FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

CARDIOPULMONARY BYPASS DURING MINIMALLY INVASIVE CARDIAC SURGERY

QUALITY PARAMETERS AND CLINICAL CONSEQUENCES

Aantal woorden: 5277

Korneel Vandewiele
Stamnummer: 01511648

Promotor: Prof. dr. Filip De Somer

Masterproef voorgelegd voor het behalen van de graad master in de richting Verpleegkunde & Vroedkunde

Academiejaar: 2018 – 2019

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Inhoudsopgave

WOORD VOORAF

Als full-time werkend student is het enkel dankzij de ondersteuning van velen dat dit werk tot stand is kunnen komen. Vooreerst wil ik mijn echtgenote en 2 kinderen daarvoor uitvoerig bedanken. Zij hebben zichzelf maandenlang onvoorwaardelijk uit de weg gecijferd en mij de nodige tijd gegund om in alle rust te kunnen verder werken. Zonder hun begrip en geduld was deze masterproef ongetwijfeld nooit verwezenlijkt.

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1. Abstract

Background: Research concerning the management of cardiopulmonary bypass (CPB) during minimally invasive cardiac surgery (MICS) is rather scarce. This study compares the quality parameters of CPB-management and their association with clinical outcome and organ function between MICS and the median sternotomy (MS).

Methods: 356 patients undergoing a MICS or MS for mitral or tricuspid valve surgery between 2006 and 2017 were retrospectively analyzed. Propensity score analysis matched 70 patients in the MS-group for comparison with 215 in MICS. A binary logistic regression analysis was carried out to investigate the independent predictors of cardiac surgery associated acute kidney injury (CSA-AKI).

Results: In MICS, CPB (136.2±38.7 vs 93.1±31.2 minutes; $p<0.001$) and aortic crossclamp duration (84.8±31.8 vs 58.4±22.1 minutes; $P<0.001$) were significantly prolonged although no differences were detected in clinical outcome. The pump flow index (PFI) was lower (2.2±0.2 vs 2.4±0.1 $L\cdot(min\cdot m^2)^{-1}$; $p<0.001$) while the intraoperative hematocrit was higher (28.4±3.7 vs 26.9±4.1; $p=0.004$) during MICS because of the higher usage of blood conservation techniques. As a consequence, the oxygen delivery did not differ. Regression analysis revealed that the nadir hematocrit was an independent predictor of CSA-AKI (β: -0.105; Odds Ratio: 0.9; p=0.018). Based on ROC-curve analysis, a nadir hematocrit of 26.3% in MICS and 24.8% in MS were predictive for CSA-AKI.

Conclusion: CPB-management during MICS has some distinct differences as compared to MS. As the PFI is limited in MICS, it is recommended to preserve the hematocrit above 26.3% in order to reduce the incidence of CSA-AKI in this specific patient population.

Abstract

Inleiding: Evidentie omtrent het management van de cardiopulmonaire bypass (CPB) tijdens minimaal invasieve hartchirurgie (MICS) is eerder schaars. Dit onderzoek vergelijkt de kwaliteitsparameters van het CPB-management en diens associatie met klinische outcome en orgaanfunctie tussen MICS en de mediane sternotomie (MS).

Methode: 356 volwassen patiënten die een mitralis of tricuspiedklepintgreep ondergingen tussen 2006 en 2017 werden retrospectief geselecteerd. Op basis van de propensity score werden het CPB-management, de klinische outcome en orgaanfunctie bij 70 patiënten in de MS groep vergeleken met 215 in MICS. Een binaire logistische regressie-analyse werd uitgevoerd om de onafhankelijke predictoren voor cardiochirurgisch gerelateerde acute nierinsufficiëntie (CSA-AKI) te bepalen.

Resultaten: De significant langere CPB- (136.2±38.7 vs 93.1±31.2 minuten; p<0.001) en aortaklem-tijden (84.8±31.8 vs 58.4±22.1 minuten; P<0.001) bij MICS brachten evenwel geen verschillen in klinische outcome teweeg. De pomp flow index (PFI) (2.2±0.2 vs 2.4±0.1 $L\cdot(min\cdot m^2)^{-1}$; p<0.001) was significant lager tijdens MICS terwijl het intraoperatief hematocriet hoger was (28.4±3.7 vs 26.9±4.1; p=0.004). Dit resulteerde in een gelijk zuurstofaanbod in beide groepen. De regressieanalyse toonde dat, naast patiëntgerelateerde factoren het laagste hematocriet tijdens CPB een onafhankelijke predictor is van CSA-AKI (β: -0.105; Odds Ratio: 0.9; p=0.018). Een ROC-curve analyse toonde aan dat een laagste hematocriet van 26.3% tijdens MICS en 24.8% tijdens MS predictief zijn voor CSA-AKI.

Conclusie: MICS induceert enkele belangrijke verschillen in CPB-management in vergelijking met MS. De onderzoek toont aan dat het voorkomen van excessieve hemodilutie tijdens MICS om het hematocriet boven 26% te houden aan te raden valt bij deze patiëntenpopulatie.

This thesis has been written in the form of a scientific article. An extensive report of the systematic literature review is not a part of this written article. The literature review was previously judged in the eponymous course unit.

2. Introduction

During the last two decades, minimally invasive cardiac surgery (MICS) for mitral or tricuspid valve surgery through a right mini-thoracotomy has gradually become common practice in many hospitals throughout the world. It is beyond doubt that this technique entails an important decrease in surgical trauma and has important esthetical advantages for patients (Massetti, Nataf, & Babatasi, 1999). However, the clinical benefits of MICS as compared to the classical median sternotomy (MS) are still under debate as convincing agreement between study results seems to be lacking.

Only eight randomized controlled trials were carried out to investigate the differences between the classical and the minimal invasive approach, probably because of ethical considerations. On the other hand, we found 36 retrospective studies which tried to address the same issue. The large degree of heterogeneity between and the high risk of bias within most studies make confident comparisons rather untrustworthy. Nevertheless, most research groups did not reveal any differences in survival between MICS and MS, both in the short and long-term (Iribarne et al., 2010; Losenno et al., 2016; Qiu et al., 2018; Ryan et al., 2010; Speziale et al., 2011). Therefore, MICS is often stated as being “non-inferior” to the sternotomy approach (Q. Wang et al., 2018), albeit shorter intubation times and length of hospital stay (LOS), and improved mid-term functional status and quality of life (Suri et al., 2012) in favor of MICS suggested that this technique is more than just a reduced incision.

Conversely, MICS has been criticized because it is associated with some clear additional intraoperative complexities (Holzhey, Seeburger, Misfeld, Borger, & Mohr, 2013) which is translated into significantly prolonged cardiopulmonary

bypass (CPB) and aortic crossclamp (AoX) duration in most studies (Downs et al., 2016; Lebon et al., 2018; Nishi et al., 2015; Qiu et al., 2018; Q. Wang et al., 2018). It seems evident that MICS requires higher levels of technical skill and expertise of the entire cardiosurgical team.

Because of the reduced operational space, peripheral access for the institution of CPB is one of the key features to make this surgical challenge a success. As the groin is the preferable cannulation site, venous and arterial cannulas are longer and have a reduced internal diameter resulting in higher cannula resistances. In order to achieve sufficient venous drainage, perfusionists are required to apply a negative pressure to the venous cannulas. This can be done by attaching a vacuum source to the cardiotomy reservoir (Vacuum Assisted Venous Drainage (VAVD)) or by incorporating a centrifugal pump in the venous line (kinetically assisted venous drainage (KAVD)) (Riley, FitzGerald, & Cohn, 2007). Unfortunately, it has been shown that assisted venous drainage is carrying some risks with its use, causing hemolysis (Cirri et al., 2001) and the entrance of micro-embolic air bubbles into the system (S. Wang & Undar, 2008). Despite these adjustments, CPB-management during MICS has thus become more challenging, which most perfusionists would probably confirm empirically.

It is remarkable that there are no reported data of CPB-management during MICS except for CPB- and AoX-duration and some short descriptions in the methods section of some articles (Antonic & Gersak, 2007; Hanedan et al., 2017; Kang, Yoon, Kim, & Kim, 2011; Matzelle et al., 2014), particularly since patient management during CPB has been repetitively associated with adverse outcome. Excessive hemodilution, the degree of CPB-hematocrit drop and the consequential increase in transfusion rate, are all independent predictors of major adverse events in adult patients (Engoren et al., 2002; Habib et al., 2003, 2005; Loor et al., 2012, 2013). What's more, the renowned studies by the research group of Dr. Ranucci revealed that maintaining the oxygen delivery (DO_2) above a certain threshold during CPB reduces the risk for postoperative acute renal failure (de Somer et al., 2011; Ranucci et al., 2005). Consequently, the concept

of goal directed perfusion (GDP), advancing the flow policy during CPB to optimize DO_2, was recognized as a major marker of perfusion quality (Ranucci et al., 2018). It should be questioned whether these goals are achievable during MICS with its additional complexities.

Therefore, the primary purpose of this study is to investigate if there are any differences in perfusion-related quality parameters in mitral and/or tricuspid valve surgery between the right mini-thoracotomy or the median sternotomy approach. As a secondary goal we will explore if these perfusion related differences, if any, are associated with clinical outcome and major organ dysfunction through analysis of biochemical parameters.

3. Methods

3.1 Population sample

In this retrospective cohort study, all adult patients above 18 years of age undergoing elective mitral and/or tricuspid valve surgery, with or without concomitant atrial fibrillation surgery, in the University Hospital Ghent, Belgium, were selected from January 2006 until the end of June 2017. Patients undergoing procedures for ASD closure, excision of cardiac tumors, congenitally related valve surgery were excluded as were patients on dialysis, patients with acute infective endocarditis and those with New York Heart Association (NYHA) class IV. The selected cohort was divided into two groups based on the surgical approach, being either through a standard median sternotomy (MS-group) or a right mini-thoracotomy (MICS-group). MICS-patients who needed to undergo a peri-procedural conversion to a median sternotomy, for any reason, were assigned to the MICS-group in an intention-to-treat-analysis.

3.2 Surgical techniques

The mitral and tricuspid valve were approached through a left and right atriotomy, respectively. In the MS-group, a complete median sternotomy was performed. Direct bicaval and central aortic cannulation was used for institution of CPB.

In the MICS-group, a submammarian incision was made to approach the heart. A single femoral venous or a combination of a jugular and femoral venous cannula were used for venous drainage. Arterial cannulation was accomplished through the femoral artery by a standard femoral arterial cannula in case the Chitwood aortic clamp was utilized. When the ascending aorta was internally occluded by the Intraclude® endoaortic-balloon, the EndoReturn® arterial cannula was used (Edwards, Irvine, CA, US). As a consequence, retrograde arterial flow was established in all MICS patients. The choice of the arterial and venous cannula type and size was at the discretion of the treating surgeon. In all patients, cold crystalloid modified St-Thomas cardioplegia was used to arrest the heart.

3.3 Cardiopulmonary bypass techniques

Before cannulation, 3 $mg \cdot kg^{-1}$ of porcine heparin (Leo Pharma, Lier, Belgium) was administered. During CPB, the activated clotting time was maintained above 480 seconds with the Hemotec® system (HR-ACT, Medtronic, Brussels, Belgium) or above 330 seconds accompanied by a clot rate below 6.0 in case the Sonoclot device ((Sonoclot® (Romed, Zoersel, Belgium) was used (since 2014).

The disposable CPB system consisted of roller pumps, a closed collapsible venous reservoir and a membrane oxygenator (Avant®, Eos®, or Inspire® 6F, Livanova, Mirandola, Italy). The entire system, with exception of the cannulas, was phosporylcholine-coated (Phisio® coating, Livanova, Mirandola, Italy). A mixture of 800 - 1300 ml gelatin solution (Geloplasma®, Fresenius Kabi, Schelle, Belgium), mannitol (0,5 $mg \cdot kg^{-1}$; Baxter, Lessines, Belgium) and 2500 IU of porcine heparin (Leo Pharma, Lier, Belgium), to achieve a total priming volume of 1000 - 1500 ml, was used.

In the MS group, venous drainage was attained by standard gravity while KAVD was applied in all MICS patients by means of a centrifugal pump (Revolution®, Livanova, London, UK). A negative pressure down to -85 mmHg on the venous line was tolerated to achieve the desired pump flow during CPB.

Mild or moderate hypothermia was employed, depending on the complexity of the surgical procedure and was at the discretion of the surgeon. A CPB blood flow of 2.4 $L \cdot min^{-1} \cdot m^{-2}$ was targeted while maintaining mixed venous saturation above 70% and the hematocrit level at 25%. Failure to maintain these targets during the procedure, was followed by an increase in CPB-blood flow or, if not possible, with the addition of homologous packed red blood cells (PRBC) if metabolic parameters were deflecting. The mean arterial blood (MAP) pressure was kept above 50 mmHg at all times during CPB.

To collect intraoperative blood loss an autotransfusion device was installed in each case. Whenever possible, pleuro-pericardial aspirations were collected separately and transfused back to the patient after autotransfusion device processing. At the end of CPB, the residual blood volume of the extracorporeal circuit was slowly infused back to the patient. If necessary, any residual blood in the extracorporeal circuit was collected by the autotransfusion device.

Heparin reversal was achieved by a calculated protamine dose based upon the Bull heparin sensitivity curve (Gravlee, 2008). The coagulation status of the patient before and after CPB was monitored by means of a viscoelastic whole blood test (Sonoclot® (Romed, Zoersel, Belgium)).

3.4 Anesthetic techniques

Standardized anesthetic induction included the administration of diazepam 0.1 $mg \cdot kg^{-1}$, fentanyl 5 $\mu g \cdot kg^{-1}$, propofol 1 $mg \cdot kg^{-1}$ and rocuronium 1 $mg \cdot kg^{-1}$. The lungs were ventilated mechanically with oxygen enriched air (fractional inspired oxygen 0.5) adjusted to keep the end-tidal carbon dioxide ($ETCO_2$) around 30-35

mmHg. Anesthesia was maintained with boluses of fentanyl up to a total dose of 20-30 $\mu g \cdot kg^{-1}$ and sevoflurane at a minimum concentration of 1.5%. Standard American Society of Anesthesiology-recommended monitoring was used throughout the procedure combined with invasive arterial and central venous pressure measurements. After intubation, a multiplane transesophageal echocardiographic probe was placed to monitor intraoperative cardiac function, cannula and endo-aortic balloon positioning.

In the MICS group patients were intubated with a double lumen endotracheal tube. The appropriate position of the bronchial balloon was confirmed by fiberoptic bronchoscopy. Once the right mini-thoracotomy was made, the patient was placed on single lung ventilation up until the start of CPB, during which the lungs were not ventilated. Since 2014, an intercostal nerve block by means of an elastomeric pump (ropivacaine, 0.2%) was inserted adjacent to the mini-thoracotomy incision at the end of surgery.

3.5 Data collection

Patient characteristics, pre- and intraoperative data were collected by extracting records from the cardiac surgical and perfusion database. If data were missing in these archives, they were collected from the written perfusionists, anesthesiology and intensive care records. Additional intra-operative perfusion quality parameters of interest were the patient's Mean Arterial Pressure (MAP) during CPB, CPB pump flow, intra-operative urine output, diuretics use (furosemide) and venous blood temperature, all registered within 15-minute intervals, from commencement of CPB up until the removal of the venous cannula(s).

Biochemical data were extracted from the hospital's laboratory database program. The blood tests were part of the hospital's routine protocols used for every cardio-surgical patient with the given pathology. The patient's hemoglobin, hematocrit, serum lactate, glycemia, arterial blood oxygen tension (PaO_2), arterial blood saturation, were collected from each blood gas analysis from the start of CPB up until 24 hours of Intensive Care Unit (ICU)-stay.

Ventilator support settings (FiO_2), the volume of chest tube drainage, transfusion of packed red blood cells, fresh frozen plasma and platelet concentrates, observed at the time of 4, 8 and 12 hours of ICU-stay postoperatively were extracted from the intensive care program's database. The hospital and ICU length of stay, revision for bleeding, NYHA class, Logistic Euroscore and the in-hospital survival were extracted from the cardiac surgical database.

3.6 Clinical outcome parameters: Estimates of organ function

The subsequent calculations were performed for each 15 minute-interval, to determine the indexed oxygen delivery (DO_{2i}) of the patient during CPB:

- $CaO_2 = (1.34 * Hb * SaO_2) + (PaO_2 * 0.003)$;
- $PFI = \frac{Absolute\ CPB\ Pump\ Flow}{BSA}$;
- $DO_2i = CaO_2 * 10 * PFI$;

with CaO_2 being the arterial oxygen content (mlO_2/dl), 1.34 the Hüfner constant, Hb the hemoglobin (g/dl), SaO_2 the arterial oxygen saturation (%), PaO_2 the partial tension of oxygen in arterial blood (mmHg), 0.003 the Bunsen solubility coefficient for oxygen, PFI the pump flow index ($L/min/m^2$), BSA the Body Surface Area (m^2) and DO_{2i} the indexed systemic oxygen delivery ($mlO_2/min/m^2$).

Cardiac surgery associated acute kidney injury (CSA-AKI) during the first 72 hours postoperatively was determined according to the KDIGO guidelines (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group, 2012). These criteria are used to evaluate the postoperative renal function as a change from the baseline preoperative renal function based on the evolution of serum creatinine (SCr) (or glomerular filtration rate) and/or urine output (UO).

Postoperative pulmonary function was assessed using the PF-ratio (PaO_2/FiO_2) as a projection of the diffusion capacity of the lungs. The evolution of the biochemical liver parameters (AST, ALT, LDH) until the first postoperative day were observed as estimates of liver function.

3.7 Statistical analysis

Continuous variables are presented as means ± standard deviations and categorical variables as frequencies and percentages. Differences in continuous variables between the two groups were analyzed using the independent samples T-test if data were normally distributed. If data were not normally distributed after log-transformation, a Mann-Whitney-U test was executed. To detect differences in categorical variables between the two groups Chi-square or Fisher's-exact test was performed.

Due to significant differences in baseline covariates between groups, a propensity score analysis was performed. The chance of being assigned to MICS, known as the propensity score (PS), was calculated using logistic regression analysis. All possible known confounders which could have influenced group assignment or outcome parameters being the type of surgery, reoperations (yes/no), gender, age, the preoperative hematocrit and the preoperative serum creatinine level were included as predictors of the PS. A PS matching procedure was executed with a match tolerance of 0.0025. The distribution of the PS of both groups was examined for acceptable overlap. Thereafter, the balance of all baseline characteristics was tested between groups using independent sample T-tests for continuous and Chi-square or Fisher's-exact test for categorical variables.

If statistically significant differences in biochemical parameters were detected between the two groups, a two-way repeated measures ANOVA was performed to assess possible the differences in evolution of these parameters depending on the treatment group.

A binary logistic regression analysis was carried out to assess the independent predictors of postoperative CSA-AKI during the first three postoperative days for the entire matched cohort. All perioperative perfusion-related parameters that were significantly different between groups, together with preoperative risk factors for CSA-AKI, being age, gender, pre-operative creatinine level, the type of procedure and diabetes were investigated for multicollinearity by the correlation coefficients. If collinearity was observed ($r^2 \geq 0.6$), the factor that correlated the most with the dependent variable was included in the multivariate model. To achieve parsimony, a backward stepwise model selection was used with a critical *p*-value of ≥.1 for removal of covariates. To assess the predictive accuracy of the nadir hematocrit for CSA-AKI, a Receiver Operator Characteristic (ROC) curve was constructed. The nadir hematocrit with the best predictive value for CSA-AKI in both groups was calculated for each coordinate point of the ROC-curve by the Youden's J statistic (sensitivity + specificity-1). For the cut-off values of both groups, the sensitivity, specificity and negative and positive predictive values were reported.

Statistical analysis was performed with SPSS software, version 25.0 (SPSS Inc., Chicago, Illinois). A p-value less than 0.05 was considered to be statistically significant.

3.8 Ethical considerations

Data collection was started after the hospital's ethical committee approval (B670201734253). All patient-related data were collected with the highest confidentiality. Personal information such as patient names, ID-numbers, hospital admission and operation date were coded by the researcher before statistical analysis.

4. Results

4.1 Baseline Characteristics

The final population sample consisted of 360 patients of which four were excluded post-hoc: one patient because of a severe protamine reaction after CPB, another one because of severe hemodynamic instability after induction of anesthesia and one patient who suffered from a severe septic shock preoperatively. A fourth patient was excluded because of an urgent reoperation a few hours after the primary procedure.

Of the 356 remaining patients, 141 underwent surgery through a median sternotomy and 215 through the minimal invasive approach. Two patients, which were intended to receive a MICS-procedure, received a sternotomy because a safe peripheral vascular access site was not attainable before incision; consequently, these two cases were included in the MS group.

Baseline characteristics of the unmatched study groups are provided in table one. No differences were detected in age or body surface area between groups. However, patients in the MS group underwent more complex procedures (multiple valve-surgery: 52(36.9%) vs 38(17.7%); redo-surgery: n=42(29.8%) vs 7(3.3%); p<0.001 for both variables) and had a higher NYHA-class (p<0.001) as compared to the MICS-group. Consequently, the operative risk score was significantly higher in the MS group (Logistic Euroscore: 6.1±72 vs 4.10±4.5; p<0.001). MICS patients had a higher preoperative hematocrit as compared to the MS group (39.9±4.3 vs 38.5±4.4, respectively; p=0.005). Because of these differences in baseline covariates between both groups, a propensity score matching analysis was performed.

Table 1

Baseline characteristics of the unmatched and propensity matched groups

Variable	Unmatched cohort (*n*=356)			Propensity score matched groups (*n*=285)		
	MS (*n*= 141)	MICS (*n*=215)	*p*-value	MS (*n*=70)	MICS (*n*=215)	*p*-value
Male sex, *n*(%)	54 (38.3)	103 (47.9)	.081	29 (41.4)	103 (47.9)	.408
Age, years	64.4 (14.2)	65.2 (12.9)	.583	64.1 (14.5)	65.2 (12.9)	.545
Height, cm	166.2 (9.5)	168.6 (9.6)	.022	166.9 (10.1)	168.6 (9.6)	.225
Weight, kg	72.1 (14.2)	72.6 (14.1)	.741	72.7 (15.1)	72.6 (14.1)	.957
BSA, m^2	1.78 (0.21)	1.81 (0.21)	.200	1.80 (0.22)	1.81 (0.21)	.603
BMI	26.1 (4.6)	25.5 (4.3)	.225	26.0 (4.6)	25.5 (4.3)	.372
Obese patients *n*(%)	28 (19.9)	34 (15.8)	.391	14 (20.0)	34 (15.8)	.462
Procedures *n*(%)			<.001			.166
Single Valve	*89 (63.1)*	*177 (82.3)*		*52 (74.3)*	*177 (82.3)*	
Multiple valves	*52 (36.9)*	*38 (17.7)*		*18 (25.7)*	*38 (17.7)*	
Redo Procedures, *n*(%)	42 (29.8)	7 (3.3)	<.001	4 (5.7)	7 (3.3)	.473
Atrial ablation, *n*(%)	11 (7.8)	25 (11.6)	.283	7 (10)	25 (11.6)	.829
Endo-aortic Clamp, *n*(%)	-	114 (53.0)	-	-	114 (53.0)	-
Conversion MS, *n*(%)	-	8 (3.7)	-	-	8 (3.7)	-
Logistic Euroscore	6.1 (7.2)	4.1 (4.5)	<.001	4.9 (5.3)	4.1 (4.5)	.087
NYHA-class, *n*(%)			<.001			.065
NYHA I	*3 (1.8)*	*19 (8.3)*		*3 (4.3)*	*19 (8.3)*	
NYHA II	*51 (30.2)*	*109 (47.8)*		*28 (40.0)*	*109 (47.8)*	
NYHA III	*87 (51.5)*	*87 (38.2)*		*39 (55.7)*	*87 (38.2)*	
NYHA IV	-	-		-	-	
AHT, *n*(%)	69 (48.9)	89 (41.4)	.191	31 (44.3)	89 (41.4)	.678
Diabetes, *n*(%)	12 (8.8)	10 (4.8)	.176	5 (7.4)	10 (4.8)	.536
COPD, *n*(%)	23 (16.3)	11 (5.1)	.001	10 (14.3)	11 (5.1)	.017
A-fib / flutter, *n*(%)	52 (39.1)	78 (37.0)	.732	27 (39.7)	78 (37.0)	.921
Diuretics use, *n*(%)	58 (51.3)	85 (40.3)	.061	22 (40.0)	85 (40.3)	1
Hematocrit pre-op, *n*(%)	38.5 (4.4)	39.9 (4.3)	.005	40.0 (3.9)	39.9 (4.3)	.896
Creatinine pre-op, mg/dl	0.93 (0.28)	0.93 (0.25)	.901	0.90 (0.26)	0.93 (0.25)	.239
Creatinine clearance	68.9 (23.0)	67.6 (21.1)	.584	71.7 (22.6)	67.6 (21.1)	.172
Renal function, *n*(%)			*.06*			.226
KDOQI Stage I	*26 (18.4)*	*23 (10.7)*		*13 (18.6)*	*23 (10.7)*	
KDOQI Stage II	*58 (41.1)*	*110 (51.2)*		*33 (47.1)*	*110 (51.2)*	
KDOQI Stage > III	*57 (40.4)*	*82 (38.1)*		*24 (34.3)*	*82 (38.1)*	

BSA, Body Surface Area; BMI, Body Mass Index; Redo, Reoperative surgery; NYHA, New York Heart Association; AHT, Arterial Hypertension; COPD, Chronic Obstructive Pulmonary disease; A-Fib, Atrial Fibrillation; KDOQI, Kidney Disease Outcomes Quality Initiative. Data presented as Mean (Standard Deviation) or n(%).

In the propensity score model, five patients were excluded because of missing data, resulting in a final sample of 351 patients of which 285 were selected based on the propensity score analysis (*n*(MS)=70; *n*(MICS)=215). The mirrored histogram in figure one shows an equal propensity score distribution across a range of propensity scores in both groups. The distribution of the baseline characteristics between the propensity score matched groups, as shown in table one, did not reveal any significant differences between both groups except for chronic obstructive pulmonary disease (COPD) prevalence (*p*=0.017). In the MICS group, there was an equal usage of both aortic clamping techniques. Eight patients (3.7%) had to undergo a conversion from MICS to MS which were included in the MICS group in an intention-to-treat analysis.

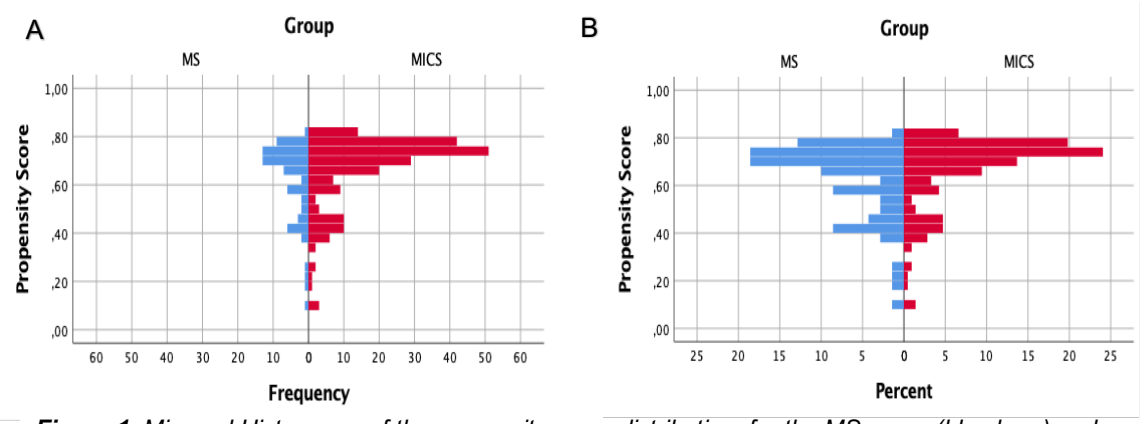

***Figure 1**: Mirrored Histograms of the propensity score distribution for the MS group (blue bars) and the MICS group (red bars). A: Bars represent frequencies; B: Bars represent percentages. MS, Median Sternotomy; MICS, Minimal Invasive Cardiac Surgery.*

4.2 Cardiopulmonary Bypass & Intraoperative Parameters

Important intraoperative and CPB parameters are listed in table two. Among the propensity matched cohorts, aortic cross-clamp time (84.8±31.8 vs 58.4±22.1 minutes; *P*<0.001) and duration of CPB (136.2±38.7 vs 93.1±31.2 minutes; *p*<0.001) were significantly longer with the minimal invasive approach. Consequently, these patients received a higher dose of crystalloid cardioplegia (14.4±4.8 vs 12.2±3.5 ml/kg; *p*<0.001). Furthermore, in MICS, CPB was conducted at a significantly lower blood temperature (28.4±1.7 vs 29.4±1.9 °Celsius; *p*<0.001).

Table 2

Peri-operative data of matched cohort

Variable	MS (*n*=70)	MICS (*n*=215)	MS - MICS MD / OR (95% CI)	*p*-value
ECC time, minutes	93.1 (31.2)	136.2 (38.7)	-43.1 (-53.1 – -33.8)	<.001
AOX time, minutes	58.4 (22.1)	84.8 (31.7)	-26.4 (-34.1 – -19.5)	<.001
CPB temperature, °C	29.4 (1.9)	28.4 (1.7)	1.1 (0.6 – 1.5)	<.001
Cardioplegia, ml/kg	12.2 (3.5)	14.4 (4.8)	-2.3 (-3.4 – -1.2)	<.001
Average PFI, L/min/m^2	2.38 (0.14)	2.23 (0.18)	0.15 (0.10 – 0.20)	<.001
Nadir PFI, L/min/m^2	2.33 (0.16)	2.15 (0.21)	0.18 (0.13 – 0.24)	<.001
Mean MAP CPB, mmHg	66.2 (6.2)	63.0 (6.1)	3.3 (1.6 – 4.9)	<.001
Nadir MAP CPB, mmHg	58.9 (7.5)	54.3 (7.0)	4.6 (2.7 – 6.5)	<.001
Mean CPB hematocrit, %	26.9 (4.1)	28.4 (3.7)	-1.5 (-2.6 – -0.4)	.004
Nadir CPB hematocrit, %	25.8 (4.4)	26.8 (4.1)	-1.1 (-2.2 – 0.1)	.064
End of CPB hematocrit, %	28.1 (3.2)	28.7 (3.2)	-0.6 (-1.5 – 0.3)	.188
Mean DO_2, mlO_2/min/m^2	295.7 (45.1)	294.1 (37.7)	1.5 (-9.3 – 12.4)	.780
Nadir DO_2, mlO_2/min/m^2	277.9 (49.9)	266.0 (45.1)	11.9 (-0.7 – 24.6)	.064
CPB Priming Volume, ml	1234 (206)	1235 (145)	-1.6 (-54 – 51)	.953
RAP, n(%)	20 (28.6)	92 (43.2)	1.9 (1.1 – 2.3)	.035
RAP volume, ml	502 (192)	497 (202)	5.8 (-92 – 103)	.908
Diuresis, ml/kg/hour ECC	5.1 (6.6)	3.6 (3.6)	2.0 (1.0 – 3.0)	.004
Furosemide ECC, mg/kg	0.16 (0.11)	0.19 (0.12)	-0.04 (-0.07 – -0.007)	.018
Transfusion				
PRBC, n (%)	26 (37.1)	64 (29.8)	0.7 (0.4 – 1.3)	.249
PRBC, Units	0.73 (1.14)	0.63 (1.18)	0.1 (-0.2 – 0.4)	.544
FFP, n (%)	3 (4.3)	4 (1.9)	0.4 (0.1 – 1.9)	.368
PLC, n (%)	1 (3.6)	8 (4.2)	1.2 (0.1– 9.8)	1
Autotransfusion n(%)	10 (37.0)	74 (40.2)	1.1 (0.5 – 2.6)	.853
PAB, n (%)	2 (7.1)	12 (6.2)	0.9 (0.2 – 4.1)	1
CPB lactate levels, mg/dl				
Mean	18.9 (6.9)	19.0 (6.2)	-0.1 (-1.8 – 1.5)	.866
Peak	23.6 (8.6)	23.6 (7.5)	0.0 (-2.1 – 1.9)	.956

ECC, ExtraCorporeal Circulation; AoX, Aortic Clamp; CPB, Cardiopulmonary Bypass; PFI, Pump Flow Index; MAP, Mean Arterial Pressure; DO_2, Oxygen Delivery; RAP, Retrograde Autologous Priming; PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma; PLC, Platelet Concentrate; PAB, Predonation Autologous Blood. MD, Mean Difference; OR, Odds Ratio (MICS vs MS). Data presented as Mean (Standard Deviation) or n (%).

Average Pump Flow Index (PFI) (2.2±0.2 vs 2.4±0.1 L·(min·m^2)$^{-1}$; *p*<0.001) and mean arterial pressure (63.0±6.1 vs 66.2±6.2 mmHg; *p*<0.001) were significantly lower in MICS. On contrary, the mean hematocrit during CPB was higher in this group (28.4±3.7 vs 26.9±4.1; *p*=0.004) while the difference in nadir hematocrit was borderline significant (26.8±4.1 vs 25.8±4.4 in MICS vs MS, respectively; *p*=0.064). Retrograde autologous priming techniques (RAP) were used more frequently in MICS patients (43.2 vs 28.6%; *p*=0.035). No differences in perioperative transfusion rate or serum lactate was observed between both groups. The average DO_2 was equivalent in both groups (figure 2), while there was a trend towards a significantly lower nadir DO2 in the MICS group (266.0±45.1 vs 277.9.2±49.9; *p*=0.064). A higher dosage of diuretics was used in MICS patients but nevertheless they had a lower perioperative urine output (3.6±3.6 vs 5.1±6.6 ml/kg/h; *p*<001).

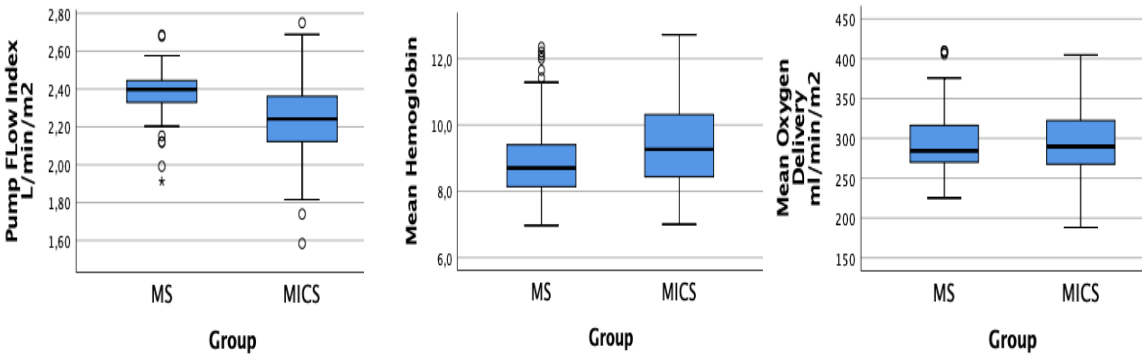

***Figure 2**: Boxplots comparing Pump Flow Index, Mean Hemoglobin and Mean Oxygen Delivery during CPB between both groups.*

4.3 Postoperative outcome & organ function

Postoperative data are presented in table three. MICS patients had a shorter hospitalization duration and time to extubation as compared to the MS group (8.7±2.0 vs 9.8±2.1 days; *p*=0.002 & 8.5±2.9 vs 10.0±3.1 hours; *p*=0.018, respectively), although ICU length-of-stay was not different. No dissimilarities were detected in blood loss or transfusion rate. Data concerning total Fresh Frozen Plasma (FFP) transfusion during ICU-stay were missing in the database records.

Table 3

Postoperative outcome data

Variable	MS (*n*=70)	MICS (*n*=215)	MD / OR (*95% CI*)	*p*-value
Survival, In hospital, *n*(%)	69 (98.6)	212 (98.6)	1.0 (.1 – 9.5)	1
Hospital LOS, days	9.8 (2.1)	8.7 (2.0)	1.1 (0.3 - 1.7)	.002
ICU stay, hours	31.8 (10.7)	30.6 (10.7))	1.2 (-3.1 - 5.1)	.599
Time to extubation, hours	10.0 (3.1)	8.5 (2.9)	1.5 (0.3 - 2.4)	.018
Chest tube drainage, ml cum				
4h	217.3 (194.1)	230.5 (442.0)	-13.2 (-58.4 – 24.6)	.520
8h	285.8 (282.0)	304.0 (261.9)	-18.2 (-76.8 – 30.9)	.491
12h	387.6 (378.1)	427.0 (350.2)	-39.4 (-119.2 – 27.8)	.267
Blood loss > 1000 ml, *n*(%)	4 (5.9)	16 7.7)	1.3 (0.4 – 4.1)	.790
Revision for bleeding *n*(%)	4 (5.9)	10 (4.7)	0.8 (0.2 – 2.6)	.750
Transfusion				
PRBC, *n*(%)	13 (18.8)	33 (15.5)	.8 (0.4 – 1.6)	.574
FFP	-	-	-	
PLC, *n*(%)	1 (1.4)	14 (6.6)	4.8 (0.6 – 37.1)	.127
KDIGO AKI, *n*(%)				
POD 1 Stage 1	8 (11.4)	25 (11.6)		.809
Stage 2	0 (0.0)	1 (0.5)		
Stage 3	-	-		
POD 2 Stage 1	6 (8.7)	26 (12.1)		.488
Stage 2	4 (5.8)	8 (3.7)		
Stage 3	1 (1.4)	0 (0.0)		
POD 3 Stage 1	4 (13.3)	14 (17.3)		.960
Stage 2	3 (10.0)	6 (7.4)		
Stage 3	2 (6.7)	6 (7.4)		
Any KDIGO pod 1,2,3	16 (22.9)	45 (20.9)	0.89 (.47 – 1.71)	.739
New onset dialysis	0 (0.0)	6 (2.8)	-	.341
PF-ratio ICU				
Arrival (*n*=67/212)	311.9 (146.0)	264.1 (129.1)	47.8 (11.0 – 84.6)	.011
2h (*n*=66/195)	410.3 (172.8)	358.2 (168.1)	52.0 (4.6 – 99.5)	.032
6h (*n*=57/151)	321.8 (197.0)	272.4 (152.7)	49.4 (8.8 – 84.8)	.019
12h (*n*=26/53)	303.9 (134.0)	318.5 (122.0)	-14.7 (-74.8 – 45.4)	.628
Liver Function				
AST pre, U/L	21.5 (7.4)	23.2 (10.3)	-1.7 (-3.8 – 3.1)	.104
AST post, U/L	59.0 (48.7)	66.2 (49.6)	-7.2 (-19.0 – 2.8)	.167
ALT pre, U/L	21.3 (14.4)	22.6 (17.3)	-1.3 (-4.9 – 1.8)	.429
ALT post, U/L	18.3 (16.0)	23.1 (22.7)	-4.8 (-9.3 – -1.1)	.010
LDH pre, U/L	301.2 (154.4)	225.7 (95.9)	75.5 (51.0 – 97.6)	<.001
LDH post, U/L	487.8 (288.7)	340.1 (187.4)	147.7 (100.6 – 189.1)	<.001

LOS, Length Of Stay; ICU, Intensive Care Unit; Cum, Cumulative; PRBC, Packed Red Blood Cells; FFP, Fresh Frozen Plasma; PLC, Platelet Concentrate; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, Acute Kidney Injury; POD, Post-Operative Day; PF-ratio, PaO_2/FiO_2 ratio; AST, Aspartate Transaminase; ALT, Alanine Transaminase; LDH, Lactate Dehydrogenase. MD, Mean Difference; OR, Odds Ratio (MICS vs MS). Data presented as Mean (Standard Deviation) or n(%).

Pulmonary diffusion capacity, assessed by calculating the PF-ratio, was significantly lower in MICS at the time of ICU-arrival (311.9±146.0 vs 264.1±129.1; p=0.011) and at two and six hours of ICU-stay (410.3±172.8 vs 358.2±168.1 & 321.8±197.0 vs 272.4±152.7; p=0.032 & p=0.019, respectively). Data concerning FiO_2 and modalities of oxygen supplementation following patient extubation were insufficiently documented to construct a reliable further analysis. There were no differences in renal function during the first three postoperative days as evaluated by the KDIGO criteria. The evolution of AST and ALT was not significantly different depending on study groups in a two-way repeated measures ANOVA of liver function (*Wilks' Lambda*; AST: p=0.616; ALT: p=0.084). However, there was a significant difference in evolution of LDH depending on the group (*Wilks' Lambda*=0.954; p=0.002) and between-subjects depending on the group (F=32.8; p<0.001). LDH was higher and increased more prominently in the MS-group.

4.4 Biochemical data

Biochemical data are presented in table four. There were no differences in postoperative hematocrit, leucocyte count, platelet count, fibrinogen and CRP on ICU. Postoperative creatinine phosphokinase (CK) levels were significantly higher in the MICS group. A two-way repeated measures ANOVA exposed a significant difference in the evolution of CK depending on the treatment group (*Wilks' Lambda*=0.980; p=0.020); there was a significantly stronger increase in

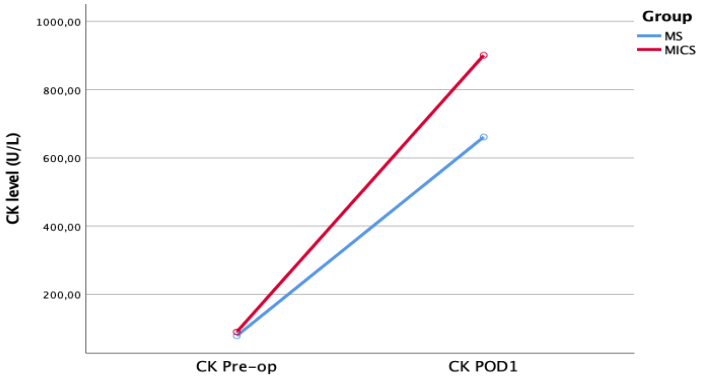

***Figure 3**: Two-Way Repeated Measures ANOVA Plot: Evolution of Creatininephosphokinase levels (U/L) pre vs postoperative day one depending on study group; MS vs MICS.*

CK in MICS. Serum lactate was significantly higher in the MICS group at arrival and after two hours of ICU-stay as was peak serum lactate during the first 24 hours postoperatively.

Table 4
Biochemical data

Variable	MS (n=70)	MICS (n=215)	MD (95% CI)	p-value
Hematocrit ICU, %				
Arrival	31.2 (3.6)	31.5 (3.9)	-0.3 (-1.4 - 0.7)	.535
2h	31.6 (4.3)	31.2 (4.0)	0.5 (-0.7 – 1.6)	.436
6h	29.9 (3.7)	31.0 (4.0)	-1.1 (-2.2 – -0.03)	.057
12h	31.3 (3.2)	31.6 (3.8)	-0.3 (-1.5 – 0.8)	.556
24h	32.2 (3.7)	32.4 (3.8)	-0.2 (-1.7 – 1.3)	.822
Leucocyte Count*10^3/µL				
Pre	6.7 (2.6)	6.4 (2.1)	0.3 (--0.3 – 0.8)	.345
Post	9.3 (5.5)	8.7 (5.7)	0.7 (--0.6 – 1.8)	.334
POD1	9.9 (3.8)	10.7 (4.3)	-0.8 (-1.8 – 0.1)	.094
Platelet Count*10^3/mm^3				
Pre	222.8 (58.4)	232.2 (64.1)	-9.5 (-26.8 – 7.9)	.284
Post	123.0 (33.0)	126.1 (38.6)	-3.1 (-13.2 – 7.0)	.541
Fibrinogen, mg/dl				
Pre	363.2 (84.6)	370.4 (94.0)	7.2 (--31.1 – 15.3)	.541
Post	212.7 (65.0)	220.4 (74.5)	-7.7 (-25.4 – 8.7)	.367
CRP (non-par)				
Pre (mean rank)	131.8	111.5	-	.095
POD1 (mean rank)	140.0	141.3	-	.912
CK, U/L				
Pre	63.8 (56.1)	73.8 (65.8)	-10.0 (-24.2 – 16.6)	0.106
POD1	486.5 (445.0)	730.3 (615.6)	-243.8 (--377.6 - -130.7)	<.001
Serum Lactate ICU, mg/dl				
Arrival	16.7 (11.0)	19.9 (10.9)	-3.2 (-5.8 – -17.5)	.006
2h	13.7 (10.7)	16.0 (10.5)	-2.3 (-5.0 – -0.03)	.048
6h	15.0 (11.5)	16.4 (11.7)	-1.4 (-4.1 – 1.0)	.294
Peak 24h	22.0 (14.5)	26.0 (15.9)	-4.0 (-7.7 - -0.8)	.015
Peak glycemia 24h, mg/dl	158.7 (28.1)	151.3 (183.9)	7.4 (-0.5 – 14.9)	.064

ICU, Intensive Care Unit; CRP, C-Reactive Protein; CK, Creatininephosphokinase; POD, Post-Operative Day. Hyperlactatemia defined as Serum Lactate >22.5 mg/d (=2.5 mmol/L). MD, Mean Difference. Data presented as Mean (Standard Deviation) or n(%).

4.5 Multivariate analysis

Because of the relatively high incidence of postoperative CSA-AKI (21.4% for the entire matched cohort), a multivariate analysis was performed with any stage of KDIGO CSA-AKI during the first three postoperative days as a dependent dichotomous variable. Severe multicollinearity was detected between the hematocrit variables and the calculations of DO_2 (r^2=0.662 & 0.797 between the nadir hematocrit and the nadir and average DO_2, respectively). The nadir hematocrit had the strongest correlation with CSA-AKI (r^2= -0.177) and was finally chosen to be implemented in the multivariate model together with the other variables. Of note, during the multicollinearity procedure a positive correlation between CPB-temperature and the mean PFI was also detected (r^2=0.293; p=<0.001), although this did not reach the criterium for removal from the model. A higher preoperative creatinine level (OR=17.5; p<0.001), older patient age (OR=1.03; p=0.044); more complex procedures (OR=2.4; p=0.022) and a lower nadir hematocrit during CPB (OR=0.9; p=0.018) were independent predictors of CSA-AKI during the first three postoperative days. The higher the nadir hematocrit, the lower the risk will be for CSA-AKI during the first three postoperative days. Further details and the parsimonious model of this analysis are presented in table five.

Table 5
Results of Binary Logistic Regression analysis

Predictor	β	S.E. β	p-value	OR	OR 95% CI
Preoperative Creatinine Level	2.862	.67	<.001	17.491	4.715 – 64.885
Age	.033	.016	.044	1.033	1.001 – 1.067
Nadir Hematocrit	-.105	.044	.018	.901	.826 – .982
Multiple valves vs single valve	.869	.38	.022	2.384	1.132 – 5.020
Constant	-3.775	1.771	.034	.023	

OR, Odds Ratio; S.E., Standard error; CI, Confidence Interval. Dependent variable: Any CSA-AK (KDIGO). Independent variables entered on step 1: CPB-Temperature, Mean Arterial Pressure during CPB, CPB-time, Pre-op Creatinine level, Gender, Age, Diabetes Y/N, COPD Y/N, Cardioplegia Volume (ml/kg), Furosemide dose (CPB), Nadir Hemoglobin & Nadir Pump Flow Index, type of procedure. Cutoff value for covariate removal: p≥.01. χ^2: 49.637 (p-value<.001); -2 Loglikelihood: 231.9. Nagelkerke r^2: 0.261.

The predictive accuracy of the nadir hematocrit for CSA-AKI was explored using a ROC-curve analysis and the relative area under the curve (AUC). The nadir

hematocrit had an AUC of 0.63 for the entire matched cohort. We hypothesized that, because of the limited pump flow in MICS, the nadir hematocrit during CPB would have a higher predictive value in that patient group. Therefore, ROC-curves were constructed for both groups separately, confirming this hypothesis with an AUC of 0.65 vs 0.56 for MICS and MS, respectively. According to the Youden's J-statistic, cut-off values of the nadir hematocrit for their impact on CSA-AKI were determined. A nadir hematocrit of less than 26.3% in the MICS group (AUC: 0.65; sensitivity: 0.69; specificity: 0.61; negative predictive value: 0.88; positive predictive value: 0.32) and 24.8% in the MS group (AUC: 0.56; sensitivity: 0.60; specificity: 0.61; negative predictive value: 0.85; positive predictive value: 0.30) were predictive of an increased risk for CSA-AKI.

5. Discussion

The principal finding of this retrospective cohort study is that, despite the distinct differences in CPB parameters, there are no important clinical differences in outcome or organ function between MICS and MS for mitral or tricuspid valve surgery.

In the past, MICS has been frequently reported to be more time-consuming as compared to the classical approach (Gammie et al., 2010; Nishi et al., 2015). Our study confirms these results with an increase in CPB and AoX duration of 43 and 20 minutes, respectively. The groin cannulation, endo-aortic balloon occlusion and the more challenging surgical exposure in MICS have been suggested as the main reasons for this observation (Dogan et al., 2005). Although prolonged CPB and myocardial ischemic-time have been previously associated with a higher incidence of postoperative adverse events (Kumar, Suneja, Bayman, Weide, & Tarasi, 2012), we could not identify any differences in in-hospital outcome between these two groups as assessed by survival, organ function, blood loss, transfusion rate and revision for bleeding. Nevertheless, our study revealed some marked dissimilarities in CPB management between MICS and MS.

The PFI was reduced by approximately 8% in MICS. One of the flow-limiting factors could be the venous return during CPB as it is directly correlated to the arterial pump flow. In order to compensate for the increased flow resistance of the smaller cannulas in MICS, assisted venous drainage is used, generating a more negative pressure to the venous line. However, these techniques have been shown to induce additional risks for CPB management. For example, increasing venous line suction can counterintuitively reduce venous return because of caval vein collapse (Kurusz, Deyo, Sholar, Tao, & Zwischenberger, 1999). This can result in excessive negative line pressures which causes hemolysis and the entrance of micro-embolic air into the extracorporeal circuit (Cirri et al., 2001; LaPietra et al., 2000). These CPB complexities and suboptimal cannula choice may provide an explanation for the reduced PFI. Unfortunately, corresponding data were lacking in this study. Better research is needed to identify the factors influencing the PFI, creating possibilities to optimize flow during MICS.

Although the PFI is directly related to DO_2, we did not identify a significant difference in the latter between the two groups, although there was a trend towards a lower nadir DO_2 in MICS (p=0.064). The higher usage retrograde autologous priming (RAP) at the initiation of CPB in MICS might have influenced this result. RAP has been shown to have beneficial effects on both the intraoperative hematocrit and transfusion rate in cardiac surgical patients (Severdija et al., 2011; Vandewiele et al., 2013). Indeed, the average hematocrit was higher in MICS in this study correcting for the reduced PFI. Similar observations have been reported with the use of minimized extracorporeal circuits. Despite the limited pump flow, the DO_2 was preserved by the inherent reduction in hemodilution of their CPB system (Bennett et al., 2013). Likewise, these researchers could not identify any differences in postoperative renal function.

The relatively high incidence of CSA-AKI across both groups of 21.4% is rather concerning as even a mild stage 1 AKI was independently associated with poorer outcome (Elmistekawy et al., 2014). A better prevention of CSA-AKI could

generate a substantial clinical benefit for our patients. In a binary logistic regression analysis for the entire matched cohort, the preoperative renal function, was shown to be the most important predictor of CSA-AKI. Remarkably, the nadir hematocrit was the only perfusion-related independent predictor of CSA-AKI in this patient group. It has been demonstrated by others in the past that the hematocrit level during cardiac surgery has an impact on several objective outcome parameters (Habib et al., 2003, 2005; Loor et al., 2012, 2013). However, while the nadir DO_2 during CPB has been shown to have a higher predictive value for postoperative CSA-AKI (Ranucci et al., 2018), our data could not confirm this.

Interestingly, the cutoff value of nadir hematocrit was higher in the MICS group (26.3 vs 24.8%). This means that during MICS the preservation of the perioperative hematocrit above a level of 26% is of major importance to optimize patient outcome as the feasibility of a flow-guided goal directed perfusion management is restricted. Perfusionists should consider using blood conservation techniques such as circuit size reduction, RAP and hemofiltration in order to reduce the risk for CSA-AKI in this patient group.

In this study, CPB-temperatures were relatively low in both groups and even lower in MICS, which might be an indication of the higher complexity of these procedures. Interestingly, CPB-temperature was not shown to be an independent predictor for CSA-AKI. Nevertheless, we detected a positive correlation between the CPB-temperature and the average PFI (r^2=0.293) which might mean that the temperature was requested to be lower by the surgeon because of intraoperative concerns and, as a consequence, PFI was reduced. However, these variables are very likely to be interrelated and unfortunately, with our data, the correct causal link of this phenomenon is not possible to determine.

There is a vast amount of literature showing that minimally invasive surgery results in a faster postoperative recovery, presented as a shorter ‘time to extubation’ (TTE) and a shorter ICU and hospital LOS (Gammie et al., 2010; Hawkins et al., 2018; Q. Wang et al., 2018). In our study, TTE was shorter in

MICS, despite the longer CPB-duration and the accompanying longer period of uninflated lungs and despite a lower postoperative PF-ratio. The usage of continuous intercostal nerve block has been shown to be associated with reduced postoperative stress and pain, a shorter TTE and a faster postoperative recovery (Zhan et al., 2017). Unfortunately, we did not collect sufficient data to investigate this topic. Therefore, these somewhat conflicting data illustrate why one should be very careful interpreting these results. Importantly, we could only find one RCT that clearly defined objective criteria for extubating their patients, based on oxygenation, blood pH, and CO2 removal (Kang et al., 2011). As a result, these authors did not see any difference in 'time to extubation' or ICU LOS between MS and MICS. We are not aware of such criteria being used in our ICU during this study period nor did we have any indication of pain measurements or patient comfort, which could also have influenced the TTE. Therefore, shorter TTE might also be addressed to performance bias due to the unfeasibility to blind the nursing and medical staff.

Another finding was the higher postoperative increase in CK in MICS. The exact explanation for this phenomenon is rather unclear although the longer CPB duration and the partial occlusion of the femoral artery because of the arterial cannula are possibly associated with this result. Finally, we also found some significant differences in postoperative serum lactate levels. The clinical relevance of these relatively small differences should be questioned. Depending on its definition, severe hyperlactatemia has been associated with a high morbidity and mortality (Lopez-Delgado et al., 2015). However, the modest and often transient increases in serum lactate as presented in our study have recently been shown to have very little predictive value on postoperative outcome in mitral valve surgery (Evans et al., 2018). Although prolonged CPB-duration has been associated with hyperlactatemia, the higher dosage of the lactate-containing cardioplegia in MICS patients might also have influenced our observation.

Limitations

By its retrospective nature, this study has several limitations, including the inherent selection bias. By using a propensity score analysis, we tried to address this problem. However, where RCT's implicate random group assignment, which should theoretically equalize all possible preoperative covariates, even the unmeasured ones, propensity score matching can work only with known variables (Winger & Nason, 2016). Hence, such analysis cannot correct for unknown or unmeasured covariates, which means that there will probably be a persisting degree of selection bias. Moreover, as has been shown in our study, propensity matched analyses tend to exclude patients with higher risk profiles, reducing the generalizability of their results. Obviously, this study is covering a study period of 11 years, thus the risk of history bias should not be neglected. During this period, the technique of MICS was implemented. It has been noted by others that every cardiac surgical team will encounter an important learning curve during the first 75 to 125 procedures (Chitwood et al., 2008; Holzhey et al., 2013). We have not addressed this issue in our methodology because we think our insights might help making this learning curve a little steeper for MICS teams. As a third limitation, the interpretation of the liver function was not reliable as AST, ALT and LDH were not specific enough to fully associate them with liver function. LDH-isoenzyme measurements could possibly clarify the difference in postoperative LDH between groups.

6. Conclusion

In conclusion, this study showed that, despite the longer CPB duration, there were no differences in postoperative outcome between the minimally invasive and the classical median sternotomy approach for mitral or tricuspid valve surgery. However, the added technical complexity in MICS resulted in a lower pump flow during CPB in MICS. Therefore, the preservation of the perioperative hematocrit above 26% during MICS can reduce the risk for CSA-AKI. The application of blood conservation techniques is highly recommended in this patient group, especially when pump flow is limited.

7. References

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