Individually Optimized Hemodynamic Therapy Reduces Complications and Length of Stay in the Intensive Care Unit

A Prospective, Randomized Controlled Trial

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ABSTRACT

Background: The authors hypothesized that goal-directed hemodynamic therapy, based on the combination of functional and volumetric hemodynamic parameters, improves outcome in patients with cardiac surgery. Therefore, a therapy guided by stroke volume variation, individually optimized global end-diastolic volume index, cardiac index, and mean arterial pressure was compared with an algorithm based on mean arterial pressure and central venous pressure.

Methods: This prospective, controlled, parallel-arm, open-label trial randomized 100 coronary artery bypass grafting and/or aortic valve replacement patients to a study group (SG; n = 50) or a control group (CG; n = 50). In the SG, hemodynamic therapy was guided by stroke volume variation, optimized global end-diastolic volume index, mean arterial pressure, and cardiac index. Optimized global end-diastolic volume index was defined before and after weaning from cardiopulmonary bypass and at intensive care unit (ICU) admission. Mean arterial pressure and central venous pressure served as hemodynamic goals in the CG. Therapy was started immediately after induction of anesthesia and continued until ICU discharge criteria, serving as primary outcome parameter, were fulfilled.

Results: Intraoperative need for norepinephrine was decreased in the SG with a mean (±SD) of 9.0 ± 7.6 *versus* 14.9 ± 11.1 μg/kg (P = 0.002). Postoperative complications (SG, 40 *vs.* CG, 63; P = 0.004), time to reach ICU discharge criteria (SG, 15 ± 6 h; CG, 24 ± 29 h; P < 0.001), and length of ICU stay (SG, 42 ± 19 h; CG, 62 ± 58 h; P = 0.018) were reduced in the SG.

Conclusion: Early goal-directed hemodynamic therapy based on cardiac index, stroke volume variation, and optimized global end-diastolic volume index reduces complications and length of ICU stay after cardiac surgery.

What We Already Know about This Topic

- To date, no individually optimized hemodynamic therapeutic strategy has been shown to improve postoperative outcomes after cardiac surgery.
- The current study investigated whether goal-directed hemodynamic therapy, based on the combination of functional and volumetric hemodynamic parameters, improves outcome in patients with cardiac surgery. Specifically, guided therapy using stroke volume variation, individually optimized global end-diastolic volume index, cardiac index, and mean arterial pressure was compared with an algorithm based on mean arterial pressure and central venous pressure.

What This Article Tells Us That Is New

- Early goal-directed therapy using stroke volume variation, cardiac index, and optimized global end-diastolic volume index reduces intensive care unit stay after cardiac surgery.

THERE is an increasing evidence that in high-risk surgical patients, hemodynamic optimization oriented on goals to maintain and improve tissue oxygenation improves outcome.[1] However, treatment strategies using "supranormal" hemodynamic goals have failed.[2,3] One major factor

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most likely contributing to these disappointing results was the factor "timing": the shorter the time period between tissue trauma and/or circulatory failure and successful resuscitation with adequate oxygen delivery, the better the clinical outcome.[4–6] This was impressively shown in 2001 in patients with sepsis.[7] In parallel, several groups have investigated the treatment concepts for intra- and perioperative hemodynamic care based on the optimization of cardiac output,[8,9] and the seemingly easiest way to increase cardiac function by volume loading maneuvers in order to optimize cardiac preload. These concepts gained more acceptances when less invasive monitoring techniques for continuous measurement of cardiac output became available, without the risk of pulmonary artery catheterization.[10–13] Strengthening the importance of the factor timing, most of the studies already initiated the preload-optimizing concept during surgery and showed benefits in patients' outcome, including reduction in postoperative complications or a shortening in postoperative intensive care unit (ICU) or hospital stay. However, when treatment protocols were initiated after surgery, *e.g.*, with admission on the ICU, heterogeneous results were reported.[2,12,14–17] To further complicate matters, monitoring approaches that only allow assessment of stroke volume or cardiac output can only quantify the success or failure of volume loading *post hoc*, *i.e.*, prediction of volume responsiveness is impossible. This may expose patients with a reduced cardiac and pulmonary function to ineffective, unnecessary, and potentially dangerous volume application. Such situations are particularly imminent in cardiac surgical patients. In this study, so-called functional parameters of cardiac preload, *i.e.*, pulse pressure variation or stroke volume variation (SVV), have shown promising results.[18–20] Unfortunately, their use is restricted to patients under controlled mechanical ventilation, and with regular cardiac rhythm. This discounts their use in many circumstances in the ICU, where restoring spontaneous breathing is also an early therapeutic goal.

In this study, volumetric parameters of cardiac preload, such as the global end-diastolic volume index (GEDI) by transcardiopulmonary thermodilution (TCPTD), have shown promising results.[13,21] However, although the GEDI allows quantification of preload volume, it does not reliably predict fluid responsiveness.[22–24] This becomes obvious when it is considered that under various physiological conditions, "normal values" of those volumetric parameters show relevant variability, which is even more pronounced in the presence of cardiac disease.[25–28] By turning a methodological weakness to a potential conceptional strength, we therefore speculated that in a heterogeneous patient group, as in cardiac surgery, a titrated, "individually optimized GEDI (optGEDI)" could serve as a landmark for preload optimization during and after surgery, despite assisted ventilation and/or cardiac arrhythmias. We hypothesized that combining the use of a functional parameter of volume responsiveness (SVV) during the perioperative phase of preload optimization, and postoperatively by using the patients' individualized optGEDI, leads to improved hemodynamics and results in less postoperative complications, facilitating earlier discharge from the ICU.

Materials and Methods

This study was performed as a single-site, prospective, controlled, randomized, parallel-arm, open-label trial in Hamburg, Germany. It was designed to investigate a potential superiority of a new hemodynamic treatment algorithm in elective patients with cardiac surgery. After the approval by the local government ethics committee (Ethics Committee, Hamburg Medical Board, Project Nr. 2509), 100 elective patients, scheduled either for coronary artery bypass grafting with the use of cardiopulmonary bypass (CPB) or aortic valve replacement or combined surgery (coronary artery bypass grafting and aortic valve replacement), were prospectively recruited by our clinical service and randomized into two groups directly before induction of anesthesia. A block randomization was performed containing 10 blocks each with 10 patients. Allocation to the study group (SG) or control group (CG) was performed in 1:1 proportion by randomly shuffled envelopes by a study nurse. The investigators were unaware of the randomization technique until end of data acquisition was reached. All patients were informed in detail of the aims of this study and gave signed written informed consent. Exclusion criteria were age less than 18 yr, pregnancy, any contraindications for catheterization of the femoral artery, kidney injury requiring dialysis therapy, valve insufficiency of more than II° and preexisting atrial fibrillation.

Anesthesia and Hemodynamic Measurements

All patients orally received 7.5–15 mg of midazolam 1 h before surgery. After getting peripheral venous access, patients had a 5-French thermistor-tipped catheter (PV2025 L20, Pulsiocath; Pulsion Medical Systems, Munich, Germany) inserted into a femoral artery connected to a monitor for TCPTD and arterial pulse contour analysis (PiCCOplus; Pulsion Medical Systems). Intravenous anesthesia was then induced with 0.7 μg/kg of sufentanil and 2.0–2.5 mg/kg of propofol. Orotracheal intubation was facilitated by pancuronium bromide 0.1 mg/kg. A 7-French triple lumen central venous catheter was then inserted into an internal jugular vein. All pressure transducers were positioned at the level of the midaxillary line and calibrated to zero atmospheric pressure. During surgery, ventilation was performed in a volume-controlled mode (Zeus IE; Draeger Medical, Luebeck, Germany) using tidal volumes of 8 ml/kg of ideal body weight and a positive end-expiratory airway pressure of 5–7 mbar. Inspiratory oxygen content and respirator frequency were adjusted to achieve normoxemia and normocapnia. Anesthesia was maintained by continuous administration of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of sufentanil and inspiratory 1.3–1.6 vol% of sevoflurane. During surgery, the trigger for transfusion of packed erythrocytes was set to a hematocrit of 22%. Values of cardiac output, stroke

volume, global end-diastolic volume, and extravascular lung water were all measured by TCPTD. All parameters were indexed to body surface area to give cardiac index (CI), stroke volume index and GEDI, and to patients' ideal body weight to give an extravascular lung water index (ELWI). Furthermore, continuous cardiac output and ventilation-induced left ventricular SVV were assessed by arterial pulse contour analysis.[29,30] In the CG, the hemodynamic monitor was blinded to the treating physician throughout the entire study period while all hemodynamic data and measurements were recorded.

Hemodynamic Management during Surgery

In the SG, the hemodynamic status was assessed by SVV, GEDI, ELWI, CI, and mean arterial pressure (MAP). Measurements were performed after induction of anesthesia, immediately after termination of CPB, and at the end of surgery (defined as end of skin suture [EOS]). Hemodynamics were optimized according to the treatment algorithms immediately after each of these routine assessments or in cases of hemodynamic instability. In detail, SVV was used to optimize cardiac preload: volume loading was performed as long as SVV remained more than 10%. After volume optimization (SVV <10%), GEDI was measured and noted as optGEDI (fig. 1). This individually titrated optGEDI served as the goal for preload optimization in clinical situations where SVV was not feasible, *i.e.*, in the presence of cardiac arrhythmias, spontaneous respiration, and motion artefacts. To avoid pulmonary edema and excessive fluid overload, ELWI was measured in parallel with GEDI. ELWI of more than 12 ml/kg, indicating risk of pulmonary edema, induced immediate termination of further fluid loading.[31,32] Furthermore, if CI was less than 2.0 $l \cdot min^{-1} \cdot m^{-2}$ after preload optimization, catecholamine support with epinephrine was initiated. If MAP was still less than 65 mmHg, norepinephrine was administered. Heart rate (HR) was kept between 50 and 110 beats/min by epicardial pacing, pharmacological intervention, and increase in hemoglobin concentration or deepening of anesthesia when necessary (fig. 2). Hemodynamic goals were defined according to the revised joint guidelines for ICU therapy for patients with cardiac surgery of the German Society of Anaesthesiology and Intensive Care Medicine and the German Society of Cardiothoracic Surgeons.[33]

In the CG, the care-giving anesthesiologist was blinded to the data provided by TCPTD and arterial pulse contour analysis. Hemodynamic management followed a protocol based on the assessment of central venous pressure (CVP), MAP, and HR, as illustrated in figure 3. On the basis of the mentioned guidelines,[33] preload was assessed by the CVP. If CVP decreased less than 8 mmHg, volume loading was performed until the target was reached. When MAP was still less than 65 mmHg, catecholamines (epinephrine and norepinephrine) were administered. As with the SG, HR was kept between 50 and 100 beats/min using respective interventions.

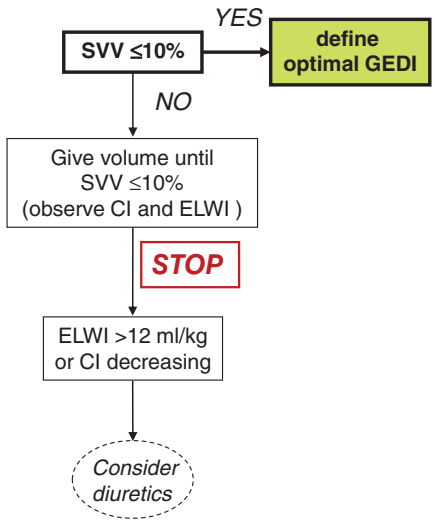

Fig. 1. Hemodynamic algorithm to define patient individually titrated optimal global end-diastolic volume index (optGEDI). Definition of optGEDI was performed directly after induction of anesthesia, after weaning from cardiopulmonary bypass, and at intensive care unit admission. CI = cardiac index; ELWI = extravascular lung water index; SVV = stroke volume variation.

In both groups, for volume loading maneuvers hydroxyethyl starch (HES) 6% 130/0.4 (Fresenius Kabi, Bad Homburg, Germany) up to a maximum daily dose of 120 g was used. If an interstitial fluid deficit was suggested and for replacement of diuresis, Ringer's lactate solution was given. In case of acute hemodynamic instability, norepinephrine was used as a bridging therapy in both groups until fluid loading or other appropriate interventions according to the study algorithms were performed.

CPB

During CPB, sevoflurane was replaced by propofol 2.5 $mg \cdot kg^{-1} \cdot h^{-1}$ and midazolam 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. Surgery was performed using CPB under mild hypothermia (31–32°C) with a pumpflow of 2.5 $l \cdot min^{-1} \cdot m^{-2}$. If MAP decreased to 50 mmHg, norepinephrine was administered. The transfusion trigger during CPB was a hematocrit less than 22%. Priming volume was standardized. Fluid management during CPB was performed at the discretion of the attending perfusionist.

Hemodynamic Management during ICU Therapy

Patients were ventilated using intermittent positive pressure support to achieve normocapnia and normoxemia. Initially after admission to the ICU, patients were, if clinically necessary, sedated and received analgesia according to the institutional standards. In all patients, hemodynamics were routinely measured immediately after ICU admission, 6 h after EOS, and then every 12 h until reaching criteria for ICU discharge or in any periods of hemodynamic instability according to the treatment algorithms (figs. 2 and 3). If necessary, treatment was initiated according to the respective algorithms

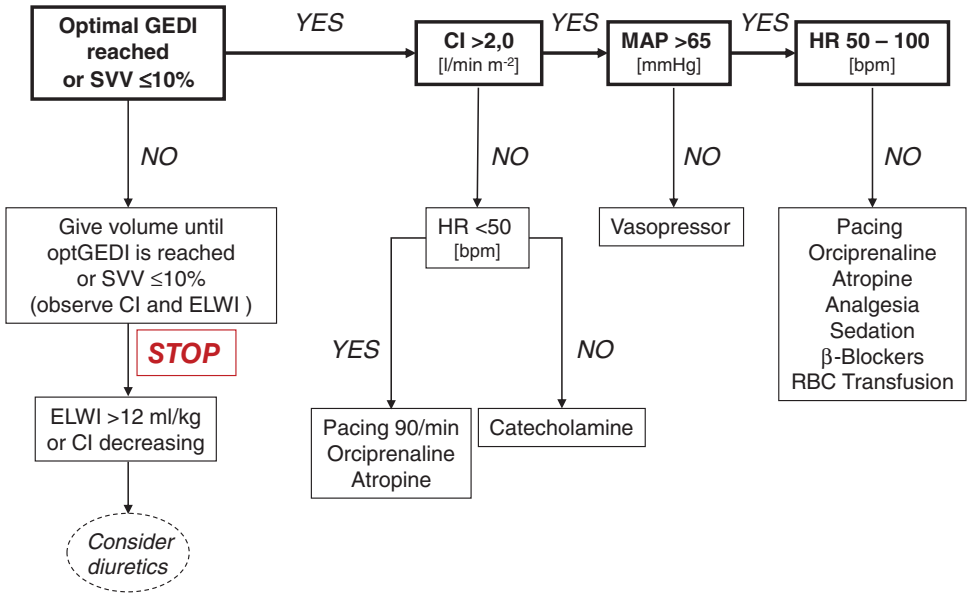

Fig. 2. Hemodynamic algorithm for patients of the study group. CI = cardiac index; ELWI = extravascular volume index; HR = heart rate; MAP = mean arterial pressure; optGEDI = optimal global end-diastolic volume index; RBC = erythrocyte concentrate; SVV = stroke volume variation.

as described above during surgery. Suspected interstitial fluid deficits were compensated by the administration of Ringer's lactate solution. Intravascular volume deficits, in particular due to obvious bleeding *via* wound drainages or nonvisible suspected bleeding, were replaced by HES 6% 130/0.4. In addition, for the algorithm-driven preload optimizing maneuvers HES 6% 130/0.4 was used. A maximum daily dose of 120 g of HES 6% 130/0.4 was given. If further fluids were necessary, albumin 5% or Ringer's lactate solution were used. The trigger for packed erythrocytes transfusion during ICU therapy was a hematocrit of less than 22%.

Assessment of Postoperative Complications, ICU Discharge, and Hospital Discharge

In all patients, an independent investigator assessed postoperative complications after hospital discharge according to the categories, which were predefined by the study protocol: arrhythmias, hemorrhage, respiratory, neurological, postoperative myocardial damage, ischemic reperfusion damage, infection, and acute kidney injury. Arrhythmic complications were comprised of any episode of atrial fibrillation, ventricular arrhythmia, or fibrillation which required therapeutic interventions. Hemorrhagic complications were defined as drainage

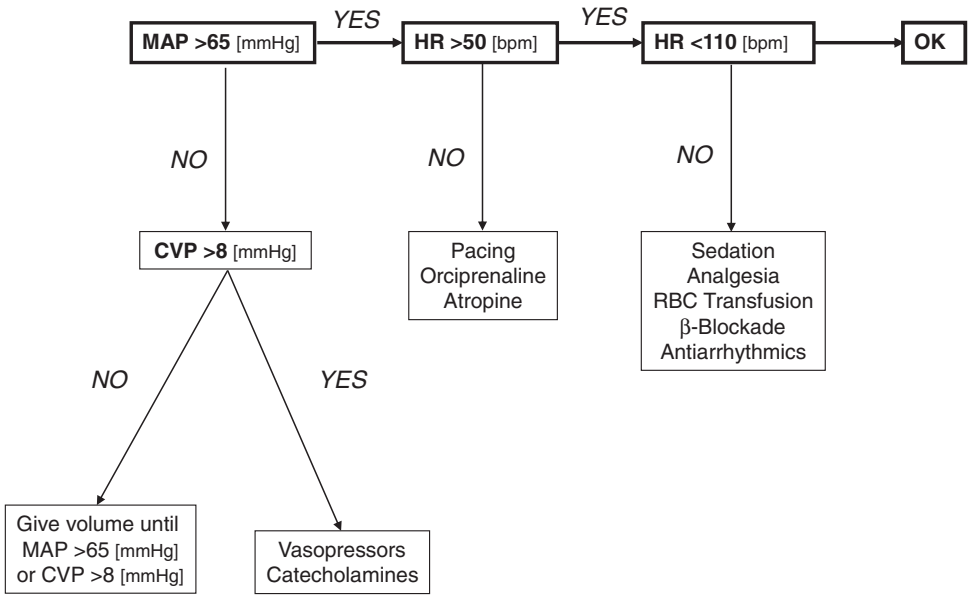

Fig. 3. Hemodynamic algorithm for patients of the control group. CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; RBC = erythrocyte concentrate.

of blood of more than 200 ml/h for 3 consecutive hours or rethoracotomy, where no surgical bleeding source could be identified. Respiratory complications were reintubation, need for noninvasive respiratory support, or a pneumothorax. Neurological complications were defined as postoperative delirium according to the nursing delirium screening scale[34] or postoperative stroke. Postoperative myocardial damage was defined as an increase in the level of creatinine kinase muscle brain mass of more than 50 pg/ml. For ischemia/reperfusion damage, a postoperative level of more than 3,000 U/l creatinine kinase had to be achieved. Infectious complications were defined as infective wound dehiscence or other infectious diseases (*e.g.*, urinary tract infections). Renal complications were defined as a postoperative serum creatinine concentration according to the Acute Kidney Injury Network criteria. In brief, acute kidney injury stage-1 is defined as a peak postoperative creatinine concentration of 150–200% from baseline value, acute kidney injury stage-2 when 200–300% from baseline value are reached, and acute kidney injury stage-3 as serum creatinine more than three times the baseline value.[35] Furthermore, in both groups an independent investigator monitored the period required to achieve the predefined and previously published "fit for ICU discharge" criteria: cooperative patient, Spo_2 greater than 90% with Fio_2 less than 0.5, no ventricular arrhythmias, chest tube drainage less than 50 ml/h, urine output more than 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$, no inotropes or vasopressors, no signs of ischemia on electrocardiography, all to be achieved within 3 successive hours.[13,36] The "fit for hospital discharge" criteria were defined as follows: patient is fully oriented and able to move without nursing support, hemodynamically stable, laboratory parameters with no sign of increasing organ dysfunction or infection, and no clinical sings of active wound infection. In addition to these "fit for discharge criteria," the real time to ICU and hospital discharge was documented.

Statistical Analysis

Primary outcome parameters of this study were the real duration of postoperative ICU therapy and time to fulfilment of predefined ICU discharge criteria.[13,36] For these two parameters, statistical significance was held to a strict rate type I error rate of 0.05; hence significance level for each primary outcome parameter was adjusted to 0.025 using the Mann–Whitney rank sum test. Secondary outcome parameters were the need for vasopressor and catecholamine support and predefined clusters of postoperative complications. For primary and secondary outcome parameters, an intention to treat (ITT) analysis was performed on all randomized patients. Sample size calculation: according to our institutional database an expected mean duration of 72-h ICU therapy with an SD of 35 h was applied for a representative collective. For the study, we hypothesized a mean ICU stay of 54 h with an SD of 26 h. Anticipating a type I error of 5% and a type II error of 20%, sample size calculation revealed 96 patients divided into two groups of equal size. No interim analysis was performed. All data are provided as mean ± SD and median in brackets or as indicated. For comparisons between groups, an unpaired two-tailed *t* test was used if data were distributed normally; otherwise the Mann–Whitney rank sum test was used. For parametric data, the Fisher exact test was used. To compare the total amount of complications between groups, the Poisson Regression was used. Statistics were performed using SPSS 20.0 (IBM SPSS Statistics, New York, NY).

Results

All patients tolerated the study regimen well. No complications were noted from the femoral arterial catheterization. Eight patients (4 in the SG and 4 in the CG) had to be excluded from per protocol analysis: one patient in the CG showed signs of acute cardiac ischemia postoperatively and was transferred to the catheter laboratory. In this study, occlusion of one graft was detected. In three patients, intraoperative transesophageal echocardiography showed massive aortic regurgitation (aortic insufficiency >III°). In two patients, the central venous catheter turned out to be incorrectly placed. In one patient, puncture of the femoral artery was unsuccessful and in one patient the catheter for TCPTD showed a technical defect at the beginning of surgery. Data of these eight patients were added to the ITT analysis. Demographic and surgical data of the 92 per protocol patients (19 female and 73 male) are listed in table 1.

Hemodynamics

Detailed hemodynamic data during surgery and ICU treatment are listed in table 2. The course of MAP and HR were similar in both groups, solely 6 h after EOS HR was higher in the CG. SVV was lower in the SG at any time during surgery until ICU admission. In addition, CVP was higher in the SG at ICU admission, 12 and 36 h postoperatively. $ScvO_2$ was higher in the SG before CPB. In addition, CI was higher after induction of anesthesia, before starting CPB, at 24 and 36 h after EOS. As a result of the hemodynamic algorithm, stroke volume index was higher in the SG at all measurements except at baseline and directly after weaning from CPB (table 2).

Due to the fact that not all patients were measured until 36 h after EOS because they were discharged from ICU before, statistical analysis was conducted as pair-wise comparisons on all available data at distinct time points and not, as appropriate, using a mixed model with time × group interaction and adjustment for multiple comparisons. However, following this, more conservative approach on the reduced data set on available patients at every time point would yield significantly different courses of CVP ($P = 0.047$), SVV ($P < 0.001$), GEDI ($P = 0.044$), CI ($P = 0.001$), and stroke volume index ($P = 0.020$) between the groups. The findings above can be confirmed, except the different CVP 36 h postoperatively.

Table 1. Demographic and Surgical Data

Parameter	Study Group	Control Group	*P* Value
Age, yr	67.3 ± 7.6 [67]	65.5 ± 9.9 [69]	0.68
Sex, F/M	11/35	8/38	0.61
BMI, kg/m^2	28.2 ± 3.3 [27.5]	27.7 ± 4.1 [27.0]	0.56
Ejection fraction, %	63.0 ± 11.3 [64.6]	61.9 ± 9.4 [60.0]	0.46
Euroscore (additive)	3.15 ± 1.7 [3.0]	2.78 ± 1.7 [3.0]	0.19
ASA physical status	III: 42 IV: 4	III: 43 IV: 3	
Creatinine clearance, ml/min	96.6 ± 30.5 [92.1]	97.8 ± 27.3 [95.1]	0.85
Bypass time, min	121.2 ± 29.2 [118]	126.7 ± 40.0 [127]	0.45
Cross-clamping time, min	80.4 ± 22.3 [78]	85.7 ± 30.9 [81]	0.35
Duration of surgery, min	259.1 ± 61.2 [263]	270.2 ± 68.0 [270]	0.41
Number of anastomoses	2.1 ± 1.5 [3]	2.46 ± 1.1 [3]	0.31
LIMA grafts	30	40	
RIMA grafts	12	13	
Radial artery grafts	9	8	
Venous grafts	40	43	
Surgical procedures			
ACB only	28	32	
AVR only	12	4	
ACB and AVR	6	10	

Preoperative creatinine clearance was calculated by the Cockroft–Gault formula. Parameters are shown as mean ± SD [median] or absolute numbers.

ACB = aortocoronary bypass; ASA = American Society of Anesthesiologists; AVR = aortic valve repair; BMI = body mass index; LIMA = left internal thoracic artery; RIMA = right internal thoracic artery.

Vasopressor and Catecholamine Support

Circulatory support with norepinephrine was higher in the CG during surgery in the per protocol and ITT population. SG patients intraoperatively received norepinephrine for 214 ± 110 [213] min; ITT: 218 ± 110 [217] min. In the CG, norepinephrine was necessary for 278 ± 113 [283] min (P = 0.008); ITT: 280 ± 145 [297] min (P = 0.010). Cumulative norepinephrine dosage in the SG was 9.0 ± 7.6 [7.7] μg/kg and 14.9 ± 11.1 [13.2] μg/kg in the CG (P = 0.002) during surgery; ITT: 8.9 ± 7.4 [7.7] μg/kg *vs.* 14.8 ± 10.8 [13.4] μg/kg (P = 0.001). No difference in norepinephrine medication was seen during ICU therapy: 5.1 ± 8.4 [0.9] μg/kg in the SG *vs.* 6.7 ± 12.3 [1.4] μg/kg in the CG (P = 0.618); ITT: 5.5 ± 9.1 [1.1] μg/kg *vs.* 7.2 ± 13.0 [1.4] μg/kg (P = 0.457). Inotrope medication with epinephrine showed no differences during surgery: 0.34 ± 0.83 [0] μg/kg in the SG *vs.* 0.42 ± 1.62 [0] μg/kg in the CG (P = 0.77); ITT: 0.32 ± 0.80 [0] μg/kg *vs.* 0.40 ± 1.55 [0] μg/kg (P = 0.783) or during ICU therapy: 0.09 ± 0.59 [0] μg/kg in the SG *vs.* 0.54 ± 3.39 [0] μg/kg in the CG (P = 0.57); ITT: 0.09 ± 0.57 [0] μg/kg *vs.* 0.50 ± 3.25 [0] μg/kg (P = 0.992).

Fluid Therapy, Urine Output, Blood Loss, Transfusion Requirements, and Fluid Balance

Fluid Therapy. All over, from the induction of anesthesia to ICU discharge, there was no significant difference in fluid intake between both groups (11,701 ± 2,175 [11,325] ml [SG] *vs.* 12,313 ± 3,281 [11,746] ml [CG]; P = 0.221). There was also no significant difference in the total amount of crystalloids (SG, 3,698 ± 1,121 [3,700] *vs.* CG, 4,451 ± 2,608 [4,000] ml; P = 0.34). Solely regarding the application of colloids (SG, 3,067 ± 1,165 [3,000] *vs.* CG, 2,117 ± 1,062 [2,000] ml; P < 0.001), a significant difference was detected.

More significant differences appeared in the timing of application of the respective fluids (fig. 4): In the SG, intraoperatively 1,293 ± 501 [1,500] ml of colloids were administered *versus* 880 ± 397 [1,000] ml in the CG (P < 0.001). Application of crystalloids during surgery was not different between both groups (SG, 2,168 ± 554 [2,000] ml *vs.* CG, 2,028 ± 535 [2,000] ml; P = 0.36).

During CPB, fluid therapy was performed at the discretion of the perfusionist. Priming volume was identical in all patients. During CPB, a total of 4,029 ± 873 [3,939] ml of fluids was applied in the SG *versus* 4,608 ± 1,824 [4,268] ml in the CG (P = 0.10).

Also, during ICU therapy, patients of the SG received more colloids 1,774 ± 996 [1,500] ml compared with patients in the CG receiving 1,237 ± 988 [1,000] ml (P = 0.008). Application of crystalloids during ICU was not different between both groups (SG, 1,529 ± 947 [1,500] ml *vs.* CG, 2,423 ± 2,470 [2,000] ml; P = 0.16).

Urine Output. Urine output did not differ between both groups during surgery (1,220 ± 661 [1,060] ml [SG] *vs.* 1,212 ± 540 [1,075] ml [CG]; P = 0.812) or during ICU therapy (2,918 ± 1,249 [2,675] ml [SG] *vs.* 3,695 ± 2,456 [2,945] ml

Table 2. Hemodynamic Parameters

Variables	Group	After Induction of Anesthesia Baseline	After Induction of Anesthesia Optimized	Before Starting CPB	Directly after CPB	ICU Admission	6 h after EOS	12 h after EOS	24 h after EOS	36 h after EOS
MAP, mmHg	SG	66 ± 11.7 [67]	71 ± 9.6 [68]	76 ± 11.6 [76]	71 ± 7.7 [70]	81 ± 13.0 [78]	77 ± 11.0 [75]	79 ± 10.5 [77]	80 ± 10.8 [79]	80 ± 13.0 [78]
	CG	68 ± 10.4 [68]	70 ± 7.7 [69]	76 ± 10.4 [72]	70 ± 7.0 [68]	81 ± 13.8 [77]	78 ± 12.1 [76]	78 ± 8.5 [76]	83 ± 9.8 [84]	82 ± 11.1 [83]
	P Value	0.176*	0.594†	0.777*	0.388†	0.956†	0.770†	0.622†	0.549*	0.685*
HR, beats/min	SG	60 ± 9.4 [60]	59 ± 8.5 [60]	66 ± 14.0 [65]	88 ± 6.2 [88]	86 ± 10.0 [87]	84 ± 12.0 [87]	83 ± 12.1 [83]	82 ± 10.2 [84]	83 ± 10.0 [84]
	CG	58 ± 11.4 [57]	59 ± 11.2 [57]	66 ± 13.8 [62]	90 ± 5.4 [90]	90 ± 9.5 [88]	89 ± 9.8 [90]	87 ± 9.6 [89]	84 ± 12.8 [81]	85 ± 12.3 [83]
	P Value	0.386*	0.950*	0.940*	0.109†	0.212†	0.024†	0.089*	0.665*	0.895*
CVP, mmHg	SG	9.1 ± 3.3 [8.0]	9.8 ± 3.3 [9.5]	9.2 ± 3.7 [9.0]	8.7 ± 2.8 [8.0]	11.7 ± 3.1 [12.0]	10.9 ± 3.2 [11.0]	10.2 ± 3.5 [10.0]	8.9 ± 4.7 [8.0]	7.9 ± 1.2 [8.0]
	CG	8.5 ± 2.7 [9.0]	9.2 ± 1.7 [9.0]	9.2 ± 2.4 [9.0]	9.4 ± 1.9 [9.0]	10.3 ± 2.3 [10.0]	10.1 ± 2.6 [10.0]	8.9 ± 2.7 [9.0]	9.8 ± 3.1 [9.5]	10.8 ± 2.7 [12.0]
	P Value	0.340*	0.816†	0.947†	0.173†	0.011*	0.195*	0.041†	0.505*	0.015*
SVV, %	SG	9.5 ± 4.7 [8.5]	6.6 ± 2.2 [7.0]	7.3 ± 2.7 [7.0]	8.2 ± 2.4 [8.0]	8.4 ± 2.1 [9.0]	n.d.	n.d.	n.d.	n.d.
	CG	10.6 ± 5.7 [9.0]	9.8 ± 4.7 [9.0]	11.5 ± 6.1 [10.0]	11.3 ± 4.0 [11.0]	14.6 ± 4.9 [14.0]				
	P Value	0.500†	<0.001†	<0.001†	<0.001†	<0.001†				
GEDI, ml/m^2	SG	650 ± 123 [637]	673 ± 112 [650]	667 ± 122 [631]	656 ± 118 [600]	701 ± 137 [682]	711 ± 144 [679]	734 ± 130 [762]	807 ± 137 [789]	920 ± 179 [887]
	CG	661 ± 156 [620]	668 ± 155 [621]	638 ± 137 [616]	658 ± 133 [656]	663 ± 134 [641]	683 ± 133 [672]	725 ± 120 [728]	726 ± 133 [741]	828 ± 178 [740]
	P Value	0.818†	0.545†	0.210†	0.960†	0.186*	0.337*	0.757*	0.060*	0.459†
ELWI, ml/kg	SG	7.3 ± 2.0 [7.0]	7.3 ± 2.1 [7.0]	7.2 ± 2.2 [7.0]	7.3 ± 1.6 [7.0]	7.2 ± 1.7 [7.0]	6.2 ± 1.5 [6.0]	6.1 ± 1.7 [6.0]	6.6 ± 1.7 [6.0]	7.9 ± 1.7 [9.0]
	CG	7.0 ± 2.1 [7.0]	7.0 ± 2.1 [7.0]	6.9 ± 2.0 [7.0]	7.6 ± 2.1 [7.0]	7.2 ± 2.1 [7.0]	6.2 ± 1.7 [6.0]	6.6 ± 1.8 [6.0]	6.7 ± 1.7 [6.0]	7.5 ± 1.2 [7.5]
	P Value	0.586†	0.691†	0.649†	0.791†	0.740†	0.796†	0.293†	0.928†	0.597*
CI, l·min^{-1}·m^{-2}	SG	2.3 ± 0.4 [2.3]	2.5 ± 0.3 [2.5]	2.8 ± 0.5 [2.8]	3.2 ± 0.6 [3.1]	3.1 ± 0.7 [3.0]	3.2 ± 0.6 [3.1]	3.3 ± 0.6 [3.2]	3.6 ± 0.5 [3.6]	3.9 ± 1.0 [3.7]
	CG	2.2 ± 0.5 [2.1]	2.2 ± 0.5 [2.1]	2.5 ± 0.5 [2.4]	3.2 ± 0.6 [3.1]	2.9 ± 0.7 [2.8]	3.0 ± 0.5 [3.1]	3.2 ± 0.6 [3.2]	2.9 ± 0.6 [2.9]	3.1 ± 0.5 [3.1]
	P Value	0.106*	<0.001†	0.003*	0.669*	0.186†	0.363*	0.230*	<0.001*	0.046*
SVI, ml/m	SG	39.3 ± 8.9 [38.9]	43.7 ± 7.8 [42.9]	43.2 ± 8.6 [42.9]	36.1 ± 7.2 [34.4]	35.9 ± 7.2 [34.0]	38.0 ± 7.6 [36.1]	40.6 ± 8.4 [41.4]	43.9 ± 5.0 [43.6]	46.6 ± 8.1 [48.3]
	CG	38.1 ± 10.2 [37.3]	38.9 ± 9.9 [37.8]	38.0 ± 8.3 [37.4]	36.0 ± 7.1 [36.1]	32.5 ± 7.6 [32.2]	34.5 ± 6.3 [34.6]	36.7 ± 6.8 [37.5]	35.0 ± 6.6 [35.6]	37.8 ± 9.6 [35.8]
	P Value	0.559*	0.005†	0.004*	0.941*	0.027*	0.020*	0.041†	<0.001*	0.046*
$ScvO_2$, %	SG	n.d.	82.3 ± 6.1 [82.3]	85.3 ± 4.8 [85.5]	85.8 ± 6.2 [85.9]	71.2 ± 9.0 [71.9]	67.6 ± 7.3 [69.5]	70.0 ± 8.5 [70.5]	66.9 ± 6.3 [67.0]	72.7 ± 10.8 [70.9]
	CG		80.5 ± 5.9 [81.0]	81.6 ± 6.7 [82.4]	83.9 ± 7.1 [84.3]	71.1 ± 8.4 [71.8]	66.2 ± 6.8 [66.1]	69.9 ± 5.4 [70.7]	68.1 ± 8.5 [67.1]	69.3 ± 16.7 [69.1]
	P Value		0.144*	0.004*	0.173*	0.954*	0.317*	0.880†	0.593*	0.668*
Norepinephrine, μg/kg	SG	n.d.	n.d.	2.5 ± 2.6 [1.7]	6.9 ± 6.4 [5.5]	9.0 ± 7.6 [7.7]	12.0 ± 9.8 [9.8]	13.6 ± 11.9 [9.8]	14.0 ± 12.2 [10.2]	14.1 ± 12.4 [10.2]
	CG			5.0 ± 3.2 [4.7]	11.0 ± 8.7 [8.6]	14.9 ± 11.1 [13.2]	19.2 ± 14.2 [15.9]	21.3 ± 16.9 [16.5]	21.6 ± 17.8 [16.5]	21.7 ± 17.8 [16.5]
	P Value			<0.001†	0.004†	0.002†	0.005†	0.012†	0.017†	0.018†
Epinephrine, μg/kg	SG	n.d.	n.d.	0.2 ± 0.6 [0.0]	0.2 ± 0.7 [0.0]	0.3 ± 0.8 [0.0]	0.4 ± 1.0 [0.0]	0.4 ± 1.0 [0.0]	0.4 ± 1.0 [0.0]	0.4 ± 1.0 [0.0]
	CG			0.0 ± 0.1 [0.0]	0.1 ± 0.5 [0.0]	0.4 ± 1.6 [0.0]	0.9 ± 4.9 [0.0]	1.0 ± 5.0 [0.0]	1.0 ± 5.0 [0.0]	1.0 ± 5.0 [0.0]
	P Value			0.086†	0.448†	0.770†	0.469†	0.469†	0.469†	0.469†

Norepinephrine and Epinephrine are presented as cumulative doses. All values are presented as mean ± SD [median]. *P* values are unadjusted for multiple testing. The level of significance is 0.05.

* Unpaired *t* test; † Mann–Whitney rank sum test.

CG = control group; CI = cardiac index; CPB = cardiopulmonary bypass; CVP = central venous pressure; ELWI = extra vascular lung water index; EOS = end of surgery; GEDI = global end-diastolic volume index; HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure; n.d. = not determined; $ScvO_2$ = central venous oxygen saturation; SG = study group; SVI = stroke volume index; SVV = stroke volume variation.

[CG]; $P = 0.211$). Neither groups required renal replacement therapy postoperatively.

Blood Loss. Intraoperative blood loss was not quantified because large amounts of shed blood were collected by the suction of the CPB. Postoperative blood loss, quantified as the cumulative amount of fluid loss from the wound drainages, did not differ between both groups (628 ± 493 [525] ml [SG] *vs.* 635 ± 439 [600] ml [CG]; $P = 0.806$).

Transfusion Requirements. There were no significant differences regarding transfusion of packed erythrocytes (2.13 ± 2.83 units in the SG *vs.* 1.83 ± 2.75 units in the CG; $P = 0.47$), platelet concentrates (0.09 ± 0.28 units in the SG *vs.* 0.07 ± 0.25 units in the CG; $P = 0.977$), or fresh-frozen plasma (0.37 ± 1.14 units in the SG *vs.* 0.46 ± 1.36 units in the CG, $P = 0.702$) between both groups during and after surgery.

Overall Fluid Balance. Overall fluid balance during the study period did not differ between both groups (5,718 ± 1,730 [5,460] ml [SG] *vs.* 5,598 ± 1,653 [5,679] ml [CG]; $P = 0.734$).

Mechanical Ventilation and ELWI

Between the groups, there were no differences in pulmonary function, defined as $Pa_{O_2}/F_{I_{O_2}}$ ratio during surgery or at ICU admission, or arterial partial pressure of carbon dioxide (data not shown). In addition, no difference in ELWI could be detected between both groups at any measurement (table 2). Duration of postoperative mechanical ventilation did not differ significantly between both groups (SG, 10.8 ± 4.7 [10.0] h *vs.* CG, 12.5 ± 6.0 [11.0] h; $P = 0.12$).

Laboratory Data

Hemoglobin concentration was lower in the SG after induction of anesthesia (SG, 11.8 ± 1.5 [11.6] mg/dl *vs.* CG, 12.5 ± 1.4 [12.7] mg/dl; $P = 0.012$), before starting CPB (SG, 11.0 ± 1.4 [11.0] mg/dl *vs.* CG, 11.7 ± 1.4 [11.8] mg/dl; $P = 0.008$), 12 h after EOS (SG, 9.5 ± 1.2 [9.2] mg/dl *vs.* CG, 10.3 ± 1.3 [10.1] mg/dl; $P = 0.003$), and 24 h after EOS (SG, 9.6 ± 1.0 [9.4] mg/dl *vs.* CG, 10.3 ± 1.2 [10.1] mg/dl; $P = 0.046$).

Levels of blood lactate were lower in the SG at 12 h (SG, 1.23 ± 0.65 [1.0] mM *vs.* CG, 1.42 ± 0.62 [1.25] mM; $P = 0.048$), 24 h (SG, 1.48 ± 0.48 [1.5] mM *vs.* CG, 1.89 ± 0.48 [1.8] mM; $P = 0.002$), and 36 h (SG, 1.14 ± 0.25 [1.2] mM *vs.* CG, 1.64 ± 0.43 [1.6] mM; $P < 0.001$) after EOS.

Lower levels of alanin aminotransferase and interleukin-6 were detected within the SG reaching statistical significance for alanin aminotransferase (SG, 28.4 ± 14.9 [28.0] U/l *vs.* CG, 43.1 ± 36.9 [32.0] U/l; $P = 0.047$) and interleukin-6 (SG, 116.4 ± 68.0 [104.5] ng/l *vs.* CG, 155.8 ± 81.8 [143.9] ng/l; $P = 0.027$) at 24 h after EOS and for interleukin-6 at 36 h after EOS (SG, 101.1 ± 65.3 [85.3] ng/l *vs.* CG, 177.7 ± 150.8 [139.0] ng/l; $P = 0.016$), respectively.

Postoperative Complications

Overall, less postoperative complications were observed in the SG compared with the CG (40 *vs.* 63; $P = 0.004$). A detailed analysis of complications is given in figure 5 and table 3. The ITT analysis in the SG observed 48 *vs.* 86 complications in the CG ($P = 0.001$).

ICU and Hospital Discharge

Patients in the SG reached the predefined criteria for ICU discharge faster (14.9 ± 6.3 [14.0] h *vs.* 24.0 ± 28.6 [17.0] h in the CG; $P < 0.001$) and were also discharged earlier from ICU (SG, 42.0 ± 18.7 [39.0] h *vs.* CG, 62.9 ± 58.2 [44.0] h; $P = 0.018$; fig. 6). Results from the ITT analysis for reaching ICU discharge criteria revealed 15.3 ± 6.3 [14.0] h for the SG *vs.* 24.7 ± 28.1 [17.5] h for the CG ($P < 0.001$) and for time to real ICU discharge SG, 43.7 ± 19.9 [39.0] h *vs.* CG, 62.8 ± 56.3 [45.5] h; $P = 0.016$). Patients from the SG also reached the predefined criteria for hospital discharge earlier (SG 5.3 ± 3.5 [5.0] days *vs.* CG 6.4 ± 3.3 [6.0] days; $P < 0.001$).

Discussion

This study demonstrates for the first time that a goal-directed hemodynamic therapy initialized immediately before surgery and continued throughout ICU treatment using CI, SVV, and an individualized optGEDI as primary targets led to a clinically significant reduction in postoperative complications in elective cardiac surgical patients. A statistically significant effect in achieving ICU and hospital discharge criteria, and time to real ICU discharge was observed in the per protocol and ITT collective.

In specialized centers, mortality after elective cardiac surgery is known to be low.[37] However, postoperative complications, such as bleeding, cardiovascular, gastrointestinal, or renal impairment, neurological deficits, infections, or disturbances in wound healing often cause protracted need for intensive care treatment and hospital stay. There is an increasing evidence of early optimization of cardiac output, and thus organ blood flow contributes to a reduction in postoperative complications. Furthermore, Hamilton *et al.*[6] recently demonstrated that such a preemptive strategy of hemodynamic optimization may also lead to an improved survival.

A few earlier studies have pointed out that this strategy also holds true for elective cardiac surgery. Mythen *et al.*[8] showed in 1994 that intraoperative optimization of cardiac output increased splanchnic blood flow. Ten years later, McKendry *et al.*[11] demonstrated that a flow-directed hemodynamic algorithm applied postoperatively after cardiac surgery in the ICU reduced complications and length of hospital stay. Our group showed that a concept based on preload and cardiac output optimization commenced during cardiac surgery reduced vasopressor and catecholamine support, and patients met ICU discharge criteria earlier compared with a historical CG.[13] A similar concept, mainly

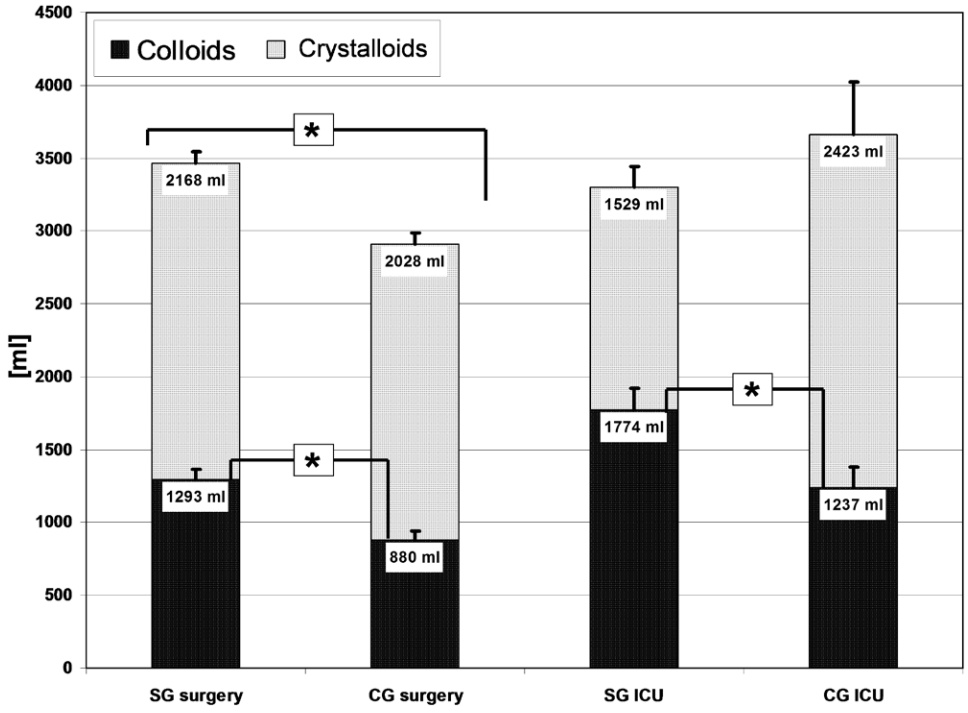

Fig. 4. Cumulative, algorithm-driven crystalloid and colloid infusion during surgery (excluding cardiopulmonary bypass) and intensive care unit (ICU) treatment. Data are presented as mean + standard error of the mean. CG = control group; SG = study group. **P* < 0.001.

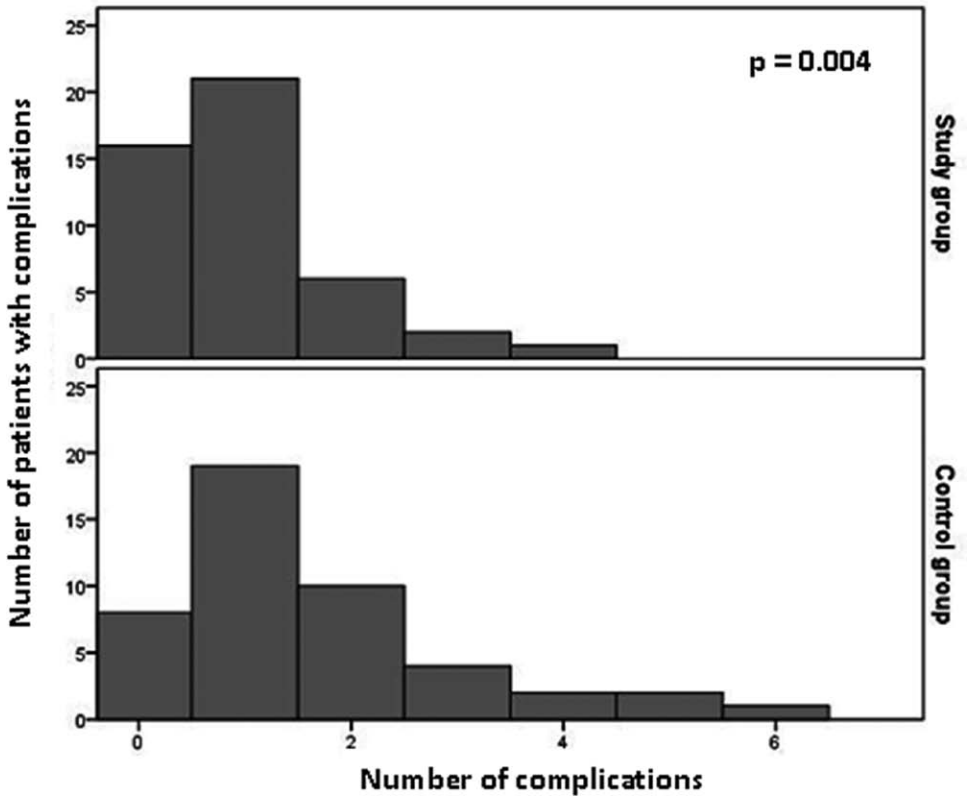

Fig. 5. Postoperative number of complications per patient in each group.

Table 3. Postoperative Complications

Complications	Study Group	Control Group	*P* Value
Total	43	75	0.004
Arrhythmias	18	22	0.41
Hemorrhagic	7	8	1.0
Respiratory	2	3	1.0
Neurological	3	9	0.12
PMD	5	10	0.26
I/R damage	1	7	0.06
Infection	2	6	0.27
ICU readmission	2	2	1.0
Acute kidney injury	3	8	0.2

ICU = intensive care unit; I/R damage = ischemia/reperfusion damage; PMD = postoperative myocardial damage.

based on $ScvO_2$, was described by Smetkin *et al.*[38] in off-pump cardiac surgery. All those studies, however, compared a treatment algorithm implementing parameters of flow or oxygen consumption and compared this with a CG where hemodynamic management was not algorithm driven. We know from both perioperative and intensive care medicine that the implementation of a treatment algorithm and early follow-up of adequate goals lead to improvement of care.[7,13,16,39] Or, as impressively shown by Takala *et al.*[40] in a recent multi-center study, simple implementation of cardiac output monitors fails to improve outcome if no adequate treatment goals are determined. For this investigation, we aimed to also implement a treatment algorithm for the CG with goals that meet broad consensus in critically ill and cardiac surgery patients.[33,41] Thus, our results point toward the fact that the improved outcomes seen in the SG do not simply result from the implementation of a goal-directed strategy, but from the implementation of more appropriate goals.

A high proportion of patients present already before cardiac surgery a compromised cardiac function, and in consequence renal and/or gastrointestinal impairment due to decreased organ perfusion. In addition, CPB used during cardiac surgery leads to ischemia and reperfusion injury, predisposing the patient to cardiac and renal failure, hepatic dysfunction, and postoperative cerebral deficits.

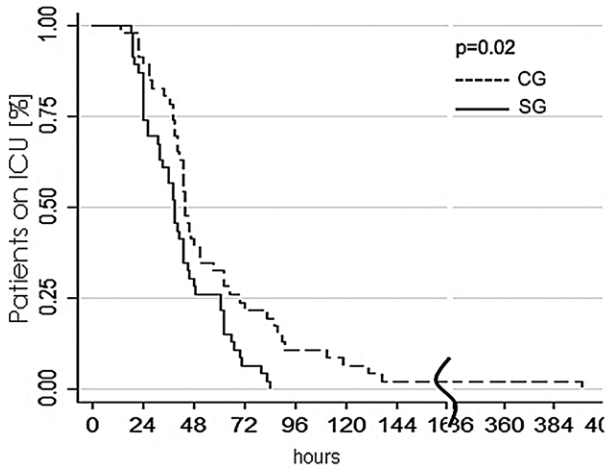

Fig. 6. Duration of intensive care unit (ICU) therapy. CG = control group; SG = study group.

To anticipate organ damage by optimizing preload and blood flow before organ injury, we chose to initiate the algorithm-guided treatment at the beginning of surgery, before CPB. Jhanji *et al.*[17] recently published data on goal-directed hemodynamic optimization in high-risk noncardiac surgery patients. Although their data demonstrated that peripheral, and therefore, most probably organ perfusion was improved in the treatment groups, there was no significant effect on the rate of postoperative complications. In our study, we did not measure peripheral perfusion patterns but moreover assessed the surrogates of cell and organ damage by the enzymatic increases in creatinine kinase and alanin aminotransferase. Although only significant for alanin aminotransferase at a single point of measurement, the overall trend in reduction of the cumulative postoperative amounts highlights the same organ protective effect of our strategy. But in contrast to Jhanji *et al.*, the preemptive optimization, before organ damage, seems to have led to the significant reduction in complications in our study. This clearly emphasizes that peri- and postoperative hemodynamic treatment strategies in high-risk patients and during high-risk procedures must form a conceptional continuum.

The fundamental cornerstone of hemodynamic optimization represents optimization of cardiac preload. However, the discussion about the "optimal tool" to guide preload optimization remains controversial. The cardiac filling pressures, CVP and pulmonary artery occlusion pressure used for decades for this purpose have been decisively questioned regarding their validity.[21–24] Dynamic deviations of the myocardial compliance from the "normal" explain the inappropriateness of CVP and pulmonary artery occlusion pressure to serve as fixed goals for preload optimization. But the so-called volumetric parameters of preload, such as left ventricular end-diastolic area by transesophageal echocardiography or measurement of intrathoracic blood volume or GEDI by thermodilution, also loose their validity in terms of "normal values" as a high variation of these parameters have recently been described for healthy individuals[25] and patients with cardiac surgery.[20,42–44]

More helpful in this regard are the so-called functional parameters of preload, SVV, or pulse pressure variation, which allow individual titration of the patients' optimal preload. Unfortunately, their major limitations are that they are dependent on controlled mechanical ventilation without any spontaneous breathing effort, and that they are invalid in the presence of arrhythmias. Therefore, on their own, these parameters are not useful to guide fluid therapy, if the treatment concept is to be followed not only during surgery but also on the ICU. We therefore chose a two-step concept of hemodynamic assessment within the study: during mechanical ventilation and in the presence of sinus rhythm, SVV

was used to optimize preload. In parallel with this situation, the individual optGEDI was titrated. In all situations where SVV could not be used, *i.e.*, in particular on the ICU when the weaning process from mechanical ventilation was initiated, the individual optGEDI was then used alternatively. This allowed us to follow an individually tailored fluid optimization goal in all clinical circumstances during the perioperative and postoperative treatment.

Recently, in the Scandinavian 6S trial, the use of HES 130/0.42 in patients with sepsis was found to be associated with a higher mortality rate and a higher need for renal replacement therapy.[45] Although with HES 130/0.4 another pharmacon was used and with cardiac surgery patients another collective as in the 6S trial was investigated, a very important issue on the use of synthetical colloids is stressed by taking both, this investigation here and the 6S trial into common consideration: synthetical colloids, and in particular low molecular HES preparations, such as HES 130/0.4 deserve a clear indication, *i.e.*, hypovolemia and a suspected positive volume responsiveness—this was not ensured in the 6S trial. Interestingly, the recently published results of the Australian–New Zealand CHEST trial could not confirm these negative results.[46] But indeed, in the light of the 6S trial, the safety of low molecular HES preparations in cardiac surgery should be addressed by appropriate trials, where—as in the current study—clear indications for their application are part of the protocol.

Of course, our study has limitations. First of all, a blinding of the care-giving physicians regarding the treatment groups was impossible. To reduce a potential bias, assessment of complications and outcome was performed by an independent and blinded investigator, after patients were discharged from hospital. We did not include a second CG that was treated without an algorithm to clarify, if there was any influence on outcome only by the fact that early treatment goals were set by an algorithm. However, this was already shown earlier in different clinical scenarios, so we purposely omitted this approach. Furthermore, we could have compared, whether the same effects could have been reached when such a treatment algorithm was initiated only postsurgery in the ICU, as done by McKendry *et al.*[11] But here also, the clinical rationale for preemptive avoidance of organ damage favored the complete perioperative approach. Finally, we did not evaluate the question whether the goals of fluid status, CI, and perfusion pressure alone or, as proposed by Pearse *et al.*, an additional increase in the oxygen demand to highly physiologic levels should be sought.[16] We did not follow this approach, which was so far described for patients undergoing major abdominal surgery, because of the higher need of catecholamines required for such a regimen seemed inadvisable in cardiac surgery patients with ischemic heart disease. Furthermore, the number of patients who underwent coronary artery bypass grafting, aortic valve replacement, or combined surgery was not identical in both groups. These differences were not statistically significant, thus potential influences on the results remain speculative. The study was not intended to detect differences in single postoperative organ functions, and therefore cannot give definitive answers to this. Here, a higher sample size would be necessary. However, the reduction in predefined categories of complications, and the difference in surrogate parameters of organ dysfunction point toward this direction. In the ITT analysis, data were included while the validity of hemodynamic measurements was not assured. This has to be taken into account when interpreting these ITT results. Finally, a larger scaled, multi-center study is desirable to prove the presented concept in daily clinical practice.

Conclusion

This study has demonstrated for the first time that in elective cardiac surgery, an early goal-directed hemodynamic therapy based on the combination of functional and volumetric parameters of preload, initialized immediately before surgery and continued throughout ICU treatment, can help to reduce postoperative complications. Criteria for ICU and hospital discharge were reached earlier, and ICU discharge time was reduced. Whether long-term outcomes can be improved by such treatment strategies needs further clarification.

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