Original Article

Effects of colloid-based (hydroxyethylstarch 6% 130/0.42, gelafundin 4%) and crystalloid-based volume regimes in cardiac surgery: a retrospective analysis

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Background: The restriction of hydroxyethylstarch (HES) necessitated changes in volume management in cardiac surgery, increasing the use of gelatin (GELA) and crystalloid (CRYS) mono strategies.

Methods: This retrospective study evaluated the effects of changed volume replacement management to a GELA or CRYS mono therapy on mortality, acute kidney injury (AKI), blood loss, and transfusion in cardiac surgery patients with at least one coronary artery bypass grafting (CABG) at a university hospital. Three groups (HES n=938, GELA n=397, CRYS n=205) were derived from 1,540 patients with complete data sets. Data were analyzed by multiple regression models.

Results: Patients had similar risk profiles, comorbidities, and preoperative routine diagnostics prior to surgery. No difference was observed in mortality and AKI. HES treated patients showed highest blood loss, followed by GELA while CRYS patients had the lowest (P<0.0001). Patients in the HES group had highest transfusion of packed red blood cells (PRBCs) and platelet concentrates (PCs), followed by GELA, whereas CRYS had the lowest (P<0.0001). Fresh frozen plasma (FFP) transfusion, administration of fibrinogen, and prothrombin complex concentrates (PCCs) were highest in HES group. CRYS showed the shortest time of mechanical ventilation (P<0.0001) and left the intensive care unit (ICU) significantly earlier (P<0.0001). Multivariable regression analysis found that colloid volume significantly predicted hospital mortality and renal replacement therapy (RRT), but not AKI.

Conclusions: Administration of crystalloids without any colloid showed no differences in mortality or AKI, but less blood loss and transfusion. Colloids should be considered critically and further studies should investigate effects of GELA in cardiac surgery.

Keywords: Gelatin; hydroxyethylstarch (HES); blood loss; transfusion; mortality; acute kidney injury (AKI)

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Introduction

Crystalloids and colloids are given to maintain blood pressure and also to avoid blood product transfusions, in which even moderate bleeding is seen to be associated with an increased morbidity and mortality especially after cardiac surgery (1). Colloids have been used during cardiac surgery because of longer perseverance intravascularly compared to crystalloids (2,3). Especially hydroxyethylstarch (HES) had been used during cardiac surgery for decades, but in 2013, the European Medical Association (EMA) restricted its application which mandated changes in common used volume regimes (4). The restriction was based on higher mortality rates and acute kidney injury (AKI) in septic and critically ill patients receiving HES (5,6). But the use of last generation HES (6% 130/0.42 tetrastarch) has been discussed to be safe in comparison to other colloids or crystalloids especially for cardiac surgery (7). After the restriction for HES, the overall administration of colloids decreased of which gelatin (GELA) was increasingly used (8). But GELA is also critically discussed to be associated with need of higher noradrenalin dosages compared to tetrastarches (9), bleeding and the need for transfusion (3,10,11). The effectiveness and safety of GELA is currently being investigated in an ongoing multi-center study in critically ill patients (12).

In this retrospective study, we aimed to evaluate the effects of changed volume replacement management after the restriction of HES to GELA or to CRYS mono regimen. Because the EMA restricted HES due to death and kidney injury, we focused primarily on mortality and AKI and secondarily on blood loss, transfusions, hemodynamic support, and intensive care unit length of stay (ICU LOS). We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-450/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of the University of Ulm (approval ID 50-17) and individual consent for this retrospective analysis was waived. Relying entirely upon existing data, the committee waived the need for retroactive study-specific patient consent. All consecutive patients who were treated at least by coronary artery bypass grafting (CABG) between January 2012 and December 2014 were assessed for eligibility to cover similar pre- and post-restriction periods in clinical practice. Patients with insufficient data coverage or various colloid administration were excluded. Study data were extracted from routine patient records and anonymized.

The observation period ended on postoperative day (POD) 3, except mortality which was additionally calculated at the end of intensive care and at discharge from hospital, as well as the length of ICU stay. Primary outcomes were mortality and AKI [according to the Acute Kidney Injury Network (AKIN) criteria] (13). Secondary outcomes were blood loss, transfusions, hemodynamic support (vasopressor administration per time normalized to body weight), mechanical ventilation, and the ICU LOS.

The determinants were type and volume of the administered volume replacement solutions. Three subgroups were selected for the present analysis based on the exposure:

(I) Patients who received just crystalloid but no colloid (CRYS);
(II) Patients who received gelafundin 4% (B.Braun, Gelafundin 4%, Melsungen), but no other colloid in addition to crystalloid (GELA); and
(III) Patients who received tetraspan 6% (B.Braun, Tetraspan® 6 % Infusionslösung, Melsungen, Germany), but no other colloid in addition to crystalloid (HES).

The standard of blood product administration was carried out according to the currently applicable cross-sectional guidelines of the German Medical Association for therapy with blood components and plasma derivatives with a focus on patient-specific threshold values based especially on a combined diagnosis of laboratory parameters, echocardiography and course of operation. The standard surgical procedure was also the administration of tranexamic acid in all operations with at least one coronary artery bypass.

Statistical analysis

Data were analyzed with the software R (R Foundation for Statistical Computing, Vienna, Austria) and add-on packages as specified below. Statistical tests and effects of factors were considered significant if P was less than 0.05.

Univariate analyses

Normalized data such as doses per body weight, cumulative

data as the sum of administered substances or of excreted/drained volumes within the observation period, and other derived data were computed from the recorded data. Normality of continuous numeric data was assessed with the Shapiro-Wilk test and visualized by Q-Q plots. Non-normally distributed data are reported as median (first quartile to third quartile). Groups were compared with the Conover-Iman test using a Holm correction for post-hoc tests (conover.test package). Count data were evaluated with χ^2 tests followed by pairwise two-proportion z-tests with Bonferroni correction for multiple testing. Ordinal data were assessed with cumulative link models and Tukey post-tests (ordinal and emmeans packages).

Longitudinal data

Time courses of continuous numeric data were fitted with linear mixed-effects models (nlme package) using time and group with an interaction term as fixed effects and patients as random intercepts. If there were significant effects of group or of the time: group interaction, data were further investigated for each level of time using the Conover-Iman test to identify pairwise differences between the groups. Colloid volumes were compared with the Wilcoxon rank sum test at each level of time as the CRYS patients did not receive colloids per definition. Longitudinal data of vasopressor and volume administration were characterized by increasing numbers of patients over time who did not receive further doses owing to improving hemodynamic stability or ICU discharge. Count data were derived from the dose data indicating the number of patients receiving a particular compound at each level of time. These data were evaluated as binary longitudinal data using generalized estimating equations (geepack package) to assess effects of group and time. Differences between groups at individual time points were identified by χ^2 tests. The doses of patients still receiving them were then analyzed with mixed-effects models as described above.

Multiple regression analysis

The primary outcome parameters hospital survival, renal replacement therapy (RRT), and AKI were analyzed by calculating multiple logistic regression models (generalized linear regression using the logit link function). Selection of factors for the initial models was guided by clinical experience and by univariate correlation analyses. Correlations between numerical factors and the dichotomous outcome variables were assessed with point-biserial correlation coefficients. Correlations between dichotomous or categorical factors and the outcome variables were analyzed by χ^2 tests. Potential confounders that were considered in regression analyses included the baseline data age, gender, acute coronary syndrome, chronic obstructive pulmonary disease (COPD), dialysis, ejection fraction, emergency surgery, hyperlipidemia, insulin-dependent and non-insulin-dependent diabetes mellitus, myocardial infarction within the last two weeks, previous myocardial infarction, heart failure according to the New York Heart Association (NYHA) classification, RRT, reoperation, stroke, serum creatinine, platelet count, antiplatelet therapy, and vasopressors. Perioperative factors included concomitant valve surgery, the number of anastomosed vessels during CABG, hematocrit, cumulative blood losses and vasopressor doses, as well as administration of blood products including packed red blood cells (PRBCs), platelet concentrates (PCs), prothrombin complex concentrate (PCC), and fresh frozen plasma (FFP). The initial models were simplified step-wise until a minimum of Akaike's information criterion was reached. Regression results are reported as exponentiated estimates (adjusted odds ratios) calculated from the raw data and from scaled/centered continuous numeric data. Confounding was assessed by removing potential confounding factors from the minimal adequate model one at a time. Confounding was assumed to be present if the scaled/centered estimate β of the exposure variable changed by 10% or more when removing a factor.

Results

Patient population

A total of 1,540 patient datasets were included covering >98.8% of all CABG patients in the predefined time range (*Table 1*). Groups were comparable in all preoperative parameters except antiplatelet therapy (P=0.021).

Mortality

Mortality was without differences between groups (*Table 2*, *Figure 1*). We calculated a multiple logistic regression based on demographic and perioperative factors from sufficiently complete datasets of n=1,432 patients to assess the role of colloids in hospital survival. The minimal adequate model {χ^2[14]=161.075, P<0.001, McFadden Pseudo-R^2=0.620} is

Table 1 Characteristics at baseline of patients who received CRYS, GELA, and HES as sole volume replacement

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Age (years)	69 (61 to 76)	70 (63 to 75)	71 (62 to 76)	0.75
Weight (kg)	84 (75 to 93)	83 (71 to 92)	81 (72 to 92)	0.27
BMI (kg/m^2)	28.0 (25.0 to 31.2)	27.8 (24.9 to 30.5)	27.4 (24.9 to 30.5)	0.30
Gender				0.74
Male	160 (78%)	319 (80%)	738 (79%)	
Female	45 (22%)	78 (20%)	200 (21%)	
EuroScore II	1.82 (1.08 to 3.46)	2.13 (1.17 to 3.97)	2.06 (1.17 to 3.83)	0.21
SAPS II	28.0 (24.0 to 32.5)	29.0 (25.0 to 33.0)	29.0 (24.0 to 33.0)	0.85
NYHA				0.17
I	18 (9%)	21 (5%)	44 (5%)	
II	51 (25%)	114 (29%)	246 (26%)	
III	117 (57%)	237 (60%)	551 (59%)	
IV	18 (9%)	23 (6%)	90 (10%)	
EF				0.53
>50%	145 (71%)	262 (66%)	651 (68%)	
31% to 50%	52 (25%)	89 (22%)	207 (22%)	
21% to 30%	5 (2%)	23 (6%)	54 (6%)	
20% and less	1 (0%)	8 (2%)	24 (3%)	
Emergency	64 (32%)	128 (32%)	273 (29%)	0.09
Dialysis prior	6 (3%)	3 (1%)	15 (2%)	0.12
Antiplatelet therapy prior	180 (88%)	346 (87%)	771 (82%)	0.021
Marcumar prior	10 (5%)	21 (5%)	56 (6%)	0.36
Vasopressors prior	1 (0%)	7 (2%)	14 (1%)	0.19
Hypertension	191 (93%)	365 (92%)	848 (90%)	0.46
Diabetes mellitus	67 (33%)	137 (35%)	281 (30%)	0.24
Hemoglobin ($g \cdot dL^{-1}$)	14.0 (12.7 to 15.0)	13.7 (12.5 to 14.9)	14.1 (12.7 to 15.0)	0.16
Hematocrit (%)	41 (38 to 44)	41 (38 to 44)	42 (38 to 44)	0.30
Thrombocytes ($10^9 \cdot L^{-1}$)	195 (166 to 236)	202 (167 to 244)	201 (168 to 242)	0.61
Glomerular filtration rate ($mL \cdot min^{-1}$ per 1.73 m^2)	50 (31 to 57)	50 (40 to 55)	51 (40 to 56)	0.58
Creatinine ($\mu mol \cdot L^{-1}$)	88 (77 to 102)	86 (75 to 104)	85 (74 to 99)	0.07
ALT ($U \cdot L^{-1}$)	27.5 (21.0 to 38.0)	26.0 (19.0 to 35.0)	26.0 (19.0 to 37.0)	0.78
AST ($U \cdot L^{-1}$)	24.0 (21.0 to 30.0)	26.0 (21.0 to 33.0)	25.0 (21.0 to 32.0)	0.41
γ-GT ($U \cdot L^{-1}$)	37.0 (25.0 to 57.0)	38.5 (25.0 to 68.8)	36.0 (25.0 to 56.0)	0.25
AP ($IU \cdot L^{-1}$)	68.5 (57.8 to 83.0)	67.0 (57.0 to 82.0)	66.5 (56.0 to 80.0)	0.26

Data indicate frequencies as number of patients (% within group) unless specified otherwise. Continuous data are presented as median (1st quartile to 3rd quartile). P values <0.05 indicate significant differences between groups. CRYS, crystalloids; GELA, gelafundin; HES, hydroxyethyl starch; BMI, body mass index; SAPS, Simplified Acute Physiology Score; NYHA, New York Heart Association; EF, ejection fraction; ALT, alanine-aminotransferase; AST, aspartate-amino-transferase; γ-GT, gamma-glutamyl-transferase; AP, alkaline phosphatase.

Table 2 Peri- and postoperative data of patients who received CRYS, GELA, and HES as sole volume replacement

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Mortality				
72 h	2 (1%)	4 (1%)	8 (1%)	0.958
ICU	2 (1%)	7 (2%)	24 (3%)	0.305
hospital	2 (1%)	7 (2%)	24 (3%)	0.305
ICU stay (d)	a	b	c	<0.0001
0 to 2	47 (23%)	70 (18%)	109 (12%)	
3 to 5	129 (63%)	232 (58%)	520 (55%)	
6 to 10	26 (13%)	82 (21%)	247 (26%)	
>10	2 (1%)	11 (3%)	59 (6%)	
Mechanical ventilation (h)	11.0 (9.0 to 13.3)a	11.0 (9.0 to 16.0)b	12.0 (10.0 to 17.3)c	<0.0001
Acute kidney injury				0.061
none	143 (70%)	260 (65%)	574 (61%)	
AKIN stage 1	43 (21%)	90 (23%)	230 (25%)	
AKIN stage 2	6 (3%)	14 (4%)	45 (5%)	
AKIN stage 3	10 (5%)	26 (7%)	64 (7%)	
Renal replacement therapy	8 (4%)	24 (6%)	62 (7%)	0.341
PRBC units	a	b	c	<0.0001
0	150 (73%)	230 (58%)	422 (45%)	
1 to 5	51 (25%)	149 (38%)	414 (44%)	
6 to 10	4 (2%)	13 (3%)	84 (9%)	
>10	0 (0%)	5 (1%)	18 (2%)	
PC units	a	a	b	<0.0001
0	196 (96%)	375 (94%)	760 (81%)	
1 to 3	7 (3%)	20 (5%)	156 (17%)	
4 to 10	2 (1%)	2 (1%)	20 (2%)	
>10	0 (0%)	0 (0%)	2 (0%)	
Fibrinogen units	a	a	b	<0.0001
0	199 (97%)	380 (96%)	825 (88%)	
1 to 5	6 (3%)	15 (4%)	943(10%)	
6 to 10	0 (0%)	2 (1%)	18 (2%)	
>10	0 (0%)	0 (0%)	2 (0%)	
FFP units	ab	a	b	0.0023
0	201 (98%)	388 (98%)	881 (94%)	
1 to 3	3 (1%)	5 (1%)	14 (1%)	
4 to 10	1 (1%)	4 (1%)	35 (4%)	
>10	0 (0%)	0 (0%)	8 (1%)	

Table 2 (*continued*)

Table 2 (*continued*)

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
PCC	3 (1%)a	11 (3%)a	69 (7%)b	<0.0001
PCC (IU)	3,500 (3,250 to 4,750)	3,000 (2,000 to 4,000)	2,000 (2,000 to 4,000)	0.45
Hematocrit (%)				0.0001
Baseline	41 (38 to 44)	41 (38 to 44)	42 (38 to 44)	0.30
Postoperative	31 (28 to 34)a	29 (27 to 31)b	28 (26 to 31)c	<0.0001
6 h postoperative	33 (30 to 35)a	31 (29 to 33)b	31 (28 to 33)c	<0.0001
Postoperative day 1	32 (30 to 35)a	30 (28 to 33)b	31 (28 to 33)b	<0.0001
Postoperative day 2	29 (26 to 32)ab	28 (26 to 31)a	29 (27 to 32)b	<0.0001
Postoperative day 3	29 (26 to 31)ab	28 (26 to 31)a	29 (26 to 31)b	0.01
Hemoglobin ($g \cdot dL^{-1}$)				<0.0001
Baseline	14.0 (12.7 to 15.0)	13.7 (12.5 to 14.9)	14.1 (12.7 to 15.0)	0.16
Postoperative	10.5 (9.6 to 11.3)a	9.7 (9.0 to 10.6)b	9.6 (8.9 to 10.4)b	<0.0001
6 h postoperative	11.2 (10.1 to 12.0)a	10.5 (9.8 to 11.3)b	10.3 (9.5 to 11.2)c	<0.0001
Postoperative day 1	10.9 (10.0 to 11.9)a	10.3 (9.5 to 11.1)b	10.5 (9.6 to 11.2)b	<0.0001
Postoperative day 2	9.7 (8.9 to 11.0)a	9.5 (8.7 to 10.3)b	9.8 (9.1 to 10.6)a	<0.0001
Postoperative day 3	9.6 (8.9 to 10.7)a	9.3 (8.6 to 10.3)b	9.6 (8.9 to 10.3)a	0.01
Platelets ($10^9 \cdot L^{-1}$)				0.136
Baseline	195 (166 to 236)	202 (167 to 244)	201 (168 to 242)	0.61
Postoperative	148 (123 to 175)a	133 (106 to 162)b	126 (101 to 160)c	<0.0001
6 h postoperative	161 (128 to 192)a	151 (122 to 186)b	144 (115 to 180)b	<0.0001
Postoperative day 1	156 (128 to 190)	150 (121 to 183)	148 (124 to 183)	0.20
Postoperative day 2	138 (115 to 167)	138 (113 to 169)	137 (112 to 171)	0.99
Postoperative day 3	145 (116 to 178)	143 (115 to 176)	140 (112 to 173)	0.22
Creatinine ($\mu mol \cdot L^{-1}$)				0.462
Baseline	88 (77 to 102)	86 (75 to 104)	85 (74 to 99)	0.07
Postoperative	91 (77 to 108)	91 (77 to 107)	89 (76 to 107)	0.78
6 h postoperative	88 (76 to 107)	89 (75 to 106)	89 (76 to 108)	0.96
Postoperative day 1	86 (74 to 108)	90 (74 to 113)	90 (74 to 112)	0.58
Postoperative day 2	92 (79 to 118)	94 (76 to 124)	95 (77 to 125)	0.86
Postoperative day 3	94 (78 to 125)	93 (75 to 137)	98 (78 to 137)	0.35
Urea ($mmol \cdot L^{-1}$)				0.406
Baseline	5.60 (4.70 to 7.15)	5.80 (4.70 to 7.40)	5.70 (4.60 to 7.40)	0.56
Postoperative	5.30 (4.30 to 6.10)	5.30 (4.40 to 6.60)	5.40 (4.40 to 6.80)	0.30
6 h postoperative	5.50 (4.40 to 6.60)	5.60 (4.60 to 7.20)	5.70 (4.60 to 7.40)	0.06
Postoperative day 1	5.50 (4.50 to 7.23)	5.90 (4.60 to 7.98)	5.90 (4.60 to 8.10)	0.17

Table 2 (*continued*)

Table 2 (*continued*)

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Postoperative day 2	6.50 (5.30 to 9.20)	6.80 (5.10 to 9.50)	6.95 (5.00 to 9.50)	0.86
Postoperative day 3	7.30 (5.40 to 10.88)	7.20 (5.10 to 10.90)	8.10 (5.60 to 11.70)	0.08
GFR (mL·min^{-1} per 1.73 m^2)				0.011
Baseline	50 (31 to 57)	50 (40 to 55)	51 (40 to 56)	0.58
Postoperative	54 (43 to 70)	51 (42 to 55)	52 (42 to 57)	0.11
6 h postoperative	53 (42 to 71)a	48 (37 to 54)b	49 (40 to 56)ab	0.01
Postoperative day 1	47 (32 to 57)ab	42 (31 to 51)a	47 (38 to 54)b	0.02
Postoperative day 2	39 (28 to 51)	41 (29 to 51)	43 (32 to 51)	0.15
Postoperative day 3	40 (28 to 51)	39 (29 to 46)	40 (31 to 49)	0.50
MAP (mmHg)				0.0002
Preoperative	98 (90 to 107)	95 (87 to 106)	97 (88 to 106)	0.26
Intraoperative	76 (72 to 79)a	73 (68 to 77)b	74 (70 to 78)a	<0.0001
Postoperative	77 (73 to 83)	78 (73 to 86)	77 (70 to 85)	0.09
6 h postoperative	78 (73 to 83)a	77 (72 to 84)ab	77 (72 to 83)b	0.01
12 h postoperative	80 (77 to 87)a	78 (73 to 83)b	78 (73 to 83)b	<0.0001
18 h postoperative	82 (77 to 87)a	80 (73 to 87)b	80 (75 to 86)b	<0.0001
Postoperative day 1	81 (77 to 87)a	78 (73 to 83)b	78 (73 to 83)b	<0.0001
Postoperative day 2	81 (76 to 88)	80 (73 to 87)	80 (75 to 86)	0.34
Postoperative day 3	83 (78 to 90)	82 (73 to 88)	81 (75 to 90)	0.07

Data indicate frequencies as number of patients (% within group) unless specified otherwise. Continuous data are presented as median (1st quartile to 3rd quartile). P values <0.05 indicate significant differences between groups. Pairwise comparison post test results are indicated as letters (a, b, c); values of groups not sharing a letter are significantly different. CRYS, crystalloids; GELA, gelafundin; HES, hydroxyethyl starch; ICU, intensive care unit; AKIN, acute kidney injury network; PRBC, packed red blood cells; PC, platelet concentrate; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; GFR, glomerular filtration rate; MAP, mean arterial pressure.

summarized in Tables S1,S2. Each liter of colloid solution decreased the adjusted odds of survival by a factor of 0.501 (95% CI : 0.354 to 0.710, P<0.001). The type of colloid was not part of the minimal adequate model, indicating similar effects of both tetraspan and gelafundin. Total infusion volume exerted a protective effect. Each liter of total volume increased the adjusted odds of survival by a factor of 1.216 (95% CI: 1.007 to 1.468, P=0.042). Cumulative blood losses at 18 h postoperative, intraoperative PRBC transfusions, cumulative norepinephrine administration on the operative day, and PCC administration were tested as potential confounders which are known to affect mortality, but may also have influenced colloid administration. The scaled and centered estimate of the effect of total colloid volume were altered by factors of 1.0, 0.92, 1.06, and 1.09, respectively, indicating that none of these factors acted as a confounder.

AKI

GFR differed between groups (P=0.011), but AKI (P=0.061) and RRT (P=0.341) did not differ between groups (*Table 2*, *Figure 2*). A multiple logistic regression model of AKI as a function of demographic and perioperative factors was calculated to estimate the influence of volume therapy. Sufficiently complete datasets of 996 patients were available for this analysis. Tables S3,S4 summarize the minimal adequate model {χ^2[19]=274.594, P<0.001, McFadden

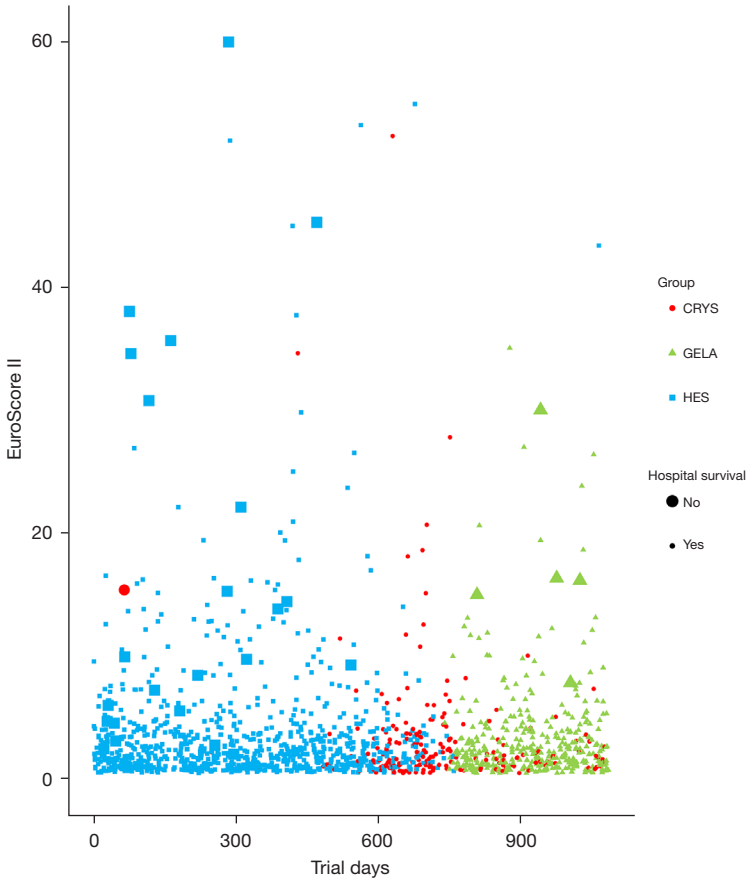

Figure 1 Volume regimen (CRYS, crystalloid, red points; GELA, gelatin, green triangle; HES, tetraspan, blue square) depicted in context with pre-operative assessment of EuroScore II and outcome (survivors small/non-survivors big symbols) over time. CRYS, crystalloids; GELA, gelatin; HES, hydroxyethylstarch.

Pseudo-R^2=0.210}. Total volume and total colloid volume were retained in the model, but their respective adjusted odds ratio estimates of 1.037 (95% CI: 0.994 to 1.082, P=0.089) and 1.097 (95% CI: 0.987 to 1.221, P=0.087) for each liter administered were not considered significant.

Blood loss

The type of volume replacement was associated with different volumes of blood loss over time (P<0.0001) (*Table 3*, *Figure 3*). HES showed the highest fraction of patients losing blood at 18h postoperative and later (P<0.0001) (*Table 3*). Platelet counts were lowest in HES and highest in CRYS postoperatively (P<0.0001) (*Figure 4*).

HES patients had the lowest hematocrit, and GELA was lower than CRYS postoperative and 6h postoperative (P<0.0001, *Figure 4*). Hemoglobin concentrations were lower in colloids compared to CRYS postoperatively until POD1 (P<0.0001) and were lowest in GELA on POD2 and POD3 (P<0.0001).

Blood products

Patients receiving PRBC transfusions were highest in the HES group (55%) followed by GELA (42%) and CRYS (27%) groups (P<0.0001, *Table 2*). PCs were administered by 19% of the HES patients, 6% of the GELA patients, and 4% of the CRYS patients (P<0.0001). Fibrinogen was administered to a higher fraction of HES patients (12%, P<0.0001) compared to GELA (4%) and CRYS (3%). PCC was administered more frequently in HES than in GELA or CRYS patients (P<0.0001) (*Table 2*).

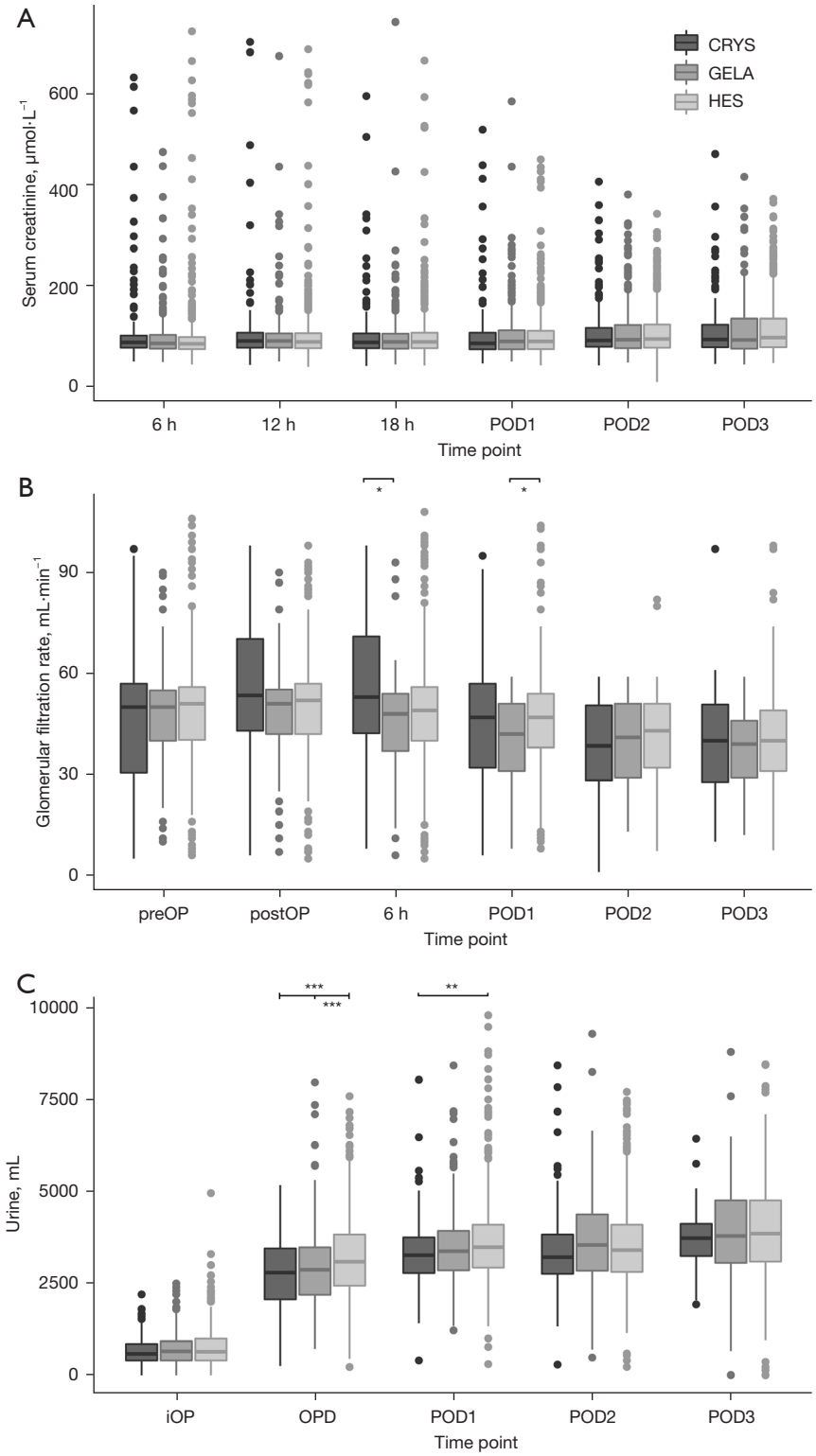

Figure 2 Time courses of renal function markers in patients who received only CRYS, crystalloids and GELA, and crystalloids and HES as volume replacement. (A) Serum creatinine levels; (B) glomerular filtration rate; (C) urine excretion. *, P<0.05; **, P<0.01; ***, P<0.001. Time point definitions: preOP, preoperative; postOP, postoperative; times in hours (h) indicate time after end of surgery; OPD, operation day; POD, postoperative day; iOP, intraoperative. CRYS, crystalloids; GELA, gelatin; HES, hydroxyethylstarch.

Table 3 Fluid input, output, and balance in patients who received CRYS, GELA, and HES as sole volume replacement

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Patients receiving crystalloids				<0.0001
Intraoperative	204 (100%)	396 (100%)	934 (100%)	0.9
OP day	204 (100%)ab	394 (99%)a	938 (100%)b	0.04
Postoperative day 1	157 (77%)a	328 (83%)a	889 (95%)b	<0.0001
Postoperative day 2	92 (45%)a	198 (50%)a	688 (73%)b	<0.0001
Postoperative day 3	53 (26%)a	129 (32%)a	500 (53%)b	<0.0001
Crystalloid administration (mL)				<0.0001
Intraoperative	2,000 (2,000 to 2,512)a	2,000 (2,000 to 2,000)a	2,000 (1,000 to 2,000)b	<0.0001
OP day	3,850 (3,125 to 4,625)a	3,750 (3,000 to 4,625)a	2,900 (2,125 to 3,750)b	<0.0001
Postoperative day 1	3,465 (2,721 to 4,000)a	3,392 (2,738 to 4,143)a	3,000 (2,400 to 3,874)b	<0.0001
Postoperative day 2	2,016 (1,504 to 2,802)a	2,418 (1,750 to 3,016)b	2,313 (1,721 to 3,000)ab	0.04
Postoperative day 3	1,624 (1,224 to 2,460)	2,016 (1,320 to 3,000)	2,050 (1,472 to 2,701)	0.05
Total crystalloid administration (mL)	9,829 (7,510 to 11,862)	10,055 (7,641 to 13,460)	10,543 (8,234 to 12,756)	0.05
Patients receiving colloids				<0.0001
Intraoperative	n/a	339 (85%)	795 (85%)	0.83
OP day	n/a	157 (40%)	754 (80%)	<0.0001
Postoperative day 1	n/a	71 (18%)	573 (61%)	<0.0001
Postoperative day 2	n/a	18 (5%)	307 (33%)	<0.0001
Postoperative day 3	n/a	7 (2%)	148 (16%)	<0.0001
Colloid administration (mL)				<0.0001
Intraoperative	n/a	500 (500 to 1,000)	500 (500 to 1,000)	0.05
OP day	n/a	500 (500 to 1,000)	1,000 (500 to 1,500)	<0.0001
Postoperative day 1	n/a	500 (500 to 500)	1,000 (500 to 1,000)	<0.0001
Postoperative day 2	n/a	500 (500 to 500)	500 (500 to 1,000)	0.38
Postoperative day 3	n/a	500 (500 to 500)	500 (500 to 1,000)	0.48
Total colloid administration (mL)	n/a	1,000 (500 to 1,500)	2,000 (1,000 to 3,038)	<0.0001
Overall volume replacement (mL)				<0.0001
Intraoperative	2,000 (2,000 to 2,500)a	2,500 (2,000 to 3,000)b	2,500 (1,500 to 3,000)c	<0.0001
OP day	3,825 (3,125 to 4,625)	4,000 (3,100 to 4,922)	3,750 (3,000 to 4,625)	0.05
Postoperative day 1	3,000 (1,225 to 3,960)a	3,170 (2,016 to 4,057)b	3,500 (2,814 to 4,500)c	<0.0001
Postoperative day 2	0 (0 to 2,016)a	0 (0 to 2,482)b	2,130 (0 to 3,016)c	<0.0001
Postoperative day 3	0 (0 to 480)a	0 (0 to 1,298)b	809 (0 to 2,343)c	<0.0001
Total overall volume replacement (mL)	9,829 (7,510 to 11,862)a	11,125 (8,500 to 14,468)b	12,746 (10,326 to 15,576)c	<0.0001

Table 3 (*continued*)

Table 3 (*continued*)

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Patients with blood loss				<0.0001
6 h postoperative	203 (99%)	395 (99%)	933 (99%)	0.70
12 h postoperative	202 (99%)	391 (98%)	925 (99%)	1.0
18 h postoperative	195 (95%)a	372 (94%)b	920 (98%)c	0.0002
Postoperative day 1	154 (75%)a	325 (82%)a	863 (92%)b	<0.0001
Postoperative day 2	41 (20%)a	110 (28%)a	454 (48%)b	<0.0001
Postoperative day 3	11 (5%)a	41 (10%)a	201 (21%)b	<0.0001
Blood loss (mL)				0.0001
6 h postoperative	190 (130 to 260)a	210 (155 to 320)b	260 (200 to 420)c	<0.0001
12 h postoperative	110 (70 to 160)a	120 (72 to 170)a	130 (90 to 210)b	<0.0001
18 h postoperative	110 (60 to 170)a	110 (63 to 180)a	120 (70 to 190)b	0.01
Postoperative day 1	275 (160 to 440)	250 (170 to 420)	270 (150 to 420)	0.87
Postoperative day 2	0 (0 to 128)a	20 (0 to 275)a	60 (0 to 270)b	<0.0001
Postoperative day 3	0 (0 to 0)	0 (0 to 100)	0 (0 to 140)	0.06
Total blood loss (mL)	660 (410 to 940)a	750 (500 to 1,090)b	940 (670 to 1,400)c	<0.0001
Urine (mL)				<0.0001
Intraoperative	580 (400 to 850)	650 (400 to 925)	640 (400 to 995)	0.09
OP day	2,790 (2,065 to 3,455)a	2,870 (2,190 to 3,485)a	3,090 (2,440 to 3,830)b	<0.0001
Postoperative day 1	3,270 (2,780 to 3,750)a	3,380 (2,855 to 3,930)ab	3,490 (2,930 to 4,100)b	<0.0001
Postoperative day 2	3,215 (2,758 to 3,830)	3,550 (2,845 to 4,383)	3,410 (2,810 to 4,100)	0.14
Postoperative day 3	3,730 (3,248 to 4,125)	3,790 (3,060 to 4,760)	3,855 (3,095 to 4,760)	0.54
Total urine (mL)	7,610 (5,450 to 11,670)a	8,540 (6,110 to 13,420)b	12,250 (8,386 to 15,098)c	<0.0001
Cumulative volume balance (mL)				<0.0001
Intraoperative	1,350 (840 to 2,010)a	1,910 (1,342 to 2,620)b	1,550 (851 to 2,260)c	<0.0001
OP day	2,235 (1,335 to 3,090)a	2,860 (1,850 to 3,945)b	2,126 (1,176 to 3,148)a	<0.0001
Postoperative day 1	2,110 (1,080 to 3,050)a	2,669 (1,525 to 3,920)b	2,024 (858 to 3,335)a	<0.0001
Postoperative day 2	1,630 (405 to 2,630)a	2,313 (866 to 3,590)b	1,442 (31 to 2,899)a	<0.0001
Postoperative day 3	1,393 (–70 to 2,460)a	1,896 (245 to 3,267)b	708 (–873 to 2,343)c	<0.0001

Data indicate frequencies as number of patients (% within group) unless specified otherwise. Continuous data are presented as median (1st quartile to 3rd quartile). P values <0.05 indicate significant differences between groups. Pairwise comparison post test results are indicated as letters (a, b, c); values of groups not sharing a letter are significantly different. CRYS, crystalloids; GELA, gelafundin; HES, hydroxyethyl starch; OP, operative.

Hemodynamic therapy

Mean arterial pressure (MAP) was lowest intraoperatively, with GELA patients slightly below other groups (P<0.0001) (*Table 2*).

Total replacement volumes were higher in colloid groups compared to CRYS in POD1 and later (P<0.0001) (*Table 3*). HES received more often noradrenaline than both groups on POD1 through POD3 (P<0.0001), requiring the

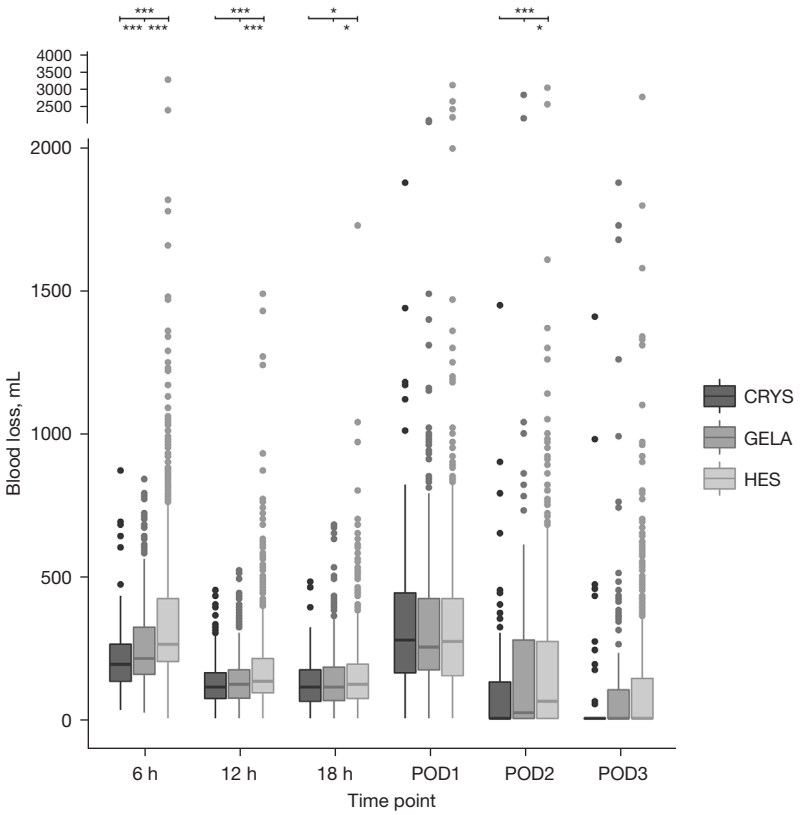

Figure 3 Time courses of blood losses in patients who received only CRYS, crystalloids and GELA, and crystalloids and HES as volume replacement. *, P<0.05; ***, P<0.001. Time point definitions: times in hours (h) indicate time after end of surgery; POD, postoperative day. CRYS, crystalloids; GELA, gelatin; HES, hydroxyethylstarch.

highest doses from operation to POD2 (P≤0.01) (*Figure 5*). Cumulative noradrenaline doses were higher in both colloid groups compared to CRYS (P<0.0001). Application of colloids increased the cumulative noradrenaline dose by 0.0158 and 0.0320 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, controlling for all other factors of the model (Tables S1-S4). Adrenaline was administered more often in colloid groups compared to CRYS (P=0.0003, *Table 4*). Cumulative adrenaline doses were higher in HES compared to both groups (P=0.03).

Mechanical ventilation and ICU LOS

Mechanical ventilation differed significantly between all groups (P<0.0001) with shortest duration in the CRYS and longest duration in the HES group. CRYS had the shortest ICU LOS, HES the longest (P<0.0001, *Table 2*).

Discussion

This retrospective study focused on the effects of volume management changes on GELA or CRYS in cardiac surgery at a university hospital. Main results are: (I) no difference in mortality was observed; (II) no differences were detected for AKI and RRT; (III) HES treated patients showed the highest blood loss, CRYS patients the lowest; (IV) HES had the highest transfusion of PRBCs and PCs and CRYS the lowest; (V) FFP, fibrinogen, and PCC were highest in HES; (VI) both colloids showed higher cumulative noradrenaline doses compared to CRYS; (VII) adrenaline was administered more often in colloid groups; (VIII) CRYS patients showed the shortest time of mechanical ventilation and ICU LOS, while HES patients had the longest ventilation and ICU LOS.

Due to the small number of deaths in our study and in

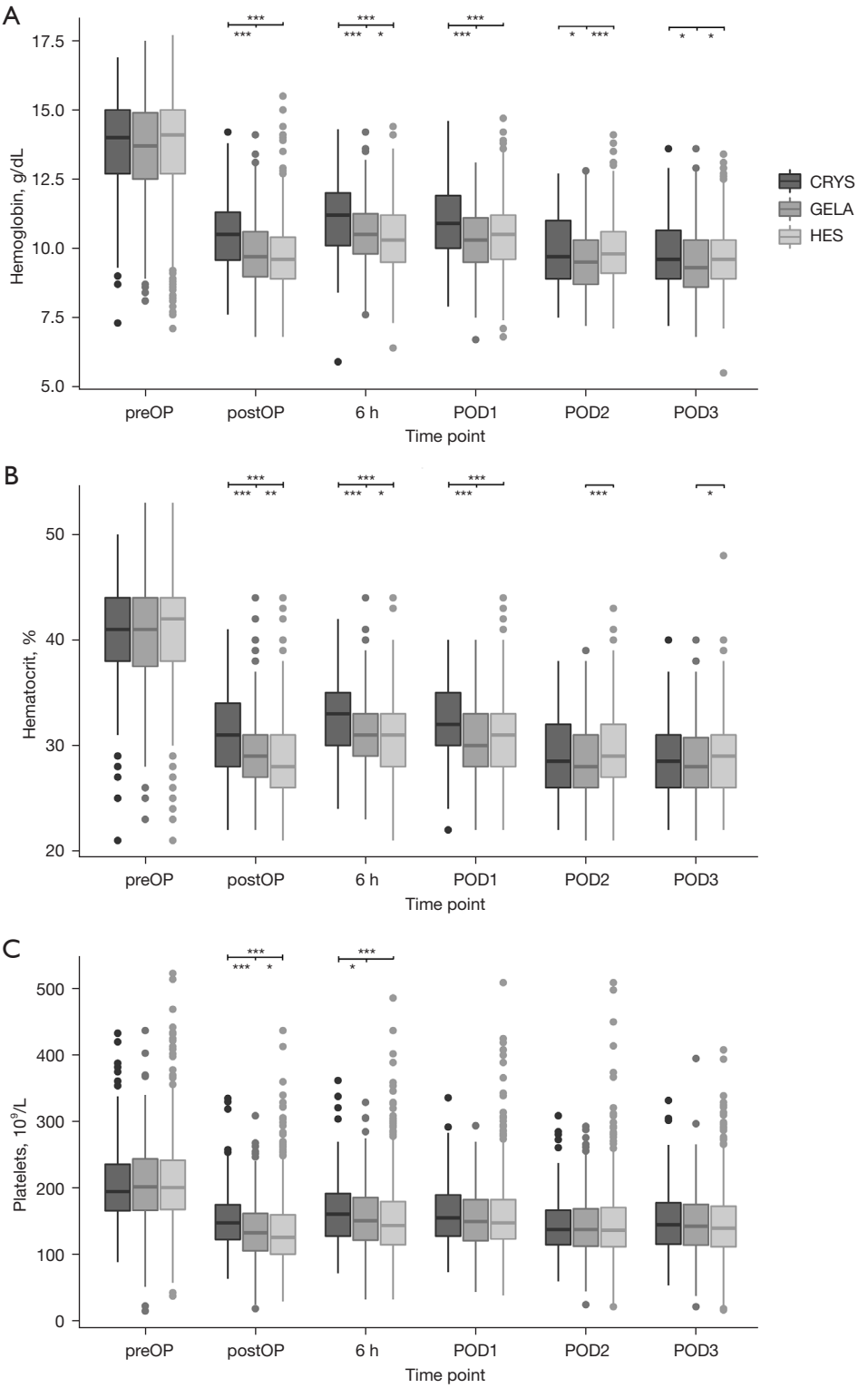

Figure 4 Time courses of blood count data in patients who received only CRYS, crystalloids and GELA, and crystalloids and HES as volume replacement. (A) Hemoglobin levels; (B) hematocrit; (C) platelet counts. *, P<0.05; **, P<0.01; ***, P<0.001. Time point definitions: preOP, preoperative; postOP, postoperative; 6 h, 6 h after end of surgery; POD, postoperative day. CRYS, crystalloids; GELA, gelatin; HES, hydroxyethylstarch.

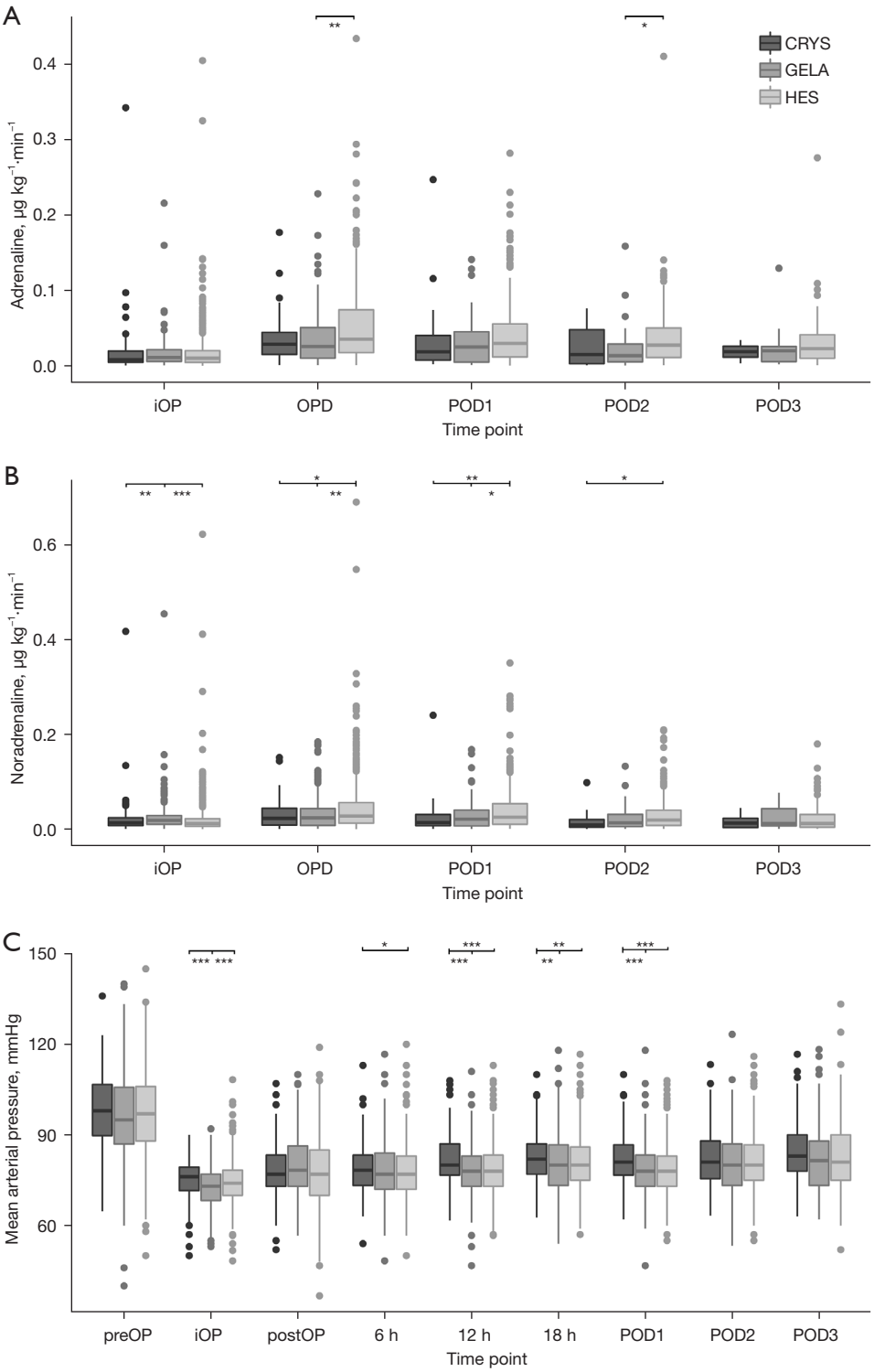

Figure 5 Time courses of vasopressor administration and mean arterial pressure in patients who received only CRYS, crystalloids and GELA, and crystalloids and HES as volume replacement. (A) Adrenaline, and (B) noradrenaline administration normalized to body weight. (C) Mean arterial pressure. *, P<0.05; **, P<0.01; *** P<0.001. Time point definitions: iOP, intraoperative; OPD, operation day; POD, postoperative day; preOP, preoperative; postOP, postoperative; times in hours (h) indicate time after end of surgery. CRYS, crystalloids; GELA, gelatin; HES, hydroxyethylstarch.

Table 4 Vasopressor administration of patients who received CRYS, GELA, and HES as sole volume replacement

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Patients receiving adrenaline at any time	72 (35%)a	215 (54%)b	455 (49%)c	0.0003
Patients receiving adrenaline				<0.0001
Intraoperative	71 (35%)a	201 (51%)b	430 (46%)b	0.0009
OP day	43 (21%)a	125 (32%)b	293 (31%)b	0.01
Postoperative day 1	27 (13%)a	76 (19%)ab	212 (23%)b	0.008
Postoperative day 2	13 (6%)a	41 (10%)ab	131 (14%)b	0.005
Postoperative day 3	4 (2%)a	19 (5%)ab	79 (8%)b	0.0007
Adrenaline administration ($\mu g \cdot kg^{-1} \cdot min^{-1}$)				0.008
Intraoperative	0.0080 (0.0047 to 0.0195)	0.0108 (0.0057 to 0.0213)	0.0100 (0.0045 to 0.0200)	0.35
OP day	0.0284 (0.0150 to 0.0441)ab	0.0255 (0.0100 to 0.0506)a	0.0351 (0.0174 to 0.0741)b	<0.0001
Postoperative day 1	0.0184 (0.0074 to 0.0401)	0.0249 (0.0049 to 0.0450)	0.0297 (0.0117 to 0.0554)	0.04
Postoperative day 2	0.0148 (0.0028 to 0.0478)ab	0.0134 (0.0052 to 0.0287)a	0.0273 (0.0109 to 0.0500)b	0.02
Postoperative day 3	0.0186 (0.0114 to 0.0258)	0.0199 (0.0055 to 0.0254)	0.0227 (0.0099 to 0.0410)	0.24
Total adrenaline administration ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.0238 (0.0054 to 0.0609)	0.0241 (0.0082 to 0.0695)	0.0337 (0.0076 to 0.1134)	0.03
Patients receiving dobutamine at any time	12 (6%)a	23 (6%)a	124 (13%)b	0.0001
Dobutamine administration				<0.0001
Intraoperative	8 (4%)a	22 (6%)a	98 (10%)b	0.0006
OP day	3 (1%)	6 (2%)	37 (4%)	0.02
Postoperative day 1	1 (0%)ab	1 (0%)a	23 (2%)b	0.006
Postoperative day 2	0 (0%)ab	0 (0%)a	13 (1%)b	0.01
Postoperative day 3	1 (0%)	0 (0%)	7 (1%)	0.2
Dobutamine administration ($\mu g \cdot kg^{-1} \cdot min^{-1}$)				n/a
Intraoperative	1.263 (0.922 to 1.534)	0.975 (0.601 to 2.233)	0.771 (0.377 to 1.311)	0.04
OP day	0.650 (0.563 to 1.466)	0.735 (0.357 to 3.693)	1.494 (0.567 to 2.206)	0.88
Postoperative day 1	0.384	2.688	1.190 (0.770 to 1.913)	0.3
Postoperative day 2	n/a	n/a	2.06 (0.977 to 3.586)	n/a
Postoperative day 3	2.773	n/a	0.662 (0.422 to 2.550)	0.28
Total dobutamine administration ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	1.315 (0.729 to 2.051)	1.086 (0.612 to 3.112)	1.083 (0.489 to 2.043)	0.62
Patients receiving milrinone at any time	7 (3%)	22 (6%)	57 (6%)	0.52
Milrinone administration				0.125
Intraoperative	2 (1%)	10 (3%)	21 (2%)	0.44
OP day	4 (2%)	17 (4%)	28 (3%)	0.26

Table 4 (*continued*)

Table 4 (*continued*)

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Postoperative day 1	4 (2%)	11 (3%)	28 (3%)	0.72
Postoperative day 2	2 (1%)	8 (2%)	21 (2%)	0.51
Postoperative day 3	1 (0%)	5 (1%)	17 (2%)	0.33
Milrinone administration (μg·kg^{-1}·min^{-1})				0.197
Intraoperative	0.0375 (0.0335 to 0.0414)	0.0484 (0.0340 to 0.0984)	0.0370 (0.0312 to 0.0495)	0.51
OP day	0.0914 (0.0612 to 0.1854)	0.0543 (0.0472 to 0.0874)	0.0684 (0.0413 to 0.1146)	0.59
Postoperative day 1	0.0771 (0.0672 to 0.0834)	0.0399 (0.0232 to 0.0705)	0.0522 (0.0292 to 0.1017)	0.40
Postoperative day 2	0.0869 (0.0519 to 0.1219)	0.0611 (0.0426 to 0.1070)	0.0246 (0.0118 to 0.0462)	0.22
Postoperative day 3	0.0914	0.0351 (0.0219 to 0.0707)	0.0472 (0.0232 to 0.0910)	0.66
Total milrinone administration (μg·kg^{-1}·min^{-1})	0.191 (0.049 to 0.270)	0.112 (0.068 to 0.233)	0.105 (0.045 to 0.174)	0.39
Patients receiving noradrenaline at any time	192 (94%)	379 (95%)	900 (96%)	0.63
Noradrenaline administration				<0.0001
Intraoperative	175 (85%)	362 (91%)	846 (90%)	0.07
OP day	134 (65%)a	313 (79%)b	704 (75%)b	0.001
Postoperative day 1	60 (29%)a	168 (42%)b	487 (52%)c	<0.0001
Postoperative day 2	23 (11%)a	64 (16%)a	315 (34%)b	<0.0001
Postoperative day 3	8 (4%)a	20 (5%)a	162 (17%)b	<0.0001
Noradrenaline administration (μg·kg^{-1}·min^{-1})				0.037
Intraoperative	0.0133 (0.0077 to 0.0238)a	0.0183 (0.0105 to 0.0290)b	0.0117 (0.0059 to 0.0221)a	<0.0001
OP day	0.0229 (0.0087 to 0.0442)a	0.0239 (0.0079 to 0.0436)a	0.0279 (0.0126 to 0.0561)b	<0.0001
Postoperative day 1	0.0138 (0.0074 to 0.0309)a	0.0213 (0.0070 to 0.0404)a	0.0252 (0.0105 to 0.0538)b	<0.0001
Postoperative day 2	0.0091 (0.0044 to 0.0202)a	0.0132 (0.0054 to 0.0312)ab	0.0192 (0.0077 to 0.0401)b	0.01
Postoperative day 3	0.0127 (0.0036 to 0.0231)	0.0116 (0.0068 to 0.0433)	0.0119 (0.0042 to 0.0310)	0.9
Total noradrenaline administration (μg·kg^{-1}·min^{-1})	0.032 (0.014 to 0.061)a	0.043 (0.021 to 0.087)b	0.049 (0.019 to 0.107)b	<0.0001
Patients receiving furosemide at any time	160 (78%)a	323 (81%)a	852 (91%)b	<0.0001
Furosemide administration				<0.0001
Intraoperative	20 (10%)a	77 (19%)b	143 (15%)ab	0.007
OP day	104 (51%)	178 (45%)	456 (49%)	0.3
Postoperative day 1	122 (60%)a	269 (68%)a	745 (79%)b	<0.0001
Postoperative day 2	60 (29%)a	123 (31%)a	458 (49%)b	<0.0001
Postoperative day 3	28 (14%)a	66 (17%)a	259 (28%)b	<0.0001

Table 4 (*continued*)

Table 4 (*continued*)

Parameters	CRYS (n=205)	GELA (n=397)	HES (n=938)	P
Furosemide administration (mg)				0.45
Intraoperative	10 (5 to 13)a	10 (10 to 20)a	20 (10 to 20)b	0.01
OP day	20 (10 to 30)	20 (10 to 40)	20 (10 to 40)	0.05
Postoperative day 1	40 (20 to 68)	40 (20 to 80)	40 (20 to 60)	0.71
Postoperative day 2	40 (20 to 178)	40 (20 to 160)	30 (20 to 90)	0.11
Postoperative day 3	60 (38 to 123)	40 (20 to 178)	40 (20 to 162)	0.37
Total furosemide administration (mg)	50 (25 to 115)a	50 (30 to 140)ab	70 (30 to 150)b	0.01

Data indicate frequencies as number of patients (% within group) unless specified otherwise. Continuous data are presented as median (1st quartile to 3rd quartile). P values <0.05 indicate significant differences between groups. Pairwise comparison post test results are indicated as letters (a, b, c); values of groups not sharing a letter are significantly different. CRYS, crystalloids; GELA, gelafundin; HES, hydroxyethyl starch; OP, operative.

the literature, no firm conclusion can be drawn for cardiac surgery. Large randomized studies in critically ill patients showed increased risk of AKI and need of RRT for the HES (5,6). GELA was rarely used, but some data describe no effects (14), other deleterious effects on kidney function in cardiac surgery (15). However, our data are consistent to a meta-analysis in cardiac surgery which did not find evidence for increased AKI or RRT in tetrastarch (7).

Controversial data are available investigating blood loss in terms of different volumes in cardiac surgery: some data comparing tetrastarch and crystalloids did not observe any differences (16-20), while others reported higher blood loss for tetrastarch (21,22); data comparing tetrastarch and GELA also range from a higher blood loss observed initially in one study in the tetrastarch group (23) to no difference reported in most studies (20,24-26). Results of blood product administration are in line with other data: patients with crystalloids received fewer transfusions compared to tetrastarch (17,21), and GELA received less transfusion than tetrastarch treated (23,24,26).

Despite differences of a few mmHg of MAP in our study, HES and GELA showed the highest cumulative doses of noradrenaline. These findings are in line with other data comparing HES and CRYS (27-29). Higher noradrenaline requirements were described in GELA treated patients compared to tetrastarch (9). Few data are available for catecholamine requirements focused on GELA and crystalloids in cardiac surgery: no difference was observed for noradrenaline and dobutamine requirement in a study of forty patients comparing GELA and 0.9% saline (30).

Despite reports of allergic or anaphylactic reactions after GELA exposure (31), no such reaction was observed in this study, but must be kept in mind as a potential risk.

Keeping in mind that just few data in cardiac surgery are available, our results match existing data that neither differences in mechanical ventilation (18,20,21) nor in ICU LOS (17,18,21) were observed.

Limitations of our study are the retrospective design, the almost linear sequence of volume regimens, and the fact that the decision for a volume regimen was at the discretion of the physician which could thus be prone to confounders and/or misinterpretations.

Overall, this retrospective investigation of three volume replacement managements showed no difference in mortality or AKI. The administration of crystalloids without any colloid was associated with less blood loss, transfusion, and mechanical ventilation having similar effects on MAP and ICU LOS. The administration of colloids in cardiac surgery should be considered critically due to the lack of evidence for benefits but severe concerns. Because of the restriction of hydroxyethylstarch and the subsequent GELA use in many places in cardiac surgery, further studies should investigate the effects of GELA in comparison to crystalloids.

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Footnote

Reporting Checklist: The authors have completed the

STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-450/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-450/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-450/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of the University of Ulm (approval ID 50-17) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Multiple logistic regression model of hospital survival using raw continuous numeric data from n=1,432 patients

	AOR	2.5%	97.5%	z	P
(Intercept)	104,834,872.767	30,943.864	355,170,588,521.637	4.453	<0.001
Age (y)	0.888	0.827	0.954	–3.274	0.001
Total volume (L)	1.216	1.007	1.468	2.034	0.042
Total colloid volume (L)	0.501	0.354	0.710	–3.892	<0.001
Emergency					
No	Reference				
Yes	0.271	0.078	0.944	–2.050	0.04
Preoperative ejection fraction					
>50%	Reference				
31% to 50%	3.930	0.480	32.164	1.276	0.202
21% to 30%	0.209	0.049	0.901	–2.099	0.036
20% and less	0.480	0.056	4.108	–0.670	0.503
NIDDM					
No	Reference				
Yes	12.412	1.404	109.726	2.265	0.024
Reoperation					
No	Reference				
Yes	0.050	0.008	0.303	–3.261	0.001
Cumulative blood loss 18 h (mL)	1.002	1.000	1.003	2.482	0.013
Intraoperative PRBC (mL)	0.999	0.998	1.000	–3.130	0.002
Cumulative norepinephrine OPD ($ng \cdot kg^{-1} \cdot min^{-1}$)	0.999	0.983	0.996	–3.017	0.003
PCC (L)	0.999	0.999	1.000	–3.809	<0.001
Postoperative hematocrit	0.000	0.000	4.139	–1.795	0.073

$\chi^2[14]=161.075$, $P<0.001$, McFadden Pseudo-$R^2=0.620$. AOR, adjusted odds ratio; 2.5% and 97.5%, lower and upper bounds of 95% confidence interval; NIDDM, non-insulin-dependent diabetes mellitus; PRBC, packed red blood cells; OPD, operating day; PCC, prothrombin complex concentrate.

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Table S2 Multiple logistic regression model of hospital survival using scaled and centered continuous numeric data from n=1,432 patients

	AOR	2.5%	97.5%	z	P
(Intercept)	1,252.854	207.221	7,574.719	7.770	<0.001
Age (y)	0.328	0.169	0.640	–3.274	0.001
Total volume (L)	2.222	1.030	4.796	2.034	0.042
Total colloid volume (L)	0.323	0.183	0.570	–3.892	<0.001
Emergency					
No	Reference				
Yes	0.271	0.078	0.944	–2.050	0.04
Preoperative ejection fraction					
>50%	Reference				
31% to 50%	3.930	0.480	32.164	1.276	0.202
21% to 30%	0.209	0.049	0.901	–2.099	0.036
≤ 20%	0.480	0.056	4.108	–0.670	0.503
NIDDM					
No	Reference				
Yes	12.412	1.404	109.726	2.265	0.024
Reoperation					
No	Reference				
Yes	0.050	0.008	0.303	–3.261	0.001
Cumulative blood loss 18 h (mL)	1.772	1.128	2.784	2.482	0.013
Intraoperative PRBC (mL)	0.618	0.457	0.835	–3.130	0.002
Cumulative norepinephrine OPD ($ng \cdot kg^{-1} \cdot min^{-1}$)	0.543	0.365	0.807	–3.017	0.003
PCC (L)	0.541	0.395	0.742	–3.809	<0.001
Postoperative hematocrit	0.567	0.305	1.054	–1.795	0.073

$\chi^2[14]=161.075$, $P<0.001$, McFadden Pseudo-R^2 =0.620. AOR, adjusted odds ratio; 2.5% and 97.5%, lower and upper bounds of 95% confidence interval; NIDDM, non-insulin-dependent diabetes mellitus; PRBC, packed red blood cells; OPD, operating day; PCC, prothrombin complex concentrate.

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Table S3 Multiple logistic regression model of acute kidney injury using raw continuous numeric data from n=996 patients

	AOR	2.5%	97.5%	z	P
(Intercept)	0	0	0	−10	<0.001
Age (y)	1.059	1.039	1.080	5.888	<0.001
NYHA score	1.246	0.991	1.566	1.881	0.060
CABG distal anastomoses (n)	1.142	0.978	1.335	1.677	0.093
Total volume (L)	1.037	0.994	1.082	1.702	0.089
Total colloid volume (L)	1.097	0.987	1.221	1.711	0.087
Emergency					
No	Reference				
Yes	1.660	1.173	2.350	2.859	0.004
Preoperative ejection fraction					
>50%	Reference				
31% to 50%	1.158	0.813	1.650	0.813	0.416
21% to 30%	1.708	1.109	2.630	2.431	0.015
20% and less	2.551	1.318	4.935	2.781	0.005
Preoperative serum creatinine ($\mu mol \cdot L^{-1}$)	1.019	1.012	1.025	5.783	<0.001
Aortic valve replacement	1.412	0.920	2.167	1.577	0.115
IDDM					
No	Reference				
Yes	1.503	0.942	2.398	1.711	0.087
Preoperative antiplatelet therapy					
No	Reference				
Yes	0.603	0.398	0.914	−2.383	0.017
Body mass index ($kg \cdot m^2$)	1.088	1.049	1.127	4.584	<0.001
Peripheral artery disease					
No	Reference				
Yes	1.476	0.990	2.200	1.910	0.056
Cumulative norepinephrine OPD ($ng \cdot kg^{-1} \cdot min^{-1}$)	1.012	1.006	1.018	3.796	<0.001
PCC (L)	1.436	1.068	1.931	2.397	0.017
Intraoperative FFP (mL)	1.003	1.000	1.006	2.319	0.017
Interaction preoperative serum creatinine: cumulative norepinephrine OPD	1.000	1.000	1.000	−2.744	0.006

$\chi^2[19]=274.594$, $P<0.001$, McFadden Pseudo-R^2 =0.210. AOR, adjusted odds ratio; 2.5% and 97.5%, lower and upper bounds of 95% confidence interval; IDDM, insulin-dependent diabetes mellitus; OPD, operating day; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

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Table S4 Multiple logistic regression model of acute kidney injury using scaled and centered continuous numeric data from n=996 patients

	AOR	2.5%	97.5%	z	P
(Intercept)	0.510	0.321	0.810	-2.849	0.004
Age (y)	1.703	1.426	2.033	5.888	<0.001
NYHA score	1.167	0.994	1.371	1.881	0.060
CABG distal anastomoses (n)	1.156	0.976	1.370	1.677	0.093
Total volume (L)	1.161	0.978	1.379	1.702	0.089
Total colloid volume (L)	1.160	0.979	1.374	1.711	0.087
Emergency					
No	Reference				
Yes	1.660	1.173	2.350	2.859	0.004
Preoperative ejection fraction					
>50%	Reference				
31% to 50%	1.158	0.813	1.650	0.813	0.416
21% to 30%	1.708	1.109	2.630	2.431	0.015
20% and less	2.551	1.318	4.935	2.781	0.005
Preoperative serum creatinine ($\mu mol \cdot L^{-1}$)	2.651	1.873	3.754	5.496	<0.001
Aortic valve replacement					
No	Reference				
Yes	1.412	0.920	2.167	1.577	0.115
IDDM					
No	Reference				
Yes	1.503	0.942	2.398	1.711	0.087
Preoperative antiplatelet therapy					
No	Reference				
Yes	0.603	0.398	0.914	-2.383	0.017
Body mass index ($kg \cdot m^2$)	1.458	1.241	1.714	4.584	<0.001
Peripheral artery disease					
No	Reference				
Yes	1.476	0.990	2.200	1.910	0.056
Cumulative norepinephrine OPD ($ng \cdot kg^{-1} \cdot min^{-1}$)	1.405	1.157	1.707	3.424	0.001
PCC (L)	1.359	1.057	1.746	2.397	0.017
Intraoperative FFP (mL)	1.490	1.064	2.088	2.319	0.020
Preoperative serum creatinine: cumulative norepinephrine OPD	0.815	0.704	0.943	-2.744	0.006

$\chi^2[19]=274.594$, $P<0.001$, McFadden Pseudo-$R^2=0.210$. AOR, adjusted odds ratio; 2.5% and 97.5%, lower and upper bounds of 95% confidence interval; IDDM, insulin-dependent diabetes mellitus; OPD, operating day; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

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