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Research Paper

Continuous Postoperative Pericardial Flushing: A Pilot Study on Safety, Feasibility, and Effect on Blood Loss

Johan S.J. Manshanden [a,1], Chantal L.I. Gielen [b,1], Corianne A.J.M. de Borgie [c], Robert J.M. Klautz [b], Bas A.J.M. de Mol [a], David R. Koolbergen [a,b,*]

[a] Department of Cardiothoracic Surgery, Academic Medical Center (AMC), Amsterdam, The Netherlands
[b] Department of Cardiothoracic Surgery, Leiden University Medical Center (LUMC), Leiden, The Netherlands
[c] Clinical Research Unit, University of Amsterdam, Amsterdam, The Netherlands

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ABSTRACT

Background: Prolonged or excessive blood loss is a common complication after cardiac surgery. Blood remnants and clots, remaining in the pericardial space in spite of chest tube drainage, induce high fibrinolytic activity that may contribute to bleeding complications. Continuous postoperative pericardial flushing (CPPF) with an irrigation solution may reduce blood loss by preventing the accumulation of clots. In this pilot study, the safety and feasibility of CPPF were evaluated and the effect on blood loss and other related complications was investigated.
Methods: Between November 2011 and April 2012 twenty-one adult patients undergoing surgery for congenital heart disease (CHD) received CPPF from sternal closure up to 12 h postoperative. With an inflow Redivac drain that was inserted through one of the chest tube incision holes, an irrigation solution (NaCl 0.9% at 38 °C) was delivered to the pericardial cavity using a volume controlled flushing system. Safety aspects, feasibility issues and complications were registered. The mean actual blood loss in the CPPF group was compared to the mean of a retrospective group (n = 126).
Results: CPPF was successfully completed in 20 (95.2%) patients, and no method related complications were observed. Feasibility was good in this experimental setting. Patients receiving CPPF showed a 30% (P = 0.038) decrease in mean actual blood loss 12 h postoperatively.
Conclusions: CPPF after cardiac surgery was found to be safe and feasible in this experimental setting. The clinically relevant effect on blood loss needs to be confirmed in a randomized clinical trial.

1. Introduction

Prolonged or excessive bleeding is one of the most common complications after cardiac surgery. Postoperative bleeding requiring transfusions and surgical re-exploration remains an important complication because it is associated with short- and long-term postoperative mortality, morbidity, prolonged hospitalization, and higher societal healthcare costs (Murphy et al., 2007).

The mechanisms involved in perioperative bleeding are complex and involve disturbances in various physiologic systems including primary hemostasis, coagulation, and fibrinolysis. This may be caused by several surgical factors including cardiopulmonary bypass (CPB) and operative trauma. Together with primary fibrinolysis, platelet dysfunction, and hemodilution these mechanisms contribute to dysfunction of the coagulation, fibrinolytic, and inflammatory systems with postoperative coagulopathy and bleeding as a result (Paparella et al., 2004; Despotis et al., 2001). Consequently, the normal or generally accepted amount of blood loss after cardiac surgery is higher than most other surgical specialties and varies between 300–1500 ml during the first 12 h.

The standard operating procedure is to insert chest tubes in order to evacuate this blood from the pericardial cavity postoperatively. However, if blood loss or clot formation is excessive the chest tubes often fail due to partial or complete blockage. The resulting stasis of blood and clots in the pericardial cavity leads to high fibrinolytic activity and consequently, maintenance of blood loss (Despotis et al., 2001; Philippou et al., 2000; Illig et al., 1997; Yavari and Becker, 2009; Vallely et al., 2009). This is also supported by the finding that during re-exploration for postoperative bleeding, removal of accumulated blood and clots by solely irrigating the pericardial space with a warm saline solution is enough to stop the bleeding instantly in a significant number of cases (Pelletier et al., 1998). Following on from this, a method of preventing

* Corresponding author at: Department of Cardiothoracic Surgery, Academic Medical Center at the University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: d.r.koolbergen@amc.uva.nl (D.R. Koolbergen).
[1] Both authors contributed equally to the manuscript.

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blood and clots from accumulating in the pericardial space could hypothetically stop postoperative bleeding at an earlier stage and reduce bleeding complications. Continuous postoperative pericardial flushing (CPPF) was developed for this purpose.

CPPF works by continuously flushing the pericardial cavity with a warm saline irrigation solution starting towards the end of surgery just before sternal closure. Continuous flushing will result in a lower viscosity mixture that will prevent chest tube blockages and promote the evacuation of blood and clots from the pericardial cavity. This pilot study evaluates the safety and feasibility of CPPF. In addition, its effects on blood loss and other related complications are investigated and discussed. To our knowledge, the continuous pericardial flushing method post-cardiac surgery has not been used or described before.

Abbreviations

ACT	activated clotting time
AMC	Academic Medical Center, Amsterdam, The Netherlands
CHD	congenital heart disease
CPB	cardiopulmonary bypass
CPPF	continuous postoperative pericardial flushing
CRP	C-reactive protein
FFP	fresh frozen plasma
ICU	intensive care unit
IU	international unit
MCTD	mediastinal chest tube drainage
METC	medical ethics committee
PRBC	packed red blood cell
TTE	transthoracic echocardiogram

2. Methods

2.1. Study Design

In this pilot study, a prospective cohort of patients who underwent surgery and CPPF between November 2011 and April 2012 (n = 21, over a 6-month inclusion period) was compared to a retrospective group of patients who underwent surgery and no CPPF (non-CPPF group) between January 2010 and December 2011 (n = 126). The study protocol was approved by the internal review board of the Academic Medical Center (AMC) Amsterdam, protocol number METC 2011_270. All adult patients undergoing surgical correction for congenital heart disease (CHD) were eligible to participate in this prospective cohort study. Exclusion criteria were emergency surgery, a history of bleeding diathesis or coagulopathy, participation in any study involving an investigational drug or device, and the inability to understand the study information or give informed consent. Informed consent was obtained one day preoperatively from all patients in the CPPF group and data were gathered prospectively. Data from the non-CPPF group were obtained retrospectively by analyzing consecutive patient records before the use of CPPF for a period of 24 months. All patients underwent cardiac surgery at the AMC, which is a quaternary care university hospital. A single surgeon performed surgery on all included patients in the CPPF group and almost all of the patients in the non-CPPF.

2.2. Continuous Postoperative Pericardial Flushing

The method of inserting chest tubes in the CPPF group was the same as routinely used in the non-CPPF group; one chest tube (Ch30 Redivac drain, Medica Europe, Oss, The Netherlands) in the pericardial space, one chest tube (Ch30 Redivac drain, Medica Europe, Oss, The Netherlands) in the anterior mediastinum and in case of opened pleural spaces they were each drained separately (Ch30 Redivac drain, Medica Europe, Oss, The Netherlands). In the CPPF group an extra infusion tube (Ch10 Redivac drain, Dispo Medical, Hattemerbroek, The Netherlands) was inserted through the incision hole of one of the standard chest tube incisions and positioned in the pericardial space. This extra infusion tube was directly connected to the CPPF system that comprises a bag of irrigation solution (NaCl 0,9%) connected to infusion line that runs through a volumetric pump (Infusomat® Space by B. Braun, Melsungen, Germany) and through a fluid heating device (Enflow® fluid warmer by GE Healthcare, Hoevelaken, The Netherlands). CPPF was started at sternal closure and continued for 12 h postoperatively. The irrigation solution NaCl 0.9%, was delivered to the pericardial cavity at a flow rate of 500 ml/h for the first two postoperative hours. It was then set to volume controlled for the next ten hours so that the volume corresponded with the patients' actual blood loss at a 1:1 ratio, with a minimum flow rate of 100 ml/h. The irrigation solution was delivered to the patient at a constant temperature of 38 °C to avoid changes in patient core temperature. Irrigation solution volume and total mediastinal chest tube drainage (MCTD) volume were monitored every 15 min for the first two postoperative hours and thereafter hourly until chest tube removal. Actual blood loss was calculated at the same time intervals by subtracting irrigation solution volume from the total MCTD volume. In this way, a secondary manually written record was kept to monitor actual blood loss and trace fluid accumulation. If MCTD volume was >200 ml less than the infused irrigation solution volume, the CPPF system was stopped to prevent accumulation of fluid in the pericardial and/or pleural spaces. One and the same research assistant facilitated both preparation of the CPPF system and the safeguarding and control of the system during the CPPF window.

2.3. Operative Procedures and Cardiopulmonary Bypass Management

Routine anesthetic procedures were employed making circumstances standardized and equal for both groups. All patients underwent full median sternotomy; CPB (Stöckert S5, Sorin Group, Italy) was instituted in all patients using mild hypothermia (30–32 °C). Before initiation of CPB, all patients received a standard heparin dosage of 150 IU/kg bodyweight with an additional optional bolus of 50 IU/kg before cannulation. Anticoagulation was monitored by serial measurements of the activated clotting time (ACT), which was kept above 450 s at all times during CPB. The heparin was reversed by administration of 1 ml protamine for each 1000 IU heparin and ACT return to baseline served as confirmation.

2.4. Transfusion Policies

A standardized transfusion protocol was followed in all patients. Intraoperative blood management included reinfusion of residual blood from the cardiotomy reservoir and packed red blood cell (PRBC) transfusion during CPB were given at hemoglobin levels <4.0 mmol/l. Postoperative blood management on the ICU included PRBC transfusions for hemoglobin level <5.0 mmol/l; platelet concentrate for platelet count $<50 \times 10^9$/l or $<100 \times 10^9$/l if blood loss exceeded 150 ml/h and fresh frozen plasma (FFP) was transfused if the activated partial thromboplastin time and prothrombin time were prolonged >150% during active bleeding.

2.5. Primary Endpoints

The primary endpoints of this pilot study were to evaluate the safety and feasibility of CPPF procedure and its effect on actual blood loss. Safety endpoints during hospitalization were defined as chest tube competence, pericardial and/or pleural fluid accumulation, infection, and adverse events. Adverse events between discharge from hospital until most recent follow-up were also recorded. Feasibility endpoints were defined as system functionality and labor-intensiveness. Transthoracic echocardiograms (TTE) and chest radiographs were the imaging modalities of choice that were used to evaluate pericardial and pleural effusions on arrival in ICU, at 5–7 days postoperatively, and on discharge. Pericardial or pleural effusions that were clinically significant and required drainage were registered.

2.6. Secondary Endpoints

Secondary endpoints included transfusion requirements, time to chest tube removal, time to extubation and length of ICU and hospital stay. Transfusion requirements were defined as total PRBC, total FFP, and total platelet concentrate transfusions as well as the proportion of patients requiring blood product transfusion. The time frames between operation and chest tube removal and between operation and extubation were recorded in postoperative hours.

2.7. Statistical Analysis

Variables are presented as mean (±standard deviation) or as number (percentage), unless otherwise noted. An independent-samples t-test was conducted to compare mean actual blood loss between the CPPF and non-CPPF group; a P value < 0.05 was considered statistically significant. All data analyses were performed using SPSS 20.0 for Macintosh (IBM® SPSS® Software). Mean actual blood loss curves were plotted using GraphPad Prism® 6.0 software for Macintosh.

2.8. Funding

This study was funded intramural with resources from the department of cardiothoracic surgery of the Academic Medical Center, Amsterdam, The Netherlands.

3. Results

3.1. Demographic and Preoperative Clinical Data

Preoperatively we registered there were two significant differences between the CPPF and the non-CPPF group of patients with respect to demographic and clinical characteristics as shown in Table 1.

Table 1
Clinical characteristics of the CPPF and non-CPPF groups.

	CPPF	Non-CPPF	P value
	n = 21 (%)	n = 126 (%)	
Mean age (years ± SD)	43.8 ± 13.6	40.5 ± 15.0	0.353
Male/female	11/10	73/53	0.637
Body mass index (mean ± SD (kg/m^2))	27.5 ± 7.0	24.3 ± 4.6	0.057
Diagnoses:			
Tetralogy of Fallot	6 (28.6)	14 (11.1)	0.109
Transposition of the great arteries	1 (4.8)	8 (6.3)	0.781
Univentricular heart	0 (0.0)	3 (2.4)	0.478
Connective tissue disease	0 (0.0)	16 (12.7)	<0.001*
Fabry syndrome	1 (4.8)	1 (0.8)	0.420
Factor V Leiden	1 (4.8)	1 (0.8)	0.420
Associated diseases:			
BMI >30 kg/m^2	5 (23.8)	11 (8.7)	0.142
Diabetes	1 (4.8)	4 (3.2)	0.518
Renal insufficiency (at least moderate)	6 (28.6)	18 (14.3)	0.189
Chronic obstructive lung disease	2 (9.5)	7 (5.6)	0.486
Urgent/emergency surgery	0 (0.0)	1 (0.8)	0.685
Left ventricular ejection fraction:			
>50%	14 (66.6)	106 (84.1)	0.127
30–50%	7 (33.3)	18 (14.3)	0.096
<30%	0 (0.0)	2 (1.6)	0.564
Euroscore I (logistic) (mean ± SD)	6.14 ± 7.27	7.51 ± 6.67	0.389
Euroscore II (mean ± SD)	2.90 ± 2.97	2.84 ± 2.63	0.916
Preoperative anticoagulant use:[a]			
Acetylsalicylic acid	6 (28.6)	23 (18.3)	0.274
Vitamin K antagonists	4 (19.0)	10 (7.9)	0.235
Other	0 (0.0)	1 (0.8)	0.685
Preoperative laboratory values:			
Hemoglobin (mmol/l)	8.8 ± 0.7	8.9 ± 0.9	0.831
CRP (mg/l)	4.0 ± 4.4	3.6 ± 6.4	0.903
Leukocytes (×10^9/l)	7.5 ± 2.1	6.4 ± 1.7	0.009*
Platelet count (×10^9/l)	221 ± 70	219 ± 55	0.869
INR (median; Q1; Q3; IQR)	1.08 (0.98; 1.62; 0.64)	0.99 (0.96; 1.08; 0.12)	0.160

[a] Use of all antiplatelet agents was discontinued 5 days prior to surgery. CRP = C-reactive protein; INR = international normalized ratio.

3.2. Surgical Procedures and Operative Data

On comparison with the CPPF group patients in the non-CPPF group had undergone significantly more procedures for left-sided lesions (P = 0.030), aortic root surgery (P = <0.001), aortic valve replacement (P = 0.008), and Bentall procedure (P = 0.008). Patients in the CPPF group underwent significantly more procedures for right-sided lesions (P = <0.001). The complexity of surgical procedures is shown in Table 2. Intraoperative variables such as the duration of CPB and aortic cross-clamping were similar in both groups and are presented in Table 3.

3.3. CPPF Safety and Feasibility

Postoperative safety aspects of the CPPF group and historic group of patients are summarized in Table 4. CPPF was successfully completed in 20 (95.2%) patients. In 1 (4.8%) patient, CPPF was stopped as a precaution 3.5 h postoperatively as there was a >200 ml lag in MCTD volume as fluid had accumulated in the right pleural cavity. On extubation the patient spontaneously evacuated all accumulated fluid, which was confirmed by chest radiography. All irrigation solution was successfully evacuated from the pericardial and/or pleural cavities in all patients before the chest tubes were removed. There were no significant differences between groups in pleural effusions (P = 0.272) or pericardial effusions (P = 0.486) at discharge. Postoperative inflammatory markers were not significantly different between groups.

No system-related or other serious problems were encountered. Monitoring of inflow and outflow volumes was considered time-consuming but feasible in this experimental setting where the monitoring was safeguarded and controlled by a research assistant. However, it was considered to be a major drawback for normal clinical setting as it would be a significant increase in workload for the ICU nurse and repeated calculation will be error prone. Especially in case of bleeding problems when a more frequent monitoring and calculation of actual blood loss is required. Also, the normal clinical assessment of blood content of MCTD is disturbed as the blood is constantly diluted in varying degrees.

3.4. Effect on Mean Actual Blood Loss

Differences in mean actual blood loss on arrival at ICU, at 6 and 12-h postoperatively, and the total postoperative blood loss between the CPPF group and non-CPPF group are presented in Table 5. The magnitudes of the significant decrease in means were 41% (mean difference = 57 ml, 95% CI: 12 to 102) on arrival at ICU and 30% (mean difference = 162 ml, 95% CI: 9 to 315) at 12 h postoperatively; both had a moderate effect (eta squared = 0.04 and 0.03 respectively). Within the non-CPPF group, those who underwent aortic root surgery had 65 ml (P = 0.286) less blood loss at 12 h postoperatively compared to the non-aortic root surgery group. Postoperative mean actual blood loss over hourly intervals and the cumulative total over the first 12 postoperative hours is shown in Fig. 1.

3.5. Secondary Endpoints

Differences in allogeneic transfusion requirements between the two groups were not statistically significant as shown in Table 5. No significant differences in means between the two groups were found with respect to the time to extubation (P = 0.535), time to chest tube removal (P = 0.762), length of ICU stay (P = 0.746), and total hospitalization (P = 0.472).

Table 2
Surgical procedures of the CPPF and non-CPPF groups.

	CPPF	Non-CPPF	P value
	n = 21 (%)	n = 126 (%)	
Aortic surgery:			
AVP	0 (0.0)	1 (0.8)	0.685
AVR+Asc. Repl. (0|2); +PVR (0|1); +MVP, PVI (0|1); +VSD repair (0|1)	0 (0.0)	7 (5.6)	0.008*
Bentall+PVR (1|4); +Hemiarch Repl. (0|1); +MVP, TVP (0|3); +VSD repair (0|2)	1 (4.8)	27 (21.4)	0.008*
VSRR+AVP (0|3); +MVP (0|2)	1 (4.8)	20 (15.9)	0.061
Ascending aorta replacement+MVP (0|1)	0 (0.0)	4 (3.2)	0.411
Hemiarch replacement + ductus closure	0 (0.0)	1 (0.8)	0.685
Atrioventricular valve surgery:			
MVP+PVI (1|3); +TVP (0|6); +VSD repair (0|2)	1 (4.8)	12 (9.5)	0.480
MVR	0 (0.0)	5 (4.0)	0.356
TVP	0 (0.0)	4 (3.2)	0.411
Septal defects:			
ASD I, MVP, TVP	2 (9.5)	1 (0.8)	0.201
ASD II+MVP, TVP (2|1); +TVP (1|3); +PVP (0|1)	2 (9.5)	6 (4.8)	0.377
VSD+TVP (1|1); +DCRV (1|0)	2 (9.5)	3 (2.4)	0.298
Pulmonary venous anomalies:			
PAPVC repair+ASD (1|4); +TVP (1|1)	2 (9.5)	5 (4.0)	0.422
Coronary artery anomalies:			
ALCAPA/ARCAPA repair+PA plasty (0|2); +CABG (0|1)	2 (9.5)	3 (2.4)	0.298
Other:			
PVR+PA plasty (5|16); +TVP (1|4); +MVP (1|0)	7 (33.3)	20 (15.9)	0.127
AP plasty + hybrid stent placement	0 (0.0)	1 (0.8)	0.685
DSAS repair/morrow	0 (0.0)	1 (0.8)	0.685
Atrial baffle + TVP	1 (4.8)	2 (1.6)	0.344
TCPC	0 (0.0)	3 (2.4)	0.478

ALCAPA = anomalous left coronary artery from the pulmonary artery; ARCAPA = anomalous right coronary artery from the pulmonary artery; Asc. = ascending aorta; ASD = atrial septal defect; AVP = aortic valve plasty; DCRV = double-chambered right ventricle; DSAS = discrete subaortic stenosis; MVP = mitral valve plasty; MVR = mitral valve replacement; PA = pulmonary artery; PAPVC = partial anomalous pulmonary venous connection; PVI = pulmonary vein isolation; PVP = pulmonary valve plasty; PVR = pulmonary valve replacement; Repl. = replacement; TCPC = total cavopulmonary connection; TVP = tricuspid valve plasty; VSD = ventricular septal defect.

4. Discussion

There are several techniques available that aim to reduce blood loss and associated exposure to allogeneic blood after surgery. These include minimally invasive surgical techniques, blood conservation strategies (Hardy et al., 1996), extracorporeal circulation systems (Abdel Aal et al., 2011) and, the systemic (Henry et al., 2011; Levi et al., 1999) and topical (Ker et al., 2013) pharmacological correction of hemostasis. Despite the improvements achieved by these techniques we still tend to accept a considerable amount of blood loss as being inherent to cardiac surgery. Moreover, all techniques available have different targets and/or time of action than the CPPF. Therefore, regardless of their effects, the result of CPPF is always an additional improvement to the current state of the art.

Review of literature revealed only a few studies that were focused on chest tube functionality and improvement of the postoperative drainage

Table 3
Operative data of the CPPF and non-CPPF groups.

	CPPF	Non-CPPF	P value
	n = 21 (%)	n = 126 (%)	
Reoperation	10 (47.6)	57 (45.2)	0.841
Left sided lesions	9 (42.9)	85 (67.5)	0.030*
Right sided lesions	17 (81.0)	56 (44.4)	<0.001*
Aortic root surgery	2 (9.5)	65 (51.6)	<0.001*
Septal defects	6 (28.6)	21 (16.7)	0.274
Pulmonary venous anomalies	2 (9.5)	5 (4.0)	0.422
Coronary artery anomalies	2 (9.5)	3 (2.4)	0.298
Single procedure	8 (38.1)	63 (50.0)	0.320
Double procedure	11 (52.4)	43 (34.1)	0.110
Triple procedure	1 (4.8)	18 (14.3)	0.103
Quadruple procedure	1 (4.8)	2 (1.6)	0.344
Mean surgical procedures per patient	1.76	1.67	0.230
Mean CPB time (min) ± SD	140 ± 72	151 ± 63	0.443
Mean cross-clamp time (min) ± SD	86 ± 41	101 ± 46	0.186

Table 4
Postoperative safety aspects of the CPPF and non-CPPF groups.

	CPPF	Non-CPPF	P value
	n = 21 (%)	n = 126 (%)	
In-hospital adverse events:			
Cardiac tamponade	0 (0.0)	4 (3.2)	0.411
Reexploration for bleeding	0 (0.0)	9 (7.1)	0.002*
Subxyphoidal drainage	0 (0.0)	3 (2.4)	0.478
Mortality	0 (0.0)	2 (1.6)	0.564
In-hospital infection:			
Sternal wound infection	0 (0.0)	3 (2.4)	0.478
Mediastinitis	0 (0.0)	2 (1.6)	0.564
Pneumonia	1 (4.8)	3 (2.4)	0.538
Urine tract infection	1 (4.8)	1 (0.8)	0.420
Fever >38.5 °C	2 (9.5)	9 (7.1)	0.703
Max. CRP	138	182	0.057
(mg/l, median; Q1; Q3; IQR)	(95;200;105)	(136;231;95)	
Max. Leukocytes	13.5	12.6	0.867
($\times 10^9$/l, median; Q1; Q3; IQR)	(11.1;15.9;4.8)	(10.7;15.8;5.1)	
In-hospital data:[a]			
Time until extubation (hours ± SD)	7.6 ± 6.1	6.8 ± 5.2	0.535
Time until chest tube removal (hours ± SD)	21 ± 8	22 ± 14	0.762
ICU stay (days ± SD)	1.4 ± 0.9	1.7 ± 3.8	0.746
Total hospitalization (days ± SD)	7.7 ± 2.4	9.0 ± 8.6	0.472
Fluid accumulation at discharge:			
Pleural effusion (trace to mild)	10 (47.6)	77 (61.1)	0.272
In a surgically opened pleural cavity	5 (23.8)	23 (18.3)	0.563
Pericardial effusion (trace to mild)	7 (33.3)	38 (30.2)	0.486
Circular (≥50%/≥6 mm)	1 (4.8)	10 (7.9)	0.606
Adverse events after discharge:			
Late cardiac tamponade	1 (4.8)	3 (2.4)	0.477
For which subxyphoidal drainage	1 (4.8)	2 (1.6)	0.344
For which re-sternotomy	0 (0.0)	1 (0.8)	0.685
Reoperation	1 (4.8)	4 (3.2)	0.718
3-year mortality	0 (0.0)	6 (4.8)	0.014*
Mean follow-up (years ± SD)	2.9 ± 0.1	4.1 ± 1.0	<0.001*

[a] Time until extubation and chest tube removal were defined as the mean number of hours between surgery and the time of removal. Length of ICU and hospital stay were defined as the mean number of days between the date of surgery and the date of ICU and hospital discharge, respectively.

Table 5
Blood loss and PRBC transfusion requirements of the CPPF and non-CPPF groups.

	CPPF	Non-CPPF	P value
	n = 21 (%)	n = 126 (%)	
Postoperative blood loss: (mean ± SD)			
T0: ICU arrival	83 ± 74	140 ± 100	0.014*
T6: 6 h postoperative	310 ± 195	415 ± 297	0.131
T12: 12 h postoperative	376 ± 249	538 ± 330	0.038*
Total postoperative	608 ± 422	768 ± 630	0.263
PRBC transfusion requirements:			
Patients transfused PRBC intraoperatively	7 (33.3)	38 (30.2)	0.772
Patients transfused PRBC postoperatively	1 (4.8)	19 (15.0)	0.080

system (Bjessmo et al., 2007; Frankel et al., 2003; Perrault et al., 2012). None of the studies reported a technique similar to CPPF as described in our paper. In addition, none of the postoperative drainage systems initially aimed for the complete cleaning of the pericardial space of blood and clots and, also, did not have reduction of blood loss as a primary study end point. Thus, to our knowledge, a flushing system that has specifically been designed to promote the evacuation of contaminated blood and clots out of the pericardial cavity in order to reduce postoperative blood loss has not been used or described before.

CPPF showed a 30% reduction in 12-hour postoperative blood loss and there were no re-explorations for bleeding complications in the CPPF group. The non-CPPF group included significantly more aortic root surgery but within the non-CPPF group, procedures on the aortic root showed even less blood loss when compared to those that had non-aortic root surgery. With respect to important bleeding parameters (percentage of redo surgery, cross-clamp and CPB time, single and multiple procedures, use of anticoagulants, EUROSCORES) no significant differences were found between the groups. None of the other significant differences between the two groups, as depicted in Tables 1–3, are known to have implications with respect to more or less bleeding tendency. Overall, the mean postoperative blood loss in both the CPPF and non-CPPF group can be considered to be low given the surgical complexity and high percentage of reoperations; this makes the difference that we found stronger. However, the evidence from this pilot study (prospective cohort in comparison with a historic group of patients) is not strong enough to draw definitive conclusions with respect to blood loss and bleeding complications. Currently, two randomized clinical trials are ongoing at our institution that need to provide proof of concept by confirmation of these pilot findings.

On the contrary, one can also put forward that flushing a fresh wound carries the risk of disturbing the normal coagulation process, which therefore may lead to increased blood loss. Considering the little

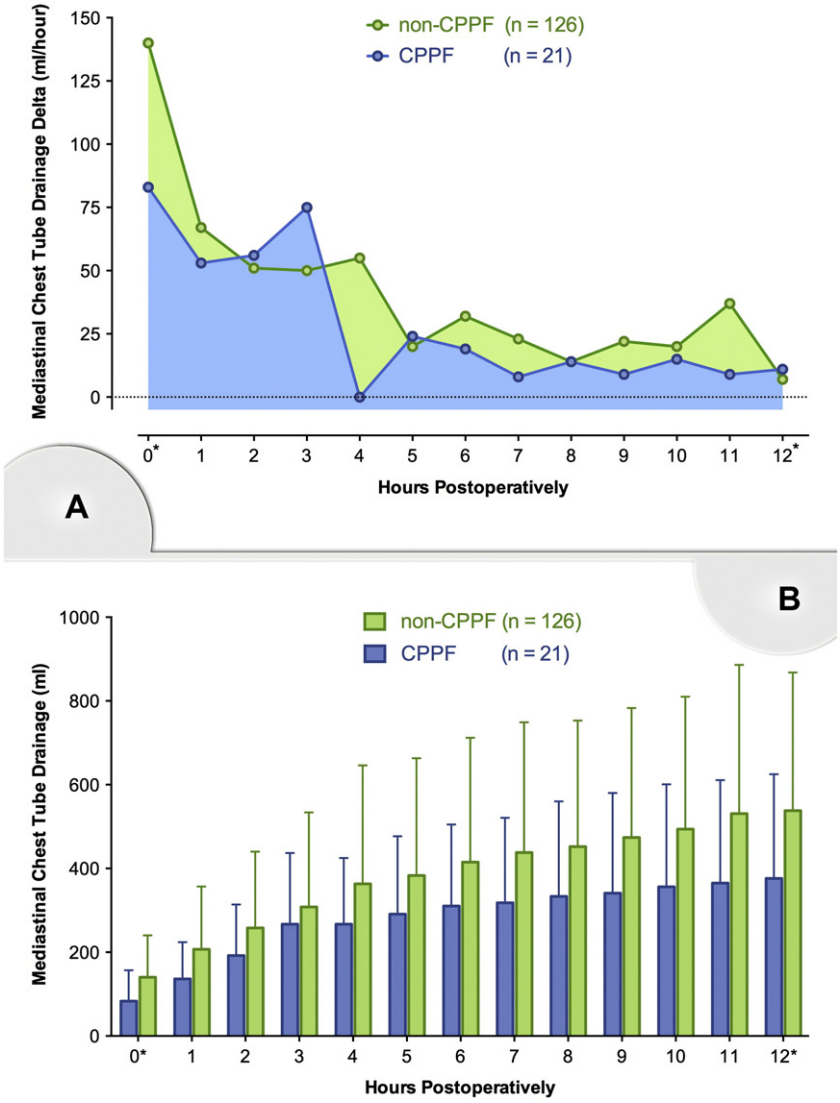

Fig. 1. Postoperative actual blood loss over hourly intervals (A) and total cumulatively (B) during the first 12 postoperative hours.

amount of blood loss that we observed in the CPPF group (mean 376 ml) and the fact that no continued bleeding was observed, we may abstract that CPPF patients did not tend to have more blood loss when compared to the "normal" non-CPPF patients. It is likely that this phenomenon did not occur is because our flushing method includes a slow continuous irrigation of flushing fluid rather than hosing the wound using strong mechanical forces. CPPF works mainly by dilution and lowering the viscosity of the blood and clot mixture in the wound, which enhances evacuation through the chest tubes.

Surgical re-exploration bleeding or suspected or acute cardiac tamponade is associated with increased mortality and morbidity (Haneya et al., 2015) and is still needed in 2–6% of patients (Karthik et al., 2004; Biancari et al., 2012). As well as its effect on blood loss, CPPF may have an important impact on the prevention of acute cardiac tamponade, which was not seen in the CPPF group. As stated above, CPPF lowers the viscosity of drainage fluid and prevents abundant formation of clots, thereby preventing the chest tubes from blocking and promoting chest tube patency. Even the use of multiple rather than single mediastinal chest tubes is known not to solve this problem (Le et al., 2015).

In theory, partial or complete chest tube blockage can never be completely eliminated, which emphasizes the need for careful monitoring of inflow and outflow volumes. Intrapericardial pressure monitoring could serve as an extra safety assurance. CPPF requires real-time accurate quantification of MCTD volume within the CPPF window in order to monitor actual blood loss and to trace possible fluid accumulation in the pericardial and/or pleural cavity. The manual monitoring procedure at time intervals that was used in this study was considered labor intensive and should ideally be automated for future clinical use. For the clinical assessment of actual blood loss and the detection of surgical hemorrhage, the blood content of MCTD must be known at any time. Therefore, real time monitoring of hematocrit values of MCTD seems indispensable.

On TTE on discharge no significant differences in pericardial effusion were found between the CPPF group and non-CPPF group of patients, and no clinically significant pericardial effusions were encountered in the CPPF group. CPPF was stopped in one patient 3.5 h postoperatively as a precautionary measure due to a lag of >200 ml of fluid drainage from the right pleural cavity. As long as the protocol is followed strictly, i.e., the maximum accumulation volume does not exceed 200 ml, these pericardial or pleural effusions may be considered as clinically insignificant.

CPPF requires insertion of an extra drain and infusion of a saline solution into a fresh wound area, thereby theoretically increasing the risk of infection. However, since both the infusion solution and drain are sterilized and the same incision is used as for the standard chest tubes, this risk is considered to be negligible. No manifest clinical infections were seen in the CPPF group. Continuous irrigation of the wound area may reduce bacterial load and in theory decrease the risk of infection. In addition, by evacuating all blood and clots an important nutrient medium for potential bacterial infections is eliminated. Besides this, blood outside the vascular system i.e., in the pericardial cavity, may itself induce a serious local inflammatory reaction. Aiming for a cleaner pericardial space, CPPF may reduce postoperative complications related to this inflammatory process. In this context, the effect of CPPF on atrial fibrillation (Bruins et al., 1997), the development of adhesions (Nkere et al., 1995; Cannata et al., 2013) and impaired postoperative right ventricular function (Bailey et al., 1984; Schuuring et al., 2012) will be the subject of future studies.

In summary, so far CPPF can be regarded as safe since no postoperative adverse events that could be related to the CPPF were encountered in this study. In this experimental setting the CPPF method was considered feasible. However, in our judgment the CPPF method must be automated and the system should be equipped with an intra-pericardial pressure sensor and real-time hematocrit analysis of MCTD to provide the required high level of safety and feasibility in the clinical setting.

A limitation of this study is the retrospective group comparison. Results regarding the clinical impact on blood loss reduction are not yet conclusive at this stage and therefore randomized clinical trials are mandatory for a final conclusion. For instance, the surgical procedures in the CPPF group may have been biased towards "dryer surgery". Also, the difference between inflow and outflow volumes may not be an accurate measure for actual blood loss while the composition of MCTD fluid is both variable in time and patient-dependent.

5. Conclusion

From our study findings we conclude that CPPF after cardiac surgery is safe and feasible in this experimental setting. A positive effect on blood loss and related complications may be anticipated, but standardized randomized clinical trials are necessary to draw definitive conclusions.

Author Contributions

CG and DK wrote the study protocol. RK and BdM provided expert clinical perspective to content of study protocol and manuscript. CdB provided expert methodological and clinical feedback to protocol and manuscript, providing methodological perspective and data analysis. JM was responsible for inclusion of study participants, execution of study, and data collection. All authors were involved in the data analyses and discussion. JM, CG and DK wrote the manuscript.

Conflict of Interest Disclosure

Based on the experiences from this pilot study, a new medical device was invented that has been patented (WO2015086857A1) by the Academic Medical Center, Amsterdam, The Netherlands. Authors DK and JM are team members of a spinoff company (Haermonics B.V.) that will develop a new medical device, and in this capacity they may have future benefits from this.

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References

Abdel Aal, M., ElNahal, N., Bakir, B.M., Fouda, M., 2011. Mini-cardiopulmonary bypass impact on blood conservation strategy in coronary artery bypass grafting. Interact. Cardiovasc. Thorac. Surg. 12 (4), 600–604. http://dx.doi.org/10.1510/icvts.2010.243055 (PubMed PMID: 21252208).

Bailey, L.L., Ze-jian, L., Schulz, E., Roost, H., Yahiku, P., 1984. A cause of right ventricular dysfunction after cardiac operations. J. Thorac. Cardiovasc. Surg. 87 (4), 539–542 (PubMed PMID: 6708574).

Biancari, F., Mikkola, R., Heikkinen, J., Lahtinen, J., Airaksinen, K.E., Juvonen, T., 2012. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. Eur. J. Cardiothorac. Surg. 41 (1), 50–55. http://dx.doi.org/10.1016/j.ejcts.2011.04.023 (PubMed PMID: 21640602).

Bjessmo, S., Hylander, S., Vedin, J., Mohlkert, D., Ivert, T., 2007. Comparison of three different chest drainages after coronary artery bypass surgery—a randomized trial in 150 patients. Eur. J. Cardiothorac. Surg. 31 (3), 372–375 (PubMed PMID: 17234425).

Bruins, P., te Velthuis, H., Yazdanbakhsh, A.P., et al., 1997. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 96 (10), 3542–3548 (18, PubMed PMID: 9396453).

Cannata, A., Petrella, D., Russo, C.F., et al., 2013. Postsurgical intrapericardial adhesions: mechanisms of formation and prevention. Ann. Thorac. Surg. 95 (5), 1818–1826. http://dx.doi.org/10.1016/j.athoracsur.2012.11.020 (PubMed PMID: 23566646).

Despotis, G.J., Avidan, M.S., Hogue Jr., C.W., 2001. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann. Thorac. Surg. 72 (5), S1821–S1831 (PubMed PMID: 11722116).

Frankel, T.L., Hill, P.C., Stamou, S.C., et al., 2003. Silastic drains vs conventional chest tubes after coronary artery bypass. Chest 124 (1), 108–113 (PubMed PMID: 12853511).

Haneya, A., Diez, C., Kolat, P., et al., 2015. Re-exploration for bleeding or tamponade after cardiac surgery: impact of timing and indication on outcome. Thorac. Cardiovasc. Surg. 63 (1), 51–57. http://dx.doi.org/10.1055/s-0034-1390154 (PubMed PMID: 25264605).

Hardy, J.F., Bélisle, S., Janvier, G., Samama, M., 1996. Reduction in requirements for allogeneic blood products: nonpharmacologic methods. Ann. Thorac. Surg. 62 (6), 1935–1943 (PubMed PMID: 8957437).

Henry, D.A., Carless, P.A., Moxey, A.J., et al., 2011. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst. Rev. 16 (3), CD001886. http://dx.doi.org/10.1002/14651858.CD001886.pub4 (PubMed PMID: 21412876).

Illig, K.A., Green, R.M., Ouriel, K., et al., 1997. Primary fibrinolysis during supraceliac aortic clamping. J. Vasc. Surg. 25 (2), 244–251 (PubMed PMID: 9052559).

Karthik, S., Grayson, A.D., McCarron, E.E., Pullan, D.M., Desmond, M.J., 2004. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. Ann. Thorac. Surg. 78 (2), 527–534 (PubMed PMID: 15276512).

Ker, K., Beecher, D., Roberts, I., 2013. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database Syst. Rev. 23 (7), CD010562. http://dx.doi.org/10.1002/14651858.CD010562.pub2 (Review, PubMed PMID: 23881695).

Le, J., Buth, K.J., Hirsch, G.M., Légaré, J.F., 2015. Does more than a single chest tube for mediastinal drainage affect outcomes after cardiac surgery? Can. J. Surg. 58 (1). http://dx.doi.org/10.1503/cjs.006814 (1, 006814-6814, PubMed PMID: 25598178).

Levi, M., Cromheecke, M.E., de Jonge, E., et al., 1999. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 354 (9194), 1940–1947 (4, PubMed PMID: 10622296).

Murphy, G.J., Reeves, B.C., Rogers, C.A., Rizvi, S.I., Culliford, L., Angelini, G.D., 2007. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 116 (22), 2544–2552 (PubMed PMID: 17998460).

Nkere, U.U., Whawell, S.A., Sarraf, C.E., Schofield, J.B., Thompson, J.N., Taylor, K.M., 1995. Pericardial trauma and adhesions in relation to reoperative cardiac surgery. Thorac. Cardiovasc. Surg. 43 (6), 338–346 (PubMed PMID: 8775859).

Paparella, D., Brister, S.J., Buchanan, M.R., 2004. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med. 30 (10), 1873–1881 (PubMed PMID: 15278267).

Pelletier, M.P., Solymoss, S., Lee, A., Chiu, R.C., 1998. Negative reexploration for cardiac postoperative bleeding: can it be therapeutic? Ann. Thorac. Surg. 65 (4), 999–1002 (PubMed PMID: 9564917).

Perrault, L.P., Pellerin, M., Carrier, M., et al., 2012. The PleuraFlow Active Chest Tube Clearance System: initial clinical experience in adult cardiac surgery. Innovations (Phila) 7 (5), 354–358. http://dx.doi.org/10.1097/IMI.0b013e31827e2b4d (PubMed PMID: 23274869).

Philippou, H., Adami, A., Davidson, S.J., Pepper, J.R., Burman, J.F., Lane, D.A., 2000. Tissue factor is rapidly elevated in plasma collected from the pericardial cavity during cardiopulmonary bypass. Thromb. Haemost. 84 (1), 124–128 (PubMed PMID: 10928482).

Schuuring, M.J., Bolmers, P.P., Mulder, B.J., et al., 2012. Right ventricular function declines after cardiac surgery in adult patients with congenital heart disease. Int. J. Cardiovasc. Imaging 28 (4), 755–762. http://dx.doi.org/10.1007/s10554-011-9892-4 (PubMed PMID: 21637982).

Vallely, M.P., Bannon, P.G., Bayfield, M.S., Hughes, C.F., Kritharides, L., 2009. Quantitative and temporal differences in coagulation, fibrinolysis and platelet activation after on-pump and off-pump coronary artery bypass surgery. Heart Lung Circ. 18 (2), 123–130. http://dx.doi.org/10.1016/j.hlc.2008.08.012 (PubMed PMID: 19081297).

Yavari, M., Becker, R.C., 2009. Coagulation and fibrinolytic protein kinetics in cardiopulmonary bypass. J. Thromb. Thrombolysis 27 (1), 95–104. http://dx.doi.org/10.1007/s11239-007-0187-5 (PubMed PMID: 18214639).