

Autotransfusion system or integrated automatic suction device in minimized extracorporeal circulation: influence on coagulation and inflammatory response

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Abstract

Objective: To measure surrogate markers of coagulation activation as well as of the systemic inflammatory response in patients undergoing primary elective coronary artery bypass grafting (CABG) using either the so-called Smart suction device or a continuous autotransfusion system (C.A.T.S.[®]). **Methods:** Fifty-eight patients being operated with a miniaturized circuit (minimal extracorporeal circuit, MECC) were prospectively randomized to using a so-called Smart suction device or a routine continuous autotransfusion system (C.A.T.S.[®]) for collection of mediastinal shed blood. The coagulation response was measured by thrombin–antithrombin complex (TAT) and D-dimer. The inflammatory response was measured by Interleukin 6 (IL-6) and complement factor 3a (C3a) at three different time points, before surgery, 2 h after surgery, as well as 18 h after surgery. **Results:** No serious adverse cardiovascular event was observed. Serum levels of TAT significantly differed between both groups 2 h after surgery (Smart suction $16.12 \pm 13.51 \mu\text{g l}^{-1}$ vs C.A.T.S.[®] $9.83 \pm 7.81 \mu\text{g l}^{-1}$, $p = 0.040$) and returned to baseline values after 18 h in both groups. Serum levels of D-dimer showed a corresponding pattern with a peak 2 h after surgery (Smart suction $1115 \pm 1231 \text{ ng ml}^{-1}$ vs C.A.T.S.[®] $507 \pm 604 \text{ ng ml}^{-1}$, $p = 0.025$). IL-6 levels also significantly differed between both groups 2 h after surgery (Smart suction $186 \pm 306 \text{ pg ml}^{-1}$ vs C.A.T.S.[®] $82 \pm 71 \text{ pg ml}^{-1}$, $p = 0.072$). No significant changes in serum levels of C3a over time could be observed. **Conclusions:** Despite no differences in the clinical course of patients with either Smart suction or C.A.T.S.[®] being observed, surrogate markers of coagulation and inflammation seem to be less pronounced in patients where cardiotomy blood is not being directly reinfused. As such, C.A.T.S.[®] should be preferred in routine CABG, as long as no extensive volume substitution is anticipated.

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Keywords: CABG; Minimized extracorporeal circulation; Autotransfusion system; Smart suction

1. Introduction

Cardiopulmonary bypass (CPB) is known to cause coagulation activation as well as a systemic inflammatory response [1–3]. To reduce the detrimental effects of inflammatory mediators, elimination of shed blood from the wound was regarded essential and autotransfusion systems have been proven to dramatically reduce this [4,5]. Recent developments have successfully reduced the foreign surface and have established the new concept of volume-controlled perfusion [6,7]. This minimal extracorporeal circuit (MECC) has been introduced into clinical routine recently. However, the same question as in conventional CPB arose regarding coagulation activation as well as systemic inflammatory response [8].

The aim of this study was to measure surrogate markers of coagulation activation as well as of systemic inflammatory response in patients undergoing primary elective coronary artery bypass grafting (CABG) using either the so-called Smart suction device or a continuous autotransfusion system (C.A.T.S.[®]).

2. Patients and methods

2.1. Experimental setting

For the purpose of this study, 58 elective patients undergoing CABG were prospectively randomized and assigned to one of the following two treatment groups: group I ($n = 32$) was undergoing surgery using the MECCTM System (Maquet Cardiopulmonary AG, Hirrlingen, Germany) with the Smart suction device (Fumedica AG, Muri, Switzerland) and group II ($n = 26$) was undergoing CABG using the MECCTM System with

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Table 1. Demographics, intra and postoperative data.

	Smart suction	Cell saver	
Demographics			
Mean age (a)	65 ± 9	62 ± 9	0.257
EuroSCORE (add)	3.3 ± 2.4	2.9 ± 2.0	0.405
EuroSCORE (log)	3.2 ± 2.5	2.5 ± 1.5	0.202
Intraoperative data			
MECC time (min)	78 ± 33	74 ± 21	0.621
Aortic clamp time (min)	50 ± 21	47 ± 17	0.608
No of distal anastomosis	3.53 ± 1.02	3.42 ± 0.76	0.795
RPBC (units)	0	0	
Suction volume (ml)	750 ± 510	1100 ± 540	0.012
Postoperative data			
RPBC (units)	1.6 ± 1.4	1.2 ± 1.3	0.158
Chest tube output (ml)	460 ± 307	404 ± 404	0.881
Ventilation time (h)	18 ± 8	18 ± 3	0.237
In-hospital stay (day)	7 ± 2	7 ± 2	0.847

the C.A.T.S.[®] continuous autotransfusion device (Fresenius AG, Bad Homburg, Germany). Patient demographics are shown in Table 1.

2.2. CPB and suction devices

The MECC-System used is a minimal, closed and pre-connected extracorporeal circulation system consisting of a hollow-fiber membrane oxygenator (Quadrox, Maquet AG, Hirrlingen) and a centrifugal pump (RotaFlow, Maquet AG, Hirrlingen). Arterial filter and venous bubble trap are not used. In our setting, air was detected by an ultrasound probe, placed on the highest level of the venous line. If air is detected, the centrifugal pump stops immediately. Air can be easily eliminated by opening a clamp, through the conducted suction reservoir, which is permanent under vacuum.

The Smart suction device includes an optic fiber, which transmits an on/off signal to a control unit, indicating whether its end is in contact with blood. When the tip of the suction cannula is in contact with blood, the sensor will automatically open a clamp located in the control unit box,

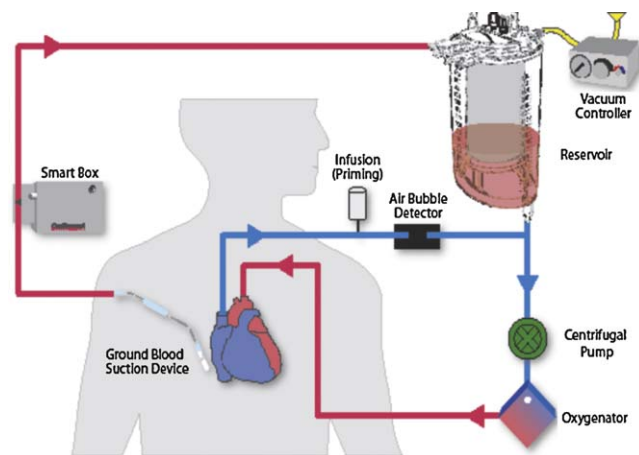


Fig. 1. Set up of the MECC Smart suction system.

which is assembled on the operating table. Blood will thus immediately be aspirated. When contact is lost, the clamp closes immediately. The aspirated fluid is conducted to a reservoir and can be returned directly into the MECC[™] circuit [9]. Fig. 1 illustrates this set-up.

The C.A.T.S.[®] suction device is a continuous autotransfusion system, which comprises a centrifugal chamber in which the blood is collected and washed. Red blood cells are separated from other blood components through washing with a saline solution.

2.3. Surgery

In all patients, CABG was performed via median sternotomy. CPB was conducted in moderate hypothermia (34 °C). After cross-clamping the aorta, 100 ml of crystalloid cardioplegia was injected into the aortic root [7]. In the first group, collected suction blood was retransfused directly into the MECC[™]-System during CPB. In the second group, suction blood was collected into the Cell Saver autotransfusion system. After processing, red blood cells (RBCs) were transfused to the patient in the operating theater after weaning of CPB. Antifibrinolytic therapy was applied according to institutional standards.

2.4. Blood sampling 1

Coagulation response was measured by the thrombin–antithrombin complex (TAT) and D-dimer. In particular, TAT was measured by microenzyme immunoassay (Enzygnost TAT micro, Dade Behring Marburg GmbH, Germany), as was D-dimer (Asserachrom[®] D-Di).

2.5. Blood sampling 2

The inflammatory response was measured by Interleukin 6 (IL-6) and complement factor 3a (C3a). IL-6 was measured by sandwich immunoassay using the Luminex fluorescent-bead technology. C3a was measured by an in-house enzyme-linked immunoassay on a Nunc MaxiSorp[®] plate of 96 wells. Abcam, 013-16 was used as detection antibody, gt-a-hu C3a from R&D was used as first-capture antibody, and mouse anti-goat-IgG-biot from Jackson Research, 205-065-108, was used as second-capture antibody.

2.6. Time points

Blood samples were taken at three different time points, before surgery, 2 h, and 18 h after surgery. In addition, hematocrit was analyzed in parallel. In-hospital data were collected, focusing on blood loss and transfusion requirements. We used ethylene diamine tetraacetic acid (EDTA) plasma and D-Phenylalanyl-L-prolyl-L-arginine Chloromethyl Ketone (C-PPACK) samples. All blood samples were centrifuged at latest 30 min after sampling with 3000 rpm for 30 min and pipetted into 0.5-ml tubes. Samples were stored at –80 °C until analysis.

2.7. Statistical analysis

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Single comparisons between treatment groups relied on the Kruskal–Wallis test; categorical data were compared by Chi-squared tests; and repeated measures analysis of variance (ANOVA) was used to analyze treatment effects over time (data were log-transformed to fulfill distributional requirements).

3. Results

3.1. Clinical results

No serious adverse cardiovascular event was observed. The number of distal anastomoses (3.5 ± 1 for group I vs 3.4 ± 0.8 for group II, $p = 0.654$) was well comparable. Furthermore, CPB times (78 ± 33 min vs 74 ± 21 min, $p = 0.637$) as well as aortic cross-clamp times (50 ± 21 min vs 47 ± 16 , $p = 0.630$) did not differ. Two patients had to be excluded from the analysis due to postoperative surgical bleeding needing revision. There were no differences with regard to ventilation time (18 ± 8 h vs 18 ± 3 h, $p = 0.686$) as well as in-hospital stay (7 ± 2 days vs 7 ± 2 days, $p = 0.985$). Need for red packed blood cell substitution was during follow-up also comparable (1.6 ± 1.4 U vs 1.2 ± 1.3 U, $p = 0.158$). Chest tube output after 6 h (460 ± 307 ml vs 404 ± 404 ml, $p = 0.881$) and 18 h (860 ± 441 ml vs 821 ± 575 ml, $p = 0.491$) was also comparable.

3.2. Coagulation response – TAT

Serum levels of TAT were comparable between both groups before surgery ($7.05 \pm 3.66 \mu\text{g l}^{-1}$ for group I vs $5.88 \pm 6.50 \mu\text{g l}^{-1}$ for group II, $p = 0.418$). Two hours after surgery, serum levels were significantly higher for group I ($16.12 \pm 13.51 \mu\text{g l}^{-1}$ vs $9.83 \pm 7.81 \mu\text{g l}^{-1}$, $p = 0.040$) as well as compared with baseline values. After 18 h, no significant difference between both groups could be observed ($7.05 \pm 3.66 \mu\text{g l}^{-1}$ vs $6.29 \pm 3.41 \mu\text{g l}^{-1}$, $p = 0.423$). Furthermore, no difference as compared with baseline values could be observed. The ANOVA with repeated measures showed a significant effect for time ($p < 0.001$), but no interaction between time and study group ($p = 0.11$) was seen (Fig. 2).

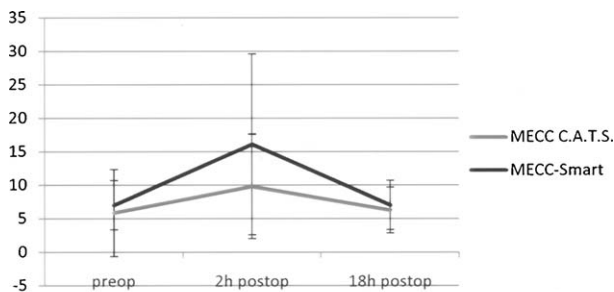


Fig. 2. TAT serum levels over time.

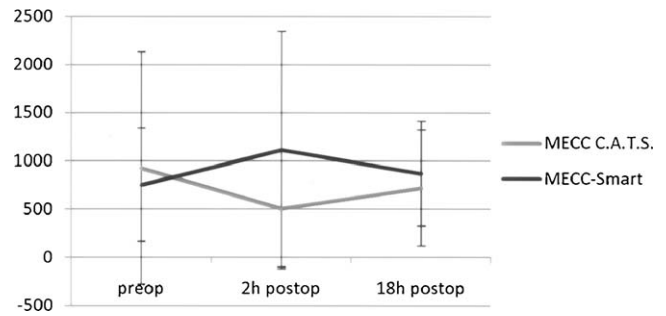


Fig. 3. D-dimer serum levels over time.

3.3. D-dimer

Serum levels of D-dimer were comparable between both groups before surgery ($756 \pm 587 \text{ ng ml}^{-1}$ for group I vs $928 \pm 1206 \text{ ng ml}^{-1}$ for group II, $p = 0.478$). Two hours after surgery, serum levels were significantly higher for group I ($1115 \pm 1231 \text{ ng ml}^{-1}$ vs $507 \pm 604 \text{ ng ml}^{-1}$, $p = 0.025$) as well as compared with baseline values. After 18 h, no significant difference between both groups could be observed ($870 \pm 442 \text{ ng ml}^{-1}$ vs $721 \pm 602 \text{ ng ml}^{-1}$, $p = 0.327$). Furthermore, no difference as compared with baseline values could be observed. The ANOVA with repeated measures showed a significant interaction between time and treatment group ($p = 0.01$) (Fig. 3).

3.4. Inflammatory response

Serum levels of IL-6 were comparable between both groups before surgery ($4 \pm 16 \text{ pg ml}^{-1}$ vs $1 \pm 3 \text{ pg ml}^{-1}$, $p = 0.220$). Two hours after surgery, serum levels were significantly higher for group I ($186 \pm 306 \text{ pg ml}^{-1}$ vs $82 \pm 71 \text{ pg ml}^{-1}$, $p = 0.072$) as well as compared with baseline values. After 18 h, no significant difference between both groups could be observed ($96 \pm 93 \text{ pg ml}^{-1}$ vs $127 \pm 164 \text{ pg ml}^{-1}$, $p = 0.375$). Still, a significant difference as compared with baseline values could be observed. The ANOVA with repeated measures showed a significant effect for time ($p < 0.001$), but no interaction between time and study group ($p = 0.073$) (Fig. 4).

Serum levels of C3a were comparable between both groups before surgery ($547 \pm 465 \text{ ng ml}^{-1}$ vs $836 \pm 933 \text{ ng ml}^{-1}$, $p = 0.130$). Two hours after surgery, serum levels neither differed between both groups ($776 \pm 506 \text{ pg ml}^{-1}$ vs $770 \pm 488 \text{ pg ml}^{-1}$, $p = 0.967$) nor as

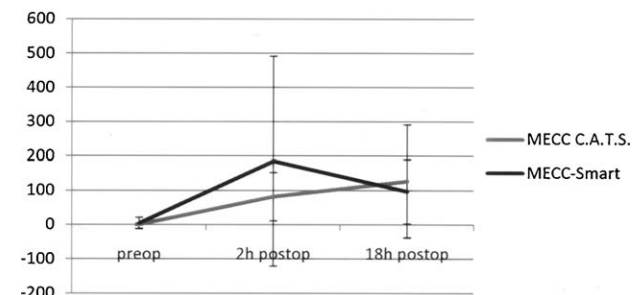


Fig. 4. IL-6 serum levels over time.

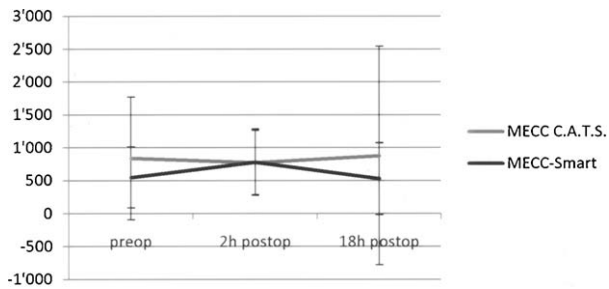


Fig. 5. C3a serum levels over time.

compared with baseline values. After 18 h, no significant difference between both groups could be observed ($526 \pm 544 \text{ pg ml}^{-1}$ vs $879 \pm 1660 \text{ pg ml}^{-1}$, $p = 0.262$). No significant difference as compared with baseline values could be observed. The ANOVA with repeated measures showed no significant effect, neither for time ($p = 0.76$) nor for the interaction between time and study group ($p = 0.383$) (Fig. 5).

4. Comment

Despite no differences in the clinical course of patients with either Smart suction or continuous autotransfusion system being observed, surrogate markers of coagulation and inflammation seem to be less pronounced in patients where cardiomy blood is not being directly reinfused. As such, C.A.T.S.[®] should be preferred in routine CABG as long as no extensive volume substitution is anticipated.

Drawbacks of using conventional CPB in patients undergoing CABG are well recognized. Primarily, due to volume shifts, substantial fluid replacement may be required, and fluid overload may affect the clinical course within the first day after surgery [1]. This fluid overload may well account for a potentially unnecessary application of red packed blood cells. Furthermore, surrogate markers of inflammation are upregulated, thereby enhancing the systemic inflammatory response of the organism [2,3]. As a consequence, alternatives to conventional CPB were developed. A miniaturized circuit has been implemented into clinical routine recently with excellent results regarding clinical outcome and simplicity of the system itself [6,7]. However, volume replacement during CABG is needed and – as the concept of the system is primarily a closed one – ways of sufficient volume substitution had to be met.

Besides the routine use of an autotransfusion system, which may – in individual situations – not be capable enough to sufficiently preserve the fluid equilibrium, a new concept has been introduced into clinical routine. To achieve a nearly perfect equilibrium, the Smart system was developed [9]. By this means, cardiomy blood is being suctioned into a reservoir that is directly connected to the tubing system but separated by a manual clamp, which is being released for fluid balancing, if needed [11]. Thereby, the concept of volume-controlled perfusion is being realized. However, the systemic effect may be no other than with conventional cardiomy suction devices, thereby leading to an increased coagulation and inflammatory response by directly reinfusing inflammatory mediators collected from the wound.

No clinical differences between both groups were seen. This was also not expected, as others, who have compared autotransfusion systems and cardiomy suction in conventional CPB did also not observe significant clinical differences regarding perioperative outcome [12,13]. Interestingly, requirement of red packed blood cells in the operating room (OR) in both groups was near zero, thereby substantiating the proof of principle of volume-controlled perfusion. Furthermore, chest tube output was well comparable. It is a fact that patients leave the OR with a stable hematocrit not necessitating any kind of RBC transfusion. However, our intensive care unit follows a strict regimen regarding fluid balancing, which is not individualized according to body surface area or weight. As such, patients with smaller body surface area or lower weight are at risk to be in need of RBC substitution, not due to bleeding but due to hemodilution. Throughout this study, we have realized, fixed, and solved this issue.

The TAT as an indirect marker of thrombin generation, was chosen as a surrogate for coagulation activation in our setting [14]. Two hours after surgery, TAT was significantly higher in the Smart group as compared with the C.A.T.S.[®] group, thereby indicating a markedly higher coagulation activation. Eighteen hours after surgery, serum levels returned to baseline values in both groups. This could have been expected as the half-value period of TAT is below this time frame.

D-dimer was used as a surrogate marker for fibrinolysis in this study [14]. As could be expected, according to the changes in serum levels of TAT, D-dimer levels developed in parallel. Therefore, a significant difference in peak values 2 h after surgery in the Smart group could be seen. Subsequently, serum levels returned to baseline after surgery.

As surrogate markers for the systemic inflammatory response, we selected as surrogate for the primary inflammatory response complement C3a as well as IL-6 as a pro-inflammatory cytokine [1]. The second time point was chosen as we expected the most intense increase in C3a levels 2 h after operation [10]. C3a serum levels in patients with a C.A.T.S.[®] remained constant throughout the observation, whereas C3a serum levels in patients with the Smart system showed a marked increase 2 h after surgery. However, due to a broad standard deviation at baseline, these values did not reach statistical significance.

IL-6 serum levels increased 2 h after surgery reaching borderline significance and then decreased again indicating a higher level of inflammation in patients with the Smart system than in patients in whom a C.A.T.S.[®] has been used. Overall, regarding surrogate markers of coagulation as well as inflammation, differences between both groups are measurable; however, serum levels return to baseline quickly. Furthermore, there was no clinical impact related our findings. As such, the manifest means of immediate volume substitution may be of higher value than a non-manifest but measurable difference in serum surrogate markers.

Clinics and surrogate markers of inflammation do not always accord. As such, it remains speculative if a switch to an autologous transfusion device may, in fact, affect outcome. To prove this hypothesis, a substantially larger

cohort of patients would be needed as – as could be shown in this study – there are no differences in outcome regarding clinical end points. Whether this change of strategy might influence more subtle parameters such as cognitive brain function, which is directly influenced by inflammation, remains the subject of further investigations [15].

Summarizing, despite no differences in the clinical course of patients with either Smart suction or C.A.T.S.[®] being observed, surrogate markers of coagulation and inflammation seem to be less pronounced in patients where cardiomy blood is not being directly reinfused. As such, C.A.T.S.[®] should be preferred in routine CABG as long as no extensive volume substitution is anticipated.

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