Gaseous Micro-Embolic Activity and Goal-Directed Perfusion Management in a Closed System for Cardiopulmonary Bypass and Minimally Invasive Extracorporeal Circulation during Coronary Artery Bypass Grafting

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ABSTRACT

Background: Cardiopulmonary bypass (CPB) techniques are becoming minimally invasive in clinical practice. The literature describes various extracorporeal techniques which seek to eliminate air-blood contact and reduce both hemodilution and the contact surface such as in Minimally invasive Extracorporeal Circulation (MiECC) and closed systems for CPB. However, the delivery of micro-embolic activity in the circuit and metabolic activity in terms of oxygen delivery for Goal-Directed Perfusion (GDP) management, in relation to the patient's blood volume and central venous pressure, have never been related and correlated. In this report, we present a cohort study that investigated these aspects between the closed SVR2000 System and modular MiECC (both from Eurosets SRL, Medolla, Italy).

Materials and Methods: Data were collected retrospectively and used to compare 60 consecutive patients who underwent isolated coronary artery bypass grafting (CABG) surgery by two surgeons using an SVR2000 oxygenator in 30 procedures, with a matched cohort of patients from the same period who underwent isolated CABG surgery by two other surgeons using a modular MiECC in 30 procedures. The primary endpoints collected were data on micro-embolic activity, including the number of gaseous micro-emboli in

the circuit during the procedure, the mean maintenance value of oxygen delivery (DO_2) and data relating to venous return volume and central venous pressure (CVP).

Results: During the CPB procedures, the following values were recorded for the closed SVR2000 and MiECC groups, respectively: the average number of gaseous micro-emboli (GME) in the venous line, 833 ± 23 vs 1221 ± 45 (p = 0.028); GME in the outlet of the pump, 375 ± 45 vs 429 ± 76 (p = 0.89; GME in the arterial line, 189 ± 36 vs 205 ± 27 (p = 0.92), and the volume of GME in the arterial line (μL), 0.32± 12 vs 0.49± 17 (p = 0.93). The mean Indexed Oxygen Delivery (DO_2i) during cross-clamp (ml/min/m^2) was 319 ±12 vs 278 ±9 (p = 0.0019), respectively. The maximum mean volume of venous return in the soft-shell venous reservoir (ml) was 1801 ±128 vs 824 ±192 (p = 0.038). The mean central venous pressure (CVP) during cross-clamp (mmHg) was 0 ± 2 vs 6 ± 2 (p = 0.019).

Conclusions: In this study, the results in the closed SVR2000 group were not statistically inferior to those in the modular MiECC group in terms of gaseous micro-embolic activity during CPB. Our analysis showed an important reduction of GME delivery in both systems. The closed SVR2000 group showed better management for GDP in terms of DO_2i, associated with the flexibility of dynamic volume management and the absence of cavitation and regulation of the rate per minute and pump flow, which were reported in the MiECC group. The SVR2000 and modular MiECC systems were both safe and effective in perioperative practice without iatrogenic problems.

INTRODUCTION

The world of extracorporeal technologies is rapidly expanding. In particular, we are trying to make cardiopulmonary bypass (CPB) more physiological for end-organ protection by reducing complications related to biocompatibility, inflammation, hemodilution, coagulation management, and gaseous micro-embolic activity.[1] This effort has led to a wide variety of systems and techniques to remedy and alleviate the pathophysiological consequences of CPB. Several studies in the literature have evaluated composite outcomes in relation to a single variable.[2] The detection and prevention of gaseous micro-emboli (GME) during CPB have attracted considerable interest. During CPB, management methods and many unexpected predisposing factors can generate micro-embolic activity (MEA). GME decrease the quality of the blood flow and capillary oxygen delivery, increasing the incidence of transient postoperative neurocognitive disorders (POCD) following cardiac surgery (i.e., postoperative delirium and agitation after anesthesia discontinuation).[3] 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, mechanical ventilation (MV) and the duration and intensive care unit (ICU) length of stay.[4] In this context, we wanted to study the superiority and non-inferiority of two systems and techniques, the closed SVR2000 system (Eurosets SRL, Modella, Italy) and a modular MiECC system (Eurosets SRL), with regard to micro-embolic activity and metabolic activity for Goal-Directed Perfusion (GDP), both in relation to venous volume management.

MATERIALS AND METHODS

This study was conducted according to the guidelines of the Declaration of Helsinki. The Internal Review Board (Anthea Hospital, GVM Care & Research review board, Bari, Italy) approved this research (March 2022) and all patients provided their written informed consent to the use of their data.

Population and study design

Between April 2022 and May 2023, 60 patients aged > 18 years with a mean EuroSCORE II of 2.1–2.8% and LVEF > 45% underwent myocardial revascularization at our institution. Patients with chronic renal failure, type 1 or 2 diabetes mellitus, septic shock or endocarditis, and patients with hemoglobin values of <8 g/dl before the procedure were excluded. Data were collected retrospectively and 60 consecutive patients who underwent isolated CABG surgery by two surgeons using the SVR2000 system were compared to a matched cohort of patients from the same period who underwent isolated CABG surgery by two other surgeons using a modular MiECC. Each set of patients was divided into two groups: 30 were treated using the SVR2000 system and 30 used the modular MiECC system. The primary endpoints were 1) micro-embolic activity in terms of the number of gaseous micro-emboli in the venous line, after the pump, and in the arterial line; 2) the mean maintenance value of oxygen delivery (DO_2) for O_2 ERi< 25% and 3) data related to the maximum and minimum venous return volume and related central venous pressure (CVP). The secondary endpoints were the perioperative and post-operative number of red blood cell units transfused. Metabolic management through blood gas analysis integrated with a metabolic parameter monitoring system during CPB was adopted in both groups.

Anaesthesia and surgical procedures

Patients were monitored by 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 Systems, 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 two surgeons.

Perfusion techniques

The closed SVR2000 system and modular MiECC were used for CPB. 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: a conventional Stöckert S5 (cHLM) and modular Stöckert S5 Hybrid (mHLM) (LivaNova, London, UK).

SVR2000 closed system components

- ◆Oxygenator AL.ONE (Eurosets);
- ◆Affinity Centrifugal Blood Pump AP40 (Medtronic Bio-Medicus, Inc., Eden Prairie, MN, USA);
- ◆SVR2000 soft-shell venous reservoir (Eurosets);
- ◆Landing monitoring systems (Eurosets).

SVR2000 management.

All patients were treated with mild hypothermic CPB (34-36 °C); 1000mL 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 rather to consider the possible integration of liquids or red blood cells. The hardware consisted of a Stöckert S5 heart-lung machine and a Stöckert Heater Cooler System 3T (LivaNova) and the same cannulae were used in both groups. For myocardial protection, a closed circuit for cardioplegia with a heat exchanger, with an infusion syringe pump in sequence and Saint Thomas solution with procaine, was used, and this was repeated every 30 min. The Landing monitoring system (Eurosets) 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.[4] On the basis of arterial blood data, we assessed the lowest Hct (percentage) under CPB; every 20 min, an arterial blood gas analysis, including a determination of blood glucose (mg/dL) and lactate (mmol/L), 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 the routine protocol. The mean arterial pressure during CPB procedures was managed for values between 55 and 70 mmHg. Extra-cavitary aspiration was managed with a cell saver and returned to the patient at the end of the operation (Fig. 1).

Modular MiECC components

- ◆Reservoir and oxygenator (RemoweLL 2 with a biopassive phosphorylcholine coating) (Eurosets);
- ◆Venous bubble trap (Eurosets);
- ◆Affinity Centrifugal Blood Pump AP40 (Medtronic);
- ◆Soft-shell venous reservoir 1800 (Eurosets);
- ◆Landing monitoring systems (Eurosets);
- ◆Vacuum-assisted venous drainage (Eurosets).

Modular MiECC management.

The circuit was filled with 500 mL crystalloid solution and 300 IU/kg of sodium heparin was added; the activated clotting time prior to CPB was 501 s. The cannulas were connected to the air-free circuit, and a bypass with a closed system was set up. The reference value for the management of venous drainage was the central venous pressure, which was maintained at around 5 mmHg using urapidil as a vasodilator for higher values, or upon a request for drainage by the sur-

Figure 1. SVR2000 system management during a CABG procedure.

Figure 2. Modular MiECC management during a CABG procedure.

geon, the Trendelenburg position was used for lower values.[5] All patients were treated with mild hypothermic CPB (34–36 °C). All patients received tranexamic acid according to the routine protocol. As in the SVR2000 group, the mean arterial pressure during CPB procedures was managed between 55 and 70 mmHg.[6] For myocardial protection, a closed circuit for cardioplegia with a heat exchanger, with an infusion syringe pump and Saint Thomas solution with procaine, was used, and this was repeated every 30 min. Extra-cavitary aspiration was managed with a cell saver and returned to the patient at the end of the operation (Fig. 2).

Metabolic management with the SVR2000 system and modular MiECC.

DO_{2i} with a target of 280 mL/min/m^2 was managed in relation to O_2ER_i (the cutoff for an increase in DO_{2i} was >25% O_2ER_i, and the cutoff for a 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.[7] 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.[8]

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

$$DO_{2i}(mL/min/m_2) = 10 \times pump\ flow(L/min/m^2) \times arterial\ O_2\ content\ (mL/100mL),$$

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 [9]

$$O_2ERi = VO_{2i}/DO_{2i} = (CaO_2 - CvO_2) / CaO_2$$

Gaseous micro-embolic activity management.

Perioperative data on micro-embolic activity were reported through a BCC 300 system (GAMPT, Zappendorf, Germany). The probes were positioned in the venous drainage line, the outlet line of the pump, and the arterial line (Fig. 3).[3] During the CPB procedures, the oxygenator filter purge was kept and managed closed. The BCC300 system was used to count GMEs. 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.[3,4] By means of different filter functions and Hilbert transformations, the signal envelope is calculated and corrected by the reference signal. The maximum amplitude of the corrected signal is used as a measure of the bubble size.[7,8] 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.[9]

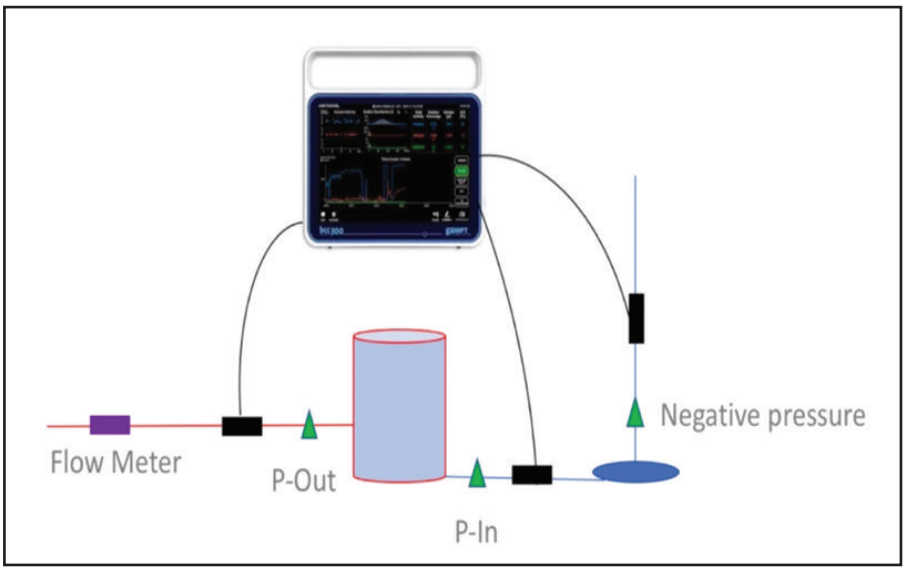

Figure 3. Probe position in the circuit for GME monitoring.

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

- ◆Cardiac index (L/min),
- ◆Indexed oxygen delivery (ml/min/m^2),
- ◆Central venous pressure,
- ◆Number (*nr*), diameter (μm) , volume (μL) of GME in the venous line, the outlet of the pump and the arterial line,
- ◆Revolutions per minute of the pump (*nr*),
- ◆Number of cavitations (*nr*),
- ◆Blood flow (L/min),
- ◆Hematocrit (Hct) (%),
- ◆Hemoglobin (gr/dl),
- ◆Maximum and Minimum venous blood volume collected in a soft-shell venous reservoir (ml).

After CPB, total red blood cell units administered intra- and postoperatively were measured in both groups.

Statistical analysis

Continuous data are expressed as a mean ± standard deviation or a median with the interquartile range, and categorical data are expressed as percentages. 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

Preoperative demographic details of the patient population are shown in Table I. During the CPB procedures, in the closed SVR2000 and MiECC groups, the average number of gaseous micro-emboli (GME) in the venous line was 833 ±23 VS 1221 ±45 (p = 0.028), that in the outlet of the pump was 375±45 vs 429 ± 76 (p = 0.89, and that in the arterial line was 189 ± 36 vs 205 ± 27 (p = 0.92). The volume of GMEs in the arterial line(μL) was 0.32± 12 vs 0.49± 17 (p = 0.93) (Fig. 4). The mean Indexed Oxygen Delivery (DO_{2i}) during cross-clamp (ml/min/m^2) was 319 ±12 vs 278 ±9 (p = 0.0019) (Fig. 5). The maximum mean volume (ml) of venous return in the soft-shell venous reservoir was 1400 ±128 vs 824 ±192 (p = 0.038). The mean central venous pressure (CVP)

Table I
Population characteristics

Procedures (n=60)	SVR2000 Closed System (n = 30)	Modular MiECC (n=30)
Age (years)	73±8	69±9
Male sex	14	38
BSA (m^2)	1.83	1.85
Pre-CPB hematocrit (%)	33.7 ± 1.9	33.9 ± 1.8
Pre-CPB Hb (g/dL)	11.9 ± 1.8	11.6±1.9
Left ventricular ejection fraction (%)	46±11	48±9
EuroSCORE II (mean)	2.1±0.7	2.8±0.7
CABG surgery	30	30

Values are presented as n (%) or mean ± standard deviation. SVR, soft-shell venous reservoir; CPB, cardiopulmonary bypass; Hb, hemoglobin; BSA, body surface area; MiECC, minimal invasive extracorporeal circulation; CABG, coronary artery bypass grafting.

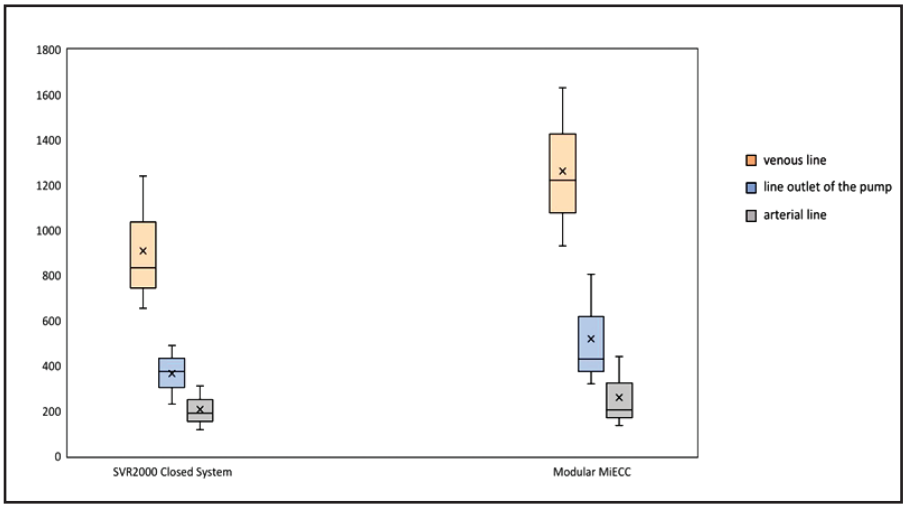

Figure 4. Box-plot distribution of the number of GMEs in the SVR200 system (N=30) and MiECC (N=30) patients who underwent CABG. The corresponding values in the venous line, the outlet line of the pump, and the arterial line were 833 ±23 vs 1221 ± 45 (p = 0.028), 375 ±45 vs 429 ±76 (p = 0.89) and 189 ± 36 vs 205 ± 27 (p = 0.92), respectively.

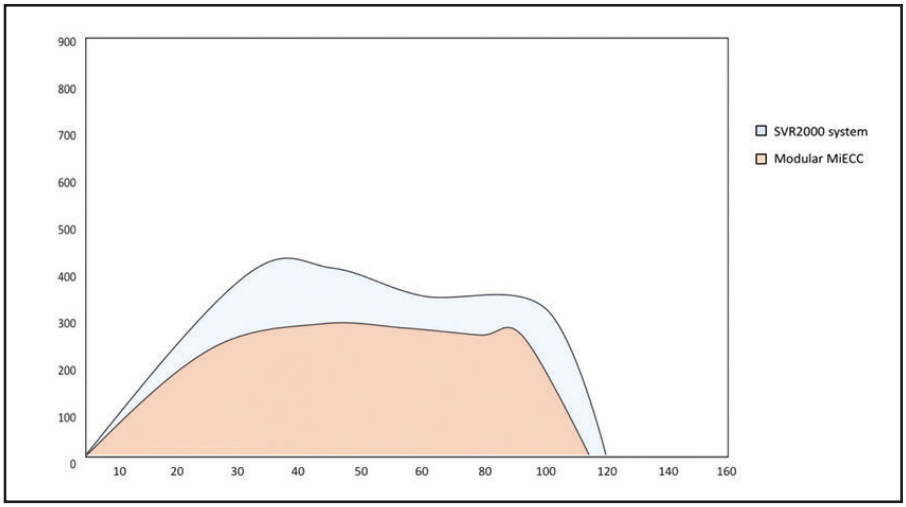

Figure 5. Distribution of DO_2i mL/min/m^2 values with the SVR200 system (N=30) and modular MiECC (N=30) in patients who underwent CABG (RAP vs. no-RAP, 319 ±12 vs 278 ±9; p = 0.0019).

Table II
Peri-operative results

Procedures (n=60)	SVR2000 Closed System (n=30)	Modular MiECC (n=30)	p-value
CBP Time (min.)	110±18	107±7	0.87
Cross-Clamp Time (min.)	86±8	76±12	0.78
Cavitation for procedure (nr)	0	4±1	0.0021
Hb (g/dL) during procedures	9.27 ± 1.17	9.13 ± 0.97	0.89
Hct (%) during procedures	27.86 ± 1.65	27.39 ± 1.25	0.99
Blood Flow (l/min) during cavitation	/	0.92±0.3	0.0019
RPM (nr) during the procedures	3900±490	3800±523	0.89
Blood Flow (l/min) during CPB	4.5±0.3	4.1±0.5	0.0033
Inlet Pressure Pump Cavitation (-mmHg)	138±43	178±28	0.023
CVP (mmHg)	0±2	6±2	0.0019
DO_2i during cross-clamp (ml/min/m^2)	319±12	278 ±9	0.0025
Crystalloid administration on CPB (ml)	328±56	598±81	0.0034
Maximum Blood volume in SVR (ml)	1801±128	824 ±192	0.0019
Minimum Blood volume in SVR (ml)	353±46	123±40	0.017
Total RBC Unit transfused (nr)	6	7	0.89
Perioperative RBC transfused (nr)	1	1	1
Postoperative RBC transfused (nr)	5	6	0.89
Venous inlet line of the pump			
n of bubbles	833 ±23	1221 ±45	0.035
bubbles > 500 µm (%)	3.4	4.1	0.57
volume (µL)	3.2 ± 1.2	3.9 ± 1.6	0.57
Outlet line of centrifugal pump			
n of bubbles	375 +/- 45	429 +/- 76	0.029
bubbles > 500 µm (%)	0.93	1.24	0.67
volume (µL)	1.22 ± 0.19	1.83 ± 0.22	0.65
Arterial line			
n of bubbles	189 ± 36	205 ± 27	0.89
bubbles > 500 µm (%)	0	0	1
volume (µL)	0.32± 12	0.49± 17	0.87

Values are presented as n (%) or mean ± standard deviation. Hb, hemoglobin; RPM, rate per minute; CVP, central venous pressure; Hct, hematocrit; MiECC, minimal invasive extracorporeal circulation; SVR, soft-shell venous reservoir; DO_2i, indexed oxygen delivery; RBC, red blood cells.

during cross-clamp (mmHg) was 0 ± 2 vs 6 ± 2 ($p = 0.019$) (Table II).

DISCUSSION

The literature describes various extracorporeal techniques that seek to eliminate air-blood contact and reduce hemodilution and the contact surface, such as Minimally invasive Extracorporeal Circulation (MiECC) and closed systems for CPB.[8,9] Organ dysfunction after cardiac surgery has been linked to a decrease in oxygen delivery during CPB.[10,11] Conventional CPB (C-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. In an interesting retrospective analysis, Bennet et al. compared 160 consecutive patients who underwent isolated CABG surgery by two surgeons using Mini-CPB with a matched cohort of patients from the same period who underwent isolated CABG surgery by four other surgeons using C-CPB. The authors concluded that, despite the same target pump flow, periodic limitations of venous return to the pump in Mini-CPB resulted in a significant reduction in average flow delivered to the patient. Less hemodilution compensated for this reduction, so that the average oxygen delivery was the same.[1] In this study, we considered the delivery of micro-embolic activity in the circuit and metabolic management in terms of oxygen-delivery Goal-Directed Perfusion (GDP), in relation to the patient's blood volume and central

venous pressure, which have not yet been correlated. Our results with the closed SVR2000 system and modular MiECC are consistent with those reported by Bennet et al.; the presence of cavitations and changes in venous return limited blood flow in the modular MiECC group, which reduced oxygen delivery compared to that in the SVR2000 group.

The main limitation of this study is the small number of patients, which was not related to post-operative outcomes but did limit the analysis of perioperative management. Furthermore, since patients with a BSA ≥ 1.8 m^2 were analysed, we do not know the effects, in terms of metabolic management and micro-embolic activity, of the two systems in patients with BSA < 1.8 m^2, and thus further studies are needed.

CONCLUSION

In this study, the results in the closed SVR2000 group were not statistically inferior to those in the modular MiECC group in terms of gaseous micro-embolic activity during CPB; we found an important reduction of GME delivery in both systems. The closed SVR2000 group exhibited better management for GDP in terms of DO_{2i}, which correlated with the flexibility of dynamic volume management and the absence of cavitation and regulation of the rate per minute and pump flow, which were reported in the MiECC group. Both the SVR2000 system and modular MiECC were safe and effective in perioperative practice without iatrogenic problems. STI

AUTHORS' DISCLOSURES

IC is a consultant for Eurosets SRL (Medolla, Italy). The other authors declare that they have no conflicts of interest.

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