective investigation with a small number of ECMO cases. An advantage of a small sample size in this case may be to contain medical, technical, and nursing management skills compared to a multicenter study. Long-term oxygenator management during post-cardiotomy ECMO procedures in the literature is limited with a high incidence of replacement due in particular to post-procedures bleeding (10 , 11). In future perspective would be interesting to explore this issue further in a larger multicenter study. In this study, we present a classification of the short, medium, long term use of the oxygenating module in relation to its certification and validation and demonstrate that the determinant that can impact the duration of the oxygenator and its failure in particular after cardiac surgery procedures does not depend exclusively on the model and design but mainly on the medical and technical management of the device in relation to the anticoagulant. The same model in this case it may have a different duration and need to be replaced depending on the suspension or continued use of heparin infusion (9,10, 12). On the other hand, replacement of an adequately functioning device requiring temporary cessation of ECMO support places the patient at unnecessary risk while consuming a limited and expensive resource. Based on the pathophysiology of the oxygenator, replacement may be required for one of three reasons: if there is (A) an associated hematologic abnormality, (B) an increasing obstruction to blood flow, or (C) inadequate gas exchange (1). In our experience we report that the continuous anticoagulation and a good balance in aPTT management is protective for the oxygenators until long-term use respect to the group that suspend the anticoagulation strategy for bleeding.

Conclusions

The performance of the Eurosets A.L.ONE ECMO Adult polymethylpentene fiber oxygenator in our experience has proven efficiency in terms of O_2 uptake and CO_2 removal, blood fluid dynamics, metabolic compensation and heat exchange in the long-term treatment. The device was safe without iatrogenic problems over a period of 14 days in the patients undergoing ECMO VA and in all patients undergoing VV ECMO with continuous administration of anticoagulation therapy, oxygenator replacement was not reported in this group of patients, compared with three replacements in the group that did not do continuous heparin infusion for bleeding.

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Chapter 7

Water Condensation and Gas Exchange Correlation in Different Models and Fibers of Blood Oxygenators: "How Can We Improve Performance?"

Ignazio Condello

Journal of Extracorporeal Technology. March 2020;52:43–51

Abstract

Creation of water condensation in blood oxygenators is a phenomenon that is constantly present during cardiopulmonary bypass and in medium- to long-term extracorporeal life support. Clinical observation of condensation at the oxygenator exit is still a common event normally associated with sudden cooling of the gas flow proximal to the outlet cover (after exiting the fiber bundle), where the warming effect of blood is no longer present. Condensation could progressively obstruct a certain number of fibers, reducing the efficiency of gaseous exchange in the membrane of the oxygenator surface. The study included 48 patients divided into four oxygenator groups of 12 each: group 1 used an Inspire 6 F oxygenator from Livanova; group 2, an Affinity Fusion from Medtronic; group 3, an Alone from Eurosets, and group 4, an ECMO Alone from Eurosets; while the last group used an ECMO Alone oxygenator from Eurosets with polymethylpentene fiber. Each group of oxygenators comprising 12 patients were divided into two groups, namely, A and B, with six patients in each group. Group A used mild hypothermia during the procedure, and group B of six patients used normothermia; Groups A and B were further subdivided into four subgroups: A1, A2, B1, and B2, each consists of three patients; subgroups A1 and B1 used negative aspiration (28 mmHg) measuring humidity (%) and temperature (°C) in the gas oxygenator output; consequently, a measurement system was necessary to be created; Subgroups A2 and B2 did not use negative aspiration in the oxygenator outlet. No statistically significant difference for PaO2 and humidity values was found in polypropylene and polymethylpentene oxygenators with mild hypothermia management with vacuum and without vacuum in the gas outlet in the first 60 minutes and 60 minutes later during cardiopulmonary bypass. In normothermia, a statistically significant difference in the PaO2–humidity relationship was observed with polypropylene and polymethylpentene fiber models. Results of this study show an inversely proportional correlation between gas exchange and condensation in statistically significant values during the use of normothermia and a reduction in oxygenation performance, in polypropylene and polymethylpentene fiber oxygenators.

Introduction

Cardiopulmonary bypass (CPB) is performed during open-heart surgeries when patients' heart and lungs need to stop functioning, as well as during extracorporeal life support for patients with severe respiratory and/or heart diseases. The blood is collected from the venous circulation and diverted to an extracorporeal circuit, where it is oxygenated and pressurized before being redirected to the arterial systemic circulation. A blood pump replaces the heart function, while a blood oxygenator provides the gaseous exchange. Blood oxygenators have experienced several changes in the past 50 years (1), and currently, the oxygenating module consists of a bundle of polymeric hollow fibers that carry the gaseous mixture (usually, nitrogen and oxygen), with the blood flowing externally around them. The microporous semipermeable membrane of the fibers allows for oxygen (O_2) and carbon dioxide (CO_2) exchange between the extraluminal (blood) and intraluminal (gas) flows. Because of the microporous nature of the membrane, blood plasma can evaporate at the liquid– membrane interface and diffuse as water vaporizes through the pores into the intraluminal gas phase. Despite the fact that the supplied gaseous mixture is dry, because of the large water vapor mass transfer coefficients of the microporous membranes, the gas is expected to become highly saturated with a short fiber length. The current study focuses on the analysis of different models of oxygenators and different types of fibers, in terms of production of water condensation to the oxygenator exhaust outlet, and oxygenation performance, in terms of PaO_2 /FiO_2 and $PaCO_2$ /LPM air/blood, and (P (E) CO_2) oxygenator exhaust PCO_2, during rewarming in CPB. Condensation could progressively obstruct a certain number of fibers, reducing the effective membrane surface area for gaseous exchange. Therefore, a number of studies investigated possible strategies for preventing or limiting water condensation: by warming the gas at the inflow, or outflow section, creating a warm environment around the whole oxygenator, or blowing off the condensed droplets from the clogged fibers by gas flushing. In this study, two different temperature managements were compared and analyzed in the four models of oxygenators, which are widely used in clinical practice during cardiopulmonary bypass: for mild hypothermia, without a heat exchanger managing temperatures leaving the oxygenator at 33.9°C and nasopharyngeal temperature at 33.8°C, whereas for normothermia, with a heat exchanger managing temperatures leaving the oxygenator at 36.4°C and nasopharyngeal temperature at 36.2°C and the two respective

heating phase nasopharyngeal temperature at 36.7°C. There are two types of management of condensation at the oxygenator output: with negative pressure (2 8 mmHg) and without negative pressure. Each oxygenator ensures a constant 50% of FiO_2 maintained as a result of the benchmark of nadir since the beginning of CPB for values in the arterial blood between 150 and 220 mmHg of PaO_2; liter per minute of air (mean value 2.6 L/min) was compared with the technical characteristics of the oxygenator and with the blood flow for the maintenance of values of (40 mmHg) $PaCO_2$. The increase in FiO_2 required to maintain PaO_2 ranges during the extracorporeal circulation was recorded within the groups, and the percentage (%) of humidity and water loss in the oxygenator outlet (mL)was measured together with (P (E) CO_2) oxygenator exhaust PCO_2.

Methods

Forty-eight patients similar in characteristics were recruited (**Table 1**), undergoing elective cardiac surgery using mild hypothermic and normothermic CPB. Surgery included both cardiac bypass grafts and aortic valve replacement. Institutional approval for the study was obtained. The study was approved without requiring informed consent for the research because all the procedures were part of the routine. A Stockert S5 (Livanova, Italy) heart and lung machine and the same circuit cannula were used in both groups. The priming volume was 1,000 mL in group A and 700 +/- 50 mL in group B ($p < .001$). Heparin reversal was obtained with .5 – 75 mg of protamine for every 100 units of heparin (2). Anesthesia was obtained by fentanyl, midazolam, and rocuronium. Concentrated red cells were transfused whenever hemoglobin (Hb) concentrations decreases below 6 g/dL during surgery or below 8 g/dL during the intensive care unit stay. A closed circuit for cardioplegia with a heat exchanger with an infusion syringe pump in series was used; Saint Thomas solution with procaine (3) and a DO2 management monitoring system (Landing Eurosets, Medolla, Italy) (4) were used. During CPB, a centrifugal (pump BioMedicus BPX80 Medtronic) was used to perfuse the patients in each model of the oxygenator (Inspire 6 F with an integrated filter Livanova, Affinity Fusion Medtronic, Alone Eurosets with an integrated filter, and Alone ECMO Eurosets). An integral heat exchanger was used, and the pump flow had a cardiac index of 2.4 L/m^2 during normothermia, and a mean nadir of DO_2 indexed (oxygen delivery index) was managed during procedures (298 $mL/min/m^2$) (4). Gas fl ow through the oxygenator was adjusted to maintain the laboratory-measured blood gas PaCO2 (partial pressure of carbon dioxide) at 40 mmHg (i.e., alpha-stat management of CPB) (5). Continuous measurement of P (E) CO_2 (oxygenator exhaust PCO_2) during CBP was performed by connecting the catheter of a side stream capnograph (Datex-Ohmeda AS3, Datex-Ohmeda, Helsinki, Finland) end to the side of the oxygenator exhaust, using a short length of silicone rubber tube and a disposable Luer-Lock T-connector (6). The calibration of the capnograph

was limited to the manufacturer' s routine recommendations (7). The blood gas samples were taken from the arterial port of the oxygenator during bypass and were measured within 10 minutes, with a blood gas analyzer (Radiometer ABL725, Radiometer Medical A/S Copenhagen, Denmark) set to measure at 37°C (8).

	Groups A and B (n = 48)
Age (year), mean	68 (68.7)
Body surface area (m^2)	1.85
Pre-CPB hematocrit (%), mean ± SEM	35
Pre-CPB Hb (g/dL)	11.5
CPB Time (min)	120
Cardiac index (L/min/m^2)	2.4
Activated clotting time in CPB (sec), mean ± SEM	525 ± 35

Table 1. Sample characteristics.

Values presented in table are mean values.

Study Design

The study included 48 patients divided into four groups of 12 each: the first group used an Inspire 6 F oxygenator from the Livanova group, the second group used an oxygenator from the Affinity Fusion Medtronic group, the third group used an Alone oxygenator from Eurosets with polypropylene fiber, and the last group used an Ecmo Alone oxygenator from Eurosets with polymethylpentene fiber (**Figure 1**). Each group of oxygenators comprising 12 patients was divided into two groups, namely, A and B with six patients in each group. Group A used mild hypothermia

during the procedure, and group B of six patients used normothermia. Groups A and B were further subdivided into four subgroups: A1, A2, B1, and B2, each made up of three patients. Subgroups A1 and B1 used negative aspiration (28 mmHg) measuring the humidity (%) and temperature (°C) in the gas oxygenator output; consequently, a measurement system was necessary to be created. The subgroups A2 and B2 did not use negative aspiration in the oxygenator outlet (9). Group A of six patients which used mild hypothermia without a warming unit were managed in the first 60 minutes with a nasopharyngeal temperature of 33.9°C and an arterial blood temperature of 33.8 and was heated after 60 minutes, which lasted for 17 minutes by setting the heater unit to 36.7°C, reaching a nasopharyngeal temperature of 36.3°C and an arterial blood temperature of 36.5. Group B of six patients were managed in normothermia, and the heater unit was set at a temperature of 36.5°C with nasopharyngeal temperature of 36.2°C and an arterial blood temperature of 36.4 for the duration of CPB. Groups A and B were subdivided into four subgroups, each made up of three patients; subgroups A1– B1 applied negative aspiration (2 8 mmHg) with measurement of humidity (%) and temperature (°C) in the gas oxygenator output with a system created (**Figures 2 and 3**) and composed of four components (Figure 4): retrofit tank of the heat exchanger for the accumulation of steam, connected to a vacuum manometer (Amvex Vacuum Regulators. Amvex®) and inside itwas placed a small tank for the loss of water and a thermo hygrometer (vanguard hydroponics). Subgroups A2– B2 did not use negative aspiration in the oxygenator outlet (**Figure 4**).

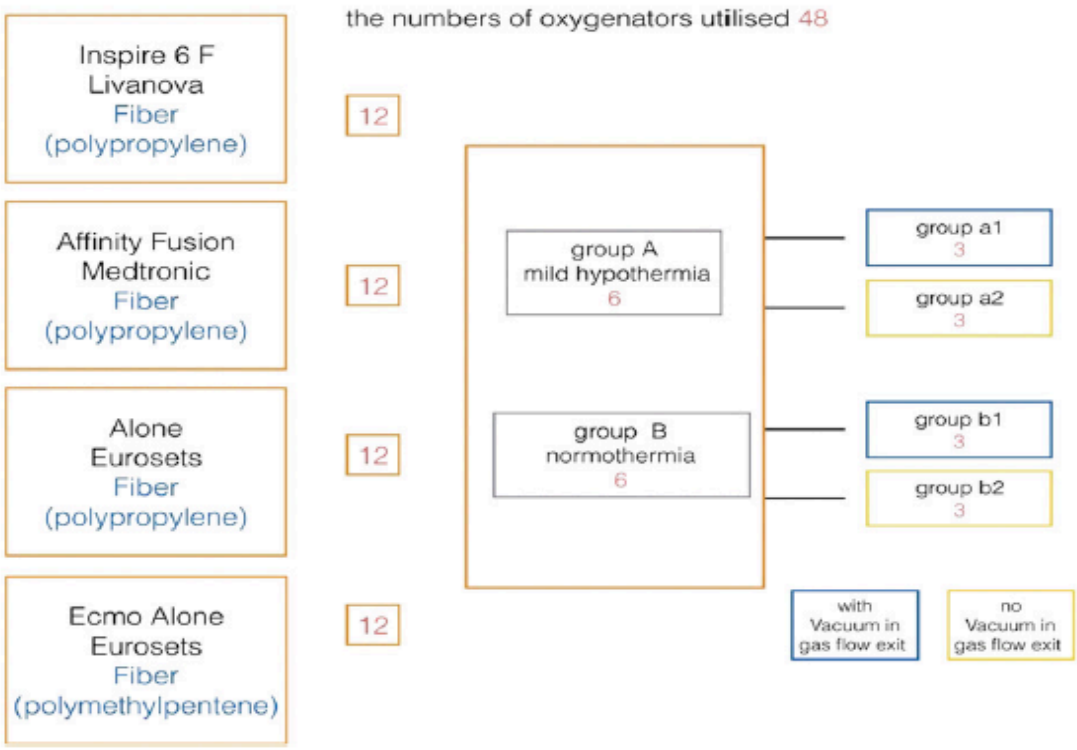

Figure 1. Study design.

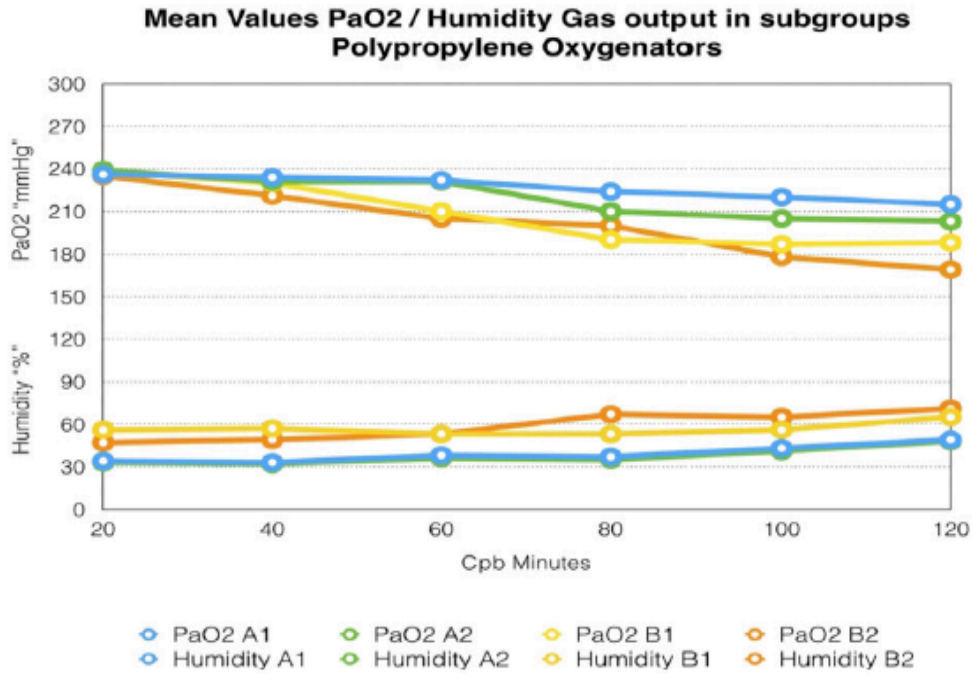

Figure 2. System for negative aspiration for measurement of humidity (%) and temperature (°C) in the oxygenator output.

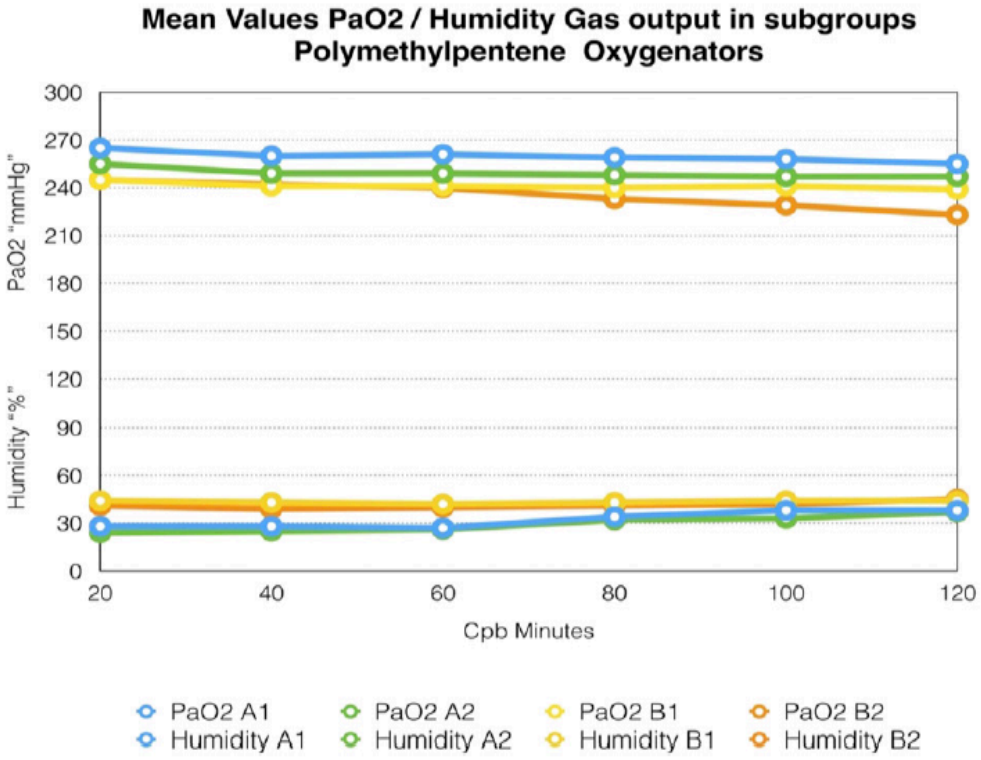

Figure 3. Measurement of humidity (%) and temperature (°C) in the oxygenator output without aspiration.

Figure 4. System for negative aspiration and measurement, which composes of four components:(1) retrofit tank of the heat exchanger for the accumulation of steam.

Statistical Analysis

The student t -test was used to compare continuous variables between groups. A p value of < .05 was considered significant. Two measurement times of the parameters were identified in the four subgroups: Time 1 in the first 60 minutes of CPB conduction (in the beginning and half of the procedure), Time 2 after 60 minutes CPB conduction (in the half and end of the procedure). The mean values of gas exchange PaO2 and PaCO2 were collected in these two time frames; temperature, exhaust PCO2, and humidity in the gas outlet of oxygenator were measured. After 10

minutes, the procedure suction was placed (2 10 mmHg) in the gas outlet of the oxygenator, storing and measuring the residual water in the tank.

Results

The gas flow temperature exiting the gas blender was reported at an average of 18°C with .01% humidity, and the temperature of the operating room was 19°C with 39% humidity. No coagulation problems in the administration of heparin and variation of pressure drop in all oxygenators were shown during the procedures in all study groups. The total time taken by the oxygenator in the four groups was 120 minutes (mean value), during the procedures, and the hematocrit values were 26% and 28%. The initial ventilation and oxygenation nadir values were set: 50% FiO2 and 1.9– 2.7 liters of air flow per minute, 4.8 L/min of blood fl ow (mean values). A different variability in the oxygenating performance and production of steam (**Tables 2 and 3**) and water loss (**Table 4**) was found in relation to temperature management and humidity evacuation in the four oxygenator models analyzed. No statistically significant difference was found in the first 60 minutes and 60 minutes later in oxygenator use, for PaO2 and humidity values in polypropylene and polymethylpentene fiber models, during mild hypothermia management with vacuum (subgroup A1) and without vacuum (subgroup A2) in the gas outlet (Table 5).A statistically significant difference for PaO2 and humidity values in polypropylene and polymethylpentene fiber models was found, in normothermia management with vacuum (subgroup B1) and without vacuum (subgroup B2) in the gas outlet (**Table 5**) (**Figures 5 and 6**).

Subgroup	PaO_2 Polypropylene *p*-Value (Times 1 and 2)	PaO_2 Polymethylpentene *p*-Value (Times 1 and 2)	Humidity in Outlet Oxygenators Polypropylene *p*-Value (Times 1 and 2)	Humidity in Outlet Oxygenators Polymethylpentene *p*-Value (Times 1 and 2)
A1	.078	.098	.086	.086
A2	.068	.071	.076	.069
B1	.046	.066	.038	.049
B2	.036	.046	.032	.048

Table 2. p-values subgroups; PaO2 and humidity during Times 1 and 2.

	Mild Hypothermia, Vacuum in Outlet Oxygenator, A1 (n = 3)		Mild Hypothermia, No Vacuum in Outlet Oxygenator, A2 (n = 3)		Normothermia, Vacuum in Outlet Oxygenator, B1 (n = 3)		Normothermia, No Vacuum in Outlet Oxygenator, B2 (n = 3)	
Oxygenators models (n = 48)	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators
Inspire 6F Livanova (n = 12) Gas blender	PaO_2 225 ± 2 mmHg $PaCO_2$ 40 ± 4 mmHg Air/oxygen (1.9 L/min/ 50%)	50%	PaO_2 218 ± 4 mmHg $PaCO_2$ 38 ± 2 mmHg Air/oxygen (1.9 L/min/ 50%)	48%	PaO_2 197 ± 4 mmHg $PaCO_2$ 38 ± 2 mmHg Air/oxygen (2.1 L/min/ 50%)	65%	PaO_2 187 ± 1 mmHg $PaCO_2$ 43 ± 3 mmHg Air/oxygen (2.1 L/min/ 50%)	71%
Affinity Fusion Medtronic (n = 12) Gas blender	PaO_2 235 ± 5 mmHg $PaCO_2$ 39 ± 3 mmHg air/ oxygen (1.8 L/min/50%) Air/Oxygen L/min/50% (1.8 L/min/50%)	44%	PaO_2 233 ± 4 mmHg $PaCO_2$ 40 ± 2 mmHg Air/oxygen (1.8 L/min/ 50%)	39%	PaO_2 205 ± 2–3 mmHg $PaCO_2$ 36 ± 2 mmHg Air/oxygen (2.2 L/min/ 50%)	61%	PaO_2 189 ± 2–3 mmHg $PaCO_2$ 37 ± 3 mmHg Air/oxygen (2.2 L/min/ 50%)	59%
Alone Eurosets (n = 12) Gas blender	PaO_2 224 ± 2–3 mmHg $PaCO_2$ 39 ± 2 Air/oxygen (2.5 L/min/ 50%)	43%	PaO_2 219 ± 2 mmHg $PaCO_2$ 38 ± 4 Air/oxygen (2.5 L/min/ 50%)	42%	PaO_2 209 ± 2 mmHg $PaCO_2$ 36 ± 2 Air/oxygen (2.7 L/min/ 50%)	52%	PaO_2 188 ± 2 mmHg $PaCO_2$ 39 ± 2 Air/oxygen (2.7 L/min/ 50%)	56%
ECMO Alone Eurosets (n = 12) Gas blender	PaO_2 255 ± 3 mmHg $PaCO_2$ 39 ± 3 Air/oxygen (2.0 L/min/ 50%)	38%	PaO_2 247 ± 2 mmHg $PaCO_2$ 36 ± 2 Air/oxygen (2.0 L/min/ 50%)	37%	PaO_2 239 ± 1 mmHg $PaCO_2$ 35 ± 2 Air/oxygen (2.2 L/min/ 50%)	44%	PaO_2 223 ± 2 mmHg $PaCO_2$ 38 ± 2 Air/oxygen (2.2 L/min/ 50%)	45%

Table 3. Time 2 (results after 60 minutes during CPB), gas exchanges/humidity gas outlet in subgroups, and mean values.

Oxygenators Models (Total n = 48)	A1 (n = 3) Total Accumulated Water Loss (mL)	A2 (n = 3) Total Accumulated Water Loss (mL)	B1 (n = 3) Total Accumulated Water Loss (mL)	B2 (n = 3) Total Accumulated Water Loss (mL)
Inspire 6F Livanova (n = 12)	2.6	3.1	5.1	6.1
Affinity Fusion Medtronic (n = 12)	2.4	2.8	4.3	5.3
Alone Eurosets (n = 12)	1.9	2.3	4.3	5.6
ECMO Alone Eurosets(n = 12)	2.1	2.2	3.2	4.2

Table 4. Total accumulated water loss (mL) in subgroups and mean values.

	Mild Hypothermia, Vacuum in Outlet Oxygenator, A1 (n = 3)		Mild Hypothermia, No Vacuum in Outlet Oxygenator, A2 (n = 3)		Normothermia, Vacuum in Outlet Oxygenator, B1 (n = 3)		Normothermia, No Vacuum in Outlet Oxygenator, B2 (n = 3)	
Oxygenators models (n = 48)	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators	Gas Exchange	Humidity in Gas Outlet Oxygenators
Inspire 6F Livanova (n = 12)	PaO_2 235 ± 3–6 mmHg	37%	PaO_2 215 ± 4 mmHg	33%	PaO_2 210 ± 2 mmHg	63%	PaO_2 201 ± 2 mmHg	59%
	$PaCO_2$ 38 ± 4 mmHg		$PaCO_2$ 39 ± 2 mmHg		$PaCO_2$ 39 ± 2 mmHg		$PaCO_2$ 39 ± 3 mmHg	
Gas blender	Air/oxygen (1.9 L/min/50%)		Air/oxygen (1.9 L/min/50%)		Air/oxygen (2.1 L/min/50%)		Air/oxygen (2.1 L/min/50	
Affinity Fusion Medtronic (n = 12)	PaO_2 255 ± 2–3 mmHg	34%	PaO_2 235 ± 2–3 mmHg	29%	PaO_2 205 ± 2–3 mmHg	59%	PaO_2 199 ± 2–3 mmHg	55%
	$PaCO_2$ 37 ± 3 mmHg		$PaCO_2$ 38 ± 3 mmHg		$PaCO_2$ 35 ± 3 mmHg		$PaCO_2$ 37 ± 3 mmHg	
Gas blender	Air/oxygen (1.8 L/min/50%)		Air/oxygen (1.8 L/min/50%)		Air/oxygen (2.2 L/min/50%)		Air/oxygen (2.2 L/min/50%)	
Alone Eurosets (n = 12)	PaO_2 234 ± 2–3 mmHg	36%	PaO_2 224 ± 2 mmHg	32%	PaO_2 209 ± 2 mmHg	51%	PaO_2 200 ± 2 mmHg	46%
	$PaCO_2$ 35 ± 3		$PaCO_2$ 38 ± 3		$PaCO_2$ 36 ± 2		$PaCO_2$ 36 ± 2	
Gas blender	Air/oxygen (2.5 L/min/50%)		Air/oxygen (2.5 L/min/50%)		Air/oxygen (2.7 L/min/50%)		Air/oxygen (2.7 L/min/50%)	
ECMO Alone Eurosets (n = 12)	PaO_2 265 ± 3 mmHg	28%	PaO_2 255 ± 2 mmHg	24%	PaO_2 245 ± 2 mmHg	42%	PaO_2 245 ± 2 mmHg	41%
	$PaCO_2$ 30 ± 3		$PaCO_2$ 38 ± 2		$PaCO_2$ 38 ± 2		$PaCO_2$ 39 ± 2	
Gas blender	Air/oxygen (2.0 L/min/50%)		Air/oxygen (2.0 L/min/50%)		Air/oxygen (2.2 L/min/50%)		Air/oxygen (2.2 L/min/50%)	

Table 5. Time 1 (results of first 60 minutes during CPB), gas exchange/humidity gas outlet in subgroups, and mean values.

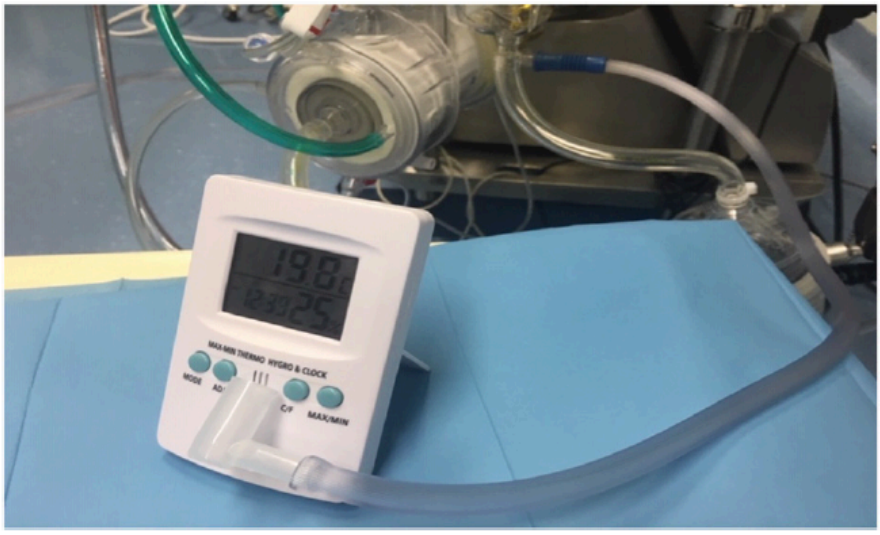

Figure 5. Mean values of PaO2/humidity gas output in polypropylene oxygenators during procedures.

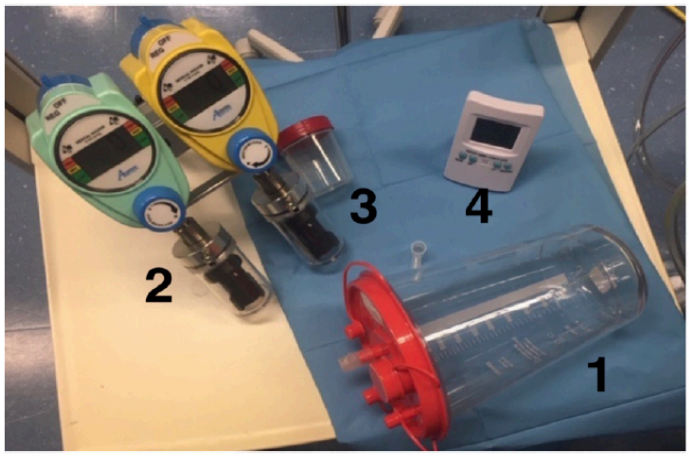

Figure 6. Mean values of PaO2/humidity gas output in polymethylpentene oxygenators during
procedures.

Discussion

The present study shows that all the oxygenator models have presented excellent quality standards during the CPB procedure, in terms of gas and thermal exchange. There are different temperature management techniques during CPB. In this study, we observe during blood heating an increase in humidity and water loss in oxygenator gas outlet and a decrease in PaO2 (10). The production of condensation and water loss from the gas oxygenator gas output has been treated in various studies (11); however, a strong correlation with gas exchange has never been highlighted (1). Above all, it would seem that each oxygenator model has different parameters and trends in humidity production and oxygenating performance (12). The goal was to describe various approaches to fi nd the most appropriate management for a type and design of the oxygenator that will ensure good gas exchange and performance for long periods of extracorporeal procedures (13). Two temperature managements and two methods have been found for evacuating the condensation from the oxygenator gas outlet, in four models of oxygenators: two types with polypropylene fi bers and two types with polymethylpentene fibers because of the microporous nature of the membrane.

According to previous studies, blood plasma can evaporate at the liquid– membrane interface and diffuse as water vapor diffuses across the pores into the intraluminal gas phase (14). Despite being supplied as a dry gaseous mixture, because of the large water vapor mass transfer coeffi cients of the microporous membranes, the gas is expected to become highly saturated within a short fi ber length (15).

Conclusion

The result of this study shows an inversely proportional correlation between gas exchange and condensation in statistically significant values. In polypropylene and polymethylpentene fiber oxygenators, the production of condensation was increased at the oxygenator gas outlet during the use of normothermia. Limiting the use of heat exchanger time during CPB would seem to reduce the production of water loss and condensation and improve the stability of exchanges in terms of PaO2 in the long-term extracorporeal circulations. The aspiration use in the gas outlet could favor the elimination of the condensation, particularly in the polymethylpentene oxygenators, and favor gas exchanges. However, further studies are needed to validate these preliminary results.

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Chapter 8

Continuous field flooding versus final one-shot CO2 insufflation in minimally invasive mitral valve repair

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Abstract

Background. Insufflation of carbon dioxide (CO_2) into the operative field to prevent cerebral or myocardial damage by air embolism is a well known strategy in open-heart surgery. However, here is no general consensus on the best delivery approach.

Methods. From January 2018 to November 2021, we retrospectively collected data of one hundred consecutive patients undergoing minimally invasive mitral valve repair (MIMVR). Of these, fifty patients were insufflated with continuous CO_2 1 min before opening the left atrium and ended after its closure, and fifty patients were insufflated with one shot CO_2 10 min before the start of left atrium closure. The primary outcome of the study was the incidence of transient post-operative cognitive disorder, in particular agitation and delirium at discontinuation of anesthesia, mechanical ventilation (MV) duration and intensive care unit (ICU) length of stay.

Results. In all patients that received continuous field flooding CO_2, correction of ventilation for hypercapnia during cardiopulmonary bypass (CPB) was applied with an increase of mean sweep gas air (2.5 L) and monitoring of VCO2 changes. One patient vs. 9 patients of control group reported agitation at discontinuation of anesthesia ($p = 0.022$). MV duration was 14 ± 3 h vs. 27 ± 4 h ($p = 0.016$) and ICU length of stay was 33 ± 4 h vs. 42 ± 5 h ($p = 0.029$). A significant difference was found in the median number of total micro-emboli recorded from release of cross-clamp until 20 min after end of CPB (154 in the continuous CO2 group vs. 261 in the one-shot CO2 control group; $p < 0.001$). Total micro-emboli from the first 15 min after the release of cross-clamp was 113 in the continuous CO_2 group vs. 310 in the control group ($p < 0.001$). In the continuous CO_2 group, the median number of detectable micro-emboli after CPB fell to zero 9 ± 5 min after CPB vs. 19 ± 3 min in the control group ($p = 0.85$).

Conclusion. Continuous field flooding insufflation of CO_2 in MIMVR is associated with a lower incidence of micro-emboli and of agitation at discontinuation of anesthesia, along with improved MV duration and ICU length of stay.

Introduction

The presence of air micro-emboli in open-heart surgery correlates with the degree of post-operative neuropsychological disorder (1, 2). Manual de-airing techniques have proved ineffective in eliminating air micro-emboli and even meticulous techniques are associated with the risk of a large number of micro-emboli (3, 4). The neurological outcome is difficult to evaluate, due to possible bias such as the status and the age of the patient and symptoms (e.g. changes in personality) (5, 6). However, it is possible that these changes are not connected with the operation itself but rather with the status of the patients, their age, sex, disease severity, or genetic factors (7, 8). The use of carbon dioxide (CO_2) in minimally invasive cardiac surgery is due to its high solubility and density in blood, allowing better tolerability of air embolism (9). The use of endo-cavitary aspirators during mitral valve surgery contributes to capture in the extra-corporeal circuit the quantity of CO2 continuously insufflated in the surgical field. This aspect is represented in the blood gas analysis and in the frequent correction of hypercapnia through ventilation in the oxygenator (10).

In this context we investigated the effect of CO_2 on two groups of patients undergoing minimally invasive mitral valve repair (MIMVR) through a right mini-thoracotomy with two different CO2 delivery techniques (continuous vs. one end shot) and we compared the peri-operatory micro-embolic activity, the impact of CO_2 in cardiopulmonary bypass (CPB) management, the incidence of transient post-operative cognitive disorder (TPOCD), mechanical ventilation (MV) duration and intensive care unit (ICU) length of stay.

Methods

Patient and data collection

A retrospective, observational study was undertaken of prospectively collected data in one hundred consecutive patients undergoing MIMVR from January 2018 to November 2021 at our Institution Anthea Hospital, GVM Care & Research, Bari, Italy. The median (interquartile range [IQR]) age was 66 (62–76) years, one hundred patients underwent MIMVR through a right thoracotomy approach. Patient characteristics are reported in Table 1. None of the study patients reported the use of psychiatric drugs, alcohol, and carotid artery stenosis prior to the procedure.

Fifty patients were insufflated with continuous CO_2 1 min before opening the left atrium and ended after its closure, and fifty patients were insufflated with one shot CO2 10 min before the start of left atrium closure, at a continuous CO_2 flow rate of 3 L/min via diffuser (**Table 1**). The main reason for performing two different methods of CO2 delivery during MIMVR was due to the different techniques used by cardiac surgeons for minimally invasive cardiac surgery. The aim and the methodology of the study was internal discussed with the ethics committee of the hospital according to the General Data Protection Regulation. Because of the retrospective nature of this study, the local ethics committees waived the need for patient consent. The transesophageal echocardiographic (TEE) protocol for the detection of micro-emboli requires to record intraoperative TEE from cross-clamping to 20 min after end of CPB. Post-operatively, a blinded assessor determined the maximal number of gas emboli during each consecutive minute in the left atrium, left ventricle, and ascending aorta. The primary outcome of the study was the incidence of TPOCD (in particular agitation and delirium occurring 5 h following weaning from anesthesia), MV duration and ICU length of stay. During the two procedures, correction for hypercapnia during CPB and monitoring of VCO2 changes were recoreded.

	All ($n=100$)	Continuous CO_2 ($n=50$)	One-shot CO_2 ($n=50$)	*P*-value
Age (years)	66 (62–76)	65 (62–78)	69 (67–79)	<0.001
Male sex	52.5%	43.9%	38.7%	<0.001
Body mass index (kg/m^2)	25.8 (22.2–28.8)	26.8 (23.4–29.0)	24.3 (21.7–28.4)	0.191
Arterial hypertension	32.2%	33.3%	36.1%	0.789
Diabetes mellitus				
Oral antidiabetic drugs	8.9%	7.2%	5.5%	0.006
Insulin	2.3%	2.8%	2.6%	0.530
Hypercholesterolemia	77.4%	38.1%	39.3%	0.899
Renal dysfunction*	1.4%	2.3%	2.1%	0.254
Respiratory or lung disease	2.1%	2.3%	1.9%	0.187
Previous disabling stroke	1.5%	1.5%	1.3%	0.687
History of cancer	1.4%	1.9%	2.5%	0.030
Atrial fibrillation	9.4%	8.3%	11.2%	<0.001
Peripheral vascular disease	1.8%	1.6%	1.9%	0.556
Coronary artery disease	0.9%	0.8%	1.1%	0.81
LVEF				0.347
>50%	93.0%	92.0%	91.2%	
30–50%	6.3%	7.5%	7.5%	
<30%	0.7%	0.5%	1.3%	
Previous surgery	2.3%	1.7%	1.9%	0.211
EuroSCORE II (%)	1.2 (1.1–2.8)	1.2 (1.1–2.7)	1.2 (1.1–2.8)	0.87

Table 1. Characteristics of the study population. Values are given as median (interquartile range) or percentage LVEF, left ventricular ejection fraction *Dialysis or creatinine>2 mg/dL

Surgical technique

Our surgical approach for minimally invasive direct view during mitral surgery was described elsewhere (11). Arterial perfusion was always retrograde and peripheral and aortic cross-clamping was external in all patients. Venous cannulation was peripheral with vacuum support and a double site insertion of the cannulas (jugular and femoral). The valve inspection and procedure were through the left atrium with direct vision and the reconstruction technique was standardized (11).

CO_2 insufflation management and CPB de-airing

A small PVC flexible drain tube was used for CO_2 insufflation as per standardized procedure (12, 13) and flow measurement was performed with a flowmeter for medical CO_2. The perfusionist regulates the flow according to pCO_2 and pH. PaO_2 during CPB was maintained between 150 and 250 mmHg, $PaCO_2$ was maintained through the sweep gas (air flow from gas blender) between 40 and 45 mmHg with pH stat management, and mean arterial pressure was maintained between 50 and 70 mmHg (14, 15). In both groups, the venting flow was maintained 800 ml/min after cross-clamping. Air embolism was managed under TEE guidance; the heart sections were filled, thus obstructing the venous return from CPB and increasing the cavity diameter, and the lungs were manually expanded using an Ambu® resuscitator (Ambu A/S,Ballerup, Denmark) at a rate of 4 inflations per minute. The ventricular and aortic intracavitary aspirators were managed at 750 ml/min and 800 ml/min after cross-clamp removal, and the aortic root vent was removed at the elimination of total gaseous micro-emboli.

Statistical analysis

Continuous data are expressed as median with IQR and categorical data as percentages. Cumulative survival was evaluated with the Kaplan–Meier method. All reported P-values are two-sided, and P-values of <_ _0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

Results

CPB duration was 78 ± _13 min and cross-clamp time was 40 ± _9 min (**Table 2**). The most predominant pathology was degenerative disease, followed by rheumatic mitral valve disease (**Table 3**). Mitral valve repair was performed in all patients with peripheral cannulation. Repair techniques included annuloplasty, leafleat resection, neochordae implantation and sliding plasty. Table 4 depicts the median number of micro-emboli during the first 15 min after release of the aortic cross-clamp in the three areas of interest taken together. All patients in both groups had micro-emboli after release of the aortic cross-clamp in all three areas of interest. The number of micro-emboli recorded with TEE was higher in the control group (**Table 4**) and remained constantly higher during all four time periods and in all three studied locations. In the continuous field flooding CO2 group, the median number of detectable micro-emboli after CPB fell to zero 9 ± 5 min after CPB versus 19 ± 3 min in the one-shot CO2 control group (p = 0.01). In patients of the continuous field flooding CO2 group, correction of ventilation for hypercapnia during CPB was applied, with an increase of mean sweep gas air (2.5 L) and monitoring of VCO2 changes. One patient of the continuous CO2 group vs. 9 patients of the control group reported agitation at discontinuation of anesthesia (p = 0.022). MV duration was 14 ± 3 h vs. 27 ± 4 h (p = 0.016) and ICU length of stay was 33 ± 4 h vs. 42 ± 5 h (p = 0.029) in the continuous CO2 vs. control group, respectively (Table 5). In the whole study population, no transient ischemic attack or stroke was reported at postoperative clinical evaluation (**Fig. 1**).

	Continuous CO_2 ($n=50$)	One-shot CO_2 ($n=50$)	*P*-value
Cardiopulmonary bypass time (min)	79 (65–85)	74 (63–79)	0.98
Cross-clamp time (min)	41 (37–45)	43 (36–47)	0.89

Table 2. Intraoperative data for surgical techniques and procedures.

Mitral valve pathology	Right thoracotomy ($n=100$)	Continuous CO_2 ($n=50$)	One-shot CO_2 ($n=50$)
Degenerative	60 (60%)	26 (52%)	34 (68%)
Functional	28 (28%)	17 (34%)	11 (22%)
Rheumatic	12 (12%)	7 (14%)	5 (10%)

Table 3. Mitral valve pathology for minimally invasive mitral valve repair.

Time period/area of interest	No. of microemboli		*P*-value
	Continuous CO_2 (n = 50)	One-shot CO_2 (n = 50)	
From release of cross-clamp until 20 min after end of CPB			
LA	59 (43–79)	98 (39–129)	< 0.001
LV	49 (45–74)	87 (59–112)	< 0.001
Ao	42 (34–58)	76 (32–88)	< 0.001
LA + LV + Ao	154 (84–195)	261(146–299)	< 0.001
First 15 min after release of cross-clamp			
LA	46 (38–96)	139 (99–159)	< 0.01
LV	65 (58–93)	96 (81–109)	< 0.001
Ao	25 (19–39)	75 (42–89)	< 0.001
LA + LV + Ao	113 (86–157)	310(290–343)	< 0.001
Last 10 min of CPB			
LA	17 (11–43)	27 (9–41)	< 0.01
LV	19 (11–29)	48 (9–59)	< 0.001
Ao	16 (12–37)	36 (25–56)	< 0.01
LA + LV + Ao	52 (42–87)	141(122–156)	< 0.001
First 20 min after end of CPB			
LA	8 (4–21)	48 (19–54)	< 0.01
LV	13 (5–25)	34 (15–41)	0.01
Ao	16 (8–28)	83 (68–98)	< 0.01
LA + LV + Ao	37 (27–58)	165(120–197)	< 0.01

Table 4. Number of microemboli on transesophageal echocardiographic evaluation of the left atrium and ventricle and the proximal ascending aorta. Values are given as median (25th–75th percentile) Ao, aorta; CPB, cardiopulmonary bypass; LA, left atrium; LV, left ventricle.

	Continuous CO_2 (n = 50)	One-shot CO_2 (n = 50)	*P*-value
Microemboli after CPB fell to zero (min)	9 ± 5	19 ± 3	0.01
Agitation at anesthesia discontinuation (no. of patients)	1	9	0.022
Mechanical ventilation (h)	14 ± 3	27 ± 4	0.016
ICU length of stay (h)	33 ± 4	42 ± 5	0.029

Table 5. Peri-operative and post-operative outcome. CPB, cardiopulmonary bypass; ICU, intensive care unit.

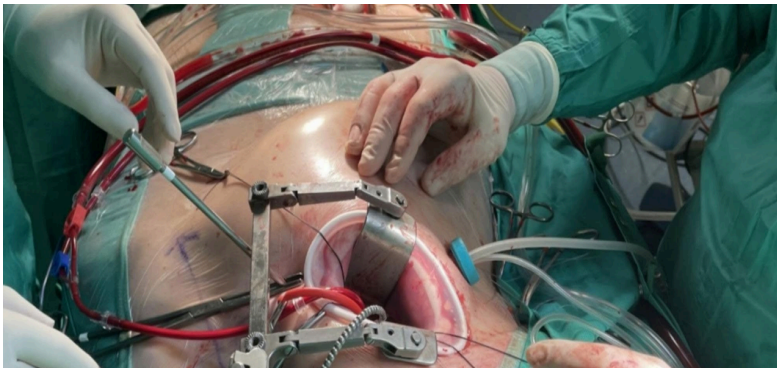

Fig. 1. Right thoracotomy for minimally invasive mitral valve repair.

Discussion

Previous studies (16, 17) demonstrated that the patients without CO_2 use had persistent air bubbles for many minutes after the end of CPB but these studies were not performed under TEE control, as in our analysis, and no cerebro-vascular outcome was reported (18, 19). Moreover, subsequent randomized studies showed no difference or were too small to demonstrate a difference in neurocognitive outcome between CO_2 and no-CO_2 use (20, 21). In other words, our study is the first that demonstrate a clinical impact of that strategy. However, the centrality of TEE use has been previously highlighted for bubble observation (19) but not yet for the clinical outcome effect. Other authors, on the other hand, demonstrated an impact on cardiac function due to less air bubbles in the heart (22). It should be noted that all these studies tried to compare the use vs. non-use of CO_2. We are the first that tried to demonstrate a difference in the use of the CO_2 strategy trying to reduce the possible site effects of CO_2 (e.g. high pCO_2) with the support of the perfusionist and a strategy that focuses the use of gas only during the phase of chamber opening. An excess of micro-embolic activity could influence the patient's awakening by giving drowsiness and transient agitation, this would seem to have an indirect impact on the lack of collaboration by prolonging the time of MV and ICU length of stay. The main limitation of our study is the quantitative assessment of gaseous micro-embolic activity with a correlation for the primary endpoint of the incidence of TPOCD (in particular agitation and delirium upon discontinuation of anesthesia), MV duration and ICU length of stay, which should be further explored in future studies with instrumental investigations (e.g. magnetic resonance imaging), and be correlated with intraoperative bispectral index, electroencephalogram, and evaluated with cognitive tests in the short, medium and long term in relation to the patient age and gender and the impact of retrograde perfusion and atherosclerotic burden (23).

Conclusion

Continuous field flooding insufflation of CO2 in MIMVR is associated with a lower incidence of micro-emboli, possibly due longer exposure to CO2, and a lower incidence of agitation at discontinuation of anesthesia as well as improved MV duration and ICU length of stay.

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Chapter 9

Clinical Evaluation of Micro-Embolic Activity with Unexpected Predisposing Factors and Performance of Horizon AF PLUS during Cardiopulmonary Bypass

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Abstract

Background. During Cardiopulmonary Bypass (CPB) gaseous micro-emboli (GMEs) decrease the quality of the blood flow and the capillary oxygen delivery, increasing the incidence of postoperative neurocognitive disorders (POCD) following cardiac surgery. In these circumstances, the use of an efficient device, could be crucial for the removal and reduction of micro-embolic activity.

Methods. From February 2022 to March 2022, we prospectively collected data from 40 consecutive patients undergoing conventional and minimally invasive cardiac surgery that used the Horizon AF PLUS (Eurosets, Medolla, Italy). We collected, during the CPB's time, the incidence of unexpected predisposing factors for micro-embolic activity reported in the literature with the GMEs count and their diameter through the GAMPT BCC 300 (Germany).

Results. The group of patients without unexpected predisposing factors for micro-embolic activity (55%) reported a GME volume of 0.59 ± 0.1 (µL) in the arterial line (*p*-value 0.67). In both groups were no reported performance deficit during the procedures for oxygenation and CO_2 removal.

Conclusions. Our clinical analysis showed that Horizon AF PLUS is an effective and safe device without iatrogenic perioperative complications, for the reduction of micro embolic activity during CPBs procedures, with high efficiency in terms of oxygenating performance and thermal exchange.

Introduction

The detection and prevention of gaseous micro-emboli (GMEs) during cardiopulmonary bypass has generated considerable interest within the cardiac surgical community. During cardiopulmonary bypass (CPB) conduction, management methods and many unexpected predisposing factors could generate micro-embolic activity (MEA). GMEs decrease the quality of the blood flow and the capillary oxygen delivery, increasing the incidence of transient postoperative neurocognitive disorders (POCD) following cardiac surgery (i.e., postoperative delirium and agitation after anesthesia discontinuation) (1). Postoperative delirium is defined as "a clinical situation in which patients think and speak incoherently, are disoriented and show impairment of memory and attention", which is not explained by a medical history of dementia, but affects the ability to focus, the mechanical ventilation (MV) and the duration and intensive care unit (ICU) length of stay (2). In these circumstances, the use of an efficient device consisting of two components, the venous reservoir and oxygenator, could be crucial in the removal, and thus reduce MEA. However, no consensus exists on when a given diameter or number of emboli becomes injurious to the patient. An important variable is the gas mixture inside the bubble. Nitrogen has a very long dissolution time that results in prolonged ischemia for tissue behind the occlusion. The pathophysiologic reaction of the body, when exposed to GMEs, is most likely based on ischemia caused by partial occlusion of the blood vessels and by endothelial damage. GMEs can be cleared mechanically by using filters, by a reduction in blood velocity, and by a rapid reduction in the nitrogen content (3). Elimination of GMEs is dependent on the design of the cardiopulmonary bypass circuit. A membrane oxygenator, although not designed for it, can remove GMEs. Arterial line filtration is not the best solution for the removal of GMEs, because larger emboli have been fractionated before reaching the arterial filter. Venous line filtration is a more efficient way of clearing gaseous micro-emboli (4). In this context, we conducted an evaluation of micro-embolic activity with unexpected predisposing factors on Horizon AF PLUS during CPB and oxygenation performance.

Materials and Methods

Population and Study Design

From February 2022 to March 2022, we prospectively collected the data of forty patients for elective cardiac surgery procedures at our institution (Department of Cardiothoracic Surgery, Anthea Hospital, Bari, Italy): isolated aortic valve replacement (*n* = 15), coronary artery bypass graft (*n* = 15) and mitral valve repair with a minimally invasive approach (*n* = 10) **(Figure 1**). The patients were aged >28 to 80 years, without chronic kidney failure and with a calculated European System for Cardiac Operative Risk Evaluation II score (mean value, 2.1–2.4%). The study protocol was approved by the local ethics committee and all patients provided written consent to the scientific treatment of their data. All 40 patients, for this study, used the Horizon AF PLUS during cardiopulmonary bypass, which consists of a hard-shell cardiotomy/venous reservoir integrated with two cardiotomy filters, designed to allow venous drainage of the patient's blood, both through the hydrostatic load (height difference between the patient and the reservoir) and the vacuum-assisted venous drainage (VAVD) technique and A.L.ONE AF PLUS **(Figure 2**). The membrane that the oxygenator uses is a microporous hollow-fiber membrane consisting of a gas exchange module with an integrated heat exchanger and an integrated 38 μm arterial filter that ensures arterial blood filtration with the removal of microaggregates and micro-emboli (Eurosets, Medolla, Italy) **(Figure 3**) with only a roller pump. HORIZON AF PLUS's inner contact surfaces are coated with the A.G.I.L.E. (Advanced Generation Inert Layer ECC) system, based on phosphorylcholine (PC), improving the device's blood compatibility by reducing platelet adhesion on the coated surface. Perioperative data included CPB duration, and the incidence of unexpected predisposing factors for micro-embolic activity reported in the literature: a low level in the venous reservoir (<250 mL), vacuum-assisted venous drainage (VAVD), accidental air embolism from the venous line, excessive suction use from aspirators with the GMEs count and their diameter through the GAMPT BCC 300 **(Figure 4 and Figure 5**). The probes were positioned: in the venous drainage line, in the outlet line of the venous reservoir and in the arterial line [1,2,3,4,5]. The primary endpoint was the evaluation of the efficiency of the venous reservoir (VR) and oxygenator (Horizon VR and Oxygenator (Oxy) A.L.ONE AF PLUS) in GME removal,

in terms of the number of total microbubbles with a diameter and air microliters in the arterial line at the end of CPB in relation to unexpected predisposing factors for micro-embolic activity. The secondary endpoint was the evaluation of oxygenation performance in terms of the mean values of PaO_2 and $PaCO_2$ for the target gas blender of 2.0 ± 0.3 L/min and 55 ± 5% FiO_2, and the evaluation of efficiency in the maintenance of thermal exchange in mild hypothermia (from 36 °C to 34 °C and vice versa for nasopharyngeal temperature) for the integrated heat exchanger unit in the A.L.ONE AF PLUS Oxygenator.

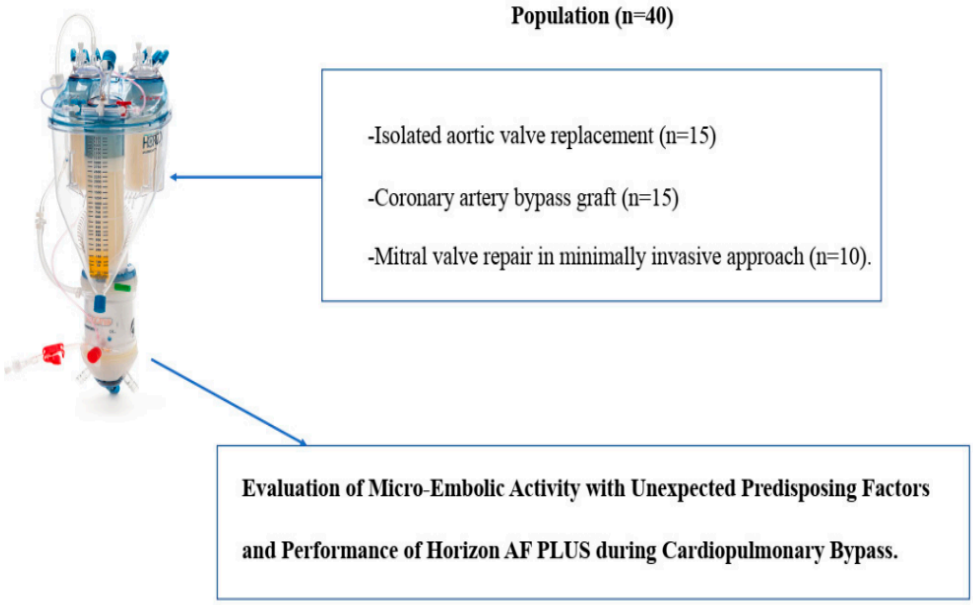

Figure 1. Study Population

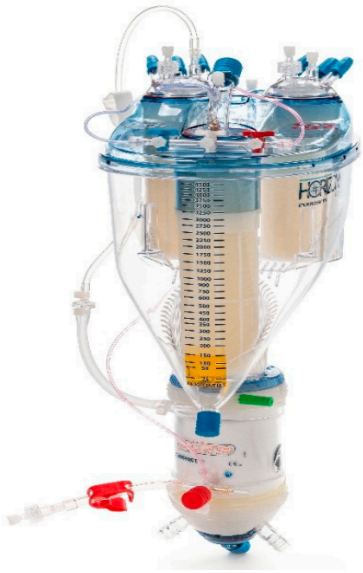

Figure 2. Horizon AF PLUS, Eurosets (venous reservoir and oxygenator).

Figure 3. A.L.ONE AF PLUS Oxygenator.

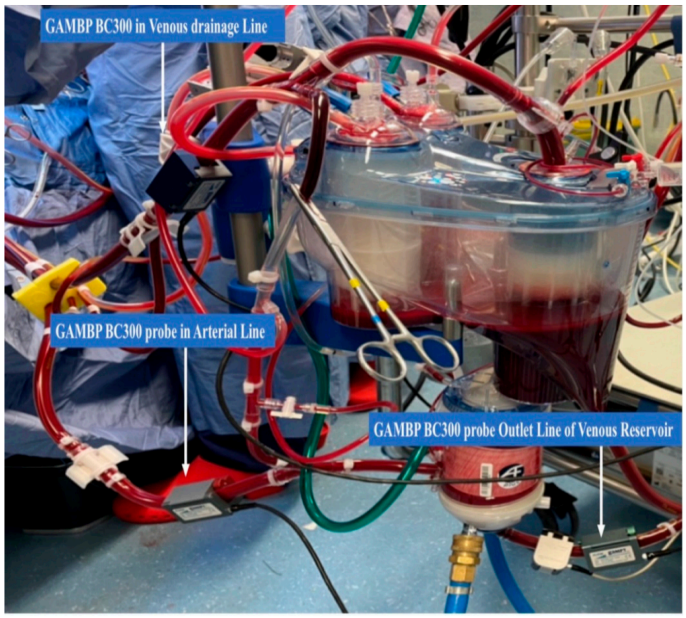

Figure 4. Probes GAMPT BC300 positioning for micro-embolic activity evaluation on Horizon AF PLUS.

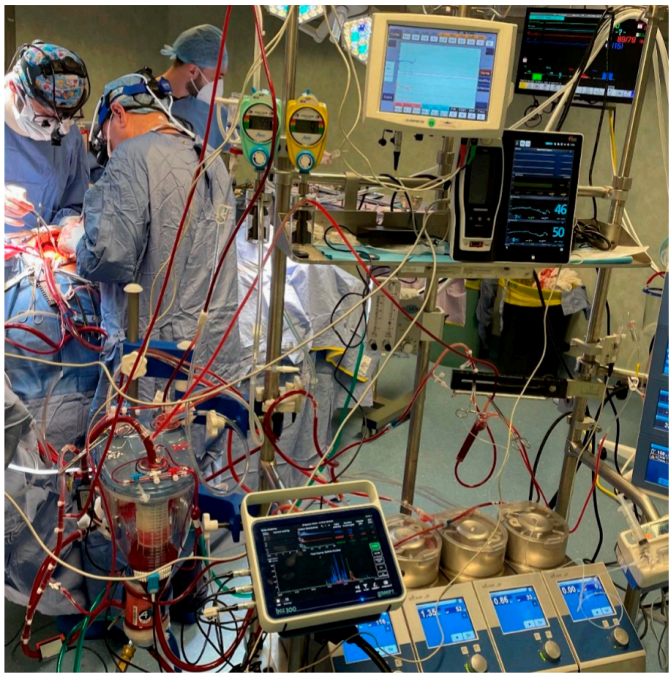

Figure 5. Horizon AF PLUS during cardiopulmonary bypass use with GAMPT BC300.

Anesthetics and Surgical Procedures

The operation was performed under general anesthesia (using propofol, fentanyl, midazolam and rocuronium) using the SedLine® brain function monitoring system (Masimo Corporation, Irvine, CA, USA). The patient was intubated and anesthetized. The arterial and venous lines were prepared. A single-lumen endotracheal tube was used for pulmonary ventilation. A transesophageal echocardiographic (TEE) probe was inserted to examine the anatomy and morphology of the aortic valve and the ascending aorta, and to evaluate aortic valve function and the removal of air before the removal of the cross-clamp. The adhesive pads of the defibrillator were correctly placed on the thoracic wall. The trigger for the administration of red blood cells (RBC) units was a hemoglobin level of less than 8 g/dL both during CPB and in the ICU. For antagonization of heparin, 0.5–0.75 mg protamine was applied for every 100 heparin units. Aortic valve replacement and coronary artery bypass graft procedures were performed in the median sternotomy with central cannulation, MVR was with the right mini-thoracotomy approach with peripheral cannulation, and surgical procedures were performed as routine by 2 surgeons. Concentrated red blood cells were transfused whenever Hb concentrations fell below 6 g/dL during surgery or below 8 g/dL during an ICU stay (2).

Cardio-Pulmonary Bypass Setting

Only the open system (Horizon VR and Oxy AF PLUS, Eurosets, Medolla, Italy) was used for CPB. All patients were treated with mild hypothermic CPB (34–36 ◦C); a volume of 1250 mL crystalloid Ringer acetate solution was used for priming. The surgical procedures selected for this study do not justify the use of moderate hypothermia by falling below 34 ◦C. For this reason, in the event of an initial increase in anaerobic metabolism, the first compensation approach was not to lower the temperature; however, possibly liquids or red blood cells were integrated. The hardware consisted of a Stöckert S5 heart-lung machine and a Stöckert 3T heater-cooler system (LivaNova), and the same cannulae were employed in both groups. The venous drainage line (3/8 inch) and the arterial delivery line (3/8) were each 180cm long, the lines to the pump (3/8 and 1/2) were each 80 cm, and the cardioplegia line (1/16) was 190 cm. The aspiration lines were 1/4. This circuit uses a serial pump with VAVD. Roller pumps were used because aspiration has a management nadir below from 800 mL/min to >2 L/min. A negative pressure of −40 mmHg VAVD was applied to the reservoir. The intracavitary aspirator managed with a roller pump was channeled into a venous reservoir, and the extra-cavitary aspirator was managed with a roller pump (1). The landing monitoring system (Eurosets) was used for DO2 management during CPB. Metabolic parameters were monitored with a DO2 system; the nadir was higher than 280 mL/min/m^2 . The security system used a level alarm, and a bubble probe was used to detect microbubbles leaving the venous reservoir. Anticoagulant therapy consisted of heparin sodium before CPB at 300 IU/kg to give an ACT of greater than 4 by 80 s. Cardioplegia was performed in an antegrade manner with normothermic blood in a 190 cm closed circuit with a bubble-trap filter by a serial micrometric pump, with St. Thomas solution with procaine and repeated every 30 min [2]. During the CPBs procedures, the oxygenator filter purge was kept and managed closed. The GAMPT system, the BCC300, was used for GMEs' count during the procedures. The BC300 uses a pulsed ultrasonic Doppler system with a transmission frequency of 2 MHz. From the Doppler signal of a bubble, one obtains an amplitude-modulated low-frequency signal depending on the size of the bubble and the time in the sound field of the sensor. By means of different filter functions and Hilbert transformations, the signal envelope was calculated and corrected by the reference signal. The maximum amplitude of the corrected signal was a measure of the bubble

size. According to the manual, the BC300 is capable of measuring GME between 5 and 500 mm. The detection limit is 1000 GME per second and it can be used with blood flows between 0.5 and 8 L/min.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation or a median with the interquartile range and categorical data as percentages. Cumulative survival was evaluated with the Kaplan–Meier method. All reported *p*-values were two-sided, and *p*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The mean age was 67 ± 15 years, 40 patients underwent cardiac surgery for conventional and minimally invasive cardiac surgery. Demographic, preoperative and operative details of the patient population are shown **in Table 1 and Table 2**. The unexpected predisposing factors for micro-embolic activity were reported in 18 patients (45%) who underwent CPB procedures, (*n* = 4) accidental air embolism from venous line time (mean values 3 ± 1 min); (*n* = 10) low levels in the venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) time (mean values 8 ± 5 min); (*n* = 4) report a combination of two excessive suctions of aspirators (>2 L/min, >77 RPM) with low levels in the venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) time (mean values 10 ± 2 min). Twenty-two patients (55%) did not report unexpected predisposing factors for micro-embolic activity **(Table 3)**. The patients that reported unexpected predisposing factors for micro-embolic activity reported mean values: n° of bubbles was 259.766 ± 193, 33% reported a diameter >500 µm, GME volume was 40.9 ± 2 (µL) in the venous inlet line of the venous reservoir; n° of bubbles was 68.053 ± 51, 2.3% reported a diameter >500 µm; GME volume was 1.31 ± 0.3 (µL) in the outlet line of the venous reservoir after pump; n° of bubbles was 1.045 ± 41, 0% reported a diameter >500 µm; GME volume was 0.71 ± 0.2 (µL) in the arterial line. The group of patients without unexpected predisposing factors for micro-embolic activity (55%) reported a GME volume of 0.59 ± 0.1 (µL) in the arterial line (*p*-value 0.67)

(Table 4 and Table 5). Mean values of PaO_2 in both groups were 260 mmHg ± 25, and $PaCO_2$ was 38 mmHg ± 4, with no reported performance deficit during the procedures for oxygenation and CO_2 removal (Table 6). The desired thermal objectives in the management of mild hypothermia during CPBs procedures were reached from 36 to 34 °C for the nasopharyngeal temperature (mean time of 5.5 min) by setting a temperature of 34 °C in the heater-cooler device (HCD) and vice versa (mean time 6.5 min), by setting a temperature in the HCD of 36.5 °C **(Figure 6) (Table 7).**

Characteristic	Conventional Cardiac Surgery (n = 30)	Minimally Invasive Mitral Valve Repair (n = 10)
Mean age (y)	69.9	72.5
Male sex	15 (50)	6 (60)
Mean body surface area (m^2)	1.73	1.78
Mean left ventricular ejection fraction (%)	45	50
Median NYHA functional class	2	2
EuroSCORE II (mean)	2.1	2.4
Pre-CPB hematocrit (%)	34.4 ± 1.2	34.4 ± 1.7
Pre-CPB Hb (g/dL)	10.4 ± 1.1	10.8 ± 1.2
No. of chronic obstructive pulmonary disease cases (mean)	27	28
Creatinine (mg/dL)	1.11 ± 0.4	1.09 ± 0.5
Obstructive coronary artery disease (%)	15	0

Values are presented as n (%) or mean ± standard deviation. NYHA, New York Heart Association; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CPB, cardiopulmonary bypass; Hb, hemoglobin.

Table 1. Preoperative profile and operative data.

Parameter	Conventional Cardiac Surgery (n = 30)	Minimally Invasive Mitral Valve Repair (n = 10)	p-Value
CPB time (min)	104 ± 11.1	102 ± 9.34	0.92
Aortic cross-clamp time (min)	78 ± 5	44 ± 6	0.75
Nadir temperature (°C) during CPB	34.9 ± 1.1	34.7 ± 2.1	0.75
Nadir hemoglobin value (mg/dL) during CPB	8.73 ± 1.53	8.6 ± 1.25	0.88
Nadir hematocrit (%) during CPB	26.6 ± 3.4	26.3 ± 3.9	0.89
Nadir DO_{2i} ($mL/min/m^2$) during CPB	294 ± 29	289 ± 14	0.99
O_2ER_i (%) during CPB	23 ± 1	23 ± 5	0.89
Nadir CI ($L/min/m^2$) during CPB	2.5 ± 0.2	2.5 ± 0.1	0.91
Nadir SvO_2 (%)	81 ± 2	80 ± 5	0.93

Table 2. Operative data

Values are presented as mean ± standard deviation. CPB, cardiopulmonary bypass.

Unexpected Predisposing Factors for Micro-Embolic Activity *n* = 18 (45%)	Conventional Cardiac Surgery (*n* = 30)	Minimally Invasive Mitral Valve Repair (*n* = 10)	Phenomena Duration (min) Mean Values
Accidental air embolism from venous line (*n* = 4)	1	3	3 ± 1
Low levels in venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) (*n* = 10)	8	2	8 ± 5
Combination of two excessive suctions of aspirators (>2 L/min, >77 RPM) with low levels in venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) (*n* = 4)	3	1	10 ± 2
Absence of predisposing factors for micro-embolic activity *n* = 22 (55%)	18	4	0

Table 3. Incidence of micro-embolic activity for procedures and duration. Values are presented as n (%) or mean ± standard deviation. CPB, cardiopulmonary bypass.

Unexpected Predisposing Factors for Micro-Embolic Activity on Horizon AF PLUS (*n* = 18)	Venous Inlet Line of Venous Reservoir	Outlet Line of Venous Reservoir	Arterial Line
Accidental Air Embolism from venous line (*n* = 4)			
Gaseous micro-emboli numbers	349.299 ± 28	129.321 ± 60	1.235 ± 73
Diameter >500 µm (%)	45	3.5	0
Volume (µL)	79.9 ± 2	1.49 ± 5	0.89 ± 1
Low levels in venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) (*n* = 10)			

Gaseous micro-emboli numbers	199.111 ± 76	35.720 ± 40	899 ± 47
Diameter > 500 µm (%)	26	1.6	0
Volume (µL)	19.2 ± 2	1.19 ± 6	0.57 ± 1
Combination of two excessive suctions of aspirators (>2 L/min, >77 RPM) with low levels in venous reservoir (<250 mL) in association with vacuum-assisted venous drainage (≥40 mmHg) (n = 4)			
Gaseous micro-emboli numbers	230.889 ± 100	39.119 ± 25	1.001 ± 37
Diameter >500 µm (%)	29	1.9	0
Volume (µL)	23.8 ± 2	1.25 ± 3	0.69 ± 2
Without predisposing factors for micro-embolic activity on Horizon AF PLUS (n = 22)			
Gaseous micro-emboli numbers	99.000 ± 35	18.000 ± 65	559 ± 56
Diameter >500 µm (%)	15	1.2	0
Volume (µL)	12.2 ± 3	0.97 ± 5	0.59

Table 4. Quantification of micro-embolic activity in the circuit for unexpected predisposing factors for micro-embolic activity on Horizon AF PLUS.

Values are presented as mean ± standard deviation.

	Unexpected Predisposing Factors for Micro-Embolic Activity on Horizon AF (n = 18)	**Without Predisposing Factors for Micro-Embolic Activity on Horizon AF (n = 22)**	***p*-Value**
Gaseous micro-emboli volume (µL) in arterial line at the end of CPB	0.71 ± 0.2	0.59 ± 0.1	0.67

Values are presented as mean ± standard deviation. CPB, cardiopulmonary bypass.

Table 6. Evaluation of oxygenation performance in terms of mean values of PaO_2 and $PaCO_2$ for the target gas blender of 2.0 ± 0.3 L/min and 55 ± 5% FiO_2 during CPBs with Horizon AF PLUS.

	PaO_2 mmHg	**$PaCO_2$ mmHg**
Unexpected predisposing factors for micro-embolic activity on Horizon AF PLUS (n = 18)	260 ± 25	38 ± 4
Without predisposing factors for micro-embolic activity on Horizon AF PLUS (n = 22)	260 ± 23	38 ± 6

Table 5. Difference for gaseous micro-emboli volume (µL) in arterial line at the end of CPBs groups with Horizon AF PLUS.

Values are presented as mean ± standard deviation. CPB, cardiopulmonary bypass.

	PaO_2 mmHg	$PaCO_2$ mmHg
Unexpected predisposing factors for micro-embolic activity on Horizon AF PLUS ($n = 18$)	260 ± 25	38 ± 4
Without predisposing factors for micro-embolic activity on Horizon AF PLUS ($n = 22$)	260 ± 23	38 ± 6

Table 6. Evaluation of oxygenation performance in terms of mean values of PaO2 and PaCO2 for the target gas blender of 2.0 ± 0.3 L/min and 55 ± 5% FiO2 during CPBs with Horizon AF PLUS.

Values are presented as mean ± standard deviation. CPB, cardiopulmonary bypass.

Nasopharyngeal Temperature	From 36 °C to 34 °C HCD Setting 34 °C (min)	From 34 °C to 36 °C HCD Setting 36.5 °C (min)
Unexpected predisposing factors for micro-embolic activity on Horizon AF PLUS (n = 18)	5.5 ± 2	6.5 ± 1
Without predisposing factors for micro-embolic activity on Horizon AF PLUS (n = 22)	5.5 ± 1	6.5 ± 2

Table 7. Thermal exchange performance for mild hypothermia during CPBs with Horizon AF PLUS.

Values are presented as mean ± standard deviation. HCD, heater-cooler device; CPB, cardiopulmonary bypass.

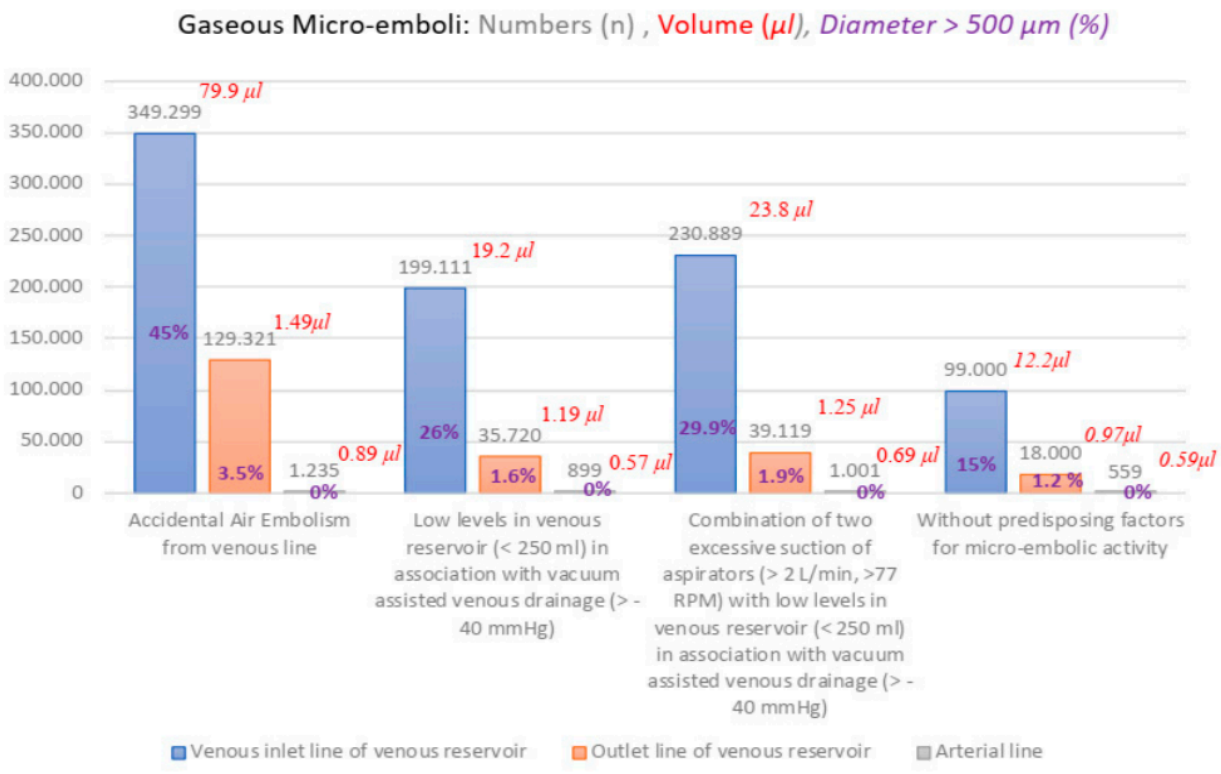

Figure 6. Graphic Representation of gaseous micro-emboli in: Numbers (n), Volume (µL), Diameter > 500 µm (%); with and without predisposing factors for micro-embolic activity during Horizon AF PLUS use.

Discussion

GMEs are considered a cause of neurocognitive deficits. The pathophysiological mechanism is multiple (3). When a microbubble occludes a blood vessel, hypoxia will occur downstream from the blockage (5). The duration of hypoxia and the deleterious effects of this hypoxia will very much depend on the size and number of GME as well as on the gas composition of these microbubbles (6). At the same time, the microbubble will induce local inflammation with edema formation, which will increase the cerebral area at risk. Finally, reperfusion injury may cause additional harm once the initial ischemia is resolved (7). Microbubbles between 20 and 60 μm will be distributed according to the blood flow since they have virtually no buoyancy in moving blood. Microbubbles of 20 μm will be absorbed quickly, depending upon the solubility coefficient and partial pressures of the gas in the bubble and the surrounding blood and tissue (8). This occurs if the bubble is not coated with lipid, which changes the rate of gas exchange between the bubble and blood (9). In this context, for the first time, we have highlighted in our sample an incidence of 45% of sudden events during the conduct of the CPB that can increase the production of GME, independent of the perfusion methodology and technique but linked to the aspect of surgical management (10). The high efficiency of the Horizon AF PLUS device, in counteracting micro-embolic activity, made the result in terms of the volume of microbubbles in the arterial line at the end of CPB, almost comparable to the group (55%) that did not report predisposing factors for the micro-embolic activity during CPB. The limitations of this study were not related to postoperative outcomes, such as (postoperative neurocognitive disorders (POCD), length of stay in ICU and postoperative quality of life) as both groups in this setting reported a low volume of gas micro-emboli in the arterial line of the CPB. However, aspects related to the gaseous micro-embolic activity are often related in cardiac surgery to the management of de-airing before and after removal of the cross-clamp, and to the CO2 management technique in the surgical field. The other limitation of this study was that we analyzed patients with coronary artery disease who are known to have atheroemboli, which could contribute to GME (11–15).

Conclusions

The patients who used Horizon VR and Oxy A.L.ONE AF PLUS (Horizon AF PLUS, Eurosets, Medolla, Italy) with unexpected predisposing factors for micro-embolic activity were not reported as statistically significant in their difference in terms of (µL) the GME volume in the arterial line at the end of the procedures compared with the group that did not report unexpected predisposing factors for micro-embolic activity. Our clinical analysis showed that Horizon AF PLUS is an effective and safe device without iatrogenic perioperative complications, for the reduction of micro embolic activity during CPBs procedures, with high efficiency in terms of oxygenating performance and thermal exchange. However, further studies and samples are needed to validate this report.

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Chapter 10

Propofol pharmacokinetics and pharmacodynamics a perspective in minimally invasive extracorporeal circulation

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Abstract

There is limited evidence as to the pharmacokinetic changes expected in adults with extracorporeal technologies. Drugs may be taken up by various components of the cardiopulmonary bypass circuit itself. Issues include the increased volume of the circuit leading to haemodilution; the sequestration of lipophilic drugs within the circuit tubing; and the absorption of proteins, especially albumin, onto the circuit, which can result in increased free drug. However, in this context, the aspect of pharmacokinetics and pharmacodynamics during minimally invasive extracorporeal circulation has not been described and evidenced by scientific studies. In this single-centre control study of 60 patients undergoing isolated coronary artery bypass grafting, we present the results focused on postoperative albumin values and intraoperative propofol dosages in patients undergoing surgery with minimally invasive ($n = 30$) versus conventional extracorporeal circulation ($n = 30$). In the minimally invasive extracorporeal circulation group, a lower propofol dosage titrated to a bispectral index of 40–45 was used during coronary artery bypass grafting, and an improvement of postoperative concentration of serum albumin was observed compared to the conventional extracorporeal circulation group.

Introduction

There is limited evidence as to the pharmacokinetic changes expected in adults with extracorporeal technologies. In particular, cardiopulmonary bypass (CPB) is associated with significant changes in the pharmacokinetics and pharmacodynamics of anaesthetic drugs (1). Drugs may be taken up by various components of the CPB circuit itself. Issues include the increased volume of the circuit leading to haemodilution; the sequestration of lipophilic drugs within the circuit tubing; and the absorption of proteins, especially albumin, onto the circuit, which can result in increased free drug (1). Various oxygenators have been reported to bind drugs *in vitro*, including volatile anaesthetic agents, propofol, opioids, barbiturates, nitroglycerine, benzodiazepines, nifedipine and antibiotics. For intravenous drugs, this phenomenon has rarely been demonstrated to be clinically important *in vivo*, likely because, depending on protein binding and lipophilicity, any free drug given intravenously and removed by the circuit is replaced from the much larger tissue reservoir (2). Nevertheless, unless the priming solution is primed with drug, and particularly for more hydrophilic drugs, the potential exists for sequestration to lower the concentration below a minimum acceptable therapeutic level when CPB is initiated (3). At present, besides the conventional extracorporeal circulation (cECC) system, which has all the aforementioned components, also minimally invasive extracorporeal circulation (MiECC) has been developed allowing a lower biological impact of CPB and, therefore, less interaction with anaesthetic drugs (4). However, many aspects of the pharmacokinetics and pharmacodynamics in the maintenance of anaesthesia during MiECC and cECC in cardiac surgery procedures are still unknown, particularly for propofol management. In this context, we present the results compared by bispectral index, for the maintenance of anaesthesia with propofol in 60 coronary artery bypass grafting (CABG) procedures managed with MiECC and cECC (5).

Materials and Methods

Patients

In this single-centre, case–control study, 60 patients undergoing isolated elective CABG between September 2019 and September 2020 at our institution were enrolled. The Internal Research Board (Anthea Hospital, GVM Care&Research, Bari, Italy) approved this research (August 2019).

Patients were randomly assigned to MiECC (*n* = 30) or cECC (*n* = 30). The study protocol was approved by the local ethics committee. Patients with chronic renal failure, type 1 or 2 diabetes mellitus, septic shock or endocarditis, and patients with haemoglobin values of <8 g/dl before the procedure were excluded.

Anaesthetics and surgical procedures

Patients were monitored with 5-lead electrocardiography, a left radial artery catheter, capnography, pulse oximeter and rectal/urine bladder temperature sensors. Transoesophageal echocardiography was performed in all patients. Anaesthesia was induced with intravenous sufentanil (0.5–1 µg/kg) and midazolam (0.08–0.2 mg/kg), and tracheal intubation was facilitated with intravenous rocuronium (0.6–1 mg/kg) (2). Anaesthesia was maintained with propofol (2–5 mg/kg) and sufentanil (0.5–2.0 µg/kg), and the depth of anaesthesia was monitored using bispectral index values (BIS XP, Aspect Medical System, Newton, MA, USA). The dosage of propofol was titrated to maintain BIS values between 40 and 45. All operations were performed in median sternotomy and the CABG procedure was performed as routine by 2 surgeons. No albumin supplementation was reported in both groups (5).

Perfusion techniques

Both MiECC and conventional circuits were used for CPB. For the procedures, normothermic CPB was instituted with aortic and double-staged venous cannulas after median sternotomy and heparin administration. Two types of heart-lung machines were

used: conventional system Stockert S5 (cHLM) and modular system Stockert S5 Hybrid (mHLM).

-MiECC Type III Circuit [6]:

- Oxygenator (Inspire® 6F with a biopassive Ph.i.s.i.o phosphorylcholine coating; LivaNova, London, UK)
- or Oxygenator RemoweLL 2 (Eurosets, Medolla, Italy); Venous bubble trap (Eurosets);
- Revolution centrifugal pump (LivaNova);
- or Centrifugal Pump (Medtronic Bio-Medicus, Inc., Eden Prairie, MN, USA);
- Soft shell venous reservoir (Eurosets);
- Landing monitoring systems (Eurosets).

-cECC [4]:

- Reservoir and Oxygenator (Inspire® 6F with a biopassive Ph.i.s.i.o phosphorylcholine coating);
- or Oxygenator RemoweLL 2 (Eurosets);
- Roller pump settings;
- Landing monitoring systems (Eurosets);
- Vacuum-assisted venous drainage (Eurosets).

Normothermic blood cardioplegia (St. Thomas solution) was used in all cases and repeated every 20 min. Oxygen delivery was calculated as follows:

CO (cardiac output) x CaO_2 (arterial oxygen concentration) x 10 (3,4).

Intensive care unit physicians were blinded to group assignment/extracorporeal techniques in the operatory theatre. No fluid restriction protocol was used (5). In both groups, the following measurements were taken: static priming volume and length of the circuits before CPB; during CPB: propofol dosage in relation to BIS index of 40–45; after CPB: postoperative albumin concentration (after 20 h).

Statistical analysis

Statistical analysis between groups was made according to the Hickey's *et al.* (7) criteria. Continuous variables are presented as mean and standard deviation. As descriptive statistics, our results are not being reported as inferential statistics. We used a routine statistical method, Student's *t*-test, which does not require extensive details (7).

Results

Patient characteristics

Baseline characteristics of both groups are reported in **Table 1**. There were no significant between-group differences. The length of the circuits differed between groups, as a result of the statistically different priming volume between MiECC and cECC (Table 2). During the procedure, no differences were recorded in CPB time and cross-clamp time; in contrast, intraoperative propofol dosage was significantly lower and the postoperative serum albu- min was significant higher in the MiECC group **(Table 2)**.

Table 1: Preoperative characteristics

	MiECC ($n = 30$)	cECC ($n = 30$)	*P*-value
Age (years)	71 ± 6.7	69 ± 5.7	0.52
Body surface area (m^2)	1.83 ± 0.6	1.82 ± 0.7	0.7
NYHA class	2 ± 0.5	2 ± 0.8	0.49
EuroSCORE II	1.5 ± 1	1.7 ± 0.9	0.12
Haematocrit (%)	34.6 ± 1.3	34.8 ± 2.1	0.67
Haemoglobin (g/dl)	11.3 ± 1.1	11.4 ± 1.2	0.76
Albumin (g/dl)	5.0 ± 0.5	5.1 ± 0.7	0.8

cECC: conventional extracorporeal circulation; MiECC: minimally invasive extracorporeal circulation; NYHA: New York Heart Association.

Table 2: Circuit details, intraoperative and postoperative results

	MiECC ($n = 30$)	cECC ($n = 30$)	*P*-value
Static priming volume (ml)	450 ± 35	1250 ± 35	0.022
Length of the circuits (m^2)	1	2.2	/
CPB time (min)	62 ± 15.2	60 ± 7.36	0.32
Aortic cross-clamp time (min)	42 ± 9	43 ± 7	0.54
Intraoperative propofol dosage (μg/kg/min)	40 ± 5	60 ± 9	0.016
Postoperative serum albumin (g/dl)	4.3 ± 0.4	2.8 ± 0.6	0.005

cECC: conventional extracorporeal circulation; CPB: cardiopulmonary bypass; MiECC: minimally invasive extracorporeal circulation.

Discussion

There is limited evidence as to the pharmacokinetic changes expected in adults with extracorporeal technologies. Drugs may be taken up by various components of the CPB circuit itself. Issues include the increased volume of the circuit leading to haemodilution; the sequestration of lipophilic drugs within the circuit tubing; and the absorption of proteins, especially albumin, onto the circuit, which can result in increased free drug [6]. Various oxygenators have been reported to bind drugs in vitro, including volatile anaesthetic agents, propofol, opioids, barbitu- rates, nitroglycerine, benzodiazepines, nifedipine and antibiotics. For intravenous drugs, this phenomenon has rarely been demon- strated to be clinically important in vivo, likely because, depend- ing on protein binding and lipophilicity, any free drug given intravenously and removed by the circuit is replaced from the much larger tissue reservoir (2). During CPB, a decrease of the total concentration of intravenous anaesthetic drugs occurs fol- lowing haemodilution. However, propofol and opioids are exten- sively bound to plasma proteins and, therefore, the protein- unbound free propofol results in offsetting the reduction in drug concentration due to haemodilution (1). Nevertheless, unless the priming solution is primed with drug, and particularly for more hydrophilic drugs, the potential exists for sequestration to lower the concentration below a minimum acceptable therapeutic level when CPB is initiated. Following injection of a single intravenous dose of a drug (e.g. induction of anaesthesia), a number of processes are initiated that serve to re- duce drug concentrations. The drug is delivered to and taken up by tissues within the body—a process known as distribution. Distribution to highly perfused tissues such as the brain, heart, lungs, liver and kidneys occurs first (3). Tissue uptake at this stage is variable, depending on factors such as protein binding (typi- cally decreased uptake with increased plasma protein binding) and lipid solubility of the drug (typically increased uptake with increased lipid solubility). Thereafter, distribution occurs into less well-perfused tissues such as muscle and fat (1). As the drug is de- livered to organs such as the liver, kidneys and lungs, elimination by biotransformation and excretion occurs. Elimination may be influenced by age, gender, disease and CPB. For most drugs employed during cardiac surgery, elimination occurs as a con- stant fraction of drug remaining in the body per unit time. This is known as first-order kinetics. Pharmacodynamics describes how a drug interacts with the body to produce changes in

patient physiology. Most drugs pro- duce these effects by interaction with a specific receptor that is the macromolecular component of the organism with which the drug interacts through a lock-and-key or other type of mechanism. This brief report results could be explained by the fact that MiECC was characterized by a reduction in the length of the cir- cuit and a reduced haemodilution [6, 8]; these variables should reduce the absorption of propofol in the extracorporeal circuit, reduce the amount of free drug, improve the quantity of postop- erative serum albumin [9] and also reduce the alteration of the glycocalyx in the microcirculation [4]. We assume that these fac- tors should help to improve pharmacokinetics and pharmacodynamics of propofol during MiECC. However, further studies and research on other drug interactions are needed to understand and strengthen our hypothesis on the improvement of pharmacokinetics and pharmacodynamics of propofol during MiECC. Our study has limitations due to the small sample size and the absence of a 'blind' design. Only future multicentre trials will be able to overcome these limitations.

Conclusion

In this single-centre, case–control study, use of MiECC was asso- ciated with a reduction of propofol dosage titrated to a bispectral index (BIS) index of 40–45 during the CABG procedure, and with an improvement of postoperative concentration of serum albu- min, compared to cECC. This is only an introductory analysis, but future larger studies may confirm the 'numerical' advantages we recorded in our study, which translate into better patient's clinical outcome.

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Chapter 11

Minimally invasive extracorporeal circulation in end-stage coronary artery disease patients undergoing myocardial revascularization

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Abstract

Background. Patients with coronary artery disease and concomitant heart failure (left ventricular ejection fraction < 35%) requiring myocardial revascularization are at risk of poor long-term prognosis and higher mortality. The benefits of minimally invasive extracorporeal circulation (MiECC), particularly in end-stage coronary artery disease patients undergoing myocardial revascularization, have not been completely described.

Materials and methods. In this single-centre control study, 60 end-stage coronary artery disease patients undergoing isolated coronary artery bypass grafting (CABG) were included. Patients were divided into two groups of 30 patients each undergoing CABG using MiECC or conventional extracorporeal circulation (cECC).

Results. In the MiECC group, oxygen delivery index (DO_{2i}) was 305 mL/min/m^2 in relation to indexed oxygen extraction ratio (O_2ER_i) 21.5%, whereas in the cECC group DO_{2i} was 288 mL/min/m^2 in relation to O_2ER_i 25.6% ($p = 0.037$). Lactate levels > 3 mmol/L were reported in 7 MiECC patients vs 20 cECC patients ($p = 0.038$), with blood glucose peak. Mean nadir hemoglobin values during cardiopulmonary bypass (CPB) were 9.7 g/dL in the MiECC group vs 7.8 g/dL in the cECC group ($p = 0.044$). Cardiac index during CPB was 2.4 L/min/m^2 in both groups. Red blood cell units administered were 8 vs 21 units in the MiECC vs cECC group ($p = 0.022$). A glycemic peak was recorded in 7 patients of the MiECC group and in 20 patients of the cECC group ($p = 0.037$).

Conclusion. In end-stage coronary artery disease, the MiECC technique was associated with a higher DO_{2i} compared to cECC. MiECC patients showed a significant reduction in red blood cell unit administration and peak intraoperative lactate levels, which correlated with better postoperative outcome.

Introduction

Patients with coronary artery disease and concomitant heart failure (left ventricular ejection fraction [LVEF] < 35%) requiring myocardial revascularization are at risk of poor long-term prognosis and higher mortality [1]. In this population, the appropriate selection of perioperative techniques and strategies is crucial for the prevention of acute kidney injury (AKI) that frequently occurs after cardiopulmonary bypass (CPB).The management and monitoring of metabolic parameters during extracorporeal circulation (ECC) has gained widespread adoption over the years, particularly in relation to the target values of oxygen delivery (DO_2) > 262 mL/min/m^2, carbon dioxide production > 5.3, indexed oxygen extraction ratio (O_2ER_i) < 25% [2–4], with average blood pressure values during CPB of 50–70 mmHg. This has made it possible to reduce the incidence of postoperative AKI and to improve the management of aerobic vs anaerobic metabolism during cardiac surgery procedures. At the same time, minimally invasive ECC (MiECC) technologies have been developed and introduced into clinical practice [5].The aim of this study was to compare MiECC vs conventional ECC (cECC) in patients with end-stage coronary artery disease undergoing myocardial revascularization.

Materials and Methods

Population and study design

Between February 2020 and May 2021, 60 patients aged > 75–83 years with a mean EuroSCORE II of 9.1–9.5% and LVEF < 35% underwent myocardial revascularization at our institution. A retrospective comparison was carried out in terms of maximum DO_2 and O_2ER_i < 25% for standard cardiac index (CI) of 2.4 (l/min/m^2). Patients were divided into two groups: 30 patients underwent coronary artery bypass grafting (CABG) using MiECC and 30 patients underwent CABG using cECC (Table 1). Metabolic management through blood gas analysis integrated with the use of a metabolic parameter monitoring system during CPB was adopted in both groups.

Table 1 Preoperative characteristics

	MiECC (n = 30)	cECC (n = 30)	*p* value
Age (years), mean	78.7	79.3	0.93
Male sex, *n* (%)	22 (73)	21 (70)	0.91
Body surface area (m^2), mean	1.79	1.78	0.99
Left ventricular ejection fraction (%), mean	28	29	0.89
EuroSCORE II (%)	9.1	9.5	0.92
Pre-CPB Hct (%), mean ± SD	32.4 ± 1.2	32.6 ± 1.9	0.92
Pre-CPB Hb (g/dL), mean ± SD	11.7 ± 1.1	11.8 ± 1.2	0.94
Chronic obstructive pulmonary disease, *n*	6	5	0.96
Creatinine (mg/dL), mean ± SD	1.14 ± 0.2	1.13 ± 0.5	0.98
Obstructive coronary artery disease	30	30	1
Peripheral arterial disease	2	3	0.98

cECC, conventional extracorporeal circulation; MiECC, minimally invasive extracorporeal circulation; CPB, cardiopulmonary bypass; Hb, hemoglobin; Hct, hematocrit; SD, standard deviation

The study protocol was approved by the local ethics committee (session June 2021) and all patients provided written informed consent to data treatment.

Data collection

Patients were selected according to the following criteria:

- Patients with coronary artery disease and concomitant heart failure (LVEF < 35%) requiring myocardial revascularization, in whom complete CPB and cardioplegic arrest had to be foreseen with an expected CPB duration > 90 min.
- Patients were excluded if they presented abnormal plasma lactate levels (> 2 mmol/L) before entering CPB, liver failure, obesity, uncompensated diabetes, autoimmune disease, active infection, any immunosuppressive therapy, or coagulation disorder. Patients undergoing combined surgery (e.g. aortic valve replacement + CABG, about 300 patients during the study period) or surgery with circulatory arrest or having preoperative hematocrit (Hct) < 27% were also excluded.

All CABG procedures (n = 100) were analyzed for this study. Preoperative data included patient demographics, baseline serum creatinine, LVEF, comorbidities (chronic obstructive pulmonary disease, previous cerebrovascular accident), baseline hemoglobin (Hb), EuroSCORE II and New York Heart Association functional class [2].

Perioperative data included type of operation, CPB duration, nadir body temperature during CPB, nadir Hct and Hb values (measured at the start of CPB and every 20 min thereafter), nadir DO_2 index (DO_{2i}), nadir DO_{2i}/O_2ER_i ratio during CPB, nadir CI, nadir CI/mixed venous oxygen saturation (SvO_2), peak serum lactate and glucose during CPB and perioperative administration of red blood cell units.

Postoperative data included peak serum creatinine, mechanical ventilation time and days spent in the intensive care unit (ICU).

The primary endpoints were: maximum DO_{2i} in relation to O_2ER_i during CPB compared between groups in terms of intraoperative lactate and glycemia trends. Secondary endpoints were total red blood cell units transfused, peak postoperative serum creatinine [6–8], mechanical ventilation time, and length of ICU stay.

Anesthetics and surgical procedures

Patients were monitored with five-lead electrocardiography, a left radial artery catheter, capnography, pulse oximetry, and rectal/urine bladder temperature sensors.

Transesophageal echocardiography was performed in all patients. Anticoagulant therapy consisted of heparin sodium before CPB at 300 IU/kg to achieve an activated clotting time of > 480 s (ACT PLUS Medtronic, Minneapolis, MN, USA); for heparin neutralization, 0.5–0.75 mg protamine was given for every 100 heparin units. Anesthesia was induced with intravenous sufentanil (0.5–1 μg/kg) and midazolam (0.08–0.2 mg/kg), and tracheal intubation was facilitated with intravenous rocuronium (0.6–1 mg/kg). Anesthesia was maintained with propofol (2–5 mg/kg) and sufentanil (0.5–2.0 μg/kg), and bispectral index values (BIS XP, Aspect Medical System, Newton, MA, USA) were used for depth of anesthesia monitoring. The dosage of propofol was titrated to maintain bispectral index values between 40 and 60. Aortic valve replacement and CABG procedures were performed in median sternotomy with central cannulation, and surgical procedures were performed as routine by two surgeons. Concentrated red blood cells were transfused whenever Hb concentrations fell below 6 g/dL during surgery or below 8 g/dL during ICU stay. The goal of hemoconcentration was to eliminate the excess of crystalloid administration.

Cardiopulmonary bypass setting

MiECC group

A closed MiECC type III circuit was employed using Stöckert S5 heart-lung machine (LivaNova, London, UK) [5], whose design presents the characteristics of a volume management circuit (MiECTiS classification). A shunted venous soft-shell reservoir (Closed, Eurosets, Medolla, Italy) was used, aortic root and pulmonary artery venous suction drainage was managed in sequence. The components (Biopassive Coating Phisio, LivaNova, London, UK) (Fig. 1) were as follows: venous-arterial line diameter (3/8), venous bubble-trap (Sherlock, Eurosets), a centrifugal pump (Biomedicus BPX80, Medtronic, Eden Prairie, MN, USA), and a polypropylene fiber oxygenator (Alone, Eurosets). A bubble detection system was used to remove the air from the bubble trap and the circuit (Stockert, LivaNova). Circuit filling volume 500 mL crystalloid solution. 300 IU/kg of sodium heparin were administered, the activated clotting time prior to CPB was 501 s, the cannulas were connected to the air-free circuit, and the bypass with a closed system was set up, the reference value of management of venous drainage was central venous pressure, maintained around 5 mmHg using urapidil as a vasodilator for higher values, or upon request of drainage by the surgeon, the Trendelenburg position was used for lower values [4, 5, 9, 10]. All patients were treated with mild hypothermic CPB (34–36 °C). For the administration of myocardial protection, a closed circuit for cardioplegia with heat exchanger, with an infusion syringe pump and Saint Thomas solution with procaine were used and repeated every 30 min. The Landing monitoring system (Eurosets, Medolla, Italy) was used for DO_2 management during CPB. In both groups, blood gas analyses were performed using alpha-stat management with a blood gas analyzer (GEM Premier 3000 IQM, Instrumentation Laboratory, Werfen Group IVD company, Munchen, Germany) set to measure at 37 °C [11]. On the basis of arterial blood data, we assessed the lowest Hct (percentage) on CPB; every 20 min, an arterial blood gas analysis, including blood glucose (mg/dL) and lactate (mmol/L) determination, was obtained. An Hb value < 6 g/dL during CPB was considered the trigger point for red blood cell transfusion. All patients received tranexamic acid according to routine protocol. Mean arterial pressure during CPB procedures was managed for values between 55 and 70 mmHg.

Fig. 1 Minimally invasive extracorporeal circulation (MiECC) during myocardial revascularization in end-stage coronary artery disease patients

cECC group

Open circuits with roller pumps (Admiral, Remo-well Eurosets, Medolla, Italy; Inspire 6 F, LivaNova, London, UK) were used for CPB. Pericardial blood was collected separately and could be processed or reinjected, if needed. The hard shell and softshell reservoir, oxygenating module and circuits were treated with phosphorylcholine (Agile Eurosets, Medolla, Italy; Phisio, LivaNova, London, UK). All patients were treated with mild hypothermic CPB (34–36 °C); a volume of 1250 mL crystalloid Ringer acetate solution was used for priming. The surgical procedures selected for this study do not justify the use of moderate hypothermia by falling below 34 °C. For this reason, in the event of an initial increase in anaerobic metabolism, the first compensation approach was not to lower the temperature but possibly liquids or red blood cells were integrated. The hardware consisted of a Stöckert S5 heart-lung machine and a Stöckert Heater Cooler System 3 T (LivaNova, London, UK) and the same cannulae were employed in both groups. For the administration of myocardial protection, a closed circuit for cardioplegia with heat exchanger, with an infusion syringe pump in sequence and Saint Thomas solution with procaine were used and repeated every 30 min. The Landing monitoring system (Eurosets, Medolla, Italy) was used for DO_2 management during CPB. In both groups, blood gas analyses were performed using alpha-stat management with a blood gas analyzer (GEM Premier 3000 IQM, Instrumentation Laboratory, Werfen Group IVD company, Munchen, Germany) set to measure at 37 °C [11]. On the basis of arterial blood data, we assessed the lowest Hct (percentage) on CPB; every 20 min, an arterial blood gas analysis, including blood glucose (mg/dL) and lactate (mmol/L) determination, was obtained. An Hb value < 6 g/dL during CPB was considered the trigger point for red blood cell transfusion. All patients received tranexamic acid according to routine protocol. As in the MiECC group, mean arterial pressure during CPB procedures was managed for values between 55 and 70 mmHg.

Statistics

Statistical analysis was made according to Hickey's criteria. Continuous variables are presented as mean and standard deviation. As descriptive statistics, our results are not reported as inferential statistics. We used a routine statistical method, i.e. Student's t-test, which does not require extensive details.

Results

Demographic, preoperative and operative details of the patient population are shown in **Tables 1 and 2**.

Table 2 Operative data

	MiECC (n = 30)	cECC (n = 30)	*p* value
CPB time (min), mean ± SD	115 ± 9.2	110 ± 6.17	0.93
Aortic cross-clamp time (min), mean ± SD	71 ± 4	69 ± 6	0.83
Nadir temperature during CPB (°C), mean ± SD	34.9 ± 1.1	34.7 ± 2.1	0.75
Nadir Hb value during CPB (mg/dL), mean ± SD	9.7 ± 1.5	7.8 ± 1.2	0.044
Nadir Hct during CPB (%), mean ± SD	29.8 ± 0.3	25.1 ± 2.1	0.043
Nadir Hb after CPB (mg/dL), mean ± SD	9.4 ± 0.1	7.2 ± 0.8	0.044
Nadir Hct after CPB (%), mean ± SD	29.2 ± 0.1	24.3 ± 0.9	0.045
Nadir DO_{2i} during CPB (mL/min/m^2), mean ± SD	305 ± 9	288 ± 6	0.037
O_2ER_i during CPB (%), mean ± SD	20 ± 1	25 ± 3	0.0029
Nadir CI during CPB (L/min/m^2), mean ± SD	2.4 ± 0.2	2.4 ± 0.1	0.94
Nadir SvO_2 (%)	81 ± 2	75 ± 5	0.038
Crystalloid solution (mL)	328 ± 41	727 ± 57	0.039
Red blood cells (units)	8	21	0.021
Red blood cells during CPB (units)	3	10	0.023
Red blood cells during ICU stay (units)	5	11	0.024

cECC, conventional extracorporeal circulation; MiECC, minimally invasive extracorporeal circulation; CI, cardiac index; CPB, cardiopulmonary bypass; DO_{2i}, indexed oxygen delivery; Hb, hemoglobin; Hct, hematocrit; ICU, intensive care unit; O_2ER_i, indexed oxygen extraction ratio; SD, standard deviation; SvO_2, mixed venous oxygen saturation

There were no difference between groups in preoperative characteristics; all patients had LVEF < 35% and underwent isolated CABG with prior risk assessment (EuroSCORE II 9.1–9.5%). In the MiECC group, oxygen delivery index (DO_{2i}) was 305 mL/min/m^2 in relation to indexed oxygen extraction ratio (O_2ER_i) 21.5%, whereas in the cECC group DO_{2i} was 288 mL/min/m^2 in relation to O_2ER_i 25.6% ($p = 0.037$). Lactate levels > 3 mmol/L were reported in 7 MiECC patients vs 20 cECC patients ($p = 0.038$), with blood glucose peak **(Table 3).** Mean nadir Hb values during CPB were 9.7 g/dL in the MiECC group vs 7.8 g/dL in the cECC group ($p = 0.044$). CI during CPB was 2.4 L/min/m^2 in both groups. As for liquid administration, including anesthesia infusions, 727 mL and 328 mL of crystalloid solution were given to MiECC and cECC patients, respectively ($p = 0.039$) **(Table 2**). Red blood cell units administered were 8 vs 21 units in the MiECC vs cECC group ($p = 0.022$). A glycemic peak was recorded in 7 patients of the MiECC group and in 20 patients of the cECC group ($p = 0.037$). Patients with hyperlactatemia during CPB showed a significant increase in serum creatinine [7], higher rate of prolonged mechanical ventilation and longer ICU stay **(Table 4).** No patient underwent ultrafiltration during CPB.

Table 3 Peak blood lactate and DO_{2i} in relation to O_2ER_i during cardiopulmonary bypass in the MiECC and cECC groups

	No hyperlactatemia or hyperglycemia	Hyperlactatemia and hyperglycemia
MiECC		
No. patients	23	7
Peak blood lactate (mmol/L)	1.08 ± 0.19	1.93 ± 0.25
Mean DO_{2i} (mL/min/m^2)	304 ± 21	275 ± 19
Mean O_2ER_i (%)	20 ± 3	38 ± 4
Blood glucose (mg/dL)	129 ± 9	205 ± 11
cECC		
No. patients	10	20
Peak blood lactate (mmol/L)	1.28 ± 0.45	3.91 ± 1.21
Highest DO_{2i} (mL/min/m^2)	289 ± 11	265 ± 19
Highest O_2ER_i (%)	25 ± 3	33 ± 4
Blood glucose (mg/dL)	149 ± 3	230 ± 11

Values are given as mean ± standard deviation. cECC, conventional extracorporeal circulation; DO_{2i}, indexed oxygen delivery; MiECC minimally invasive extracorporeal circulation; O_2ER_i, indexed oxygen extraction ratio

Table 4 Hyperlactatemia during cardiopulmonary bypass and postoperative outcome

	MiECC (n = 30)		cECC (n = 30)	
	No HL (n = 23)	HL (n = 7)	No HL (n = 10)	HL (n = 20)
Peak serum creatinine (mg/dL)	1.1 ± 0.1	1.4 ± 0.5	1.19 ± 1.1	1.7 ± 1.5
MV time (h)	19.6 ± 45	55 ± 31	22.6 ± 55	52 ± 49
ICU stay (days)	1.2 ± 2.1	5.2 ± 4.9	1.5 ± 2.1	6.1 ± 2.9

Values are given as mean ± standard deviation. cECC, conventional extracorporeal circulation; MiECC minimally invasive extracorporeal circulation; HL, hyperlactatemia; ICU, intensive care unit; MV, mechanical ventilation

Discussion

This retrospective study aimed at comparing two different CPB techniques (i.e. MiECC type III vs cECC) in end-stage coronary artery disease patients undergoing myocardial revascularization in terms of DO_{2i} values in relation to O_2ER_i with the same target CI, and of incidence of peak lactate and correlation with postoperative outcome. More specifically, the type of ECC technique can influence intraoperative DO_{2i} with blood product use but hemodilution being equal. In other words, mean DO_2i was higher in the MiECC group compared to the cECC group with higher Hb and Hct, though with less transfusions administered since the flow rate of the two circuits would have been the same. The reduced hemodilution with MiECC can also account for the better results obtained in this group in terms of lower O_2ER_i. The relationship between hyperlactatemia and hyperglycemia through the above mechanism was confirmed by Revelly et al. in 2005 [12] in an elegant study on cardiogenic or septic shock. The role of adrenergic agonists in this setting is well defined: in cardiogenic shock, these drugs are either endogenous or administered for cardiovascular therapy; in our model, they were endogenous in the majority of patients. None received epinephrine during CPB, and few received norepinephrine; however, unlike epinephrine, norepinephrine usually does not increase glucose production or induce an increase in plasma lactate concentration [13–15]. The two mechanisms leading to hyperlactatemia in various clinical conditions are therefore (1) anaerobic metabolism due to a poor DO_2, and (2) excess lactate production due to glucose failing to enter the oxidative pathway and being degraded to lactate by the glycolytic pathway [13, 15, 16]. These mechanisms, if independently considered, lead to different acid–base balance conditions, the former being accompanied by metabolic acidosis and the latter not necessarily so. However, in the clinical conditions of this observational study, the acid–base balance is constantly maintained at a normal pH value by bicarbonate corrections applied by the perfusionist whenever the base excess starts decreasing. Therefore, we were unable to identify differences in hyperlactatemia related to different values of peak blood lactate. However, the evidence that only four patients showed hyperlactatemia without hyperglycemia and that only patients with a hyperlactatemia-hyperglycemia syndrome had significantly lower DO_2 values seems to confirm that, in our specific clinical environment,

hyperlactatemia and hyperglycemia are linked by the causative factor of a poor DO_2. This leads on one hand to lactate production through the anaerobic pathway and on the other hand to a vicious cycle of lactate production due to the poor ability to use glucose through the aerobic pathway [3, 6, 11, 17]. Reduced oxygen content in cases of acute anemia is usually compensated by reduced blood viscosity with increased blood flow in the microcirculation and by a compensatory increase in cardiac output [18]. This last mechanism may be impaired during CPB, where pump flow is usually adjusted on the basis of the patient's body surface area and temperature, not the Hb value. On the basis of our data, the main rationale for explaining hyperlactatemia during CPB is a DO_2 inadequate to guarantee the needed oxygen consumption of the patient. In the present study, we investigated the role of potentially modifiable factors related to CPB during CABG surgery in determining postoperative hyperlactatemia (e.g. due to inadequate perfusion) and hyperglycemia [19]. Our results demonstrate that a $DO_{2i} < 270$ mL/min/m^2 with $O_2ER_i > 35\%$ and low CI (< 2.4 L/min/m^2) with $SvO_2 < 65\%$ during CPB are associated with hyperlactatemia and hyperglycemia and $DO_{2i} > 290$ mL/min/m^2 with $O_2ER_i < 25\%$ and CI > 2.4 L/min/m^2 with $SvO_2 > 75\%$ during CPB are associated with a low incidence of hyperlactatemia and hyperglycemia. Various preoperative factors or comorbidities may create the right environment for hyperlactatemia during CPB. Age, female gender, congestive heart failure, low LVEF, hypertension, atherosclerosis, diabetes, preoperative Hb value, redo or complex surgery, and emergency procedures were found to be risk factors for hyperlactatemia by Demers and coworkers [20], who reported an hyperlactatemia incidence of 18%. Some of these factors were confirmed in our study, and other new factors were identified. However, our study population had a significantly shorter CPB duration and a lower degree of hemodilution during CPB. Given that both these factors seem to favor the onset of hyperlactatemia, the lower hyperlactatemia rate in our population is reasonably explained. The role of CPB duration in the development of hyperlactatemia during CPB has been highlighted in other studies [2, 20, 21]. Moreover, the additional volume of crystalloid in the cECC group resulted in significant hemodilution as indicated by the mean Hb values which were more than 2 g/dL greater for the MiECC group during CABG. This factor alone could have had a large impact on the other dependent variables, including lactate levels and oxygen delivery.

Study limitations

Several limitations should be acknowledged. First, this is a single-centre study with a small sample size. Second, we did not know the microcirculation response for the higher Hb values in the MiECC group compared to the cECC group. Third, there were no inflammatory markers (cytokines) that could affect postoperative outcome, including DO_{2i}. Fourth, eight pre- and intraoperative factors were found to be significantly associated with peak blood lactate levels during CPB at univariate analysis (i.e. age, isolated coronary operation, lowest pump flow/blood pressure, requirement of vasopressor or inotropic medications, lowest temperature, Hct, and DO_{2i}) which were negatively correlated with peak blood lactate levels during CPB, whereas CPB duration and peak blood glucose were positively correlated with peak blood lactate levels during CPB. Notwithstanding this, the samples were homogeneous as for the characteristics. The Landing monitoring system was used for DO_2 management during CPB; however, we did not record time durations < 280 mL/min/m^2. Finally, the availability of perfusionists with and without skills for managing the MiECC technique is another limitation of the study.

Conclusion

End-stage coronary artery disease patients undergoing myocardial revascularization with the MiECC technique had a higher DO_{2i} in relation to O_2ER_i 20–25% compared to patients operated on with the cECC technique. MiECC patients showed a significant reduction in blood red cell units administered, in the incidence of peak intraoperative lactate, which correlated with reduced postoperative serum creatinine and shorter mechanical ventilation and ICU stay, as compared to cECC patients.

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Chapter 12

Magnetic levitation pump versus constrained vortex pump: a pilot study on the hemolysis effect during minimally invasive extracorporeal circulation

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Abstract

Background. Elevated plasma free hemoglobin is associated with multi-organ injury. In this context, minimally invasive extracorporeal technologies represent a way to reduce this complication following cardiac surgery.

Methods. We present a pilot study focused on plasma free hemoglobin levels in 40 patients undergoing isolated coronary artery bypass grafting (CABG). The same circuits for minimally invasive extracorporeal circulation (MiECC) were used in all patients. The ECMOLIFE magnetic levitation pump was used in the study group (n = 20), and the AP40 Affinity CP centrifugal blood pump was used in the control group (n = 20).

Results. In the immediate postoperative period, plasma free hemoglobin (PFH) and lactate dehydrogenase (LDH) were significantly lower in the study group than in the control group (10.6 ± 0.7 vs 19.9 ± 0.3 mg/dL, $p = 0.034$; and 99.16 ± 1.7 vs 139.17 ± 1.5 IU/L, $p = 0.027$, respectively). Moreover, patients treated with the magnetic levitation pump showed lower creatinine and indirect bilirubin (0.92 vs 1.29 mg/dL, $p = 0.030$ and 0.6 ± 0.4 vs 1.5 ± 0.9 mg/dL, $p = 0.022$, respectively) at 24 h after the procedure, and received fewer transfusions during the whole postoperative period (3 vs 9 red blood cell units (RBC), $p = 0.017$).

Conclusion. Our pilot study suggests that the use of magnetically levitated centrifugal pumps for extracorporeal circulation support is associated with a lower risk of hemolysis, though larger studies are warranted to confirm our results.

Introduction

Minimizing the risk of blood damage (i.e. hemolysis) using minimally invasive extracorporeal technologies is critical, especially if patients show higher hematocrit values during cardiopulmonary bypass (CPB). The recent generation constrained vortex pumps, with their inherent design improvements, could lead to a reduction in red blood cell trauma. However, this topic is a source of potential bias, including the use of magnetically levitated pumps [1, 2]. In particular, hemolysis and plasma free hemoglobin release during extracorporeal circulation can occur from a number of patient-related and technical factors and might be worse with high flows and/or excess negative pressures within the circuit and blood transfusions [1, 2]. Elevated plasma free hemoglobin is associated with multi-organ injury, including severe acute kidney injury [3].In this context, we present a pilot study on two different pump technologies, a magnetic levitation pump vs a constrained vortex pump, comparing 40 patients undergoing isolated coronary artery bypass grafting (CABG) using a minimally invasive extracorporeal circulation (MiECC) type IV system, which enables volume management.

Materials and Methods

Between September 2019 and September 2020, 40 consecutive elective patients undergoing isolated CABG with MiECC type IV were included in the study. The study period and the patients to be enrolled were selected on the basis of the number of magnetic levitation pumps to be tested and a request was made for comparing them in a pilot study with the centrifugal pumps normally used in our center. The study protocol was approved by the local ethics committee and informed consent was obtained from all individual participants included in the study. Patients with chronic kidney disease, type 1 or 2 diabetes mellitus, anemia or other individual risk factors for hemolysis were excluded. The decision to perform CABG with MiECC was left to the cardiac surgeon in accordance with the perfusionists team. During the study period, 196 isolated CABG operations were performed; of these, 156 were excluded based on the afore mentioned exclusion criteria and 40 patients consented to participate in the study.

Modular MiECC type IV with the ECMOLIFE magnetic levitation pump was used in the study group (Levitation Group, n = 20), and modular MiECC type IV with the AP40 Affinity CP centrifugal blood pump was used in the control group (Vortex Group, n = 20).

Closed circuit was performed with modular MiECC, whose design presents the characteristics of a volume management circuit (MiECTiS classification). A shunted venous soft-shell reservoir was used, the aortic root and pulmonary artery suction was managed in series venous return. The reference value for the management of venous drainage was the central venous pressure, maintained using urapidil as a vasodilator for higher values, or upon request of drainage by the surgeon, using the Trendelenburg position for lower values. All patients were treated with mild hypothermic CPB (34 °C to 36 °C).

All CABG procedures were performed under cardioplegic arrest through median sternotomy and oro-tracheal intubation. During surgery and postoperatively, the need for blood transfusion was established according to the institutional protocol of the heart team based on the patient's oxygenation status in addition to predefined hemoglobin levels. In any case, blood volume was never re-transfused from the cell saver.

Normothermic CPB was instituted with aortic and double-staged venous cannulas. Two types of heart lung machines were used:

In the Levitation Group, the ECMOLIFE console (Eurosets, Medolla, Italy) with the ECMOLIFE centrifugal pump (Eurosets, Medolla, Italy) was used **(Fig. 1A**);

- In the Vortex Group, Stockert S5 (cHLM) with Bio-console 560 (Medtronic Bio-Medicus, Inc., Eden Prairie, MN) with the AP40 Affinity CP centrifugal pump (Medtronic Bio-Medicus, Inc., Eden Prairie, MN, USA) was used **(Fig. 1B).**

In both groups, the following components were used for the MiECC type IV circuit (**Fig. 1**):

- Oxygenator alone (Eurosets, Medolla, Italy);
- Venous bubble trap (Eurosets, Medolla, Italy);
- Soft shell venous reservoir (Eurosets, Medolla, Italy);
- Landing monitoring systems (Eurosets, Medolla, Italy).

In both groups, the MiECC procedure was managed without using extra-cavitary suction but using a cell saver [4].

Static priming volume mean values (mv): 450 ± 35 mL; Circuit length (mv): 1 m^2; no retrograde autologous priming was made.

Normothermic blood cardioplegia (St. Thomas solution) was used in all cases and repeated every 20 min.

During CPB, the following parameters were measured and collected (every 5 min) in both groups:

- Cardiac index,
- Indexed oxygen delivery,
- Central venous pressure,
- Inlet pressure of the centrifugal pump,
- Revolution per minute of the pump and the oxygenator pressure drop,
- Pressure of arterial cannula,
- Hematocrit,
- Hemoglobin.

After CPB, the following parameters were measured in both groups:

- Plasma free hemoglobin (10 min after CPB),
- Lactate dehydrogenase (at 24 h),
- Indirect bilirubin (at 48 h),
- Creatinine (postoperative peak),
- Total red blood cell units administered intra- and postoperatively.

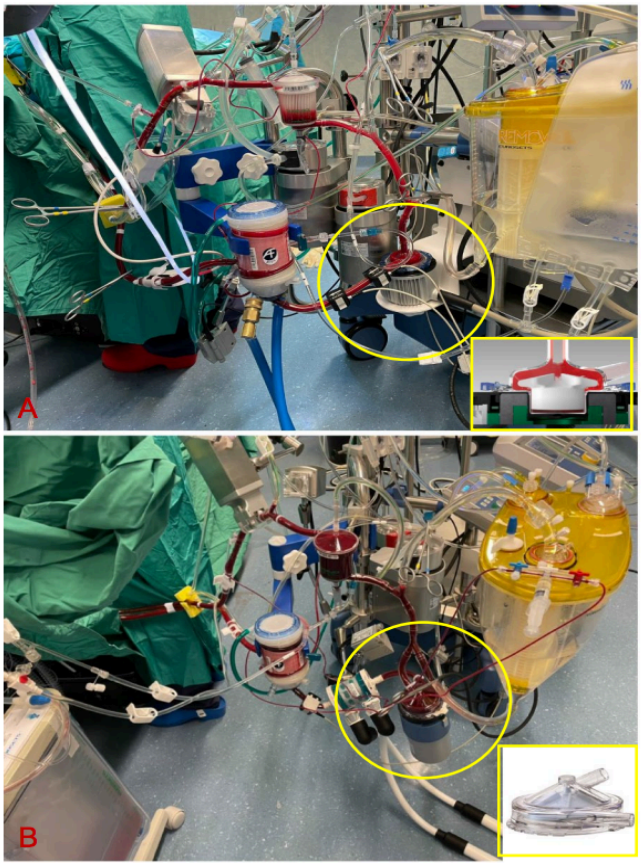

Fig. 1 **A** MiECC with magnetic levitation pump, ECMOLIFE (highlighted); **B** MiECC with constrained vortex pump, AP40 (highlighted)

Results

The patient characteristics and the perioperative results are described in **Table 1**. No deaths or major postoperative complications were recorded in the 40 patients in the postoperative period.

Table 1 Patient characteristics intra and postoperative results

	Levitation Group (n = 20)	Vortex Group (n = 20)	*P*-value
Preoperative			
Age (years) (mean ± SD)	71.0 (63.7)	69 (58.7)	0.89
Body surface area (m^2)	1.83	1.82	0.94
EuroSCORE II	1.5	1.7	0.88
Pre-CPB hematocrit (%) (mean ± SEM)	34.6 ± 1.3	34.8 ± 2.1	0.99
Hb (g/dL)	12.3 ± 1.1	12.3 ± 1.2	1
Serum creatinine (g/dL)	0.83 ± 0.5	0.85 ± 0.7	0.96
PFH (mg/L)	0.02	0.01	1
Intraoperative			
CPB time (min)	72 ± 15.2	71 ± 7.36	1
Aortic cross-clamp time (min)	52 ± 9	51 ± 7	0.93
DOi_2 ($mL/min/m^2$)	339 ± 20	338 ± 17	0.99
CI ($L/min/m^2$)	2.4 ± 0.2	2.4 ± 0.1	0.99
Pump speed (rpm)	2800 ± 140	2880 ± 160	0.98
Pump inlet pressure (mmHg)	56 ± 10	58 ± 9	0.88
CVP (mmHg)	5 ± 3	6 ± 2	0.89
Hct (%)	34 ± 2	32 ± 1	0.69
Hb (g/dL)	11.5 ± 0.5	11.3 ± 0.6	0.76
Oxygenator pressure drop (mmHg)	45 ± 4	41 ± 2	0.79
Arterial pressure cannula (mmHg)	105 ± 9	104 ± 7	0.89
MAP (mmHg)	65 ± 7	63 ± 4	0.91
Postoperative			
PFH at 10 min after CPB (mg/L)	10.6 ± 0.7	19.9 ± 0.3	0.034
LDH at 24 h after CPB (IU/L)	99.16 ± 1.7	139.17 ± 1.5	0.027
Creatinine peak after CPB (mg/dL)	0.92	1.29	0.030
RBC (units)	3 (0.15/patient)	9 (0.45/patient)	0.017
Indirect bilirubin after CPB (mg/dL)	0.6 ± 0.4	1.5 ± 0.9	0.022

CI, cardiac index; CPB, cardiopulmonary bypass; CVP, central venous pressure; DOi_2, indexed oxygen delivery; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; MAP, mean arterial pressure; PFH, plasm free hemoglobin; RBC, red blood cells; SD, standard deviation; SEM, standard error of the mean

Discussion

Our pilot study suggests that the use of magnetic levitation pumps can reduce the degree of hemolysis in patients undergoing CABG with modular MiECC type IV, though confrmation from larger studies is required. It was demonstrated that free-hemoglobin is not signifcantly increased by centrifugal pump [5]; however, no study reported a diference between the levitation pump and the centrifugal pump on this hemolysis endpoint. To the best of our knowledge, this is the frst study using this MiECC system in this patient subset. Te promising results recorded may provide direction for further research on this topic, which may have an impact on postoperative clinical outcomes as partly observed in our pilot study. Te major limitation of our study is the small sample size, as only 20 magnetic levitation centrifugal pumps were received or tested. Tat is the reason for the study design: this is not a randomized study but only a pilot study aiming to assess, as frst endpoint, the safety and feasibility of this new technology. Another limitation is the lack of haptoglobin measurement; plasma free hemoglobin and lactate dehydrogenase were used as hemolytic indices. Moreover, the higher number of transfusions in the Vortex Group can represent a bias for the increased postoperative bilirubin and lactate dehydrogenase. However, this may support the advantage of using the magnetic levitation pump. Te clinical signifcance of our study can easily be understood: current guidelines suggest that MiECC systems should be used routinely, especially in the feld of coronary surgery [6]. Furthermore, recent studies [7, 8] suggest to improve minimally invasive extracorporeal systems towards minimal biological invasiveness and greater biocompatibility. Te use of MiECC with a magnetic levitation centrifugal pump, if it confrms its ability to reduce hemolysis on larger scale samples, could represent an important technological advance in this direction.

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Chapter 13

Magnetic levitation pumps for cell-free hemoglobin prevention during VV ECMO

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Increased plasma concentrations of circulating cell-free hemoglobin (CFH) are supposed to contribute to the multifactorial etiology of acute kidney injury (AKI). In their recent article: “The role of cell-free hemoglobin and haptoglobin in acute kidney injury in critically ill adults with ARDS and therapy with VV ECMO.”, Graw et al. identified a cohort of 1044 ARDS patients with CFH and haptoglobin measurements before initiation of ECMO therapy. They concluded that in critically ill patients with ARDS requiring therapy with VV ECMO, increased plasma concentration of CFH were an independent risk factor for AKI. Among patients with increased CFH concentrations, higher plasma haptoglobin concentrations might protect from CFH-associated AKI [1]. In this context we reported our experience about the effect of Magnetic levitation pump versus Constrained vortex pump on the hemolysis effect during extracorporeal technologies for short time. We reported a pilot study focused on plasma free hemoglobin levels in 40 patients undergoing isolated coronary artery bypass grafting (CABG). The same circuits for minimally invasive extracorporeal circulation (MiECC) were used in all patients. The ECMOLIFE magnetic levitation pump was used in the study group (n = 20), and the AP40 Affinity CP centrifugal blood pump was used in the control group (n = 20). In the immediate postoperative period, cell-free hemoglobin (CFH) and lactate dehydrogenase (LDH) were significantly lower in the study group than in the control group (10.6 ± 0.7 vs. 19.9 ± 0.3 mg/dL, p = 0.034; and 99.2 ± 1.7 vs. 139.2 ± 1.5 IU/L, p = 0.027, respectively). Moreover, patients treated with the magnetic levitation pump showed lower creatinine and indirect bilirubin (0.92 vs. 1.29 mg/dL, p = 0.030 and 0.6 ± 0.4 vs. 1.5 ± 0.9 mg/dL, p = 0.022, respectively) [2]. We think that the materials selection during VV-ECMO with the use of magnetic levitation pump (Fig. 1) for long time could be crucial for the possible reduction of CFH and the indirect bilirubin, however further studies are needed to support our opinion.

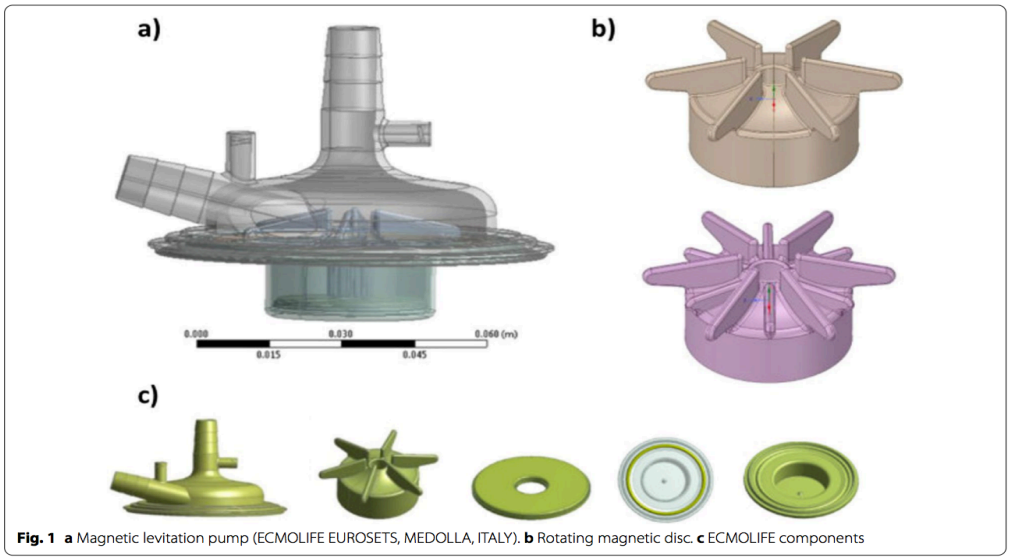

Fig. 1 **a** Magnetic levitation pump (ECMOLIFE EUROSETS, MEDOLLA, ITALY). **b** Rotating magnetic disc. **c** ECMOLIFE components

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Chapter 14

General Discussion

Extracorporeal techniques and metabolic management.

The world of extracorporeal technologies is very broad and varies in the selection of techniques and materials. This aspect of wide variability has a physiopathological impact on inflammation and metabolic management secondary to extracorporeal circulation. For instance, the use of an "active coating" is associated with better preservation of the endothelial glycocalyx compared with "passive coating" circuits. However, probably the biggest challenge for ECC in order to improve biocompatibility is the elimination of air-blood contact [1]. This is very intuitive, given that in nature blood does not come into contact with air but circulates in a closed system. A blood-air interface (BAI) in the ECC circuit causes activation of the blood elements [2] and the generation of a systemic inflammatory response syndrome (SIRS). The pros and cons in terms of air, inflammation and biocompatibility of open (conventional ECC), closed (minimally invasive ECC, or MIECC), and vacuum (Fibonacci Techniques) systems are well known and also address in the presented research project. In a future perspective, more availability of standardized flexible extracorporeal techniques in relation to the type of patient (frail and at high risk) and procedures could reduce the invasiveness of cardiopulmonary bypass [3]. The aspect of metabolic management in ensuring the correct oxygen delivery during ECC has been widely described in the literature, particularly on the prevention of acute kidney injury (4,9). However, many aspects inherent to peri-procedural ECC management appear fuzzy both in cardiopulmonary bypass and in ECMO [4]. The relationship between indexed oxygen delivery (DO_{2i}) in relation to Oxygen Extraction Ratio (O_2 ERi), for the prevention of anaerobic metabolism in terms of lactate production versus cardiac index (C.I.) and in relation to mixed venous saturation (SvO_2), has been well described (5,6,7). Such an approach has been shown more appropriate for the ECC management and monitoring in a retrospective study of 500 patients (8). The application of the metabolic approach of goal-directed perfusion to the management of ECMO has been proposed (9), although in this particular ECC setting, the perfusion management occurs more at a macro level, merely based on measured parameters (10). Our findings in this respect (11) open up a new perspective of metabolic-based management also of ECMO although there must be future studies to support it despite initial promising evidences.

Advanced Extracorporeal Techniques and Device Efficiency for Improving Patient Outcome.

The use of mechanical circulatory support, and particularly ECMO, following mitral valve surgery accounts for almost 35% of patients receiving such support for postcardiotomy shock (12). However, this aspect has been poorly investigated in the literature. The results of peri-operative extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) application in an overall population of 5901 mitral valve surgery procedures during a period of 6 years from eleven tertiary cardiac surgery institutes were analyzed (13). In this retrospective analysis, incidence for the treatment of post-carditomy shock with ECMO and IABP was 0.2% and for low cardiac output syndrome was 1.6%, confirming that such adverse vent rate in elective mitral valve surgery is very low (14). Interestingly, the patients who received the perioperative IABP in minimally invasive mitral valve surgery (MIMVS) through right minithoracotomy reported a reduced mortality compared to full-sternotlomy patients in relation to the operative risk and surgical technique. Low incidence of V-A ECMO was found in both surgical accesses, but only one patient survived after V-A ECMO after MIMVS (13). Despite this study reports a good result for mitral valve surgery both in FS and MIMVS, perioperative cardiogenic shock is a life-threatening complication and is associated with increased morbidity, short- and long-term mortality, and marked healthcare resource utilization (15,16). The presented analysis represents a pilot of our experience.

The application of ECMO is steadily increasing in various cardiovascular medicine settings (17,18)). Technology is improving and providing a series of new devices widening the choice of the device availability for such a field of mechanical circulatory support. Eight-year data from a single cardiac surgery unit on the use exceeding 14 days of the A.L.ONE ECMO adult oxygenator in polymetylpentene (Eurosets, Medolla, Italy) for ECMO procedures were collected and analyzed (19). The performance of such an ECMO oxygenator in our experience has shown efficiency in terms of O_2 uptake and CO_2 removal, blood fluid dynamics, metabolic compensation and heat exchange in protracted. The device was safe, without major malfunction-related events over a period of 14 days in patients undergoing V-A or V-V ECMO. Oxygenator replacement

need was not reported in the group of patients undergoing conventional ECMO-related anticoagulation, whereas three replacements were required in the group that did not receive continuous heparin infusion due to concomitant major bleeding (19,20). Oxygenator malfunction due to thrombosis in conditions which necessitate stopping the anticoagulation regimen is not unusual, particularly in patient experiencing major bleeding requiring massive blood transfusion, in accordance with our reported series (19). Furthermore, in this study, a classification of the short-, medium-, long-term use of the oxygenating module in relation to its certification and validation has been presented (19). This study also demonstrated that the determinant that can impact the duration of the oxygenator and its failure in particular after cardiac surgery procedures does not depend exclusively on the model and design but mainly on the medical and technical management of the device in relation to the anticoagulant (19).

Water condensation and gas exchange correlation in different models and fibers of ECC oxygenators has been a concern raised in recent studies (20). We also addressed this potential issue in ECC management in a series of adult patients undergoing cardiac surgery procedures (21). The result of this study shows an inversely proportional correlation between gas exchange and condensation in statistically significant values. Furthermore, our findings showed that, in polypropylene and polymethylpentene fiber oxygenators, the production of condensation was increased at the oxygenator gas outlet during the use of normothermia, as shown in other series (22). Limiting the use of heat exchanger time during ECC seems to reduce the production of water loss and condensation and improve the stability of exchanges in terms of PaO2 in the long-term ECC. Our findings show that during blood heating there is an increase in humidity and water loss at oxygenator gas outlet with a concomitant decrease of PaO2 (23). The production of condensation and water loss from the gas oxygenator gas output has been treated in various studies (11,22). However, a strong correlation with gas exchange has never been highlighted (21) indicating that further investigations are necessary also in this setting to elucidate such a phenomenon and its clinical implications.

Continuous field flooding insufflation of CO2 in MIMVR is associated with a lower incidence of micro-emboli, possibly due longer exposure to CO2, and a lower incidence of agitation at discontinuation of anesthesia as well as improved MV duration and ICU length of stay (24). In our study on this topic, CO_2 management in surgical field and

gaseous micro-embolic activity correlated with postoperative disfunction (POCD) on 100 consecutive minimally invasive mitral valve repair (MIMVR) procedures (25). Previous studies have demonstrated that the patients without CO2 use had persistent air bubbles for many minutes after the end of ECC but these studies were not performed under TEE control (26), as in our analysis, and no cerebro-vascular outcome was reported (27,28). Moreover, subsequent randomized studies showed no difference or investigations with very limited patient cohorts to demonstrate a difference in neurocognitive outcome between CO2 and no-CO2 use (24). Therefore, our study is the first which demonstrates a clinical impact of that strategy. However, as shown in our investigation, the centrality of TEE use has been previously highlighted for bubble observation (27) but not yet for the clinical outcome effect.

Microgaseous emboli during ECC might be generated also within the ECC-related components, and, particularly, in the oxygenator (28). Gaseous micro-emboli (GME) are considered a cause of neurocognitive deficits after ECC-related procedures. The pathophysiological mechanism is multiple. When a microbubble occludes a blood vessel, hypoxia will occur downstream from the blockage. The duration of hypoxia and the deleterious effects of this hypoxia will very much depend on the size and number of GME as well as on the gas composition of these microbubbles (30). The use of new device, specifically designed to hemofiltrate the patient blood and makedly reduce microgaseous emboli. In order to investigate the performance in this respect of a specific ECC component, the data from 40 consecutive patients undergoing conventional and minimally invasive cardiac surgery with the use of Horizon AF PLUS oxygenator (Eurosets, Medolla, Italy) were collected and analyzed (29). During ECC, The incidence of unexpected predisposing factors (low level of reservoir blood volume…..) for micro-embolic generation reported in the literature (29) with the gaseous micro-embolis count and their diameter through the GAMPT BCC 300 (Germany) were assessed and monitored. The patients who underwent ECC with the Horizon VR and oxygenator A.L.ONE AF PLUS with unexpected predisposing factors for micro-embolic activity, did not show any statistically significant difference in terms of (µL) the GME volume in the arterial line at the end of the procedures compared with the group that did not report unexpected predisposing factors for micro-embolic activity. Our clinical analysis showed, therefore, that Horizon AF PLUS is an effective and safe device for the

reduction of micro embolic activity during CPBs procedures, with high efficiency in terms of oxygenating performance and thermal exchange, as shown in other series (28,30).

The pharmacodynamics and kinetics during ECC represent another relevant aspect of CPB and ECMO management (31). Indeed, several pharmacological compounds have been shown to be absorbed with marked reduction in circulating levels and, hence, decreased therapeutic activity (32). The pharmacodynamics and pharmacokinetics of propofol was tested in 60 patients undergoing MiECC technique vs conventional CPB, respectively (33). The study findings showed a containment of propofol levels for the bispectral index correlated with the reduction of hemodilution (32) to the reduction of the contact surface and to an increase in plasma albumin values (33).

Cardiac surgery procedure in patients with diffuse coronary artery disease may pose peculiar issues and concerns (34). The impact of the ECC-related inflammatory and circulatory threats may facilitate organ dysfunction and favor perioperative complications (35). The use of MIECC has been shown to likely reduce such damages or injury (REF). To investigate such an aspect, the metabolic impact of 30 MiECC procedures were compared to 30 conventional CPB in end-stage CABG patients (36). The MiECC group showed a more effective multi-organ preservation, in accordance with other clinical series (34,35).

Finally, the type of CPB-related pumps have been shown to be responsible for specific perioperative complications, like blood element-related consumption/destruction, particularly related to red cells hemolysis due to shear stress (37,38).In a limited cohort of 40 patients, we evaluated the centrifugal magnetic levitation pump compared to the constrained vortex pump in the MiECC context (39). The patients in the magnetic levitation group reported a containment of plasma free hemoglobin and a reduction in the incidence of renal damage, as also shown in other series (40).

Further issues*:* The Generative Machine Learning on Extracorporeal Monitoring Devices.

The future research perspective on perfusion techniques will be dedicated to the study of machine learning in the planning and management of extracorporeal circulation, since the main limitation of the studies and research addressed in this thesis previously has limited numbers and samples. Machine learning has experienced a revolutionary decade with advances across many disciplines. There has been enormous interest in applying machine learning and artificial intelligence to healthcare and, in particular, to data-rich environments like the intensive care unit. In this context, we present our theoretical concept of a system based on artificial intelligence and on management algorithms designed to support operator choices during metabolic management in cardiopulmonary bypass. Intelligent systems and algorithmic supports are widely established and considered indispensable in the safety systems integrated into the extracorporeal consoles that regulate cardiopulmonary bypass and extracorporeal membrane oxygenation. They have prevented adverse events during the procedures performed in the last decade. Although management of metabolism during cardiopulmonary bypass remains crucial, no systems and algorithms exist that are integrated to support the prevention of acute kidney injury or anaerobic metabolism. This situation results in wide variability of the management procedures carried out by the operators. For example, one can achieve 280 ml/min/m^2 of indexed oxygen delivery in several ways: through an increase in the cardiac index or transfusion of blood products or ultrafiltration or diuresis. These different pathways can have different clinical impacts. Integrating management algorithms in a metabolic monitoring system in relation to the analysis of the monitored variables could provide the most appropriate predictive path. The concept that we favour and propose should be able to provide a colour code to indicate the parameter to be improved (red), the secondary parameters to be improved (orange), and the final corrective solution (green). The blue color code shows a positive correlation and the red code a negative correlation between the related parameters (Figure 1). Machine learning has experienced a revolutionary decade, with advances across many disciplines. There has been enormous interest in applying machine learning and artificial intelligence to health care and, in particular, to

cardiovascular perfusion and cardiac surgery. During CPB, the fluids in the goal-directed perfusion have an effect in increasing the flow rate and venous return but have a negative effect on the oxygen delivery, predisposing to the consumption of blood products. We think that integrating these graphs across multiple numbers will help in the future to understand the cause-and-effect relationships on various rehabilitation programs (41).

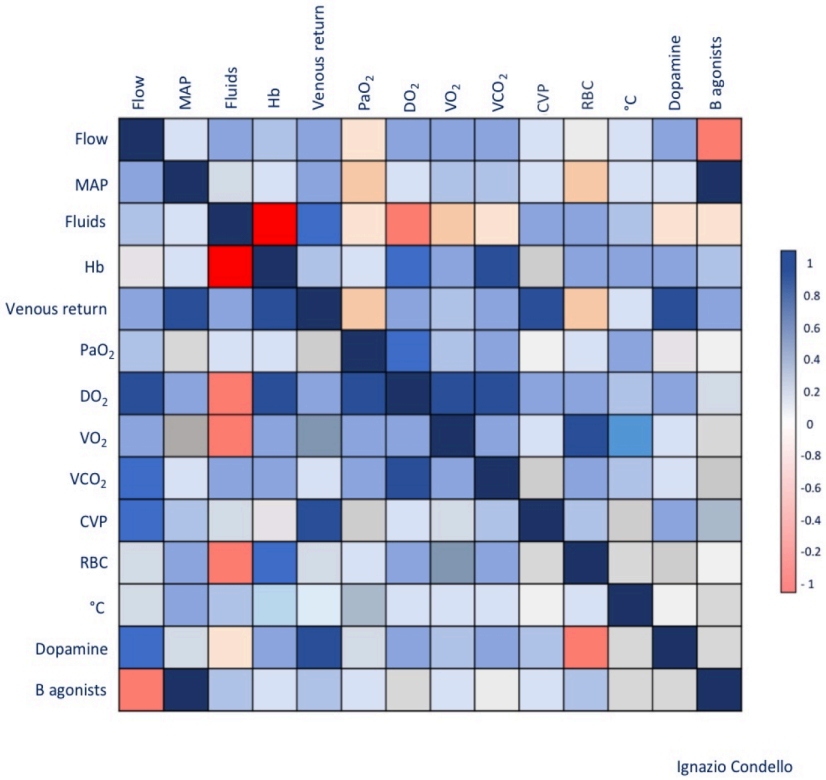

Figure 1. Machine Learning during CPB Graphical Representation.

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Chapter 15

Impact

We aimed to investigate the issue about the Effects, Management and Optimization of Extracorporeal Techniques and Technologies in Contemporary Cardiac Surgery. we have investigated all the aspects related to inflammation, biocompatibility, air-blood contact transversely to the various perfusion techniques (***chapter 2)***, a new metabolic nadir of the DO_2 relationship has been investigated and researched on the prevention of the anaerobic metabolism inherent in $ERiO_2$ (***chapter 3)***, looking in the context of 'ECMO to deepen the concept of Goal Directed Perfusion and to transfer the inherent skills on conventional extracorporeal circulation and MiECC (***chapter 4)***. We evaluated the incidence of LCOS on MIMVR and the use of ECMO and IABP was collected (***chapter 5***). On the post cardiotomy and VV ECMO VA procedures, the duration and oxygenating performance was evaluated in relation to the continuity of the anticoagulant therapy (***chapter 6***). The phenomenon of condensation in the oxygenator gas outlet was analyzed on the oxygenating modules and correlated to the exchange performance during the procedures (***chapter 7***). CO_2 management is a useful tool for the prevention of air embolism during minimally invasive mitral valve surgery procedures. We compared two techniques, demonstrating that continuous administration is superior to one shot administration (***chapter 8***). Micro-embolic activity for unexpected predisposing factors was analyzed during the conduct of cardiopulmonary bypass (***chapter 9***). The MiECC technique was studied on the management aspects of propofol pharmacodynamics and kinetics (***chapter 10***), on metabolic preservation for goal directed perfusion in end stage coronary artery disease (***chapter 11***), and on the benefits of magnetic levitation on hemolysis prevention in minimally invasive extracorporeal circulation ***(chapter 12***) and ECMO ***(chapter 13)***.

The techniques and approaches to extracorporeal circulation have a clinical impact in terms of organ protection, preservation from cerebrovascular damage and cognitive dysfunction. This thesis shows how integrating many aspects related to monitoring the selection of components can impact the post-operative outcome. Even the management of ECMO can be crucial we have introduced observations on the management and preservation of the long-term management of the oxygenator (***chapter 7***). Management of micro-embolic and embolic activity is crucial in cardiac surgery We have integrated the role of CO_2 administration technique for post-operative cognitive disorders (POCD) prevention with the appearance and utility of cardiopulmonary bypass technologies and monitoring in the prevention of micro-embolic activity (***chapter 9-10***). The MiECC technique has been studied in detail on the aspects of the pharmacodynamics of Propofol in relation to the content of albumin, hemodilution and contact surface (***chapter 11***), the metabolic impact on frail patients has been investigated compared to the conventional CPB (***chapter 12)***, and we have evaluated the benefits of the magnetic levitation pump on the reduction of hemolysis on short-term procedures (***chapter 13***).We presented this thesis with the aim of integrating the knowledge of cardiopulmonary bypass to the ECMO procedure and vice versa. In the world of research and development of new technologies, the key role of metabolic management is increasingly gaining scientific evidence, and the role of advanced techniques is increasingly crucial in reducing the adverse effects of conventional cardiopulmonary bypass. The holistic approach presented in this thesis represents an evolution of expedients on extracorporeal technologies aimed at the organic preservation of the patient by focusing on various aspects covered in the chapters of the thesis (***chapter 2, chapter 3, chapter 4***).

Chapter 16

Summary

The inflammatory response in cardiac surgery using extracorporeal circulation (ECC) has beenextensively discussed, we presented through literature research, various extracorporeal techniques that aim to reduce the impact on inflammation with the elimination of air-blood contact, the reduction of hemodilution through the length of the circuit and the use of coating in extracorporeal surfaces, such as minimally invasive extracorporeal circulation. The retrospective study associations between oxygen delivery and cardiac index with hyperlactatemia during cardiopulmonary bypass showed on 500 extracorporeal procedures that the management of DO2i in relation to O2ERi was 16% more specific in terms of negative predictive value for hyperlactatemia during CPB compared to the use of CI in relation to SvO2, patients who reported the absence of hyperlactacidemia had a low incidence of acute kidney injury and reduction in time of stay in intensive care unit. The literature review: "Goal-directed extracorporeal circulation: transferring the knowledge and experience from daily cardiac surgery to extracorporeal membrane oxygenation" described that in extracorporeal circulation, predictive target parameters have been found and consolidated, especially in terms of acute kidney injury and the prevention of anaerobic metabolism, while for ECMO management a vague path remains. In this context, we reviewed the strategies for optimal targeted therapy during CPB and ECMO, trying to transfer the knowledge and experience of daily cardiac surgery to venoarterial ECMO.

The retrospective research: "Perioperative incidence of ECMO and IABP on 5901 mitral valve surgery procedures" reported the incidence and outcomes of perioperative extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) in patients undergoing mitral valve surgery (MVS) via right mini-thoracotomy (RT) and conventional full sternotomy. FS). The ECMO and IABP incidence for the treatment of PCS was 0.2% and for Low Cardiac Output Syndrome (LCOS) 1.6% in elective mitral valve surgery was very low. The patients using the perioperative IABP in minimally invasive mitral valve surgery (MIMVS) via RT reported reduced mortality compared to FS in relation to the operative risk and surgical technique. A low incidence of VA-ECMO was found with the RT and FS approach; only one patient survived after VA-ECMO after minimally invasive mitral valve surgery.

The retrospective study: “Long-term ECMO, efficiency and performance of EUROSETS adult A.L.ONE ECMO oxygenator” collected on long-term use of more than 14 days of Eurosets A.L.ONE ECMO Adult oxygenator in polymethylpentene fiber, for ECMO procedures, including the procedures: Veno Arterial (VA) ECMO post-cardiotomy or not, veno-venous (VV) ECMO. In this research the device was safe with no iatrogenic issues over a 14-day period in the patients undergoing ECMO VA and in all patients undergoing VV ECMO with continuous administration of anticoagulation therapy. The study: “Water Condensation and Gas Exchange Correlation in Different Models and Fibers of Blood Oxygenators: How Can We Improve Performance?"presented the phenomenon of water condensation in blood oxygenators, a phenomenon that is constantly present during cardiopulmonary bypass and extracorporeal life support in the medium to long term. This perspective research found an inverse correlation between gas exchange and condensation in statistically significant values during the use of normothermia and a reduction in oxygenation performance in polypropylene and polymethylpentene fiber oxygenators. The carbon dioxide (CO2) used in the operating field to prevent brain or heart damage due to air embolism is a well-known strategy in open-heart surgery. However, there is no general consensus on the best delivery approach. In the retrospective research: “Continuous field flooding versus final one-shot CO_2 insufflation in minimally invasive mitral valve repair” showed that continuous CO2 insufflation by field flooding in MIMVR is associated with a lower incidence of microemboli and less agitation upon discontinuation of anesthesia, along with improved MV duration and intensive care unit length of stay. During Cardiopulmonary Bypass (CPB), gaseous microemboli (GMEs) reduce blood flow quality and capillary oxygen supply, increasing the incidence of postoperative neurocognitive disorders (POCD) after cardiac surgery. Our clinical analysis: “Clinical Evaluation of Micro-Embolic Activity with Unexpected Predisposing Factors and Performance of Horizon AF PLUS during Cardiopulmonary Bypass.” showed that Horizon AF PLUS is an effective and safe device without iatrogenic perioperative complications, for the reduction of microembolic activity during CPB procedures, with high efficiency in terms of oxygenation performance and thermal exchange.

There is limited evidence on the pharmacokinetic changes expected in adults with extracorporeal technologies. The study: "Propofol pharmacokinetics and pharmacodynamics-a perspective in minimally invasive extracorporeal circulation" presented that the minimally invasive extracorporeal group, used a lower dose of propofol during coronary artery bypass grafting, titrated to a bispectral index of 40–45, and an improvement in postoperative serum albumin concentration was observed compared with the conventional extracorporeal circulation group. Patients with coronary artery disease and concurrent heart failure (left ventricular ejection fraction < 35%) requiring myocardial revascularization are at risk for poor long-term prognosis and increased mortality. The study: "Minimally invasive extracorporeal circulation in end-stage coronary artery disease patients undergoing myocardial revascularization" demonstrated that in end-stage coronary artery disease, the MiECC technique was associated with a higher DO2i compared to cECC. The elevated plasma free hemoglobin is associated with multiorgan injury in the literature. The study: "Magnetic levitation pump versus constrained vortex pump: a pilot study on the hemolysis effect during minimal invasive extracorporeal circulation" presented a pilot study focused on plasma free hemoglobin levels in 40 patients undergoing isolated coronary artery bypass grafting (CABG). The pilot study suggested that the use of magnetically levitated centrifugal pumps for extracorporeal circulation support is associated with a lower risk of hemolysis. The use of magnetically levitated centrifugal pumps to support extracorporeal circulation is associated with a lower risk of hemolysis, although larger studies are warranted to confirm our results. In critically ill patients with ARDS requiring therapy with VV ECMO, increased plasma cell free hemoglobin concentration (CFH) was an independent risk factor for AKI. In patients with elevated CFH concentrations, higher plasma haptoglobin concentrations could protect against CFH-associated AKI. The choice of equipment during VV-ECMO with long-term use of a magnetic levitation pump could be crucial for the possible reduction of CFH and indirect bilirubin, but further research is needed to support our opinion.

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Chapter 17

Samenvatting

De inflammatoire reactie van het lichaam op het gebruik van extracorporele circulatie (ECC) tijdens cardiale chirurgie is uitgebreid beschreven in de literatuur. Wij beschreven meerdere technieken om de inflammatoire reactie te reduceren. Naast het elimineren van lucht-bloed-contact en reduceren van hemodilutie door de lengte van het EEC te beperken, kan het gebruik van een speciale beschermlaag in de ECC de reactie van het lichaam op het systeem verminderen. De retrospectieve studie die de associatie tussen het zuurstofaanbod en de cardiac index met hyperlactatemie legt tijdens cardiopulmonale bypass (CPB), toonde aan dat de negatief voorspellende waarde voor hyperlactatemie 16% specifieker was voor de relatie tussen het geïndexeerde zuurstofaanbod (DO2i) en de geïndexeerde zuurstof-extractie ratio (O2ERi) ten opzichte van de relatie tussen de cardiac index en de gemengde veneuze saturatie (SvO2) tijdens CPB. Patiënten zonder hyperlactatemie hadden een lagere incidentie voor acute nierinsufficiëntie en een korter intensive care unit verblijf. Metabolismemanagement is essentieel tijdens het toepassen van extracorporele technologieën. Extracorporele membraan oxygenatie (ECMO) en CPB zijn conceptueel vergelijkbaar, maar verschillen op meerdere niveaus. Zo verschilt het wetenschappelijk bewijs voor de afkapwaarden van metabole parameters. Voor CPB zijn duidelijke afkapwaarden gedefinieerd, vooral wat betreft acute nierinsufficiëntie en de preventie van anaëroob metabolisme. Dit is niet het geval voor ECMO. Derhalve wordt in het hoofdstuk “Goal-directed extracorporeal circulation: transferring the knowledge and experience from daily cardiac surgery to extracorporeal membrane oxygenation” ingegaan op strategieën voor optimale doelgerichte therapie tijdens CPB en ECMO, waarbij de opgedane kennis en ervaring tijdens CPB wordt getransleerd naar het metabolismemanagement voor veno-arteriële (VA) ECMO. Hoofdstuk 5 (“Perioperative incidence of ECMO and IABP on 5901 mitral valve surgery procedures”) rapporteert de incidentie en uitkomsten van het gebruik van perioperatieve ECMO en/of intra-aortale ballonpomp (IABP) tijdens mitralisklepchirurgie via rechtszijdige mini-thoracotomie (RT) of conventionele volledige sternotomie (VS). De ECMO- en IABP-incidentie, bij electieve mitralisklepchirurgie, voor de behandeling van post-cardiotomie cardiogene shock en

Low Cardiale Output Syndroom (LCOS) was respectievelijk 0,2 en 1,6 procent. Het perioperatief gebruik van een IABP bij minimaal invasieve mitralisklepchirurgie (MIMKC) via RT had, ten opzichte van VS, een lagere mortaliteit. Echter, VA ECMO tijdens MIMKC werd geassocieerd met een hoge mortaliteit van 92 procent. Verder werd het langdurig gebruik (>14 dagen) van de Eurosets A.L.ONE ECMO polymetylpenteenvezel oxygenator voor volwassenen beschreven. Het cohort bestond uit volwassen patiënten die werden behandeld met VA (post-cardiotomie) of veno-veneuze (VV) ECMO. De studie concludeerde dat zowel bij VA ECMO patiënten als bij VV ECMO patiënten die behandeld werden met continue antistollingstherapie, het apparaat veilig werd geacht zonder iatrogene complicaties gedurende een periode van 14 dagen. De studie: “Water Condensation and Gas Exchange Correlation in Different Models and Fibers of Blood Oxygenators: How Can We Improve Performance?” introduceert het fenomeen van watercondensatie in oxygenatoren; dit is op de middellange tot lange termijn voortdurend aanwezig tijdens CPB en ECMO. Er is, in het geval van normothermie, een omgekeerd evenredige correlatie tussen de gasuitwisselingscapaciteit (bijvoorbeeld oxygenatie-prestaties) en condensatie in oxygenatoren gebaseerd op polypropyleen en polymethylpenteenvezels**.**Het creëren van een beschermde atmosfeer binnen het operatieveld middels kooldioxide (CO2), ter preventie van cerebrale en/of cardiale schade door een luchtembolie, is een bekende strategie tijdens cardiale chirurgie. Er bestaat echter geen (algemene) consensus over de beste techniek om deze atmosfeer te creëren. Het beschreven retrospectieve onderzoek in hoofdstuk 8 bracht continue kooldioxide-toevoer via veldoverstroming tijdens MIMVR in verband met een lagere incidentie van: 1) micro-embolieën, 2) minder agitatie bij het ontwaken na algehele anesthesie, 3) een kortere duur van mechanische ventilatie en 4) kortere verblijfsduur op de intensive care. De achterliggende fysiologische gedachte voor het belang van deze studie is het feit dat de kwaliteit van de vasculaire hemodynamiek en het capillaire zuurstoftransport, gedurende CPB, negatief beïnvloed worden door gasvormige micro-embolieën. it leidt tot een hogere incidentie van postoperatieve neurocognitieve stoornissen na cardiale chirurgie.

Onze linische analyse toonde aan dat de Horizon AF PLUS effectief is voor de vermindering van micro-embolische activiteit tijdens CPB-procedures met een hoge efficiëntie in termen van oxygenatieprestaties en thermische uitwisseling, zonder iatrogene perioperatieve complicaties. Extracorporele technologieën hebben invloed op de farmacokinetiek en er zijn nog veel kennishiaten. Hoofdstuk 10 beschrijft de farmacokinetiek en -dynamiek gedurende minimaal invasieve extracorporele circulatie. In de minimaal invasieve extracorporele groep werd tijdens coronaire bypass-transplantatie, ten opzichte van de conventionele extracorporele circulatiegroep, een lagere dosering propofol gebruikt (streefwaarde bispectrale index 40-45), en werd een verbetering van de postoperatieve albumine-concentratie in het serum waargenomen. Patiënten met zowel coronairlijden als hartfalen (linkerventrikelejectiefractie < 35%) hebben een verhoogd risico op een slechte langetermijnprognose en een hogere mortaliteit na myocardiale revascularisatie. De studie: “Minimally invasive extracorporeal circulation in end-stage coronary artery disease patients undergoing myocardial revascularization” toonde aan dat minimaal invasieve extracorporele circulatie bij patiënten met eindstadium coronairlijden geassocieerd was met een hoger zuurstofaanbod vergeleken met “standaard” extracorporele circulatie opstelling. Verhoogd plasmavrij hemoglobine (PVH) wordt in verband gebracht met multiorgaanfale. Wij beschreven een pilotonderzoek met de focus op PVH-concentraties in 40 patiënten die een geïsoleerde coronary artery bypass grafting (CABG) ondergingen. Het gebruik van magnetisch zwevende centrifugaalpompen gaat gepaard met een lager risico op hemolyse, hoewel grotere onderzoeken gerechtvaardigd zijn om onze uitkomsten te bevestigen. Een verhoogd PVH was een onafhankelijke risicofactor voor acute nierinsufficiëntie bij ARDS-patiënten welke ondersteund werden met VV ECMO. Bij patiënten met verhoogde PVH-concentraties zouden hogere haptoglobineconcentraties in het plasma bescherming kunnen bieden tegen PVH-geassocieerde AKI.

Wij zijn van mening dat de apparatuurkeuze voor langdurige VV ECMO ondersteuning met een magnetische levitatiepomp cruciaal zou kunnen zijn voor de mogelijke reductie van PVH en indirect bilirubine. Echter is aanvullend onderzoek nodig.

Chapter 18

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Chapter 19

About the Author

Ignazio Condello was born in Agrigento on 12/19/1989. After obtaining his classical high school diploma at the Empedocle classical high school in Agrigento, he graduated in Pavia in Cardiocirculatory Physiopathology and Cardiovascular Perfusion Techniques and specialized in Basic and Advanced Echocardiography in Padua. Over the years, he has developed an interest in research and writing scientific articles. His career has focused on artificial intelligence applied to the critical conditions of cardiac surgery patients and he obtained a PhD on "Artificial Intelligence of Extracorporeal Technologies" at SUSL Great London, UK. This line of research was the substrate that influenced the research and development of biomedical technologies in the field of machine learning and next generation at an international level. He became a consultant on Biomedical Devices for the cardiopulmonary sector for the companies Eurosets Italy and Livanova, UK. He is currently the owner and creator of a patent, together with a colleague, for a device that studies the electrical polarization of red blood cells for the invasive calculation of cardiac output.

The continuous collection of scientific literature, 111 articles indexed on Pubmed, allowed him to be invited to the Maastricht University (UMC) Faculty of Health Medicine and Life Sciences, Cardio Thoracic Surgery and to obtain a further PhD on the role of modern extracorporeal techniques and devices on contemporary cardiac surgery.He also holds the role of Head and Lead Perfusionist at Anthea Hospital and is the Training and Quality Manager at GVM Care & Research Italian hospital network. In the meantime, he continues to carry out scientific divulgatin activities around the world upon invitation to international conferences.

Chapter 20

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