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ORIGINAL ARTICLE

# Effects of goal-directed crystalloid vs. colloid fluid therapy on microcirculation during free flap surgery

## *A randomised clinical trial*

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**BACKGROUND** Macro, and microcirculatory effects of crystalloids and colloids are difficult to compare, because interventions to achieve haemodynamic stability seldom follow similar criteria.

**OBJECTIVES** Our aim was to compare the effects of crystalloids and colloids on the microcirculation during free flap surgery when management was guided by detailed haemodynamic assessment.

**DESIGN** A randomised, controlled clinical trial.

**SETTINGS** The investigation was performed at the University of Szeged, Hungary.

**PATIENTS** Patients undergoing maxillofacial tumour resection and free flap reconstruction were randomised into groups treated with either intra-operative crystalloid (Ringerfundin, $n = 15$) or colloid (6% hydroxyethyl starch, HES, $n = 15$) solutions.

**INTERVENTIONS** Macrohaemodynamics were monitored by a noncalibrated device (PulsioFlex-PULSION). Central venous oxygen saturation, venous-to-arterial $PCO_2$-gap, lactate levels and urine output were measured hourly. Maintenance fluid was Ringerfundin ($1\,ml\,kg^{-1}\,h^{-1}$), and a multimodal, individualised, approach-based algorithm was applied to guide haemodynamic support. Hypovolaemia was treated with Ringerfundin or HES fluid boluses, respectively. The microcirculatory effects were assessed by laser-Doppler flowmetry (PeriFlux 5000 LDPM), with the probe placed on the flap and on a control area. Measurements were performed after the flap was prepared, then 1 and 12 h later.

**MAIN OUTCOME MEASURES** The primary end-point was microcirculatory perfusion as determined by laser-Doppler flowmetry.

**RESULTS** There was no difference between the groups regarding patient characteristics. Both groups remained haemodynamically stable throughout due to the use of approximately a 1.5 times higher total fluid volume in the Ringerfundin group than in the HES group: mean ± SD: 2581 ± 986 and 1803 ± 497) ml, respectively, ($P = 0.011$). There was no significant difference in the microcirculatory blood flow between the groups.

**CONCLUSION** Our results showed that when fluid management was guided by detailed haemodynamic assessment, more crystalloid than colloid was needed to maintain haemodynamic stability, but there was no difference between the effects of crystalloids and colloids on the microcirculation.

**TRIAL REGISTRATION** ClinicalTrials.gov NCT03288051.

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## Introduction

Inappropriate haemodynamic management during major surgery may lead to hypoperfusion or fluid overload, both of which are accompanied by a significant risk of impaired postoperative outcome.[1] The same holds true for unnecessary use of vasoactive medications[2] and blood transfusions.[3,4] In reducing such adverse effects, advanced haemodynamic monitoring-based management has a strong pathophysiological rationale and, indeed,

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advanced haemodynamic monitoring-based peri-operative management has been shown to improve outcomes in high-risk surgery in several studies.[5,6] These trials showed that high-risk patients, especially those undergoing bowel surgery, benefited from this approach, with reduced postoperative complications and increased survival.

In addition to haemodynamic management, the type of fluid used may also have an important effect on outcome. The crystalloid-colloid debate has a long history, and most studies conclude that colloids seem to be superior to crystalloids as far as microcirculatory perfusion was concerned.[7] Many surgeons and anaesthetists share this belief, despite the fact that none of the clinical trials that investigated this issue used detailed haemodynamic assessment.[7] Furthermore, the advantages of colloid solutions for the microcirculation have been shown in clinical studies applying goal-directed therapy, without inclusion of crystalloid group as a control.[8,9] Therefore, one cannot exclude the possibility that the observed benefit of colloids on the microcirculation was due to better global haemodynamic conditions achieved by the better volume-replacement ratio of colloids (as compared with crystalloids), and not due to their better microcirculatory properties *per se*.

Therefore, our aim was to perform a randomised clinical trial to examine the effects of intra-operative crystalloid and colloid fluid replacement on microcirculatory perfusion in patients undergoing free flap surgery for maxillofacial malignancy; fluid boluses for intra-operative hypovolemia were guided by detailed haemodynamic monitoring.

## Materials and methods

### Patient selection

This randomised, controlled study (Ethical Committee No. 44/2014) was undertaken between April 2014 and February 2018 and was approved by the Regional and Institutional Human Medical Biological Research Ethics Committee, University of Szeged, Hungary on 28 April 2014. The investigation was performed at the University of Szeged. The study was registered at ClinicalTrials.gov with the registration number: NCT03288051. Written informed consent was obtained from all participants.

Adult patients of both sexes undergoing radical forearm free flap surgery were recruited. Exclusion criteria included vulnerable individuals as defined in ISO 14155 : 2011, pregnant or lactating women, and end-stage oral cancer. The progress of participants through the study is depicted in Fig. 1.

Patients were randomised either to a crystalloid group (Ringerfundin; B. Braun Melsungen, Germany) or a colloid group [hydroxyethyl starch (HES), Voluven 6%; Fresenius Kabi Deutschland, Germany], using envelope block-randomisation in blocks of fifteen. Patient enrolment, sequence generation and assignment to interventions were performed by a responsible investigator. Only the patients were blind to group allocation.

### Intra-operative protocol

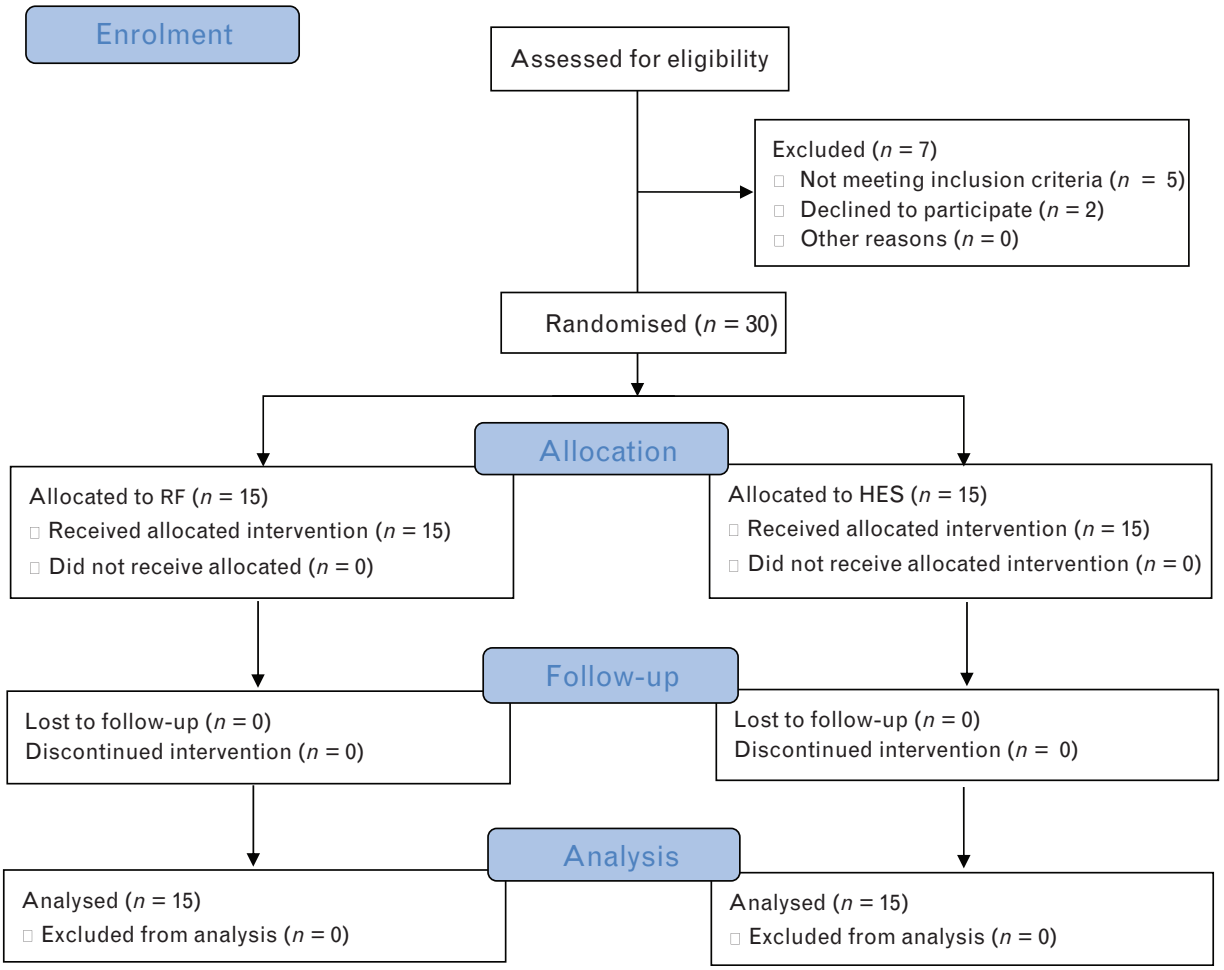
Patients received routine anaesthetic management. In addition to standard monitoring, a radial artery catheter was inserted under local anaesthesia for invasive blood pressure monitoring. This arterial line was also connected to a noncalibrated haemodynamic monitor (ProAQT; PULSION Medical Systems SE, Munich, Germany). Anaesthesia was induced with 1 to 3 $mg\,kg^{-1}$ propofol [Propofol (1%), Fresenius Kabi Deutschland, Germany], 0.6 $mg\,kg^{-1}$ rocuronium (Esmeron, MSD Pharma Hungary, Hungary), and for analgesia, morphine (Morfina Jacopo Monico, Italy) was used. Anaesthesia was maintained with sevoflurane with the minimum alveolar concentration maintained around 1.3 vol%. Patients were ventilated with an 8 $ml\,kg^{-1}$ tidal volume, in pressure control mode, in order to have a reasonable effect on pulse pressure variation (PPV).[5,10] During the operation, core temperature was measured by rectal thermometer. Maintenance fluid was Ringerfundin 1 $ml\,kg^{-1}\,h^{-1}$.

After induction of anaesthesia, a central venous catheter was inserted into the right internal jugular or the right subclavian vein based on the requirements of the surgical approach. Haemodynamic assessment during the operation was based on a multimodal concept shown in Fig. 2. This included elements of the model that had been applied and reported in a recent multicentre clinical trial, in which our institute also participated.[6]

In brief, fluid responsiveness was defined as PPV at least 10%, but this this did not mean that fluid was given immediately: fluid administration was determined by a complex, multimodal algorithm, depicted in Fig. 2. In cases when fluid loading was indicated, a bolus of 250 ml of Ringerfundin or HES, as determined by randomisation, was administered within 15 min. The aim was to maintain cardiac index (*CI*) above 2.5 $l\,min^{-1}\,m^{-2}$. If *CI* was low, and our haemodynamic model indicated that contractility had to be improved, then dobutamine (Dobutamine Hexal, Sandoz Hungária, Hungary) was administered starting at a rate of 5 $\eta g\,kg^{-1}\,min^{-1}$. In the case of a drop in blood pressure, as indicated by a mean arterial pressure of 65 mmHg or less or at least 20% drop as compared with baseline data, after excluding hypovolemia, or myocardial depression, norepinephrine was started as a continuous infusion.

Global haemodynamic assessment was complemented with measuring hourly urine output and arterial and central venous blood gas analysis. Parameters included in the haemodynamic decision algorithm were central venous oxygen saturation ($ScvO_2$), central venous-to-arterial $CO_2$-gap ($dCO_2$), arterial lactate, $HCO_3$ and

Fig. 1




Flow chart according to the CONSORT (Consolidated Standards of Reporting Trials) statement showing the progress of participants throughout the study.

pH. Normal values for these parameters were considered as $ScvO_2$: 70 to 80%, $dCO_2$ of 6 mmHg or less, $HCO_3$: 20 to 24 mmol $l^{-1}$, pH: 7.35 to 7.45. Arterial and central venous samples were taken at the same time hourly, or anytime in between, when a decision had to be supported in order to commence therapy. This approach was aimed at helping to individualise treatment, rather than following a preset target value.

Data were recorded after instrumentation at baseline ($T_0$), at incision ($T_i$) and then hourly until the end of the surgery ($T_{es}$) and 24 h after $T_0$ ($T_{24}$).

## Laser-Doppler flowmetry

All flaps were monitored with noninvasive laser-Doppler flowmetry (PeriFlux 5000 LDPM; Perimed, Järfälla, Sweden) intra-operatively, and postoperatively. A probe with a standard fibre separation of 0.25 mm, and a 780 nm wavelength laser was used. The depth of the measurements was 0.5 to 1 mm. Results are expressed as perfusion units. The first measurements were taken after the flap was prepared ($R_{bsl}$), then 1 h after reperfusion and continued hourly for up to 12 h ($R_1$–$R_{12}$). The probe was placed and fixed in a position in the centre of the forearm flap skin island. The skin in the deltoid region provided the control site. At both places, measurements were taken after active warming of the skin, at 35°C and 44°C. Data were recorded for more than 2 min at each measurement point. Quantitative assessment of the recording periods was performed off-line.

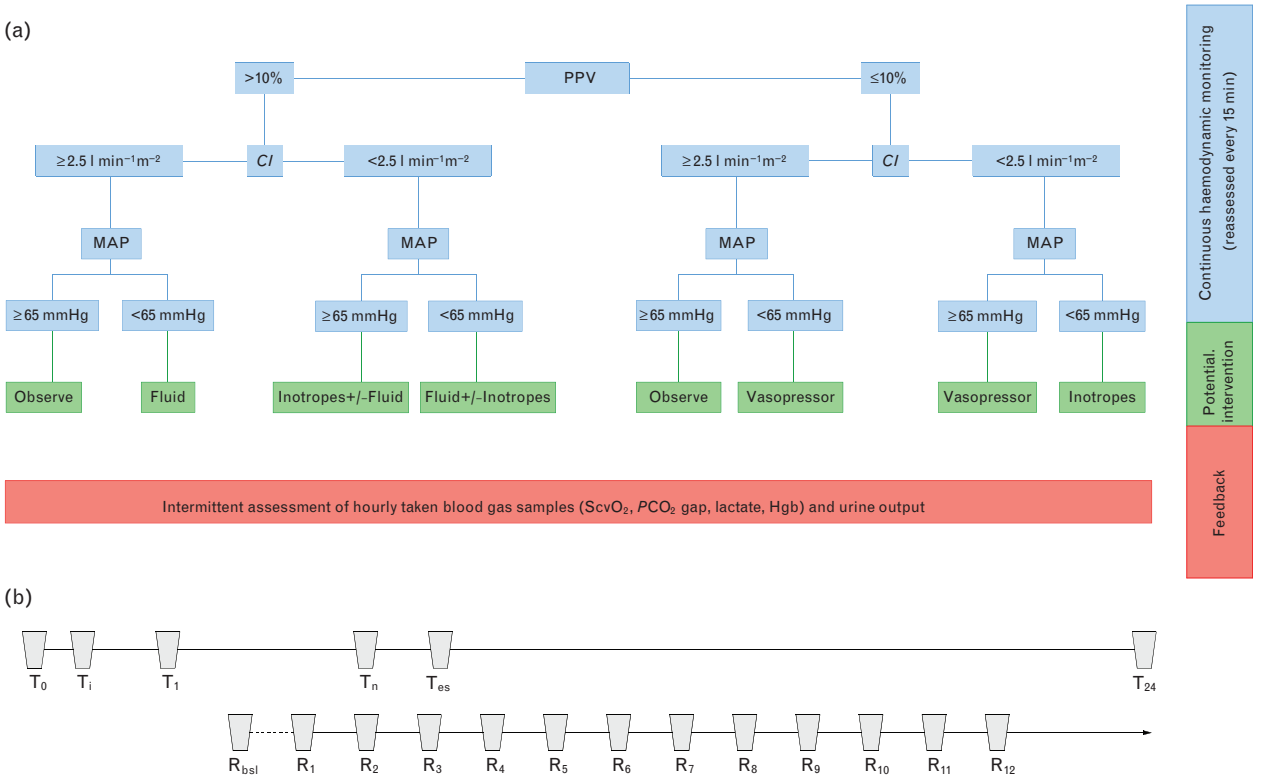
## Postoperative and ICU protocol

All patients were monitored in the ICU until they were discharged to the Maxillofacial Surgery ward. Patients received standard ICU care according to our institutional protocols.

## Data analysis and statistics

For statistical analysis, Statistical Program for Social Sciences version 23.0 for Windows (SPSS, Chicago,

**Fig. 2**




(a) Haemodynamic assessment and interventions. CI, cardiac index; Hgb, haemoglobin; MAP, mean arterial pressure; $PCO_2$ gap, central venous-to-arterial $PCO_2$-gap; PPV, pulse pressure variability; $ScvO_2$, central venous oxygen saturation; SVV, stroke volume variation. (b) Measurements and recordings: $T_0$, baseline; $T_i$, incision; $T_{es}$, end of surgery; $T_{24}$, day one. $R_{bsl}$, baseline (Laser-Doppler after flap was prepared); $R_1$, one hour after $R_{2-12}$, hourly.

Illinois, USA) was used, and $P$ value less than 0.05 was considered as significant. Data are presented as mean ± SD or median [IQR]. For testing normal distribution, the Shapiro–Wilk test was used. Independent samples were tested by independent samples $t$-test or Mann–Whitney $U$ test, as appropriate. Changes in repeated measures throughout the experiment were tested by two-way repeated measures analysis of variance (ANOVA) with Bonferroni post hoc comparisons. Categorical data were compared using $\chi^2$ tests. The Type I error probability associated with this test of the null hypothesis is 0.05.

The study's primary end-point was the difference in the perfusion units as determined by laser-Doppler at $R_{12}$. On the basis of preliminary results, for a study to have 80% power to show a significant difference in perfusion units at $R_{12}$, when the standardised difference (clinically significant difference/standard deviation) worked out to be 0.9, required a minimum of 30 patients in total (15 per group).

## Results

There was no difference in the demographics, as summarised in Table 1. Complete flap failure occurred on five occasions (one in the Ringerfundin, four in the HES group, $P = 0.142$).

### Macrohaemodynamic effects of fluid resuscitation

Patients remained haemodynamically stable throughout the observation period in both groups (Table 2). PPV was in general higher in the Ringerfundin group, which became significant at $T_3$. *CI* also showed the same pattern in both groups, with significantly higher values in HES group at $T_1$. At $T_0$, the systemic vascular resistance index values were significantly elevated in the Ringerfundin group. Several other parameters showed changes during the experiment, without any significant differences between the groups.

Intra-operative total urine output reached similar values in the HES and Ringerfundin-treated groups [355.0 (166.4) ml and 477.3 (212.5) ml, respectively, $P = 0.090$]. Creatinine values as measured 24 h after surgery were not different between the groups either [HES, 76 (19) μmol l$^{-1}$; Ringerfundin, 71 (26) μmol l$^{-1}$, $P = 0.505$].

### Respiratory parameters

Respiratory data are summarised in Table 3. Overall, all parameters showed similar values in both groups.

Table 1 Demographic variables of patients in the crystalloid (Ringerfundin) to and colloid (hydroxyethyl starch) to treated groups

| Demography | RF ($n = 15$) | HES ($n = 15$) | P |
|---|---|---|---|
| Female/Male | 5/10 | 3/12 | 0.409 |
| Age (years) | 64 ± 11 | 62 ± 10 | 0.680 |
| Height (cm) | 170.6 ± 9.0 | 168.8 ± 7.2 | 0.550 |
| Weight (kg) | 72.0 [60.0 to 83.0] | 62.0 [57.0 to 81.0] | 0.539 |
| BMI (kg m$^2$) | 24.4 [21.6 to 27.8] | 24.0 [19.6 to 31.6] | 0.775 |
| Scores | | | |
| APACHE II (point) | 13.5 [9.5 to 15.25] | 14.0 [7.75 to 16.0] | 0.946 |
| APACHE MR (%) | 17.6 ± 6.8 | 16.7 ± 8.3 | 0.731 |
| ASA 1 (*n*) | 3 | 0 | 0.250 |
| ASA 2 (*n*) | 9 | 10 | |
| ASA 3 (*n*) | 3 | 5 | |
| Procedures | | | |
| Duration of operation (min) | 354.3 ± 59.4 | 342.4 ± 79.1 | 0.644 |
| Duration of ischemia (min) | 66.9 ± 13.1 | 67.9 ± 19.3 | 0.869 |
| LOS | | | |
| ICU (days) | 2 [2 to 3] | 2 [2 to 2] | 0.389 |
| Hospital (days) | 9 [7 to 13] | 10 [8 to 15] | 0.325 |
| Organ support on ICU | | | |
| Mechanical ventilation (days) | 1 [1 to 1] | 1 [0 to 1] | 0.595 |
| Vasopressor (days) | 0 [0 to 1] | 1 [0 to 1] | 0.683 |
| Dialysis (therapy) | 1 | 0 | |

Data are presented as mean ± SD, median [IQR] and *n*. APACHE II, Acute Physiology and Chronic Health Evaluation II; APACHE MR, Acute Physiology and Chronic Health Evaluation Mortality Rate; ASA, American Society of Anaesthesiologists' classification; LOS, length of stay.

Although end-tidal $CO_2$ was significantly elevated in the HES group at $T_0$ and $T_i$, it still stayed within the normal range.

### Blood gas parameters

All parameters remained within the physiological normal range throughout the observation period and, although there were certain statistically significant differences observed, these can be regarded as clinically nonrelevant (Table 4). Haemoglobin concentration in the HES group showed a significant decrease over time, without the need for blood transfusion.

Oxygen consumption and oxygen delivery were more or less stable throughout the study and followed similar patterns in both groups. Oxygen extraction changed accordingly with no major difference between the groups.

### Total amount of intra-operative and ICU medications

As listed in Table 5, the Ringerfundin group required significantly more boluses and greater total amounts of fluid. Blood loss did not differ between the groups. During surgery, the Ringerfundin group was given 1.5 times more boluses of fluid than the HES group. There were no significant differences in the postoperative period.

Nearly half of the patients required vasopressors (Ringerfundin, $n = 8$; HES, $n = 7$) and inotropic support (Ringerfundin, $n = 6$; HES, $n = 7$), without significant difference in the required doses between the groups.

Total amount of anaesthetic and analgesic agents was similar in both groups.

### Microcirculation and corresponding macrohaemodynamics

As evidenced by laser-Doppler flowmetry, baseline perfusion values were similar at the flap areas (*in situ*, before harvesting) and at the control sites in both groups (at 35°C and 44°C) (Figs. 3 and 4). During reperfusion, however, significantly higher tissue perfusion values were observed at the free flap sites in both groups than those observed at baseline or at the control areas (at corresponding time-points) at 35°C (Fig. 3). A significant difference in the perfusion of the free flaps areas was observed only in the ninth hour of reperfusion between the groups when perfusion values appeared to be higher in the Ringerfundin group. Heat provocation (to 44°C) induced increases in tissue perfusion only at the control areas, whereas this effect was missing in the flaps during reperfusion in both groups (Fig. 4). In the macrohaemodynamic values, a significant difference was found in the DBP (Dia) and PPV during the second hour of reperfusion ($R_2$), but these changes were not accompanied by significant changes in microcirculatory perfusion at any sites. Changes in macrohaemodynamic parameters at different reperfusion measurement points varied according to the surgical section (Table 6).

## Discussion

This randomised clinical trial aimed to investigate the effects of crystalloid vs. colloid fluid replacement to treat intra-operative hypovolemia during free flap surgery on global haemodynamic parameters and microcirculation. It was found that patients in the crystalloid group required more fluid than patients in the colloid group, without any significant difference in the macrocirculation and microcirculation. To detect hypovolaemia, advanced

**Table 2** Haemodynamic parameters in the crystalloid (Ringerfundin) and colloid (hydroxyethyl starch) treated groups

| Group | $T_0$ | $T_i$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_{es}$ | $T_{24}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SAP (mmHg) | | | | | | | | | | | |
| RF | 115.1 ± 48.1 | 119.2 ± 43.6 | 111.5 ± 27.9 | 115.9 ± 17.3 | 111.7 ± 22.4 | 104.2 ± 17.3 | 104.6 ± 13.8 | 112.5 ± 14.1 | – | 113.8 ± 16.3 | 114.6 ± 15.5 |
| HES | 114.2 ± 28.5 | 113.7 ± 29.6 | 116.4 ± 21.1 | 118.5 ± 26.2 | 113.3 ± 12.0 | 106.9 ± 12.1 | 105.3 ± 12.6 | 109.3 ± 13.1 | 102.8 ± 7.13 | 115.5 ± 13.2 | 124.8 ± 17.7 |
| DAP (mmHg) | | | | | | | | | | | |
| RF | 64.3 ± 22.1 | 67.5 ± 17.4 | 59.9 ± 12.9 | 59.9 ± 7.7 | 58.3 ± 9.2 | 55.3 ± 7.4 | 54.8 ± 5.8 | 56.4 ± 8.2 | – | 57.5 ± 8.6 | 55.3 ± 9.5 |
| HES | 63.1 ± 17.5 | 62.0 ± 18.2 | 61.2 ± 11.1 | 61.9 ± 12.0 | 58.9 ± 7.4 | 56.1 ± 7.4 | 55.0 ± 5.8 | 58.9 ± 6.1 | 53.5 ± 2.4 | 59.0 ± 8.0 | 59.5 ± 9.3 |
| PP (mmHg) | | | | | | | | | | | |
| RF | 50.9 ± 29.9 | 51.7 ± 28.9 | 51.7 ± 20.7 | 56.0 ± 14.6 | 54.4 ± 11.4 | 53.3 ± 19.0 | 53.7 ± 15.3 | 56.1 ± 12.3 | – | 56.3 ± 16.6 | 59.3 ± 17.5 |
| HES | 51.1 ± 15.6 | 51.7 ± 15.6 | 55.2 ± 13.3 | 56.6 ± 17.2 | 53.5 ± 16.4 | 53.6 ± 12.8 | 52.1 ± 14.0 | 50.4 ± 9.8 | 49.3 ± 6.7 | 56.5 ± 12.6 | 65.3 ± 11.6** |
| MAP ± mmHg) | | | | | | | | | | | |
| RF | 82.4 ± 32.2 | 85.6 ± 28.3 | 75.1 ± 16.5 | 80.0 ± 9.5 | 76.8 ± 12.6 | 74.2 ± 10.4 | 73.4 ± 8.5 | 75.5 ± 8.9 | – | 76.6 ± 9.0 | 75.7 ± 9.4* |
| HES | 81.5 ± 19.1 | 80.4 ± 20.0 | 81.1 ± 15.2 | 82.9 ± 17.4 | 78.3 ± 7.3 | 75.1 ± 9.6 | 72.9 ± 8.5 | 76.3 ± 10.1 | 71.3 ± 3.5 | 78.7 ± 8.8 | 83.8 ± 11.4 |
| HR ($min^{-1}$) | | | | | | | | | | | |
| RF | 69 ± 11 | 71 ± 10 | 68 ± 8 | 66 ± 10 | 69 ± 12 | 63 ± 7 | 66 ± 10 | 68 ± 9 | – | 71 ± 10 | 71 ± 9 |
| HES | 71 ± 13 | 69 ± 9 | 74 ± 17 | 73 ± 12 | 71 ± 9 | 72 ± 12 | 73 ± 12 | 76 ± 11 | 82 ± 18 | 73 ± 14 | 78 ± 13** |
| *CI* ($l min^{-1} m^{-2}$) | | | | | | | | | | | |
| RF | 2.66 ± 0.56 | 2.76 ± 0.71 | 2.70 ± 0.56* | 2.67 ± 0.52 | 2.83 ± 0.32 | 2.56 ± 0.27 | 2.63 ± 0.42 | 2.91 ± 0.75 | – | 2.83 ± 0.40 | 3.29 ± 0.90** |
| HES | 2.77 ± 0.54 | 2.75 ± 0.54 | 3.22 ± 0.99** | 3.01 ± 0.56 | 3.01 ± 0.57 | 3.07 ± 0.82 | 3.13 ± 0.77 | 2.91 ± 0.32 | 3.39 ± 0.70 | 3.02 ± 0.63 | 3.76 ± 0.86** |
| PPV (%) | | | | | | | | | | | |
| RF | 13.07 ± 6.98 | 9.67 ± 5.00 | 9.47 ± 2.72 | 9.93 ± 3.59 | 10.87 ± 2.36* | 10.14 ± 2.73 | 9.93 ± 3.50 | 9.81 ± 5.96 | – | 8.40 ± 3.36 | 11.33 ± 4.72 |
| HES | 12.40 ± 7.50 | 10.0 ± 4.30 | 9.20 ± 5.14 | 9.27 ± 5.50 | 8.27 ± 4.28 | 10.86 ± 7.09 | 8.09 ± 3.02 | 8.43 ± 2.76 | 8.25 ± 2.63 | 9.80 ± 6.78 | 9.71 ± 3.86 |
| SVV (%) | | | | | | | | | | | |
| RF | 14.00 ± 7.17 | 11.67 ± 5.68 | 11.67 ± 6.04 | 10.13 ± 4.61 | 12.40 ± 5.19 | 10.86 ± 4.43 | 11.71 ± 5.01 | 11.00 ± 4.73 | – | 10.20 ± 5.63 | 14.83 ± 7.76 |
| HES | 13.20 ± 7.24 | 10.27 ± 3.13 | 10.47 ± 5.69 | 9.80 ± 5.04 | 11.47 ± 10.63 | 14.86 ± 7.73 | 11.18 ± 7.24 | 11.71 ± 7.67 | 11.75 ± 7.89 | 13.33 ± 7.84 | 8.57 ± 2.07 |
| SVI ($ml m^{-2}$) | | | | | | | | | | | |
| RF | 36.53 ± 8.69 | 39.60 ± 7.94** | 40.93 ± 6.44 | 40.00 ± 6.88 | 41.00 ± 5.01** | 40.14 ± 4.84 | 40.00 ± 4.87 | 41.73 ± 3.90 | – | 39.73 ± 5.89 | 40.70 ± 14.37 |
| HES | 40.40 ± 9.38 | 40.60 ± 8.52 | 43.20 ± 7.73 | 40.66 ± 4.53 | 41.13 ± 4.86 | 41.71 ± 6.09 | 41.81 ± 4.93 | 41.71 ± 5.41 | 42.50 ± 2.52 | 42.13 ± 4.10 | 48.22 ± 9.83** |
| SVRI ($dyn s cm^{-5} m^{-2}$) | | | | | | | | | | | |
| RF | 2503 ± 682* | 2378 ± 699 | 2040 ± 578 | 2236 ± 484 | 2069 ± 304** | 2113 ± 402 | 2130 ± 390 | 1926 ± 370 | – | 2028 ± 420 | 2142 ± 702 |
| HES | 1870 ± 627 | 1880 ± 669 | 1922 ± 488 | 2046 ± 459 | 1967 ± 382 | 1896 ± 484 | 1900 ± 519 | 1871 ± 656 | 1614 ± 578 | 2007 ± 450 | 1745 ± 473 |
| dPmax ($mmHg s^{-1}$) | | | | | | | | | | | |
| RF | 697 ± 295 | 671 ± 345 | 611 ± 354 | 708 ± 420** | 674 ± 290 | 645 ± 347 | 696 ± 263 | 618 ± 279 | – | 801 ± 280 | 761 ± 180 |
| HES | 563 ± 207 | 569 ± 215 | 583 ± 150 | 622 ± 201 | 576 ± 160 | 583 ± 184 | 621 ± 307 | 712 ± 238 | 590 ± 141 | 687 ± 237 | 870 ± 189** |
| T (°C) | | | | | | | | | | | |
| RF | 36.1 ± 0.9 | 36.2 ± 0.9 | 35.9 ± 0.8 | 35.7 ± 0.8** | 35.8 ± 0.9 | 35.9 ± 0.8 | 36.1 ± 0.9 | 36.4 ± 0.5 | – | 36.3 ± 1.0 | 36.6 ± 0.6 |
| HES | 36.3 ± 0.9 | 36.1 ± 0.8 | 36.0 ± 0.8** | 35.8 ± 0.7** | 35.9 ± 0.8** | 35.9 ± 0.9 | 36.2 ± 0.8 | 36.2 ± 0.7 | 36.1 ± 0.7 | 36.1 ± 0.9 | 36.9 ± 0.5 |

Data were recorded after instrumentation at baseline ($T_0$), at incision ($T_i$), then hourly until the end of the surgery ($T_{es}$) and 24 h after $T_0$ ($T_{24}$). Data are presented as mean ± SD. *CI*, cardiac index; DAP, diastolic blood pressure; dPmax, index of left ventricular contractility; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; PPV, pulse pressure variability; SAP, systolic blood pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index; SVV, stroke volume variation. * $P < 0.05$ significant difference between groups. ** $P < 0.05$ significant difference from $T_0$.

**Table 3** Respiratory variables in the crystalloid (Ringerfundin) and colloid (hydroxyethyl starch) treated groups

| Group | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_{es}$ | $T_{24}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Sat. (%) | | | | | | | | | | |
| RF | 98.5 ± 0.9 | 98.5 ± 1.1 | 98.3 ± 1.2 | 98.1 ± 1.0 | 98.4 ± 1.2 | 98.2 ± 1.1 | 98.4 ± 1.7 | 99.4 ± 0.8 | – | 99.2 ± 1.1 | 99.1 ± 1.2 |
| HES | 97.9 ± 1.9 | 97.6 ± 2.1 | 97.9 ± 1.6 | 97.7 ± 1.7 | 97.7 ± 1.3 | 98.2 ± 1.3 | 97.9 ± 1.6 | 97.7 ± 1.6 | 98.0 ± 1.6 | 98.7 ± 1.0 | 99.1 ± 1.0** |
| $FiO_2$ (%) | | | | | | | | | | | |
| RF | 42.9 ± 5.6 | 42.3 ± 4.6 | 41.5 ± 5.2 | 39.7 ± 3.2 | 39.3 ± 4.1 | 40.2 ± 2.8 | 40.7 ± 4.5 | 45.4 ± 18.7 | – | 48.6 ± 20.0 | 32.8 ± 10.7** |
| HES | 51.7 ± 16.1 | 49.5 ± 17.0** | 46.7 ± 9.4** | 43.4 ± 8.1** | 44.6 ± 11.5** | 47.9 ± 19.2 | 50.9 ± 20.8 | 54.9 ± 27.0 | 61.3 ± 34.7 | 63.2 ± 29.1 | 36.1 ± 10.5** |
| PEEP ($cmH_2O$) | | | | | | | | | | | |
| RF | 3.6 ± 1.5 | 4.0 ± 1.1 | 4.0 ± 1.4 | 4.2 ± 1.3 | 4.2 ± 1.5 | 4.4 ± 1.4 | 4.5 ± 1.4 | 4.5 ± 1.8 | – | 4.2 ± 1.3 | – |
| HES | 3.1 ± 1.8 | 3.0 ± 1.8 | 3.9 ± 1.1 | 3.9 ± 1.2 | 3.9 ± 1.2 | 3.9 ± 1.0 | 3.9 ± 0.9 | 4.3 ± 1.5 | 3.3 ± 0.5 | 4.2 ± 1.7 | 3.2 ± 2.0 |
| TV (ml) | | | | | | | | | | | |
| RF | 504.3 ± 96.3 | 496.3 ± 150.8 | 499.6 ± 79.5 | 497.0 ± 113.2 | 518.7 ± 82.5 | 515.4 ± 88.8 | 507.4 ± 111.1 | 499.3 ± 141.4 | – | 460.3 ± 158.7 | – |
| HES | 464.9 ± 113.4 | 457.6 ± 78.7 | 503.1 ± 101.8 | 514.2 ± 82.0 | 509.7 ± 101.5 | 528.5 ± 104.8 | 476.4 ± 55.0 | 468.1 ± 43.1 | 519.3 ± 129.5 | 519.5 ± 125.1 | 651.3 ± 68.5 |
| RR ($min^{-1}$) | | | | | | | | | | | |
| RF | 12 ± 2 | 12 ± 2 | 13 ± 2 | 13 ± 2 | 13 ± 2 | 13 ± 2 | 14 ± 2 | 14 ± 2 | – | 14 ± 2 | 17 ± 4 |
| HES | 12 ± 3 | 12 ± 2 | 13 ± 2 | 13 ± 2 | 14 ± 2 | 13 ± 3 | 13 ± 2 | 14 ± 2 | 12 ± 4 | 12 ± 4 | 15 ± 3 |
| $EtCO_2$ (mmHg) | | | | | | | | | | | |
| RF | 31.6 ± 3.7* | 33.1 ± 2.9* | 32.6 ± 3.4 | 31.9 ± 3.8 | 30.7 ± 4.2 | 30.6 ± 4.8 | 31.6 ± 5.9 | 32.3 ± 4.5 | – | 32.9 ± 4.4 | – |
| HES | 35.3 ± 3.6 | 36.2 ± 4.1 | 33.9 ± 4.3 | 32.9 ± 3.6 | 32.4 ± 4.4** | 31.6 ± 4.1 | 32.1 ± 3.9 | 33.4 ± 2.4 | 35.5 ± 2.6 | 32.7 ± 4.8 | – |
| MAC | | | | | | | | | | | |
| RF | 1.0 ± 0.3 | 1.1 ± 0.3** | 1.2 ± 0.3** | 1.3 ± 0.5** | 1.1 ± 0.2 | 1.1 ± 0.2 | 1.1 ± 0.2 | 1.1 ± 0.3 | – | 0.9 ± 0.3 | – |
| HES | 1.0 ± 0.2 | 1.1 ± 0.1** | 1.2 ± 0.2** | 1.2 ± 0.2 | 1.8 ± 2.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.0 ± 0.2 | 0.8 ± 0.3 | – |

Data were recorded after instrumentation at baseline ($T_0$), at incision ($T_1$), then hourly until the end of the surgery ($T_{es}$) and 24 h after $T_0$ ($T_{24}$). Data are presented as mean ± SD. $EtCO_2$, end-tidal carbon dioxide; $FiO_2$, fraction of inspired oxygen; MAC, minimum alveolar concentration; PEEP, positive end-expiratory pressure; RR, respiratory rate; Sat, arterial saturation; TV, tidal volume. * $P < 0.05$ significant difference between groups. ** $P < 0.05$ significant difference from $T_0$.

haemodynamic monitoring was applied in order to minimise the possibility of diagnostic errors and administer fluid boluses only when hypovolaemia was strongly supported by physiological parameters.

## Crystalloids vs. colloids – macrocirculation

The crystalloid-colloid controversy has been in focus for several decades. Over the last 15 years, several large, multicentre, randomised clinical trials were published mainly in critically ill patients. Most of these compared crystalloids with HES and concluded that there is no difference, or they observed worse outcome in the HES group.[11–13] On the basis of these results, current guidelines recommend strongly against the use of HES especially in septic patients.[14] Although the investigation of renal function was not the goal of this study, the finding that there was no difference in urine output, and serum creatinine levels remained in the normal range in both groups, with no patient requiring renal replacement therapy in the HES group provides support that there is no current evidence that HES causes renal insufficiency in the peri-operative period.[15]

Ernest Starling's three-compartment model, describing the distribution of total body water, forms the physiological rationale for using colloids in clinical practice. According to this hypothesis, colloids (i.e. similar to albumin) should stay within the intravascular space, while crystalloids should be distributed in the extracellular (intravascular and interstitial) space. Therefore, theoretically, one unit of blood loss can be replaced by three to four units of crystalloid or one unit of colloid solution.[16] However, several clinical trials, including thousands of critically ill patients, seem to disprove this principle, as we do not see this major difference in the required volume of crystalloids vs. colloids to stabilise these patients. On one hand, this discrepancy between physiology and clinical observations can be explained by the destruction of the glycocalyx in critically ill, septic patients, which impairs the semipermeable function of the endothelium; hence, colloids can escape into the interstitial space in substantial quantities.[17] On the other hand, none of these trials used detailed haemodynamic monitoring. In the current study, detailed haemodynamic evaluation was performed in order to detect hypovolaemia adequately. This resulted in higher amount of crystalloid infusion in the Ringerfundin group than in the HES group but, despite less colloid being administered, haemodilution was only significant in the HES group, thus indicating a better volume replacement effect. Strictly speaking, Starling's principle – suggesting that 3-4 times more crystalloid than colloid is required for the same volume replacement effect-, could not be confirmed in our trial. To some extent, these results seem to differ from the findings of our recent experiment in a bleeding-resuscitation pig model: fluids followed the Starling's distribution and this was explained by normal

**Table 4** Blood gas parameters in the crystalloid (Ringerfundin) and colloid (hydroxyethyl starch) groups during the study period

| Group | $T_0$ | $T_i$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_{es}$ | $T_{24}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a pH | | | | | | | | | | | |
| RF | 7.43 ± 0.20 | 7.42 ± 0.19 | 7.35 ± 0.05 | 7.36 ± 0.06 | 7.37 ± 0.03 | 7.36 ± 0.04 | 7.36 ± 0.04 | 7.34 ± 0.09 | – | 7.33 ± 0.08 | 7.38 ± 0.08 |
| HES | 7.33 ± 0.00 | 7.33 ± 0.03 | 7.34 ± 0.03 | 7.36 ± 0.02 | 7.35 ± 0.02 | 7.36 ± 0.03 | 7.34 ± 0.03 | 7.35 ± 0.02 | 7.33 ± 0.03 | 7.34 ± 0.03 | 7.43 ± 0.07** |
| a $PCO_2$ (mmHg) | | | | | | | | | | | |
| RF | 44.2 ± 8.3* | 44.5 ± 8.1* | 46.8 ± 6.8 | 45.4 ± 7.3 | 42.3 ± 4.9 | 43.2 ± 7.5 | 43.2 ± 7.5 | 46.6 ± 14.9 | – | 47.9 ± 12.9 | 43.2 ± 3.0 |
| HES | 50.4 ± 4.6 | 50.4 ± 4.6 | 47.3 ± 4.4 | 44.8 ± 3.9** | 44.9 ± 3.2** | 44.4 ± 3.9 | 46.4 ± 5.1 | 45.7 ± 2.2 | 51.4 ± 4.2 | 47.1 ± 6.3 | 41.0 ± 8.9** |
| a $PO_2$ (mmHg) | | | | | | | | | | | |
| RF | 148.0 ± 46.2 | 155.3 ± 41.0 | 137.3 ± 41.2 | 138.8 ± 30.9 | 143.7 ± 28.9 | 152.0 ± 34.6 | 142.7 ± 28.7 | 142.7 ± 17.9 | – | 145.5 ± 33.5 | 151.1 ± 49.3 |
| HES | 174.1 ± 54.9 | 174.1 ± 54.9 | 153.1 ± 71.2 | 131.6 ± 39.2** | 130.2 ± 33.4** | 145.9 ± 56.4 | 148.0 ± 61.7 | 123.1 ± 42.7 | 151.3 ± 100.1 | 184.4 ± 71.2 | 138.6 ± 41.0 |
| a BE (mmol $l^{-1}$) | | | | | | | | | | | |
| RF | −0.7 ± 1.6 | −0.9 ± 1.6 | −0.7 ± 1.3 | −1.1 ± 1.5 | −1.5 ± 1.5** | −1.6 ± 1.4 | −1.9 ± 1.2 | −2.3 ± 1.5 | – | −2.0 ± 1.3 | 1.2 ± 1.6** |
| HES | −1.1 ± 1.4 | −1.1 ± 1.4 | −1.0 ± 1.4 | −1.2 ± 1.1 | −1.2 ± 1.4 | −1.2 ± 1.3 | −1.3 ± 1.1 | −0.8 ± 0.9 | 0.2 ± 1.1 | −1.2 ± 1.4 | 1.0 ± 1.5** |
| a $HCO^-_3$ (mmol $l^{-1}$) | | | | | | | | | | | |
| RF | 24.8 ± 1.7 | 24.6 ± 2.0 | 25.1 ± 1.5 | 24.4 ± 1.7 | 23.7 ± 1.7** | 23.8 ± 2.2 | 23.6 ± 2.0 | 23.6 ± 2.0 | – | 24.1 ± 1.8 | 26.0 ± 1.5 |
| HES | 25.5 ± 1.4 | 25.5 ± 1.5 | 25.0 ± 1.5 | 24.6 ± 1.4** | 24.4 ± 1.4** | 24.3 ± 1.4 | 24.5 ± 1.4 | 24.9 ± 0.8 | 26.5 ± 1.0 | 24.7 ± 1.9 | 25.3 ± 2.5 |
| a $SO_2$ (%) | | | | | | | | | | | |
| RF | 98.5 ± 1.1 | 98.6 ± 1.1 | 98.3 ± 1.0 | 98.6 ± 0.7 | 98.7 ± 0.6 | 98.8 ± 0.7 | 98.7 ± 0.7 | 99.4 ± 1.6 | – | 98.6 ± 0.8 | 98.7 ± 0.8 |
| HES | 98.8 ± 1.0 | 98.8 ± 1.0 | 98.4 ± 1.1 | 98.3 ± 1.0 | 98.4 ± 0.7 | 98.5 ± 0.8 | 98.4 ± 0.9 | 97.7 ± 1.6 | 98.1 ± 1.3 | 99.0 ± 0.7 | 98.6 ± 0.9 |
| a lactate (mmol $l^{-1}$) | | | | | | | | | | | |
| RF | 1.1 ± 0.4 | 1.2 ± 0.5 | 0.9 ± 0.2 | 1.0 ± 0.3 | 1.1 ± 0.4 | 0.9 ± 0.2 | 1.1 ± 0.3 | 0.9 ± 0.4 | – | 1.0 ± 0.3 | 1.0 ± 0.4 |
| HES | 1.3 ± 1.0 | 1.3 ± 1.0 | 1.0 ± 0.3 | 1.0 ± 0.4 | 1.1 ± 0.5 | 1.1 ± 0.6 | 1.3 ± 0.9 | 1.6 ± 1.4 | 0.8 ± 0.4 | 1.6 ± 1.1 | 1.3 ± 0.6 |
| a Hb (g $dl^{-1}$) | | | | | | | | | | | |
| RF | 11.7 ± 1.1 | 11.7 ± 1.1 | 11.9 ± 1.3 | 11.8 ± 1.3 | 11.9 ± 1.5 | 11.1 ± 1.4 | 11.3 ± 1.3 | 11.2 ± 1.7 | – | 11.0 ± 1.4 | 10.6 ± 1.1** |
| HES | 12.6 ± 1.3 | 12.6 ± 1.3 | 11.3 ± 1.3** | 10.9 ± 1.5** | 10.4 ± 1.5** | 10.2 ± 2.0 | 10.1 ± 2.2 | 10.1 ± 1.3 | 9.8 ± 1.2 | 10.1 ± 2.2 | 10.4 ± 1.2** |
| cv pH | | | | | | | | | | | |
| RF | 7.33 ± 0.05 | 7.33 ± 0.05 | 7.33 ± 0.05 | 7.33 ± 0.04 | 7.34 ± 0.04 | 7.33 ± 0.03 | 7.33 ± 0.03 | 7.30 ± 0.08 | – | 7.30 ± 0.07 | 7.35 ± 0.06 |
| HES | 7.30 ± 0.03 | 7.30 ± 0.03 | 7.31 ± 0.03 | 7.33 ± 0.03** | 7.33 ± 0.02** | 7.33 ± 0.02 | 7.32 ± 0.03 | 7.32 ± 0.02 | 7.31 ± 0.02 | 7.31 ± 0.03 | 7.38 ± 0.06** |
| cv $PCO_2$ (mmHg) | | | | | | | | | | | |
| RF | 51.45 ± 8.2 | 50.8 ± 8.8 | 51.7 ± 6.5 | 50.2 ± 5.9 | 48.5 ± 5.4 | 48.6 ± 4.6 | 49.0 ± 5.7 | 53.1 ± 14.9 | – | 52.9 ± 13.2 | 50.5 ± 3.3 |
| HES | 55.6 ± 5.0 | 55.6 ± 5.0 | 52.6 ± 4.3 | 50.2 ± 4.0** | 50.0 ± 3.2** | 49.2 ± 4.1 | 51.8 ± 5.2 | 51.6 ± 2.9 | 55.4 ± 3.2 | 51.9 ± 5.8 | 46.8 ± 8.6** |
| cv $PO_2$ (mmHg) | | | | | | | | | | | |
| RF | 51.8 ± 8.8 | 53.8 ± 7.7 | 53.9 ± 9.4 | 52.4 ± 6.4 | 49.7 ± 5.6 | 48.3 ± 5.7 | 49.4 ± 5.7 | 51.2 ± 8.4 | – | 51.6 ± 7.8 | 46.0 ± 3.2 |
| HES | 55.5 ± 8.2 | 55.5 ± 8.2 | 56.5 ± 10.8 | 52.4 ± 8.0 | 53.2 ± 10.7 | 50.1 ± 5.6 | 49.1 ± 4.2 | 51.0 ± 4.0 | 50.5 ± 2.5 | 50.3 ± 4.4 | 43.3 ± 7.7** |
| cv BE (mmol $l^{-1}$) | | | | | | | | | | | |
| RF | −0.2 ± 1.9 | −0.4 ± 1.5 | −0.4 ± 1.1 | −0.7 ± 1.4 | −1.0 ± 1.5** | −1.3 ± 1.0 | −1.4 ± 0.9 | −1.9 ± 0.9 | – | −1.8 ± 1.0 | 1.9 ± 1.4** |
| HES | −0.3 ± 1.2 | −0.3 ± 1.2 | −0.7 ± 1.3 | −0.8 ± 1.2** | −0.6 ± 1.3 | −0.9 ± 1.5 | −0.9 ± 1.0 | −0.2 ± 0.9 | 0.3 ± 0.9 | −1.0 ± 1.3 | 1.7 ± 1.6** |
| cv $HCO^-_3$ (mmol $l^{-1}$) | | | | | | | | | | | |
| RF | 25.8 ± 2.1 | 25.7 ± 2.1 | 25.9 ± 1.2 | 25.2 ± 1.7 | 24.8 ± 1.8** | 24.9 ± 1.2 | 24.9 ± 1.5 | 24.9 ± 1.7 | – | 25.5 ± 1.8 | 27.4 ± 1.6 |
| HES | 26.8 ± 1.5 | 26.8 ± 1.5 | 26.1 ± 1.4 | 25.5 ± 1.4** | 25.5 ± 1.3** | 25.3 ± 1.6 | 25.6 ± 1.2 | 25.9 ± 1.4 | 27.1 ± 1.0 | 24.9 ± 1.6 | 26.5 ± 2.3 |
| $ScvO_2$ (%) | | | | | | | | | | | |
| RF | 81.8 ± 6.4 | 83.9 ± 6.5 | 83.9 ± 6.0 | 83.5 ± 3.2 | 81.6 ± 4.0 | 79.6 ± 4.5 | 79.3 ± 5.4 | 80.8 ± 5.2 | – | 81.3 ± 5.2 | 78.9 ± 3.1 |
| HES | 84.9 ± 5.0 | 84.9 ± 5.1 | 85.7 ± 5.6 | 84.1 ± 4.8 | 83.5 ± 3.6 | 83.3 ± 5.0 | 82.2 ± 3.6 | 84.1 ± 3.3 | 83.6 ± 3.1 | 82.2 ± 4.3 | 79.6 ± 4.6** |
| cv Hb (g $dl^{-1}$) | | | | | | | | | | | |
| RF | 11.7 ± 1.1 | 11.8 ± 1.1 | 12.5 ± 1.8 | 12.2 ± 1.7 | 11.6 ± 1.6* | 11.5 ± 1.3 | 11.2 ± 1.4 | 11.3 ± 1.4 | – | 10.8 ± 1.4 | 10.5 ± 1.2** |
| HES | 12.4 ± 1.4 | 12.4 ± 1.4 | 11.2 ± 1.4** | 11.0 ± 1.7** | 10.1 ± 1.1** | 9.7 ± 1.7 | 10.0 ± 1.3 | 10.4 ± 1.2 | 10.5 ± 1.0 | 10.2 ± 1.4 | 10.5 ± 1.3** |
| $CO_2$ gap (mmHg) | | | | | | | | | | | |
| RF | 6.7 ± 3.4 | 5.3 ± 2.9 | 5.3 ± 2.3 | 6.0 ± 1.1 | 6.0 ± 2.1 | 6.4 ± 2.1 | 6.4 ± 2.1 | 6.5 ± 2.2 | – | 6.1 ± 2.0 | 7.3 ± 2.7 |
| HES | 5.2 ± 2.1 | 5.2 ± 2.1 | 5.4 ± 2.2 | 5.4 ± 1.7 | 5.1 ± 1.5 | 4.8 ± 1.4 | 5.4 ± 2.6 | 6.2 ± 2.1 | 4.0 ± 3.0 | 4.9 ± 2.9 | 5.8 ± 2.0 |
| $PaO_2/FiO_2$ | | | | | | | | | | | |
| RF | 366.0 ± 121.1 | 378.1 ± 97.2 | 345.6 ± 115.0 | 351.8 ± 97.2 | 362.0 ± 97.0 | 383.7 ± 104.2 | 357.9 ± 100.4 | 345.7 ± 102.5 | – | 320.3 ± 116.0 | 511.1 ± 242.1 |

Table 4 (continued)

| Group | $T_0$ | $T_i$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ | $T_7$ | $T_{es}$ | $T_{24}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HES | 348.2 ± 125.9 | 375.7 ± 160.9 | 349.8 ± 195.1 | 314.7 ± 102.7 | 308.7 ± 99.4 | 331.8 ± 146.3 | 317.0 ± 125.0 | 297.9 ± 132.0 | 265.0 ± 92.5 | 327.4 ± 170.2 | 406.1 ± 168.0** |
| $DO_2I$ (ml min$^{-1}$ m$^{-2}$) | | | | | | | | | | | |
| RF | 445.5 ± 106.5 | 476.1 ± 124.6 | 438.4 ± 82.3 | 423.3 ± 91.6 | 451.0 ± 90.4 | 394.8 ± 80.6 | 410.5 ± 93.8 | 447.7 ± 87.0 | – | 405.4 ± 100.8 | 476.2 ± 132.1 |
| HES | 495.1 ± 118.0 | 492.2 ± 106.5 | 506.7 ± 167.9 | 449.8 ± 91.3 | 431.1 ± 92.2 | 424.1 ± 102.2 | 427.2 ± 109.2 | 439.0 ± 102.7 | 455.3 ± 107.7 | 428.2 ± 83.5 | 543.0 ± 172.3 |
| $VO_2I$ (ml min$^{-1}$ m$^{-2}$) | | | | | | | | | | | |
| RF | 76.8 ± 32.5 | 73.4 ± 35.5 | 64.5 ± 26.8 | 89.0 ± 71.0 | 78.6 ± 21.5 | 78.7 ± 24.8 | 80.0 ± 23.6 | 82.5 ± 30.2 | – | 77.4 ± 29.0 | 94.6 ± 26.0 |
| HES | 70.5 ± 30.4 | 69.3 ± 27.3 | 61.2 ± 22.3 | 65.0 ± 25.6 | 66.5 ± 23.3 | 66.7 ± 28.3 | 69.2 ± 16.0 | 64.3 ± 22.2 | 68.5 ± 24.5 | 71.6 ± 29.2 | 102.9 ± 34.8** |
| $ERO_2$ (%) | | | | | | | | | | | |
| RF | 17.1 ± 6.4 | 15.1 ± 6.2 | 14.8 ± 5.7 | 21.5 ± 18.3 | 17.5 ± 3.9 | 19.7 ± 4.4 | 19.7 ± 5.5 | 18.3 ± 5.2 | – | 17.8 ± 5.0 | 20.2 ± 3.1 |
| HES | 14.2 ± 4.8 | 14.2 ± 4.8 | 13.1 ± 5.4 | 14.6 ± 4.5 | 15.3 ± 3.4 | 15.6 ± 5.2 | 16.6 ± 3.8 | 14.5 ± 3.2 | 15.0 ± 3.2 | 17.2 ± 4.2 | 19.5 ± 5.0** |

Data were recorded after instrumentation at baseline ($T_0$), at incision ($T_i$), then hourly until the end of the surgery ($T_{es}$) and 24 h after $T_0$ ($T_{24}$). Data are presented as mean ± SD. a BE, arterial base excess; a Hb, arterial hemoglobin; a $HCO^-_3$, arterial bicarbonate; a lactate, arterial lactate; a $PCO_2$, arterial carbon dioxide partial pressure; a pH, arterial pH; a $PO_2$, arterial oxygen partial pressure; a $SO_2$, arterial oxygen saturation; cv BE, central venous base excess; cv $HCO^-_3$, central venous bicarbonate; cv Hg, central venous hemoglobin; cv $PCO_2$, central venous carbon dioxide partial pressure; Cv pH, central venous pH; cv $PO_2$, central venous oxygen partial pressure; $DO_2I$, oxygen delivery index; $ERO_2$, oxygen extraction; $PaO_2/FiO_2$, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; $PCO_2$ gap, central venous to arterial $CO_2$ gap; $ScvO_2$, central venous oxygen saturation; $VO_2I$, oxygen consumption index. * $P < 0.05$ significant difference between groups. ** $P < 0.05$ significant difference from $T_0$.

**Table 5 Total amount of intra-operative medications in the crystalloid (Ringerfundin) and colloid (hydroxyethyl starch) groups**

| Fluid balance | RF ($n = 15$) | HES ($n = 15$) | P |
|---|---|---|---|
| IOP Total Maintenance fluid (RF ml) | 731.2 ± 621.5 | 653.2 ± 229.3 | 0.654 |
| IOP Boluses (ml) | 1850.0 ± 900.4 | 1150.0 ± 580.9 | 0.017* |
| IOP Boluses (events) | 7.4 ± 3.6 | 4.6 ± 2.3 | 0.017* |
| IOP Total fluid (ml) | 2581.2 ± 986.2 | 1803.2 ± 497.9 | 0.011* |
| IOP Blood loss (ml) | 150.0 [100.0 to 225.0] | 250.0 [100.0 to 400.0] | 0.346 |
| Vasopressors, Inotropes | | | |
| IOP Noradrenalin (μg) | 10.0 [0.0 to 781.4] | 0.0 [0.0 to 450.0] | 0.870 |
| IOP Dobutamine (mg) | 0.0 [0.0 to 35.5] | 0.0 [0.0 to 79.5] | 0.967 |
| Anaesthetics, Analgesics | | | |
| IOP Propofol (mg) | 172.0 ± 62.7 | 190.7 ± 62.3 | 0.420 |
| IOP Morphine (mg) | 15.0 [13.0 to 20.0] | 20.0 [12.0 to 20.0] | 0.512 |
| IOP Fentanyl (μg) | 100.0 [0.0 to 100.0] | 100.0 [100.0 to 200.0] | 0.202 |
| IOP Rocuronium (mg) | 132.0 ± 50.6 | 139.0 ± 41.2 | 0.681 |

Data are mean ± SD or median [IQR]. * $P < 0.05$ significant difference between the groups.

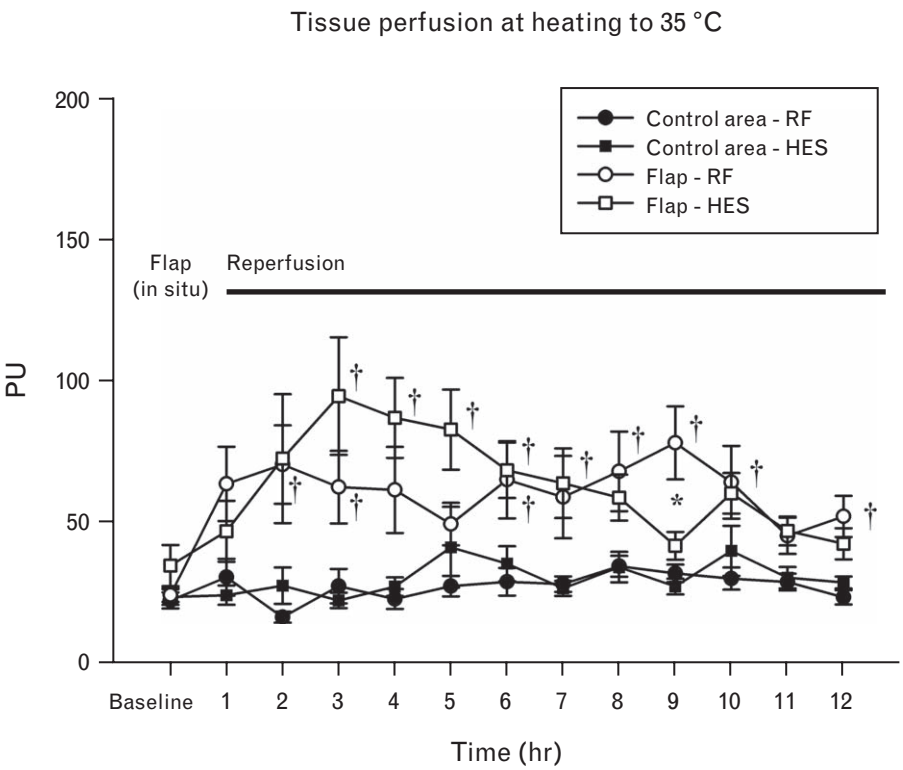
levels of glycocalyx degradation products.[18] Unfortunately, we did not have a chance to measure glycocalyx degradation products in the present clinical study. Nevertheless, our results provide further data to support the premise that during fluid therapy, to achieve similar haemodynamic goals, less colloid than crystalloid is required, therefore resuscitation could be completed faster with colloids.

## Crystalloids vs. colloids – microcirculation

Correction of systemic haemodynamics should be effective in ameliorating regional and microcirculatory perfusion.[19] The assumption that colloids, compared with crystalloids, have superior effects on the microcirculatory blood flow underestimates the importance of haemodynamic stabilisation, and gives all the credit to the better pharmacological properties of colloids.[8,20] Furthermore, most of the studies in the field did not measure cardiac output and its derivatives. Therefore, one cannot exclude that the beneficial effects of colloids on the microcirculation were due to their better volume expansion, which caused an increased cardiac output, hence better regional blood flow, rather than the features of the colloid molecules *per se*.

In the present trial, microcirculation (as examined by laser-Doppler flowmetry) showed no clinically important difference between the crystalloid and colloid groups either when the probe was placed on the control area or on the flap itself. Because the free flaps lose their innervation (including sympathetic innervation) during harvesting, significantly higher perfusion values can be observed at these sites during reperfusion.[21] Heat-induced vasodilation, which requires both intact innervation (mostly mediated by c-afferents) and endothelial function,[22] is apparently lost in the free flaps during

Fig. 3




Perfusion is expressed as the ratio of the perfused units at 44°C/PU without heating (i.e. at original temperature). The figure shows tissue perfusion on heating to 35°C in the forearm flap and at the control area (skin at the deltoid region) in the crystalloid (RF) and colloid (HES) treated patients at different time-points of the study. Recordings were taken when the flap was prepared ($R_{bsl}$), 1 h after reperfusion and continued hourly for up to 12 h. Data are presented as mean ± SD. $^{*}P < 0.05$ significant difference between groups. $^{\dagger}P < 0.05$ vs. $R_{bsl}$.

reperfusion in both treatment groups. This latter reaction, however, is present in the control areas, and reaches similar values in both groups. These results suggest that haemodynamic stability probably has a higher impact on regional microcirculation than the type of infusion fluid used to achieve this state.[8,9] Furthermore, intravenously administered vasopressors may affect denervated vessels via the endothelial nitric oxide system,[23,24] but our results suggest that norepinephrine can be used safely and does not harm the flap when its administration is controlled by appropriate haemodynamic assessment.

Although all flaps survived the study period, we observed that four flaps failed in the HES group and one in the Ringerfundin group within the first 10 days. However, in three cases, flap failure occurred most probably due to surgical complications, but our sample size is too small to draw any firm conclusions.

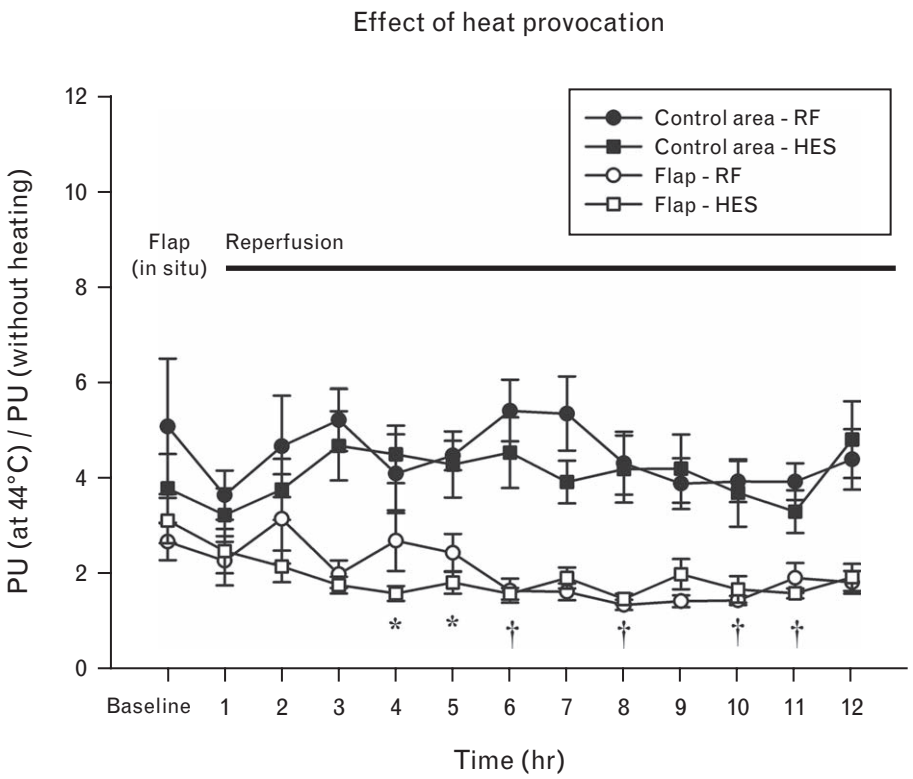
## Haemodynamic assessment

It appears that most of the clinical trials comparing the effect of crystalloids and colloids share the common feature of inappropriate haemodynamic assessment. The administration of intravenous (i.v.) fluids was mainly based on the subjective decision of the clinicians,[11,13,25–27] or on parameters such as heart rate,[12] blood pressure,[11,13,28] central venous pressure,[11,13,28] urine output,[11–13,25,28] lactate levels[12] or central venous oxygen saturation.[11,13,28] Measurements of cardiac output, stroke volume, stroke volume/PPV were typically not included.

In the current study detailed, multimodal haemodynamic evaluation was performed in order to detect haemodynamic 'instability', or more precisely to detect changes in haemodynamics, which would indicate a requirement for intervention. Furthermore, instead of targeting treatment according to fixed values (often seen in recent clinical trials), we applied a multimodal concept, including regular blood gas (both arterial and central venous) analyses. About 40% of patients needed inotropic support during surgery. This is in accordance with recent results showing that whenever advanced haemodynamic monitoring was used intra-operatively, patients required not only fluid and vasopressors but also positive inotropic support.[5]

Another important issue to note is that, according to the haemodynamic assessment, patients' intra-operative fluid requirements varied from a minimum of 500 ml to almost 3.5 l, indicating a huge individual variability and emphasising the need for advanced haemodynamic monitoring to guide fluid management in selected cases.

Fig. 4




Perfusion is expressed as the ratio of the perfused units at 44°C/PU without heating (i.e. at original temperature). The figure shows the effects on perfusion at the control site (skin at the deltoid region) and in the forearm flap in the crystalloid (RF) and colloid (HES) treated patients at different time-points. Recordings were taken when the flap was prepared ($R_{bsl}$), 1 h after reperfusion and continued hourly for up to 12 h. Data are presented as mean ± SD. $^{*}P < 0.05$ significant difference between groups. $^{\dagger}P < 0.05$ vs. $R_{bsl}$.

## Limitations

Our study has several limitations. It was a single-centre trial with a relatively small sample size and long-term effects could not be evaluated. Examination of the effects of HES on renal function would have been an important issue, but this was not among the aims of the present study. Haemodynamic monitoring was performed with a noncalibrated device. It has been reported that the accuracy and trending ability of noncalibrated devices are moderate or even poor when compared with gold standard technologies applying thermodilution measurements.[29,30] However, such results were mainly reported in critically ill patients, a very different population from that in the present trial. Although awareness and pain can exert a profound effect on haemodynamic variables, depth of anaesthesia monitoring was not used. However, in addition to clinical signs, continuous measurement of end-tidal sevoflurane was performed, and we aimed to keep the minimal alveolar concentration above 1.3 to achieve adequate depth of anaesthesia. As regards the type of fluids chosen, comparing Ringerfundin with a balanced HES-solution (Volulyte rather than Voluven) could have been a better choice. Finally, if glycocalyx degradation products could have been measured, it could have provided an important explanation for the observed difference in the amount of fluid required after crystalloid and colloid treatments.

## Conclusion

In this randomised clinical trial performed during free flap surgery, we found that compared with colloid, higher amounts of crystalloid were needed to achieve similar haemodynamic stability. There was no difference between the crystalloid and colloid groups as far as haemodynamic parameters were concerned nor was there a difference in flap perfusion either. Our results indicate that in patients without relevant blood losses and relatively low infused fluid volumes, when haemodynamic stability is maintained with the aid of detailed haemodynamic assessment, there is no measurable impact from the type of infusion fluid on free flap microcirculation.

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**Table 6** Hemodynamic parameters in the crystalloid (Ringerfundin) and colloid (hydroxyethyl starch) treated groups at baseline and during reperfusion (at matching time-points with the microcirculatory measurements)

| Group | $R_{bsl}$ | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | $R_9$ | $R_{10}$ | $R_{11}$ | $R_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SAP (mmHg) | | | | | | | | | | | | | |
| RF | 122.0 ± 28.4 | 125.9 ± 21.0 | 132.6 ± 31.1 | 131.3 ± 27.8 | 126.1 ± 21.5 | 125.4 ± 17.3 | 121.9 ± 22.2 | 119.4 ± 20.0 | 118.8 ± 27.6 | 120.8 ± 17.9 | 120.2 ± 14.6 | 118.7 ± 20.1 | 119.2 ± 19.4 |
| HES | 118.0 ± 20.8 | 117.0 ± 17.8 | 119.8 ± 29.5 | 147.0 ± 25.4[†] | 139.6 ± 31.2 | 129.2 ± 26.8 | 122.5 ± 19.4 | 114.3 ± 15.1 | 114.9 ± 13.6 | 116.2 ± 17.1 | 110.7 ± 21.1 | 122.8 ± 21.5 | 119.2 ± 15.9 |
| DAP (mmHg) | | | | | | | | | | | | | |
| RF | 60.4 ± 11.2 | 62.8 ± 11.0 | 66.2 ± 12.2[*] | 64.3 ± 15.2 | 62.7 ± 18.6 | 65.6 ± 18.5 | 64.6 ± 15.4 | 62.4 ± 14.6 | 57.3 ± 12.0 | 57.5 ± 11.6 | 59.6 ± 16.0 | 55.8 ± 12.4 | 55.9 ± 10.7 |
| HES | 61.3 ± 9.0 | 58.2 ± 8.0 | 56.6 ± 7.7 | 67.5 ± 8.8 | 61.6 ± 9.4 | 60.6 ± 8.2 | 57.6 ± 9.3 | 55.9 ± 7.0 | 56.2 ± 9.7 | 54.9 ± 6.6 | 51.8 ± 7.9[**] | 53.7 ± 8.3 | 52.8 ± 7.9[**] |
| MAP (mmHg) | | | | | | | | | | | | | |
| RF | 79.5 ± 13.2 | 85.6 ± 19.4 | 87.5 ± 19.3 | 87.1 ± 18.4 | 84.3 ± 18.3 | 88.3 ± 15.1 | 85.9 ± 12.1 | 83.2 ± 11.9 | 81.3 ± 17.5 | 80.4 ± 13.7 | 80.0 ± 13.1 | 77.9 ± 16.0 | 80.0 ± 14.0 |
| HES | 83.4 ± 13.3 | 78.9 ± 11.7 | 78.9 ± 14.9 | 101.3 ± 25.7[**] | 92.6 ± 29.6 | 84.9 ± 14.6 | 80.9 ± 11.0 | 76.3 ± 9.4 | 76.5 ± 10.0 | 76.3 ± 10.3 | 71.5 ± 9.7[**] | 78.0 ± 10.8 | 77.7 ± 10.1 |
| HR ($min^{-1}$) | | | | | | | | | | | | | |
| RF | 68.3 ± 12.3 | 66.0 ± 10.4 | 71.7 ± 11.5 | 71.0 ± 11.3 | 72.0 ± 12.8 | 69.8 ± 10.0 | 68.9 ± 9.0 | 69.1 ± 12.3 | 68.5 ± 12.3 | 68.5 ± 11.2 | 68.4 ± 11.7 | 67.8 ± 11.6 | 67.7 ± 11.6 |
| HES | 73.9 ± 9.3 | 71.2 ± 10.1 | 75.9 ± 14.3 | 83.5 ± 24.5 | 78.3 ± 21.2 | 81.8 ± 24.8 | 78.2 ± 24.1 | 78.7 ± 22.2 | 75.7 ± 18.5 | 77.2 ± 16.5 | 73.6 ± 17.1 | 75.4 ± 16.5 | 75.1 ± 16.7 |
| CI ($l min^{-1} m^{-2}$) | | | | | | | | | | | | | |
| RF | 2.8 ± 0.5 | 3.0 ± 0.3 | 3.0 ± 0.5 | 3.2 ± 0.9 | 3.2 ± 0.7 | 3.2 ± 0.8 | 3.1 ± 0.8 | 3.0 ± 0.7 | 3.2 ± 0.8 | 3.2 ± 0.8[**] | 3.0 ± 0.6 | 3.2 ± 0.7 | 3.2 ± 0.8[**] |
| HES | 3.1 ± 0.5 | 3.1 ± 0.6 | 3.2 ± 0.6 | 3.6 ± 1.2[**] | 3.6 ± 1.2[**] | 3.6 ± 1.3 | 3.3 ± 0.8 | 3.1 ± 0.6 | 3.0 ± 0.6 | 3.2 ± 0.7 | 3.2 ± 0.6 | 3.3 ± 0.8 | 3.4 ± 0.7 |
| PPV (%) | | | | | | | | | | | | | |
| RF | 9.5 ± 2.5 | 8.4 ± 3.6 | 7.5 ± 2.9[*,**] | 8.0 ± 3.6 | 8.6 ± 6.8 | 9.8 ± 6.9 | 9.5 ± 6.2 | 8.4 ± 5.3 | 9.1 ± 5.8 | 9.3 ± 4.0 | 8.0 ± 3.0 | 9.1 ± 3.7 | 9.0 ± 2.7 |
| HES | 8.6 ± 2.7 | 9.5 ± 4.2 | 10.3 ± 3.5 | 12.0 ± 6.7 | 11.4 ± 5.5 | 12.2 ± 6.7 | 11.2 ± 6.4 | 11.7 ± 5.9 | 11.0 ± 5.1 | 10.5 ± 3.8 | 11.0 ± 4.4 | 11.0 ± 5.0 | 10.1 ± 3.5 |
| SVI ($ml m^{-2}$) | | | | | | | | | | | | | |
| RF | 37.8 ± 10.9 | 41.7 ± 6.4 | 42.4 ± 7.1 | 45.0 ± 7.7[**] | 42.6 ± 8.1 | 43.5 ± 10.1 | 44.7 ± 8.8[**] | 43.2 ± 9.2 | 45.2 ± 9.6[**] | 46.7 ± 9.0[**] | 45.3 ± 10.5[**] | 46.8 ± 8.3[**] | 48.2 ± 9.1[**] |
| HES | 42.5 ± 6.2 | 43.5 ± 6.0 | 43.5 ± 5.9 | 45.7 ± 6.3 | 46.8 ± 6.4 | 44.0 ± 5.6 | 42.3 ± 4.4 | 40.8 ± 4.9 | 41.5 ± 5.3 | 42.3 ± 5.5 | 43.0 ± 6.4 | 45.7 ± 6.4 | 48.2 ± 7.9 |

Data were recorded after the flap was prepared ($R_{bsl}$), then 1 h after reperfusion and continued hourly for up to 12 h ($R_1$ – $R_{12}$). Data are presented as mean ± SD. *CI*, cardiac index; DAP, diastolic blood pressure; dPmax, index of left ventricular contractility; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; PPV, pulse pressure variability; SAP, systolic blood pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index; SVV, stroke volume variation. * $P < 0.05$ significant difference between groups. ** $P < 0.05$ significant difference from $R_{bsl}$.

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