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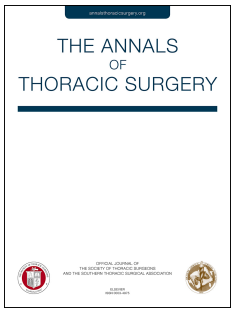

Randomized Trial of Miniaturized versus Standard Extracorporeal Circulation in Aortic Valve Surgery

Frank R. Halfwerk, MD, MSc, Kees Knol, MPA, Silvia Mariani, MD, Jan G. Grandjean, MD, PhD, FETCS, Gianclaudio Mecozzi, MD

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Randomized Trial of Miniaturized versus Standard Extracorporeal Circulation in Aortic Valve Surgery

Running head: MiECC vs AdECC : Blood loss in AVR

Frank R. Halfwerk MD, MSc [1,2], Kees Knol MPA [1], Silvia Mariani MD [1], Jan G. Grandjean MD, PhD, FETCS [1,2], Gianclaudio Mecozzi MD [1,3]

[1] Dept. of Cardio-Thoracic Surgery, Thoraxcentrum Twente, Medisch Spectrum Twente Hospital, P.O. Box 50 000, 7500 KA Enschede, The Netherlands

[2] Dept. of Biomechanical Engineering, Faculty of Engineering Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

[3] Dept. of Cardio-Thoracic Surgery, University Medical Center Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands

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Corresponding author: Corresponding author: Frank R. Halfwerk MD MSc, Dept. of Cardio-Thoracic Surgery, Thoraxcentrum Twente, Medisch Spectrum Twente Hospital, P.O. Box 50 000, 7500 KA Enschede, the Netherlands, frankhalfwerk@gmail.com

Abstract

Background. Complications related to extracorporeal circulation remain serious. While a Minimal Invasive Extra Corporeal Circulation (MiECC) system was developed to cope with these complications, its effectivity on patient-related outcomes such as blood loss remain uncertain. Therefore, the aim of this study is to compare MiECC to an advanced standard system with respect to blood loss.

Methods. A total of 128 adult patients undergoing elective isolated aortic valve replacement were enrolled in a randomized clinical trial. Patients with previous heart surgery and pre-existing kidney failure were excluded.

The primary endpoint was post-operative blood loss (mL) after 12 hours and at drain removal. Secondary endpoints included intensive care and total length of stay and intubation time. After 1 hour and 12 hours post-surgery, clinical laboratory data were determined. Early clinical outcomes and long-term survival were determined.

Results*.* MiECC patients (n=63) had a significant lower blood loss (230 mL, 95% CI: [203, 261 mL]) compared to regular patients (n=62) after 12 hours (288 mL, 95% CI: [241, 344 mL], $p = 0.04$). A preservation of hemoglobin levels 1 hour and 12 hours after surgery in the MiECC group were observed ($p < 0.001$). There was no difference in early clinical outcomes and long-term survival.

Conclusions*.* This study is the first randomized controlled trial comparing MiECC and an advanced system for aortic valve replacement with blood loss as primary endpoint. We conclude that using MiECC is clinically equal for short- and long term follow up regarding blood loss. Trial registration number: NTR3378.

Word count: 248

Since the introduction of cardiopulmonary bypass or extracorporeal circulation (ECC) in the 1950s, mortality of cardiac surgery dropped to very low levels. In the 1990s however, complications related to ECC remained serious such as the Systemic Inflammatory Response Syndrome [1].

To reduce systemic effects of ECC, a primitive Minimal Invasive ECC (MiECC) was developed. The main goal of these developments is to reduce air-blood contact and therefore reduce coagulopathies and an inflammatory response. In the early days of MiECC major concerns existed for possible air embolization, yet adequate team management, continuous CO_2 field flooding and a venous air bubble trap resolved most of the safety concerns [2-4]. The Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS) set standards to describe a MiECC and categorizes MiECC systems in four categories [5]. Main components of these systems are listed in Table 1.

Many theoretical advantages exist about using MiECC for isolated Aortic Valve Replacements (AVR). Still, in 2013 MiECC was used in only 20% of all isolated AVR cases in Germany [6].

A meta-analysis on short-term outcome of MiECC found a significant ($p=0.04$) reduction of blood loss of 114 mL and was pooled from four small early MiECC studies [7], yet these studies had blood loss as secondary endpoint.

Thus far, only small cohort studies and poorly constructed small Randomized Controlled Trials were conducted for MiECC use in isolated AVR patients [2, 3, 8]. Moreover, these studies used roller pumps which are an important factor in hemolysis and platelet activation [9]. Furthermore, these studies demonstrated equipoise on safety endpoints such as clinical laboratory data and in-hospital mortality and morbidity, yet did not include blood loss as a primary endpoint. Finally, since the introduction of MiECC, some conventional systems advanced into less invasive systems by decreasing blood-air contact.

Therefore, the aim of this study is to compare MiECC to an Advanced ECC with respect to blood loss in patients undergoing isolated Aortic Valve Replacement.

Patients and Methods

Trial Design and Study Population

This was a single center, 1:1 intention-to-treat parallel-group study conducted at Thorax Centrum Twente (Medisch Spectrum Twente Hospital, Enschede, The Netherlands), a tertiary non-academic teaching hospital. Patients were included from April 2012 to January 2016. During the trial, the original protocol was amended to extend the study period from January 2014 to January 2016 after a delay in recruiting due to unavailability of the MiECC system. This study is reported as per the Consolidated Standards of Reporting Trials (CONSORT)-guidelines [10] and standards for publishing Randomized Controlled Trials in The Annals of Thoracic Surgery [11]. Eligible participants were all adults aged 18 or over undergoing elective isolated aortic valve replacement for moderate/severe aortic valve stenosis and/or aortic regurgitation and eligible for MiECC perfusion (Body Mass Index (BMI) 20-50). Exclusion criteria were previous heart surgery and pre-existing kidney failure. Patients were recruited at the day of admission to the hospital.

Four cardio-thoracic surgeons participated in the study. All team members were previously trained for MiECC for at least one year and 50 patients. Ethical approval was acquired from a local Medical Ethical Committee (NL39386.044.12) and institutional review board. Written consent was obtained according to the declaration of Helsinki.

Anesthesiological management and Surgical approach

All eligible patients received standard preoperative care as determined by the attending physician. Anesthesia was standardized where possible and was induced by sufentanil (0.5-1µg/kg), combined with etomidate (0.2-0.3 mg/kg), rocuronium (0.6 mg/kg) and dexamethasone (1 mg/kg). Anesthetic management was maintained with propofol infusion (2

mg/kg/h), sufentanil perfusion (0.5 µg/kg/hr) and sevoflorane, according to patient's needs and bispectral index (target values: 40-50).

Surgical access was achieved through a full median sternotomy and central cannulation was established after heparinization (400 IU/kg). In all patients a target Activated Clotting Time (ACT) of 440 seconds was achieved and normothermia (35-37℃) was applied. Intermitted blood cardioplegia was given after cross clamping the aorta and repeated every 15 min after total cardiac arrest.

Heparinization was reversed with protamine sulfate (1 mg per 100 UI of heparin) to reach an ACT within 10% of baseline level in both groups. A cell Saver device (Sorin Electa, Sorin Group, Mirandola, Italy) was used in all cases to re-infuse pericardial shed blood and to remove activated platelets and coagulation factors.

All patients were admitted to the Intensive Care Unit (ICU) following surgery. Postoperative care and re-thoracotomy policy were at the discretion of the attending physician. Patients received a packed cell transfusion with hematocrit levels under 25%, and according to the 6-5-4 transfusion policy [12].

AdECC (Control)

We used an advanced conventional extracorporeal system characterized as a MiECTiS type IV-like circuit [5] with a Bioline-coated circuit (Maquet, Hirrlingen, Germany), diffusion membrane oxygenator (Quadrox-iD, Maquet, Hirrlingen, Germany) with integrated arterial filter and heat exchanger, a centrifugal pump (Rotaflow, Maquet, Hirrlingen, Germany), a soft-shell reservoir for systemic blood and a cardiotomy reservoir for shed mediastinal blood suction, aortic root and left heart venting. A suction vent was positioned in the aortic root and right superior pulmonary vein. We name this our gold standard group and refer to as AdECC. The circuit was primed with 1500 mL Ringer's lactate, 200 mL mannitol 15%, 200 mL albumin, 30 mL sodium carbonate 8.4% and 75 mg porcine heparin (7500 IU). 850 mL retropriming was applied to reduce priming volume.

MiECC

The MiECC system (MECC, Maquet, Hirrlingen, Germany) was a MiECTiS type II closed miniaturized circuit with no blood–air contact and no open venous reservoir. The system components included a centrifugal Rotaflow pump (Maquet, Hirrlingen, Germany), a diffusion membrane oxygenator (Quadrox-i, Maquet, Hirrlingen, Germany) with integrated heat exchanger and a venous bubble trap (VBT160. Maquet, Hirrlingen, Germany) located between the venous line and the centrifugal pump. A suction vent was positioned in the aortic root and pulmonary artery. All components were Bioline coated (Maquet, Hirrlingen, Germany). The MiECC circuit was primed with 800 mL physiological saline solution and retropriming was used.

Study Design and Variable Definition

The primary endpoint was post-operative blood loss (mL) measured after 12 hours or at drain removal if earlier than 12 hours. Secondary endpoints included Intensive Care Unit length of stay (days), length of total hospital stay (days) and intubation time (hours). Plasma loss was measured as plasma separated from pericardial blood after Cell Saver centrifugation. After 1 hour and 12 hours post-surgery, hemoglobin (mmol/L), hematocrit (L/L) and thrombocytes (10^9/L) levels were determined. After 12 hours post-surgery, leucocytes (10^9/L), C-reactive protein (mg/L), ureum (mmol/L), Creatine Kinase (CK, U/L), CK-MB (ng/mL) and creatinine (µmol/L) were also determined.

Further clinical relevant secondary endpoints were determined as follows. Periprocedural Myocardial Infarction (PMI) was based on CK-MB values 10 times CK and new alterations in Electrocardiography and/or Transthoracic Echocardiography, and post-operative acute kidney injury on estimated Glomerular Filtration Rate (eGFR) reduction > 50% within 48 hours post-surgery. eGFR was calculated using the Modification of Diet in Renal Disease formula. We recorded re-thoracotomy during hospital admission, post-operative atrial fibrillation and calculated Major Adverse Cardiac and Cerebrovascular Events (MACCE) as

composite endpoint of PMI, stroke and 30-day mortality. 30-120-365-day and overall mortality were determined as survival proportions.

Patients were allocated using sealed envelopes in block randomization for intervention and were equally distributed among surgeons. Random allocation sequence was done by an independent researcher with a 1:1 allocation using a block size of 5. Envelopes were opened after surgeons acquired informed consent from patients the day before surgery. Due to the nature of intervention, patients, surgeons and researchers were aware of the allocated arm.

Statistical analysis

To detect a reduction in blood loss using MiECC, we used 66 MiECC/AdECC AVR cases from our own center. With a one-sided 5% significance level and power of 80%, a sample size of 55 patients per group was necessary. Statistical analysis was performed with SPSS 23.0 (SPSS Inc, Chicago, IL). A p-value of less than 0.05 was set as statistical significant. All continuous variables were tested for normality with the Kolmogorov–Smirnov and Shapiro-Wilk test and visual inspection of histograms. Non-normal data were log-transformed. Variables were analyzed with t-tests for independent samples or with the analysis of variance (ANOVA) for repeated measures. For unsuccessful log-transformation the Mann-Whitney U test was applied and with overdispersion we used a negative binomial regression.

Categorical variables were compared using Chi-square. A Kaplan-Meier analysis estimated survival over time. Imbalances in baseline characteristics were assessed using univariate analysis for influence on blood loss, including variables with $p < 0.10$. Results are reported as mean ± Standard Deviation when normally distributed and median with interquartile range in non-normal distributions.

Results

128 patients were included in this study, with MiECC and AdECC evenly distributed among groups. Three patients were excluded after randomization based on BMI under 20 (n=2) and concomitant elective planning for Coronary Artery Bypass Graft (CABG)-surgery (n=1).

Therefore, 125 patients were included in this analysis: 63 in the MiECC-group and 62 in the AdECC group. Eligible patients were included from April 2012 – January 1st 2016. Follow-up on mortality was 100% for this analysis and ended on February 12th 2018.

Baseline characteristics

Baseline demographic and clinical characteristics of this study are demonstrated in Table 2. There were no significant differences between study groups, except for BMI (MiECC: 29 ± 4.1; AdECC: 27 ± 3.6. p = 0.008). Both BMI and ECC-type were used in an univariate analysis for influence on blood loss. Tests of between-subjects effects showed no influence of BMI on blood loss (Supplement 1).

Intraoperative characteristics

No conversions to an open ECC system nor air bubbles in the circuit were encountered and operative mortality was not observed. There were no significant differences in intraoperative characteristics (Table 3).

Plasma loss during surgery was twice as high in MiECC (841 mL ± 452) than in AdECC (409 ± 300), p < 0.001 and return of pericardial shed blood using a Cell Saver device was comparable to the former plasma loss.

In-hospital post-operative characteristics

Table 4 shows post-operative blood management, laboratory results and clinical endpoints. Blood loss, our primary endpoint, was non-normally distributed and successfully log transformed into a normal distribution. We found a significant difference in blood loss between both groups, favoring MiECC (230 mL, 95% CI: [203, 261 mL]) compared to AdECC patients (n=62) after 12 hours (288 mL, 95% CI: [241, 344 mL]), p = 0.043 (Figure 1). In 4/6 AdECC patients with blood loss over 750 mL, a rethoracotomy was performed where two minor surgical bleeding sites were discovered. For both MiECC patients with a blood loss

over 750 mL, one patient received one unit of Packed Red Blood Cells and no rethoracotomies were deemed necessary.

Simultaneously, hemoglobin (Hb) levels were significantly higher at all time points in the MiECC group (Hb 1 hour post-surgery: 6.7 mmol/L ± 0.97; Hb 12 hours post-surgery: 7.3 mmol/L ± 0.80) compared to AdECC (Hb 1 hour: 6.1 mmol/L ± 0.88; Hb 12 hours: 6.7 ± 0.77), $p < 0.001$. A distribution of Hemoglobin levels 1 hour post-surgery is displayed in Figure 2.

An analysis of variance for repeated measures showed a significant time effect as well as interaction of time and ECC-type (ANOVA, $F(1.98, 243) = 11.9$, $p < 0.001$), see Supplemental Figure S1.

C-Reactive Protein (CRP) as a marker for inflammation was slightly decreased in MiECC (35 mg/L ± 20) *vs* AdECC (43 mg/L ± 23), $p = 0.043$. No other markers for organ damage were observed (Table 4).

Because our transfusion data was over-dispersed (many zero transfusions), a negative binomial regression analysis was used. No influence of ECC-type on Packed Red Blood Cells, Fresh Frozen Plasma or thrombocyte transfusions ($p > 0.27$) was found.

Long term follow-up

We had a 30-day survival of 98.4% in both groups (Figure 3). After 120 days survival was still 96.8% in both groups. Median follow-up was 1571 days in the MiECC group and 1612 days in the AdECC group with no significant differences at all timepoints (Figure 3).

Comment

We compared a minimal invasive extracorporeal circulation (MiECC) to an advanced extracorporeal circulation (AdECC) on blood loss after aortic valve surgery in a randomized controlled trial. We found a significant reduction in our primary endpoint blood loss after 12 hours in the MiECC group (230 mL) compared to the AdECC group (288 mL, $p = 0.04$). A

preservation of hemoglobin levels 1 hour and 12 hours after surgery in the MiECC group ($p < 0.001$) was observed.

This study is the largest Randomized Controlled Trial comparing MiECC and AdECC for isolated aortic valve surgery with blood loss as primary endpoint. A pooled analysis from three trials on AVR surgery with considerable heterogeneity ($I^2 = 81\%$) showed a significant reduction of postoperative blood loss of 115 mL in MiECC procedures ranging from 36 mL to 208 mL [13]. Our blood loss difference of 58 mL is within the range of these studies. A meta-analysis of previous studies in AVR surgery was published by Wang et. al in 2016 and showed a minor reduction in Intensive Care Unit stay for 6 hours and total hospital stay for 18 hours favoring MiECC above Conventional ECC [14], which we were not able to demonstrate.

Clinical and research implications of this study

While we find a significant difference in blood loss between AdECC and MiECC of 58 mL (288 vs 230 mL), this difference has no major clinical impact for a general population. There was no difference in blood product use or other clinical endpoints. A reason for this finding could be that blood loss difference was smaller than the transfusion trigger [12]. Plasma loss was significantly higher in MiECC, where more pericardial blood drained into the Cell Saver and separated plasma was discarded. Our data suggests that this has no specific impact on patient outcome.

Unfortunately, literature about long term follow up is scarce and other studies or systematic reviews frequently mention only in-hospital or 30-day mortality [13, 7], while early mortality of cardio-thoracic surgery continues up to 120-days [15]. Our 30-day mortality is low (1.6% in both groups), as well as our in-hospital mortality (1.6% in both groups) compared to other trials (Table 5) or STS unadjusted Operative Mortality for Aortic Valve Replacement (2.4%) [16]. Although our study was not powered for this safety endpoint, our long term follow up

with median follow up over 4 years (1600 days) indicate no difference in long-term survival between both groups.

Limitations

We obtained a significantly higher BMI in the MiECC group compared to our AdECC group (29 vs 27, p = 0.008) despite our randomization of patients. A high BMI might influence hematology due to increased circulation volume and we therefore included BMI and ECC-type in an univariate analysis on blood loss. Here, we found no influence of BMI on blood loss (Supplement 1). Nolan et. al found a decreased postoperative blood loss in overweight and obese BMI in CABG patients [17]. Using their categorization, still no effect on (log transferred) blood loss was observed in our AVR study.

Furthermore, analysis of the coagulation cascade might have given insights of *in vivo* hemostasis. No differences in pre-operative aspirin or Dual Anti Platelet Therapy were observed between both groups (Table 2). For future studies, thromboelastography and thromboelastometry can be beneficial.

Comparison between both systems

In our study we used a MiECTiS type II MiECC as intervention group (MiECC) and a modified Conventional ECC with MiECC characteristics (AdECC, MiECTiS type IV-like). We define this as “MiECTiS type IV-like” because we used a fully coated circuit, a centrifugal pump, arterial filter and soft-shell reservoir with a miniaturized circuit volume due to retropriming. Therefore not fully complying to MiECTiS type IV classification (reduced priming volume) yet also not defined as Conventional ECC in most studies.

Most studies compared conventional ECC with roller pumps and uncoated circuits to MiECC in small retrospective or poorly designed randomizes studies. Here, we show that there is a small advantage in blood loss reduction even between two advanced ECC systems.

To conclude, some centers prefer a Conventional ECC system due to perceived safety concerns and training of dedicated teams. In our center, only specifically trained perfusionists and surgeons run MiECC after a training of at least 50 cases. Using an AdECC system might be an alternative to these centers, with added benefits from fully coated lines, a centrifugal pump and arterial filters.

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Table 1. Characteristics of a Minimal Invasive Extracorporeal Circulation (MiECC) as defined by MiECTiS [a] [5]

Closed Cardiopulmonary bypass circuit
Biologically inert blood contact surfaces
Reduced priming volume
Centrifugal pump
Membrane oxygenator
Heat exchanger
Cardioplegia system
Venous bubble trap
Shed blood management system

[a] MiECTiS = Minimal invasive Extra-Corporeal Technologies international Society

Table 2. Baseline characteristics

Variable	**MiECC (n = 63)**	**AdECC (n = 62)**	***p* value**
Gender (male)	48% (30)	53% (33)	0.59
Age (years)	71 ± 8.4	72 ± 8.8	0.35
BMI [a]	29 ± 4.1	27 ± 3.6	0.008
NYHA Class [e]			0.89
I	13	15	
II	30	28	
III	20	19	
IV	0	0	
CCS Class [b]			0.74
0	26	22	
1	14	18	
2	22	20	
3	1	2	
4	0	0	
Aortic Valve Area (cm^2)	0.82 ± 0.18	0.79 ± 0.19	0.35
Aortic Valve gradient (mm Hg)	79 ± 23	76 ± 20	0.37
EuroScore I (log)	5.6 ± 3.5	6.2 ± 4.0	0.38
Pre-operative Aspirin	41% (26)	45% (28)	0.72
Aspirin stopped pre-surgery (days)	2.8 ± 2.9	2.6 ± 3.0	0.89

Pre-operative DAPT [c]	4.8% (3)	4.8% (3)	1.0
DAPT stopped pre-surgery (days) [c]	4.0 ± 3.6	6.5 ± 2.1	0.45
Pre-operative Anticoagulants	21% (13)	16% (10)	0.65
Anticoagulants stopped pre-surgery (days)	3.1 ± 2.2	3.3 ± 2.0	0.87
INR [d]	1.0 [1.0-1.1]	1.0 [1.0-1.1]	0.90
Creatinine pre-surgery (µmol/L)	80 [68-92]	81 [68-97]	0.83
Hemoglobin pre-surgery (mmol/L)	8.5 ± 0.87	8.5 ± 0.86	0.92
Hematocrit pre-surgery (L/L)	0.41 ±0.04	0.41 ± 0.04	0.92
Thrombocytes pre-surgery (10^9 /L)	215 [179-249]	217 [190-267]	0.12

[a] BMI = Body Mass Index, [b] CCS = Canadian Cardiovascular Society, [c] DAPT = Dual Anti Platelet Therapy, [d] INR = International Normalized Ratio, [e] NYHA = New York Health Association. 1 mmol/L Hemoglobin = 1.61 g/dL Hemoglobin

Table 3. Intraoperative characteristics

Variable	**MiECC (n = 63)**	**AdECC (n = 62)**	***p* value**
Cardiopulmonary bypassTime (min)	74 ± 18	80 ± 26	0.14
Aortic Cross-clamp time (min)	51 ± 17	54 ± 20	0.32
Biological Aortic Valve Prosthesis	83% (52)	81% (50)	0.82
Valve size (mm)			0.45
19	1	0	
21	14	15	
23	32	25	
25	12	17	
27	4	5	

Table 4. Post-operative results and laboratory data

Variable	MiECC (n = 63)	AdECC (n = 62)	*p* value
Hematology and blood management			
Blood loss after 12 hours (mL)	230 [203-261]	288 [241-344]	0.04[a]
Plasma loss (mL)	841 ± 452	409 ± 300	< 0.001
Reinfusion of cells (mL)	776 ± 519	348 ± 262	< 0.001
Hemoglobin after 1 hour (mmol/L)	6.7 ± 0.97	6.1 ± 0.88	< 0.001
Hemoglobin after 12 hours (mmol/L)	7.3 ± 0.80	6.7 ± 0.77	< 0.001
Hematocrit after 1 hour (L/L)	0.33 ± 0.05	0.30 ± 0.04	< 0.001
Hematocrit after 12 hours (L/L)	0.36 ± 0.04	0.33 ± 0.04	< 0.001
Thrombocytes after 1 hour (10^9 /L)	131 ± 45	139 ± 54	0.42
Thrombocytes after 12 hours (10^9 /L)	151 ± 48	162 ± 44	0.18
Laboratory data			
Leucocytes after 12 hours (10^9 /L)	15 ± 3.5	14 ± 4.2	0.29
CRP after 12 hours (mg /L) [e]	35 ± 20	43 ±23	0.04
Urea (mmol/L)	7.7 ± 2.7	7.8 ± 2.4	0.87
CK (U/L) [c]	303 [226-454]	318 [254-463]	0.61
CK-MB (ng/mL) [d]	18 [14-25]	21 [14-24]	0.50
Troponin T HS (ng/L)	324 ± 171	363 ± 311	0.39

Creatinine after 24 hours (µmol/L)	72 [61-92]	75 [61-89]	0.72
eGFR reduction > 50% within 48h [f]	1.6% (1)	4.8% (3)	0.37
Clinical endpoints			
MACCE [g]	7.9% (5)	8.1% (5)	0.99
Periprocedural Myocardial Infarction [k]	6.3% (4)	6.5% (4)	0.99
Stroke	0% (0)	0% (0)	0.99
Packed Red Blood Cells Transfusion [l]	19% (12)	27% (17)	0.30[b]
Fresh Frozen Plasma Transfusion [g]	8% (5)	15% (9)	0.27[b]
Thrombocytes Transfusion	8% (5)	9.7% (6)	0.76[b]
Post-operative Atrial Fibrillation	40% (25)	37% (23)	0.86
Rethoracotomy	1.6% (1)	6.5% (4)	0.21
Intensive Care Unit stay (days)	1 [1-1]	1 [1-2]	0.55
Length of stay (days)	6 [5-7]	6 [5-7]	0.20
Ventilation time (hours)	7 [6-11]	8 [5-12.5]	0.44[b]

[a] p-value of log-transformed data, [b] p-value of negative binomial regression analysis, [c] CK = Creatine Kinase, [d] CK-MB = Creatine Kinase Myocardial Band, [e] CRP = C-Reactive Protein, [f] eGFR = estimated Glomerular Filtration Ratio, [g] MACCE = Major Adverse Cardiovascular and Cerebrovascular Event,

Table 5. In-hospital and 30-day mortality of Randomized Controlled Trials comparing MiECC with Conventional ECC in AVR surgery

First author, Year	**Patients**	**No. Patients MiECC/CECC** [f]	***MiECTiS Type***	***Conventional ECC Type***	***Mortality MiECC***	***Mortality CECC***	***P-value***
Remadi, 2004 [2]	AVR [d]	50/50	I, SC [n]	NPV [k], RP [n], NC [j], OS [l]	2% [a]	4% [a]	.2
Castiglioni, 2009 [3]	AVR [d]	60/60	I	NPV [k], RP [n], HC [h], OS [j]	0% [b]	0% [b]	.99
Rimpiläinen, 2011 [18]	AVR [d], CABG+AVR [d,e]	20/20	III	NPV [k], RP [n], PC [m], SC [p]	0% [b]	0% [b]	.99
Baumbach, 2016 [19]	AVR [d], MVR [h]	101/99	III	NPV [k], RP [n], HC [h], SC [p]	1% [b]	3% [b]	.339

This study	AVR [d]	63/62	II	RPV [o], CP [g], HC [h], SC [c, p]	1.6%[a,b]	1.6%[a,b]	.99

[a] 30-day mortality, [b] In-hospital mortality, [c] Type IV MiECC, [d] AVR = Aortic Valve Replacement, [e] CABG = Coronary Artery Bypass Grafting, [f] CECC = Conventional Extracorporeal Circulation, [g] CP = centrifugal pump, [h] HC = heparin coated, [i] MVR = Mitral Valve Replacement, [j] NC = Not Coated, [k] NPV = normal priming volume, [l] OS = open system, [m] PC = Phosphoryl choline Coated, [n] RP = roller pump, [o] RPV = reduced (retro)priming volume, [p] SC = semi-closed system

Figure Legends

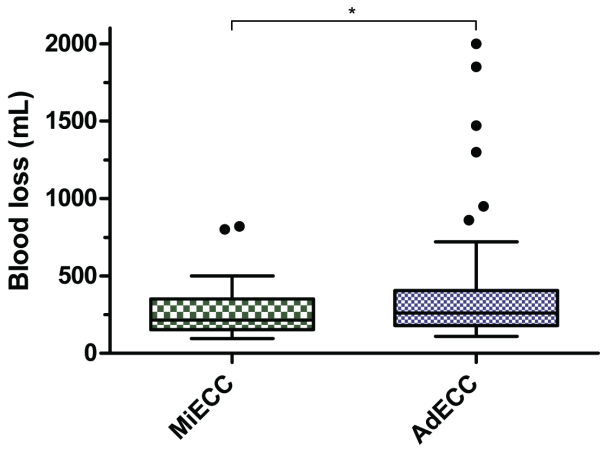
Figure 1. Blood loss (mL) 12 hours post-surgery. Blood loss was significantly higher in the AdECC group, compared to MiECC (* p = 0.043). Whiskers show the 25th and 75th percentile ± 1.5 times Inter Quartile Range (Tukey box-and-whiskers plot).

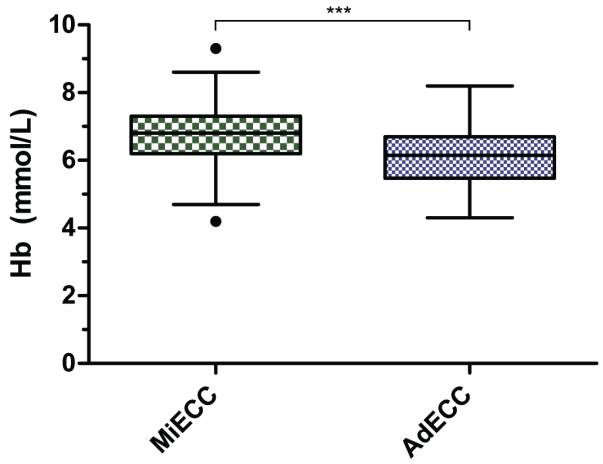
Figure 2. Boxplot of Hemoglobin levels (mmol/L) 1 hour post-surgery. Hemoglobin was significantly higher in the MiECC group compared to the AdECC group (*** p < 0.001). 1 mmol/L = 1.61 g/dL Hemoglobin

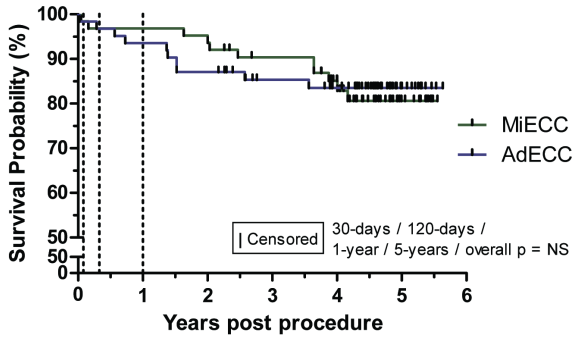
Figure 3. Survival proportions of both groups showing no significant difference in survival at all time points.

Abbreviations

Abbreviation	Description
ACT	Activated Clotting Time (seconds)
AdECC	Advanced Extra Corporeal Circulation
AVR	Aortic Valve Replacement
CECC	Conventional Extra Corporeal Circulation
CK	Creatine Kinase (U/L)
CK-MB	Creatine Kinase Myocardial band (ng/mL)
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-Reactive Protein (mg/L)
ECC	Extra Corporeal Circulation
eGFR	estimated Glomerular Filtration Rate (mL/min/1.73 m^2)
Hb	Hemoglobin (mmol/L)
ICU	Intensive Care Unit
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MiECC	Minimal Invasive Extra Corporeal Circulation
MiECTiS	Minimal invasive Extra-Corporeal Technologies international Society
PMI	Periprocedural Myocardial Infarction







Years post-procedure / Patients at risk

Year	0	1	2	3	4	5
MiECC	63	62	61	53	42	13
AdECC	62	59	56	47	42	12