

Are minimized perfusion circuits the better heart lung machines? Final results of a prospective randomized multicentre study

A El-Essawi, T Hajek, J Skorpil, A Böning, F Sabol, Y Ostrovsky, H Hausmann and W Harringer
Perfusion 2011 26: 470 originally published online 22 August 2011
DOI: 10.1177/0267659111419035

The online version of this article can be found at:
<http://prf.sagepub.com/content/26/6/470>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Perfusion* can be found at:

Email Alerts: <http://prf.sagepub.com/cgi/alerts>

Subscriptions: <http://prf.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Citations: <http://prf.sagepub.com/content/26/6/470.refs.html>

>> [Version of Record](#) - Oct 25, 2011

[Proof](#) - Aug 22, 2011

[What is This?](#)

Are minimized perfusion circuits the better heart lung machines? Final results of a prospective randomized multicentre study

A El-Essawi,¹ T Hajek,² J Skorpil,² A Böning,³
F Sabol,⁴ Y Ostrovsky,⁵ H Hausmann⁶
and W Harringer¹

Abstract

Introduction: Minimized perfusion circuits (MPCs), although aiming at minimizing the adverse effects of cardiopulmonary bypass, have not yet gained popularity. This can be attributed to concerns regarding their safety, as well as lack of sufficient evidence of their benefit.

Methods: Described is a randomized, multicentre study comparing the MPC - ROCsafeRX to standard cardiopulmonary bypass in patients undergoing elective coronary artery bypass grafting and/ or aortic valve replacement.

Results: Five hundred patients were included in the study (252 randomized to the ROCsafeRX group and 248 to standard cardiopulmonary bypass). Both groups were well matched for demographic characteristics and type of surgery. No operative mortality and no device-related complications were encountered.

Transfusion requirement (333 ± 603 vs. 587 ± 1010 ml; $p=0.001$), incidence of atrial fibrillation (16.3% vs. 24.2%; $p=0.03$) and the incidence of major adverse events (9.1% vs. 16.5%; $p=0.02$) were all in favour of the MPC group.

Conclusion: These results confirm both the safety and efficacy of the ROCsafeRX MPC for a large variety of cardiac patients. Minimized perfusion circuits should, therefore, play a greater role in daily practice so that as many patients as possible can benefit from their advantages.

Keywords

minimized perfusion circuits; coronary artery bypass surgery; aortic valve replacement; blood transfusion; atrial fibrillation

Introduction

Minimized perfusion circuits (MPCs), although no longer an innovation, have not yet become part of routine practice. In spite of following a similar philosophy as minimal invasive surgery by minimising the trauma inflicted by heart lung machines, their acceptance is still limited. The reason for this is that the clinical impact of this philosophy has not been sufficiently established. In fact, only two^{1,2} prospective, randomized studies with a group size of 100 or more have been published. Furthermore, most prospective, randomized studies have concluded that, although MPCs have their benefits in terms of reduction of transfusion requirements or inflammatory reaction, their clinical benefit remains inconclusive²⁻⁹. As most of these studies included low risk patients with a group size of 30³⁻⁷, this lack of clinical evidence is not surprising.

The purpose of this study was to verify the safety and efficacy of the ROCsafeRX MPC.

¹ Department of Thoracic and Cardiovascular Surgery, Klinikum Braunschweig, Braunschweig, Germany

² Department of Cardiac Surgery, University Hospital Pilsen, Pilsen, Czech Republic

³ Department of Cardiovascular Surgery, University Hospital Giessen and Marburg, Giessen, Germany

⁴ Heart Surgery Department, Pavol Jozef Safarik University Kosice, Kosice, Slovak Republic

⁵ Cardiovascular Surgery, Byelorussian Center of Cardiovascular Surgery, Minsk, Belarus

⁶ Cardiovascular, Thoracic and Intensive Care, Mediclin Herzzentrum Coswig, Coswig, Germany

Corresponding author:

Aschraf El-Essawi, M.D.,
Department of Thoracic and Cardiovascular Surgery,
Klinikum Braunschweig,
Salzdahlumer Str. 90,
38126 Braunschweig,
Germany.
Email: aelessawi@aol.com

Presented at the 24th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Geneva, Switzerland, September 11-15, 2010.

Patients and Methods

A prospective, randomized, multi-centre trial, comparing the ROCsafeRX MPC to conventional cardiopulmonary bypass (CCPB) in elective coronary artery bypass and/or aortic valve replacement, was initiated following the approval of the ethics committees of the participating centres. Following their written consent, 503 patients eligible for the study (Table 1) were enrolled from January 2008 to March 2010 and blindly randomized by a computer-generated algorithm to either group. Three patients were later excluded as a result of an unplanned concomitant procedure. Finally, 500 patients were evaluated, 252 in the ROCsafeRX group and 248 in the CCPB group.

Patient demographics, co-morbidities, pre-operative medication, laboratory findings and procedural characteristics are presented in Table 2.

Statistical hypothesis and power calculation

The study is powered for the main endpoint - reduction in transfusion requirements with an estimated power of more than 99%.

Concerning the secondary endpoint of atrial fibrillation, the study has shown an incidence of atrial fibrillation of about 15% in the ROCsafeRX group compared to 25% in the CCPB group. A simulation of a power for a study to put in evidence a difference of 10% in this population shows an actual power of approximately 85%.

Table 1. Exclusion criteria

| |
|--|
| Patients below 18 years of age |
| Concomitant procedure |
| Ejection fraction of 20% or less |
| Previous cardiac surgery |
| Acute endocarditis |
| Acute coronary syndrome within the last 10 days |
| Previous cerebrovascular accident |
| Knowledge of an intracardiac thrombus |
| Stenosis of an internal carotid artery exceeding 70% |
| Dialysis |
| Baseline C-reactive protein exceeding 10 mg/l or leucocytosis exceeding $12 \times 10^9/l$ |
| Patients on dual antiplatelet therapy or having received a DES within the last 6 months. |
| History of any malignancy or immunological disease. |
| Intake of warfarin, preoperative continuous heparin infusion or known coagulopathy. |
| Thrombocytic count below $100 \times 10^9/l$. |
| Patients who gave autologous pre-deposited blood |
| Intake of steroids |
| Participation in another trial |

DES = Drug eluting stent

Surgical strategy

Surgery was performed by a median sternotomy. After heparinisation with a target activated clotting time of 480 seconds, cardiopulmonary bypass was established with an arterial cannula in the ascending aorta and a two-stage venous cannula introduced through the right atrium. To minimise the risk of air aspiration, the venous cannula was secured by a ligature around the right atrial auricle in addition to a conventional snare in the MPC group. Nasopharyngeal temperature was maintained at 35°C to 37°C. Myocardial protection was achieved by intermittent warm blood cardioplegia (repeated every 20 minutes) or cold crystalloid cardioplegia (Bretschneider or St Thomas') with no difference between the groups in each centre.

Surgeons, anesthesiologists, perfusionists were the same for both groups, as was the anaesthetic and haemostatic management.

The ROCsafeRX MPC

A closed-loop circuit incorporating a Sarns™ centrifugal pump (Terumo Cardiovascular Systems, Ann Arbor, MI, USA), a hollow-fibre oxygenator (Terumo RX 15, Terumo Corporation, Tokyo, Japan) and a 40-µm arterial blood filter (AL8X, Pall, East Hills, NY, USA) in the arterial line. Integrated is a venous de-airing unit, consisting of an ultrasound-controlled bubble detector (ABD, component of System 1, Terumo Cardiovascular Systems), a 150 cc/170 µm Bubble trap (BT15X) and an electronic venous line occluder (EVO) (Terumo Corporation, Tokyo, Japan).

When air is detected by the ABD, an automatic command is given to the centrifugal pump to reduce speed to 1500 rpm, thereby creating neither forward nor reverse flow. The EVO automatically closes the venous line in response to the speed reduction. This allows for controlled manual de-airing of the bubble trap using a standard vacuum suction device (-200 mm Hg). This is usually accomplished in a matter of a few seconds.

The modular concept of the circuit permits the speedy integration of a preconnected hard-shell reservoir in case of a major air leak. This is facilitated by the quick connectors that are an integral part of the system. Likewise, a pericardiotomy suction can be integrated in case of major blood loss. Routinely, pericardial blood is aspirated into a cell-saving device. If anticipated, to reduce transfusion requirements, it was washed, centrifuged and re-transfused at the end of the operation. Venting was via the aortic root (in addition to the pulmonary vein in the case of aortic valve replacement) directly to the venous line or into a coated flexible reservoir that included a 105-µm filter screen in the case of valve surgery. Cardioplegia is delivered by an infusion pump into a side arm of the arterial line for Calafiore cardioplegia or via a roller pump for crystalloid cardioplegia.

Table 2. Demographics, co-morbidities, medication, laboratory findings and procedural characteristics

| Variables | ROCsafRX (n = 252) | CCPB (n = 248) | p Values |
|---------------------------------------|--------------------|----------------|----------|
| Age (years) | 65 ± 10 | 65 ± 10 | 0.99 |
| Gender (M/F) | 207 / 45 | 186 / 62 | 0.06 |
| Weight (kg) | 83.7 ± 15.6 | 84.8 ± 15.9 | 0.44 |
| Body mass index (kg·m ⁻²) | 28.7 ± 4.8 | 29.2 ± 4.8 | 0.22 |
| NYHA III-IV | 14.0% | 12.1% | 0.59 |
| Diabetes mellitus | 27.9% | 31.9% | 0.38 |
| Hypertension | 85.2% | 84.6% | 0.90 |
| Hypercholesterolemia | 62.7% | 63.0% | 1.00 |
| COPD | 12.3% | 7.7% | 0.10 |
| Renal insufficiency | 12.8% | 10.1% | 0.40 |
| Smoking history | 39.5% | 37.7% | 0.71 |
| History of SV arrhythmias | 8.0% | 10.2% | 0.44 |
| Peripheral vascular disease | 12.4% | 15.0% | 0.43 |
| Previous myocardial infarction | 29.7% | 31.4% | 0.69 |
| Previous PCI | 16.8% | 14.0% | 0.45 |
| Unstable angina | 11.7% | 6.7% | 0.07 |
| LVEF | 56.9 ± 12.5% | 57.0 ± 11.3% | 0.16 |
| β-blocker | 59.9% | 53.2% | 0.15 |
| Magnesium | 23.0% | 25.4% | 0.60 |
| ACE-inhibitor | 59.1% | 59.3% | 1.00 |
| Statins | 63.1% | 61.3% | 0.71 |
| Calcium antagonists | 20.6% | 14.9% | 0.10 |
| Nitrates | 23.4% | 23.8% | 1.00 |
| Digitalis | 0.8% | 0.4% | 1.00 |
| Diuretics | 21.8% | 20.6% | 0.74 |
| Type of operation | | | 0.89 |
| CABG | 75.4% | 75.8% | |
| AVR | 15.5% | 14.1% | |
| CABG + AVR | 9.1% | 10.1% | |
| Blood cardioplegia | 64% | 62.9% | 0.71 |
| ECC time (min) | 74.9 ± 26.7 | 78.5 ± 35.8 | 0.17 |
| Aortic clamp time (min) | 48.2 ± 20.5 | 49.9 ± 22.5 | 0.39 |
| Operating time (min) | 206.5 ± 50.4 | 204.9 ± 56.4 | 0.73 |
| Haemoglobin (g/l) | 14.0 ± 1.8 | 13.9 ± 1.8 | 0.47 |
| Haematocrit (%) | 41.9 ± 4.0 | 41.8 ± 4.3 | 0.96 |
| Platelets (10 ⁹ /l) | 231.1 ± 54.9 | 239.0 ± 61.2 | 0.13 |
| Granulocytes (10 ⁹ /l) | 4.4 ± 1.4 | 4.6 ± 1.5 | 0.19 |
| Lymphocytes (10 ⁹ /l) | 1.9 ± 0.6 | 2.0 ± 0.7 | 0.15 |
| Monocytes (10 ⁹ /l) | 0.5 ± 0.2 | 0.5 ± 0.2 | 0.69 |
| Creatinine (μmol/l) | 90.7 ± 18.7 | 91.2 ± 20.6 | 0.82 |
| Urea (mmol/l) | 5.9 ± 1.6 | 5.9 ± 1.6 | 0.98 |
| Creatinine kinase (U/l) | 105.6 ± 71.0 | 119.4 ± 96.1 | 0.09 |
| CK-MB (U/l) | 15.2 ± 5.4 | 15.7 ± 5.7 | 0.52 |
| Troponin I (μg/l) | 0.06 ± 0.3 | 0.08 ± 0.4 | 0.76 |
| Fibrinogen (g/l) | 3.9 ± 1.0 | 3.9 ± 1.0 | 0.77 |
| PTT (sec.) | 25.3 ± 11.5 | 25.7 ± 10.6 | 0.65 |
| INR (sec.) | 1.0 ± 0.1 | 1.0 ± 0.1 | 0.52 |
| CRP (mg/l) | 3.1 ± 3.3 | 3.3 ± 2.9 | 0.56 |
| Free haemoglobin g/l | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.77 |
| Procalcitonine (μg/l)* | 0.12 ± 0.18 | 0.10 ± 0.14 | 0.38 |

NYHA: New York Heart Association classification; COPD: chronic obstructive pulmonary disease; SV: supraventricular; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; ECC: extracorporeal circulation; PTT: partial thromboplastin time; INR: international normalized ratio; CRP: c-reactive protein. Data presented as mean ± standard deviation. * measured for 47 ROCsafe and 46 CCPB patients.

All of the components in the system are coated with a biocompatible proprietary coating (X-coating, Terumo Corporation, Tokyo, Japan). The circuit was primed with 600 ml crystalloid solution that was reduced to 100-200 ml by retrograde autologous priming following aortic cannulation.

Conventional cardiopulmonary bypass

The standard open perfusion circuit of each centre was used. The circuits were primed with 1500 ml of crystalloid solution. No retrograde autologous priming was used. Cardiotomy suction was used and aspirated blood returned into the hard-shell reservoir. A cell saver device was permitted if it was anticipated to reduce transfusion requirement after heparin reversal was established.

Postoperative Management. A transfusion protocol was recommended and a standardised regimen of prophylaxis against atrial fibrillation. The trigger for transfusion of packed red cells (RBC) was 8 g/dl of haemoglobin postoperatively and 6 g/dl on bypass. Conservative measures for haemostasis were recommended if the blood loss within one hour did not exceed 250 ml and the transfusion of fresh frozen plasma (FFP) restricted unless clinically indicated. Platelet transfusion was restricted to a count below 100 000 except when otherwise indicated.

Prophylaxis against atrial fibrillation included continuing the patient's antiarrhythmic medication up to the morning of the operation, followed by metoprolol 50 mg twice daily up to discharge. Additionally, patients received magnesium 5 mmol p.o. one day prior to surgery, 12.6 mmol/24 hrs intravenously via an infusion pump for the first 48 hrs after surgery and 5 mmol p.o. daily up to the 5th postoperative day. Furthermore, potassium was substituted to keep the serum potassium level above 4 mmol/l.

An electrocardiogramme (ECG) was recorded on arrival to the ICU, daily for the first 3 days, at discharge and when any arrhythmia was detected.

Study end points. The main end points were safety, defined as a lack of device-related complications, and efficacy regarding the reduction of transfusion requirements. Secondary end points were in-hospital results, including freedom from major adverse events - defined as death, myocardial infarction, major cerebrovascular accident or re-operation - incidence of atrial fibrillation, blood loss within the first 12 hours, inflammatory response and intubation time, as well as length of intensive care unit (ICU) and hospital stay.

Biochemical analysis

Changes in laboratory values at 6 and 16 hrs postoperatively compared to baseline were analysed. These time

points were chosen to assure the accurate timing of blood sampling as most patients were still in the intensive care units at 16 hrs postoperatively. With the exception of haemoglobin, haematocrit, partial thromboplastin time (PTT), Quick and international normalisation ratio (INR), all values were corrected for haemodilution as follows:

Corrected measurement = Measurement X (Baseline haematocrit / Measured hematocrit)

Statistical evaluation. Data were recorded in case report forms, entered into a database and queries generated for any discrepancies. Results are reported as mean \pm standard deviation. Continuous variables were compared by parametric (unpaired Student t-test) or non-parametric (Mann-Whitney) tests while Fisher's exact test was used to compare discrete variable. Multivariate logistic regression analysis was carried out to assess the effect of the perfusion circuit used on major postoperative events, taking into account other potential risk factors (the stepwise selection method was used in the model's variables selection). For all tests, a *p* value of 0.05 or less was deemed statistically significant. The SAS 9.1 statistical software was employed (SAS Institute, Cary, North Carolina).

Results

Safety

Neither operative mortality nor device-related complications were encountered. In the MPC group, cardiotomy suction was necessitated by major bleeding in 10 patients while the integration of a hard-shell reservoir was deemed necessary to ensure adequate air handling following perforation of the right atrium on venous cannulation in 1 patient. Otherwise, these patients had an uneventful peri-operative course.

Cell salvage

A cell-saver was used in all MPC procedures; however, the harvested blood was re-transfused only in 72 patients. The mean volume of the re-transfused blood was 298 \pm 277 ml. In the CCPB group, a cell-saver was used in only 2 patients.

Postoperative course (Table 3)

In-hospital mortality. One patient in the MPC group died of acute cardiogenic shock in the ICU: due to lack of autopsy, the cause remained unclear. In the CCPB group, 2 patients died of sepsis and multi-organ failure and 1 patient following tamponade and cardiogenic shock.

Table 3. Postoperative course

| Variables | ROCsafeRX (n = 252) | CCPB (n = 248) | p Values |
|--|---------------------|----------------|----------|
| In-hospital mortality (n / %) | 1 / 0.4% | 3 / 1.2% | 0.37 |
| Blood loss at 12 hr (ml) | 454 ± 351 | 495 ± 417 | 0.62 |
| Postoperative bleeding | 8.8% | 14.1% | 0.07 |
| Re-operation for bleeding | 2.4% | 6.1% | <0.05 |
| Ventilation time (h) | 9.6 ± 6.7 | 11.0 ± 11.4 | 0.16 |
| ICU stay (h) | 34.4 ± 30.2 | 43.7 ± 107 | 0.16 |
| Hospital stay (days) | 10.3 ± 4.8 | 11.8 ± 6.8 | <0.01 |
| Weight gain 2 nd postop. day (Kg) | 1.3 ± 2.5 | 1.8 ± 2.7 | 0.04 |
| Postoperative need for | | | |
| Adrenaline (n/ %) | 9 (3.6%) | 7 (2.8%) | 0.80 |
| Noradrenaline (n/ %) | 64 (25.4%) | 72 (29%) | 0.37 |
| Dobutamine (n/ %) | 64 (25.4%) | 71 (28.6%) | 0.42 |
| any of above (n/ %) | 109 (43.2%) | 116 (46.8%) | 0.47 |
| Myocardial infarction (n / %) | 4 (1.6%) | 13 (5.2%) | 0.03 |
| Cerebrovascular events (n / %) | 11 (4.4%) | 10 (4.0%) | 1.00 |
| Stroke | 2 (0.8%) | 2 (0.8%) | 1.00 |
| Delirium | 8 (4.0%) | 8 (4.0%) | 0.97 |
| TIA | (0,4) | 0 (0,0%) | 1.00 |
| Re-operations* | 9 (3.6%) | 25 (10.1%) | <0.01 |
| Freedom from major adverse events | 229 (90.9%) | 205 (83.5%) | 0.02 |
| Atrial fibrillation | 41 (16.3%) | 60 (24.2%) | 0.03 |
| Optimal outcome (n / %) | 130 (52%) | 102 (41%) | 0.02 |

Postoperative bleeding is defined as any bleeding requiring therapy; ICU: intensive care unit; AF: atrial fibrillation; Optimum outcome: defined as freedom from any complication and transfusion. Data presented as mean ± standard deviation.

*Excluding patients who received a pacemaker (2 in each group)

Postoperative morbidity. Freedom from major adverse events, defined as death, myocardial infarction, major cerebrovascular accidents or re-operation, was significantly in favour of the MPC group (90.9% vs. 83.5%, $p=0.02$).

Transfusion requirement. Overall transfusion requirement, as well as requirements for packed RBC and FFP, showed significant differences in favour of the MPC group (333 ± 603 ml vs. 587 ± 1010 ml, $p<0.001$; 199 ± 367 ml vs. 347 ± 594 ml, $p<0.001$ and 124 ± 308 ml vs. 268 ± 732 ml, $p=0.01$, respectively)

Freedom from transfusion as a whole (64.7% vs. 55.2%), transfusion of packed RBC (71.4% vs. 60.5%) and transfusion of FFP (82.5% vs. 74.6%) were all significantly higher in the ROCsafeRX patients ($p=0.04$, 0.01 and 0.04, respectively). The incidence of platelet transfusion was similar in both groups (3.6% vs. 2.8%).

Biochemical results (Fig 1a,b). The rise in polymorphonuclear leucocytes, monocytes and C-reactive protein showed no statistically significant differences between the groups at 6 and 16 hrs postoperatively while the maximum rise in procalcitonin (measured for 47 patients in the ROCsafeRX group and 46 patients in the CCPB

group) over the same duration was less pronounced in the ROCsafeRX group (9.3 ± 9.8 vs. 15.2 ± 21.7 ; $p<0.05$).

Postoperative creatinine at 6 and 16 h post-operatively as well as urea at 16 h showed a more significant rise in the CCPB patients.

The rise in creatinine kinase (CK) at 6 h and 16 h as well its isoenzyme-MB (CK-MB) at 6 h postoperatively was significantly higher in the CCPB group while the rise in troponin I was not (Figure 2). Likewise, exclusion of those patients who experienced a myocardial infarction revealed a more significant rise in CK, CK-MB and troponin I at the 6th postoperative hour as well as CK and CK-MB at the 16th postoperative hour in the CCPB group.

Comment

Eliminating the drawbacks of conventional heart lung machines has been the aim of minimized perfusion circuits. Reduction of haemodilution and foreign surface contact, as well as elimination of the blood air interface, were to achieve these goals. However, due to concerns regarding their safety and insufficient evidence of their clinical benefit, MPCs have not seen great acceptance.

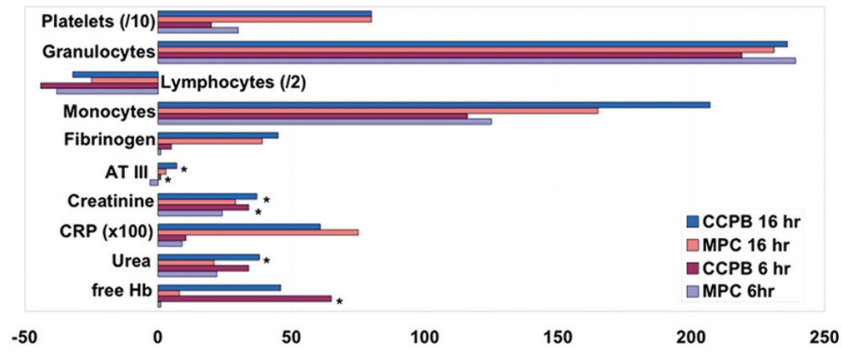


Figure 1a. Biochemical results (% change compared to baseline) corrected for haemodilution after exclusion of transfused patients n= 163 ROCsafeRX vs. 137 CCPB patients
Significant differences between groups are marked by *

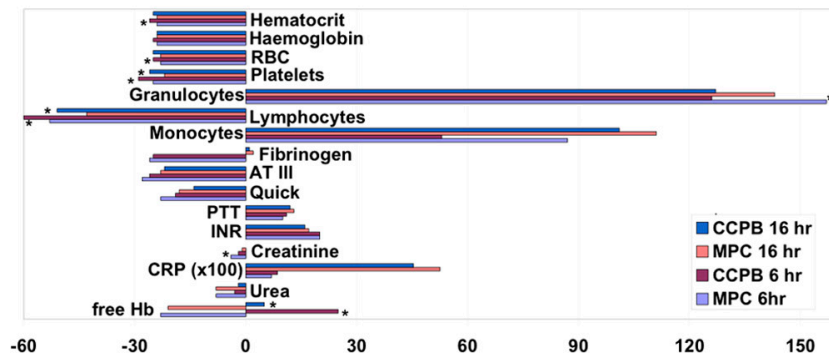


Figure 1b. Biochemical results (% change compared to baseline) n= 252 ROCsafeRX vs. 248 CCPB patients
Significant differences between groups are marked by *

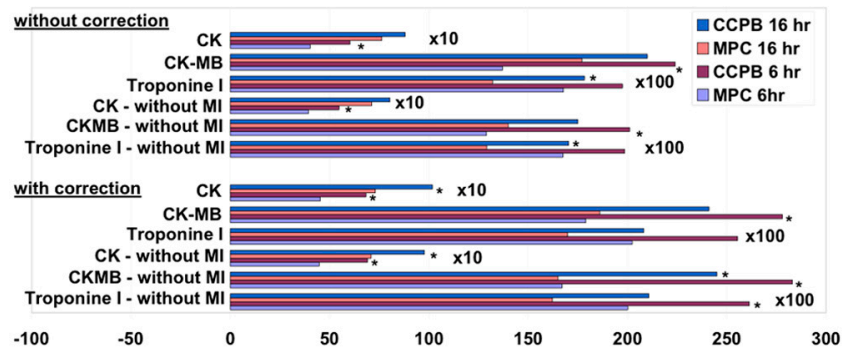


Figure 2. Markers of myocardial injury (% change compared to baseline) excluding patients with postoperative myocardial infarction (corrected and non corrected for haemodilution)
n= 252 ROCsafeRX vs. 248 CCPB patients for non corrected values and 163 vs. 137 respectively for corrected values.
Significant differences between groups are marked by *

Safety concerns are mainly related to the adequacy of air handling; Nollert et al.¹⁰ even reporting on a loss of safety margin in this context. The fact that a worst case scenario was encountered only once in 252 patients, as

well as its successful management - through the integration of a reservoir as described in detail in the interim results of the study¹¹ - without any adverse consequence to the patient, emphasises that such concerns

Table 4. Independent risk for major adverse events, postoperative atrial fibrillation and optimum outcome

| | Odds ratio | 95% Wald confidence limits | | p-value |
|---------------------------|------------|----------------------------|-------|---------|
| Major adverse events | | | | |
| Type of operation | 2.102 | 1.189 | 3.716 | 0.01 |
| Type of perfusion circuit | 1.776 | 1.015 | 3.107 | 0.04 |
| Age | 1.035 | 1.006 | 1.066 | 0.02 |
| Atrial fibrillation | | | | |
| Type of operation | 1.943 | 1.194 | 3.163 | 0.01 |
| Type of perfusion circuit | 1.655 | 1.042 | 2.630 | 0.03 |
| Age | 1.027 | 1.003 | 1.052 | 0.03 |
| Optimum outcome | | | | |
| Type of operation | 1.659 | 1.037 | 2.653 | 0.03 |
| Type of perfusion circuit | 1.560 | 1.054 | 2.309 | 0.03 |
| Gender | 0.203 | 0.114 | 0.359 | <0.0001 |
| Age | 1.038 | 1.017 | 1.059 | 0.0003 |

Multivariate logistic regression (stepwise selection method) showing complex operations, conventional cardiopulmonary bypass, male gender and advanced age as independent risk factors.

are no longer warranted. On the other hand, a reduction of the micro-embolic load through the elimination of the reservoir has already been shown experimentally¹² and clinically¹³. Reduction of haemodilution¹⁴ and avoidance of pericardiotomy suction¹⁵ further reduce micro-embolisation.

Avoidance of pericardiotomy suction has been shown to reduce the inflammatory response to extracorporeal circulation^{16,17}. Westerberg et al.¹⁸ even demonstrated a significant reduction in systemic vascular resistance (SVR) when this blood is re-transfused. However, when the amount of bleeding during cardiopulmonary bypass is significant, a cell saver may not be sufficient for hemodynamic support or may increase transfusion requirements due to a depletion of coagulation. The latter may explain why one of the largest prospective comparative studies to date² has shown no differences in RBC transfusion and a significantly higher FFP transfusion in MPCs within the first 24 hrs of surgery, the intra-operative blood losses in that group reaching 1245 ± 947 ml.

In our experience, the integration of a pericardiotomy suction was deemed necessary in 10 patients due to significant bleeding while on bypass. This was facilitated by the modular concept of the RocSafeRX.

Although comparative studies concerning MPCs are plentiful, most have been performed on low-risk patients, with low mortality and morbidity, hence, large numbers would be necessary to show a clinical impact. As most of these studies have enrolled 60 patients or less³⁻⁷, the lack of evidence to the clinical benefit of MPCs is not surprising.

Only five prospective randomized studies with a group size of 50 or more have been reported to date^{1,2,8,9,19}. Their limited exclusion criteria^{1,2,8,19}, lack of a transfusion protocol^{1,2,8,9} and lack of reference to the performing teams^{1,2,8,9,19} may explain why their results have been

inconsistent regarding clinical outcome and transfusion requirements.

Perhaps the most important result of this study is the impact of MPCs on clinical outcome as freedom of major adverse events was significantly lower in that group. In particular, the incidence of postoperative myocardial infarction and re-operation has been in favour of those patients. Similar differences have been shown by Wiesenack et al.²⁰, comparing their retrospective experience with MPCs for elective coronary artery bypass grafting (CABG) with a random group of patients undergoing elective CABG with CCPB during the same time period. As the surgeons and the type of cardioplegia in our study were similar for both groups, a better myocardial protection by MPC has to be assumed. This is further substantiated by significant differences in postoperative changes of CK, CK-MB and troponin, even on exclusion of patients with postoperative myocardial infarction. Similar effects on markers of myocardial injury have also been reported by others^{1,2,8,19-21}. This may also explain why Ramedi et al.¹⁹ have seen a significant reduction in the incidence of low cardiac output in two randomized studies comparing MPC to CCPB in CABG and aortic valve replacement. The significantly lower incidence of re-operations for bleeding in the RocSafeRX group may be explained by the better platelet preservation in minimised perfusion circuits, a finding that has also been reported by other prospective randomised studies^{1,8}.

Regarding transfusion requirements, we have demonstrated a higher overall freedom from transfusion and a lower incidence of RBC and FFP transfusion in the MPC group. Furthermore, a lower transfusion volume as a whole, as well as for RBC and FFP, has been shown. This extensive analysis demonstrates the significant impact MPCs have in this regard and allows comparison to

similar studies which have failed to show differences in transfusion requirements^{2,4-7} have shown an increased transfusion of FFP within the first 24 hours of surgery² or have limited these differences to intraoperative transfusion incidence¹, peri-operative transfusion requirement⁸ or peri-operative RBC transfusion incidence¹⁹.

A significant reduction in the incidence of atrial fibrillation within the MPC group was also seen. If one was to define optimum outcome as a freedom from adverse events and blood transfusion, then the incidence with which this goal was achieved would be substantially in favour of the ROCsafeRx patients (52% vs 41%; $p=0.02$). We suppose that this is the reason for the shorter hospital stay seen in that patient group.

In an analysis of the postoperative inflammatory reaction after different kinds of cardiothoracic surgical procedures, Frank A et al.²² demonstrated that, unlike pro-inflammatory cytokines that seem to correlate more with surgical trauma than the physiological trauma of the heart lung machine, procalcitonin liberation depended on the use of cardiopulmonary bypass. In their study, procalcitonin levels were significantly higher at 4-6 hours and day 1 postoperatively in CCPB CABG in comparison to both off-pump coronary artery bypass and thoracic surgery without cardiopulmonary bypass. Depending on these findings, we postulated that procalcitonin was a reliable marker for the physiological trauma inflicted by the heart lung machine. The fact that the maximum rise in procalcitonin level within the first 16 hrs postoperatively was significantly lower in the ROCsafeRX group seems to support this hypothesis.

Finally, the key role of the perfusion circuit as an independent risk factor for postoperative adverse events is shown by the multivariate analysis.

Limitations

Correction of the laboratory values for haemodilution may be questionable. However, the purpose of this study was to detect differences resulting from the use of two perfusion circuits on similar groups of patients. Hence, it was our concept from the start to compare differences in biochemical results in comparison to baseline values, a correction for haemodilution as previously done by Westerberg et al.²³ is, therefore, only a natural step in the same direction.

Conclusions

These results confirm that the ROCsafeRX is both safe and efficient and that MPCs can add to the quality of patient care.

Disclosure and Funding

The study was partly supported by Terumo Europe.

Conflict of Interest Statement

None Declared.

References

1. Remadi JP, Rakotoarivelo Z, Marticho P, Benamar A. Prospective randomized study comparing coronary artery bypass grafting with the new mini-extracorporeal circulation Jostra System or with a standard cardiopulmonary bypass. *Am Heart J*. 2006; 151: 198.
2. Abdel-Rahman U, Özasan F, Risteski P, et al. Initial experience with a minimized extracorporeal bypass system: is there a clinical benefit? *Ann Thorac Surg* 2005; 80: 238–244.
3. Huybregts R, Morariu A, Rakhorst G, et al. Attenuated renal and intestinal injury after use of a mini-cardiopulmonary bypass system. *Ann Thorac Surg* 2007; 83: 1760–1767.
4. Fromes Y, Gaillard D, Ponzio O, et al. Reduction of the inflammatory response following coronary bypass grafting with total minimal extracorporeal circulation. *Eur J Cardiothorac. Surg* 2002; 22: 527–533.
5. Berghi C, Nicolini F, Agostinelli A, et al. Mini-cardiopulmonary bypass system: results of a prospective randomized study. *Ann Thorac Surg* 2006; 81: 1396–1400.
6. Schötter J, Lutter G, Böning A, et al. Is there really a clinical benefit of using minimized extracorporeal circulation for coronary artery bypass grafting? *Thorac Cardiovasc Surg* 2008; 56: 65–70.
7. Bical O, Fromes Y, Gaillard D, et al. Comparison of the inflammatory response between minimized and standard CPB circuits in aortic valve surgery. *Eur J Cardiothorac Surg* 2006; 29: 699–702.
8. Castiglioni A, Verzini A, Colangelo N, Nascimbene S, Laino G, Alfieri O. Comparison of minimally invasive closed circuit versus standard extracorporeal circulation for aortic valve replacement: a randomized study. *Interact CardioVasc Thorac Surg* 2009; 9: 27–41.
9. Kutschka I, Skorpil J, El-Essawi A, Hajek T, Harringer W. Beneficial effects of modern perfusion concepts in aortic valve and aortic root surgery. *Perfusion* 2009; 24: 37–44.
10. Nollert G, Schwabenland I, Maktav D, et al. Minimized cardiopulmonary bypass in coronary artery bypass surgery: marginal impact on inflammation and coagulation but loss of safety margins. *Ann Thorac Surg* 2005; 80: 2326–2332.
11. El-Essawi A, Hajek T, Skorpil J, et al. A prospective randomised multicentre clinical comparison of a minimised perfusion circuit versus conventional cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2010; 38(1): 91–97.
12. Kutschka I, Schönrock U, El-Essawi A, Pahari D, Anssar M, Harringer W. A new minimized perfusion circuit provides highly effective ultrasound controlled deairing. *Artif Organs* 2007; 31(3): 215–220.

13. Perthel M, El-Ayoubi L, Bendisch A, Laas J, Gerigk M. Clinical advantages of using mini-bypass systems in terms of blood product use, postoperative bleeding and air entrainment: an in vivo clinical perspective. *Eur J Cardiothorac Surg* 2007; 31: 1070–1075.
14. Nollert G, Reichart B. Cardiopulmonary bypass and cerebral injury in adults. *Shock* 2001; 16(Suppl 1): 16–19.
15. Brooker RF, Brown WR, Moody DM, et al. Cardiomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg* 1988; 65: 1651–1655.
16. Westerberg M, Bengtsson A, Jeppsson A. Coronary surgery without cardiomy suction and autotransfusion reduces the postoperative systemic inflammatory response. *Ann Thorac Surg*. 2004; 78: 54–59.
17. Aldea G, Soltow L, Chandler W, et al. Limitation of thrombin generation, platelet activation, and inflammation by elimination of cardiomy suction in patients undergoing coronary artery bypass grafting treated with heparin-bonded circuits. *J Thorac Cardiovasc Surg*. 2002; 123: 742–755.
18. Westerberg M, Gäbel J, Benstsson A, Sellgren J, Eidem O, Jeppsson A. Hemodynamic effects of cardiomy suction blood. *J Thorac Cardiovasc Surg* 2006; 131: 1352–1357.
19. Remadi JP, Rakotoarivelo Z, Marticho P, et al. Aortic valve replacement with the minimal extracorporeal circulation (Jostra MECC System) versus standard cardiopulmonary bypass: a randomized prospective trial. *J Thorac Cardiovasc Surg* 2004; 128: 436–441.
20. Wiesenack C, Liebold A, Philipp A, et al. Four years' experience with a miniaturized extracorporeal circulation system and its influence on clinical outcome. *Artif Organs*. 2004 Dec; 28(12): 1082–8.
21. Skrabal C, Steinhoff G, Liebold A. Minimizing cardiopulmonary bypass attenuates myocardial damage after cardiac surgery. *ASAIO J* 2007; 53: 32–35.
22. Franke A, Lante W, Fackeldey V, et al. Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? *Eur J Cardiothorac Surg* 2005; 28: 569–575.
23. Westerberg M, Bengtsson A, Jeppsson A. Coronary surgery without cardiomy suction and autotransfusion reduces the postoperative systemic inflammatory response. *Ann Thorac Surg* 2004; 78: 54–59.