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ORIGINAL

Continual hemodynamic monitoring with a single-use transesophageal echocardiography probe in critically ill patients with shock: a randomized controlled clinical trial

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Abstract

Purpose: Mortality in circulatory shock is high. Enhanced resolution of shock may improve outcomes. We aim to determine whether adding hemodynamic monitoring with continual transesophageal echocardiography (hTEE) to usual care accelerates resolution of hemodynamic instability.

Methods: 550 patients with circulatory shock were randomly assigned to four groups stratified using hTEE (hTEE vs usual care) and assessment frequency (minimum every 4 h vs 8 h). Primary outcome was time to resolution of hemodynamic instability, analyzed as intention-to-treat (ITT) analysis at day 6 and in a predefined secondary analysis at days 3 and 28.

Results: Of 550 randomized patients, 271 with hTEE and 274 patients with usual care were eligible and included in the ITT analysis. Time to resolution of hemodynamic instability did not differ within the first 6 days [hTEE vs usual care adjusted sub-hazard ratio (SHR) 1.20, 95% confidence interval (CI) 0.98–1.46, $p = 0.067$]. Time to resolution of hemodynamic instability during the 72 h of hTEE monitoring was shorter in patients with TEE (hTEE vs usual care SHR 1.26, 95% CI 1.02–1.55, $p = 0.034$). Assessment frequency had no influence. Time to resolution of clinical signs of hypoperfusion, duration of organ support, length of stay and mortality in the intensive care unit and hospital, and mortality at 28 days did not differ between groups.

Conclusions: In critically ill patients with shock, hTEE monitoring or hemodynamic assessment frequency did not influence resolution of hemodynamic instability or mortality within the first 6 days.

Trial registration and statistical analysis plan: ClinicalTrials.gov Identifier: NCT02048566.

Keywords: Circulatory shock, Hemodynamic monitoring, Hemodynamic transesophageal echocardiography (hTEE), Randomized controlled trial

Introduction

Circulatory shock has always had a poor outcome and its treatment remains challenging [1]. The effects of shock are initially reversible, but treatment delays, repeated or prolonged hypotension, and high-dose vasopressors may all worsen the prognosis [1–4]. How the treatment of shock should be monitored is controversial [5]. To date, no monitoring technology for hemodynamically unstable patients has improved the outcomes. This has been

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attributed to the failure of coupling monitoring with therapeutic interventions [6]. However, trials comparing monitoring-coupled treatment protocols with usual care have shown no benefit [7–9].

Echocardiography is considered a primary assessment tool in acute circulatory failure. Its usefulness in the diagnosis and management of hemodynamics in shock states has been shown [10–12], but its effects on patient-centered outcomes are unclear [13].

Qualitative hemodynamic TEE assessment (hTEE) using disposable miniature echocardiography probes facilitates repeated and continual monitoring of cardiac function and response to treatment [14]. Whether the use of hTEE enhances hemodynamic stabilization in circulatory shock is not known. If earlier shock resolution is achievable, its impact on other patient-centered outcomes should be assessed.

We hypothesized that hTEE monitoring as compared to usual care expedites the time to resolution of hemodynamic instability in patients admitted to the intensive care unit (ICU) with unstable hemodynamics and tested this in a randomized controlled trial.

Methods

The Ethics Committee of the Canton of Bern, Switzerland approved the study (KEK 174/13). The study protocol has been published [15, 16].

Trial design and setting

This randomized, open label, 2×2 factorial design, controlled clinical trial comparing hemodynamic monitoring using hTEE with standard monitoring was conducted from March 2014 to October 2017. The Department of Intensive Care Medicine, Bern University Hospital is a tertiary care 37-bed multidisciplinary adult ICU.

Patient selection

Consecutive patients >18 years with unplanned ICU admission requiring mechanical ventilation and in circulatory shock of any cause were eligible. Circulatory shock was defined as mean arterial blood pressure (MAP) < 60 mmHg (or < 80 mmHg if chronically hypertensive) for > 30 min despite adequate fluid resuscitation (minimum 20 ml/kg of crystalloids) or maintaining the MAP $\geq$ 60 mmHg required any vasopressors or inotropes, and concomitant signs of hypoperfusion or organ dysfunction (capillary refilling time $\geq$ 3 s, urine output < 0.5 mL/kg/h, lactate > 2 mmol/L) [17–20]. Patients with upper gastrointestinal tract or cervical spine pathologies, severe coagulopathy (thrombocyte count < $30 \times 10e9$/l or INR > 3) precluding TEE, ICU admission after planned surgery or on mechanical circulatory support were excluded.

Take-home message

Continual hemodynamic monitoring with transesophageal echocardiography (hTEE) shortens the time to resolution of hemodynamic instability during the first 72 h after ICU admission. The use of hTEE monitoring in addition to usual care helps to stabilize patients in circulatory shock.

Randomization and procedures

The allocation sequence used computer-generated random numbers with randomly varying block sizes [21]. Intervention assignments were inside sequentially numbered, opaque sealed envelopes. Only two hTEE devices were available and recruitment for all groups was interrupted as soon as the second patient was randomized to hTEE. Subjects were assigned to one of the four groups stratified by the method of hemodynamic monitoring and frequency of hemodynamic assessments:

- hTEE protocolized monitoring (hTEEPM) group: hTEE assessment at study inclusion, when new organ system deterioration occurred or at least 4 hours
- hTEE standard monitoring (hTEESM) group: hTEE assessment at study inclusion, follow-up assessments at discretion of the treating specialist but at least 8 hours
- Control protocolized monitoring (ControlPM); hemodynamic monitoring at discretion of treating specialist, assessment at study inclusion, when new organ system deterioration occurred or at least 4 hours
- Control standard monitoring (ControlSM); assessment at study inclusion, hemodynamic monitoring and follow-up assessments at the discretion of the treating specialist but at least 8 hours

In patients with hTEE monitoring, the hTEE device (ImaCor Inc, Garden City, NY, USA) was installed and examinations were performed by the ICU specialist in charge of the patient. The hTEE had previously been introduced to clinical use [22] and specialists were trained accordingly. The device produces single-plane two-dimensional views using a 5.5 mm detachable probe for up to 72 h. Additional hemodynamic monitoring (central venous catheter, pulmonary artery catheter, and conventional echocardiography) was used at the discretion of the treating ICU specialist. Three hTEE standard views were acquired: transgastric midesophageal, midesophageal four chamber and midesophageal ascending aortic short axis view [22]. Fractional area change of left ventricle, ratio of right to

left ventricular areas, and superior vena cava collapsibility index were calculated.

The ICU specialist quantified and interpreted the hTEE findings in the context of all available hemodynamic monitoring and reported consequent changes in the treatment (Supplementary Methods 1). For control patients, monitoring was at the discretion of the treating ICU specialist. Study procedures including hTEE were stopped when resolution of hemodynamic instability occurred or latest after 72 h. All patients received usual care prescribed by the treating ICU specialist.

Data collection methods

Hemodynamic variables, use of vasopressors/inotropes, fluids, and organ support were registered in the patient data management system (PDMS; GE Centricity Critical Care, General Electrics, Helsinki, Finland) as part of routine care.

Outcomes

The primary outcome resolution of hemodynamic instability was defined as the time from study commencement to the point, when more than 90% of the 2-min median MAP values, automatically recorded in the PDMS, had been ≥ 60 mmHg for 4 h after discontinuation of vasopressors or inotropes (identified using a customized macro, Excel™ VBA, Microsoft Office). The primary analysis of the primary outcome was censored after 6 days. Secondary analysis of the primary outcome included the censoring after 3 days and after 28 days. The secondary outcomes included the time to resolution of signs of hypoperfusion (capillary refilling time < 3 s, urine output > 0.5 mL/kg/h for at least 4 h, and blood lactate < 2 mmol/L, documented at 2 h intervals), time to death, use of conventional echocardiography and hemodynamic monitoring (pulmonary artery catheter, central venous catheter) and occurrence of serious adverse events. Further outcomes of interest included the length of time on organ support (mechanical ventilation, renal replacement therapy), length of stay (LOS) and mortality in the ICU and in hospital.

Sample size calculation

Sample size calculation was based on 159 patients sampled over 3 months. Median time to resolution of hemodynamic instability as defined by discontinuation of vasopressors or inotropes was 18.5 h [interquartile range (IQR) 6.5–43.9 h]. A sample size of 458 patients was required to achieve a power of 80% at two-sided alpha level of 0.05 for the main effect (monitoring with/without hTEE) to identify a clinically relevant reduction of time to resolution of circulatory shock of 25%. Patient recruitment was continued until 500 patients, with a complete study follow-up, and approved deferred study consent were included—resulting in 550 randomized patients. During the study, the Swiss law on human research changed, allowing the primary outcome assessment also in patients, whose deferred consent was withdrawn, not accepted, or not obtainable (e.g., due to death). An amendment approved by the Ethics Committee allowed inclusion of all randomized patients in the analysis of the primary outcome.

Statistical methods

Since the study was powered only for the main effect (monitoring with/without hTEE), the results are presented as two groups according to the use of hTEE, combining group hTEEPM with hTEESM (hTEE monitoring) and group ControlPM with ControlSM (control monitoring). The primary analysis was based on intention-to-treat (ITT). We examined the association of hTEE use and monitoring interval with the time to hemodynamic stabilization using competing risk regression models according to Fine and Gray, accounting for the competing risk of death [23]. The interaction between the method and frequency of hemodynamic monitoring was also tested. The primary outcome was censored after 6 days in the primary analysis. The secondary outcome time to death was evaluated using Cox proportional-hazards regression. Other secondary time-to-event outcomes were analyzed like the primary outcome using competing risk models. Logistic regression, adjusted for monitoring frequency was used for binary outcomes. Secondary analyses included a per-protocol analysis of patients who received the allocated monitoring, and sensitivity analyses for the primary endpoint censoring after 3 days and after 28 days using the ITT data set.

Between-group comparisons for further outcomes of interest were analyzed post hoc. Variables not in the original statistical analysis plan included the number of changes in hemodynamic management and volume administration during the 72 h of monitoring and 28-day mortality. The post hoc comparisons were done using Wilcoxon rank-sum test for continuous and Chi squared test for categorical data. All analyses were done using Stata 15 (Stata Corporation, College Station, Texas, USA).

Data monitoring

The trial was externally monitored (Clinical Trials Unit, Bern, Switzerland) in accordance with Good Clinical Practice standards. All variables used in the analysis,

including the derived variables, were checked for missing values, outliers, and inconsistencies and queried.

Results

Patient characteristics

During the study, 550 patients of 8812 ICU admissions were randomized. 271 patients were allocated to hTEE monitoring and 274 patients to control monitoring in the ITT analysis (Fig. 1). Baseline characteristics were evenly distributed (Table 1).

Primary outcome

In the ITT analysis, the time to resolution of hemodynamic instability within 6 days after randomization did not differ between hTEE monitoring versus control patients [adjusted sub-hazard ratio (SHR) 1.20, 95% confidence interval (CI) 0.98–1.46, $p=0.067$] (Supplementary Table 1 for all study groups). In the prespecified secondary analysis at the maximum duration of hTEE monitoring of 72 h, time to resolution of hemodynamic instability was shortened in the hTEE monitoring group (SHR 1.26, 95% CI 1.02–1.55, $p=0.034$) (Fig. 2). In the per-protocol analysis (249 patients with hTEE monitoring, 250 control patients), the primary outcome time to resolution of hemodynamic instability at 6 days was shorter in the hTEE group (SHR 1.24, 95% CI 1.00–1.52, $p=0.045$). The per-protocol analysis at 3 days indicated earlier resolution of shock in the hTEE patients (adjusted SHR 1.30, 95% CI 1.05–1.62, $p=0.018$) (Supplementary Fig. 1). The secondary analysis of time to resolution of hemodynamic instability by monitoring frequency showed no significant difference (SHR 0.96, 95% CI 0.79–1.16, $p=0.65$ within 6 days; SHR 0.98, 95% CI 0.80–1.21, $p=0.88$ within 3 days) and no interaction between the monitoring group and the monitoring frequency ($p_{\text{interaction}}=0.66$ for the primary endpoint during 6 days, and $p_{\text{interaction}}=0.99$ for the 72 h sensitivity analysis).

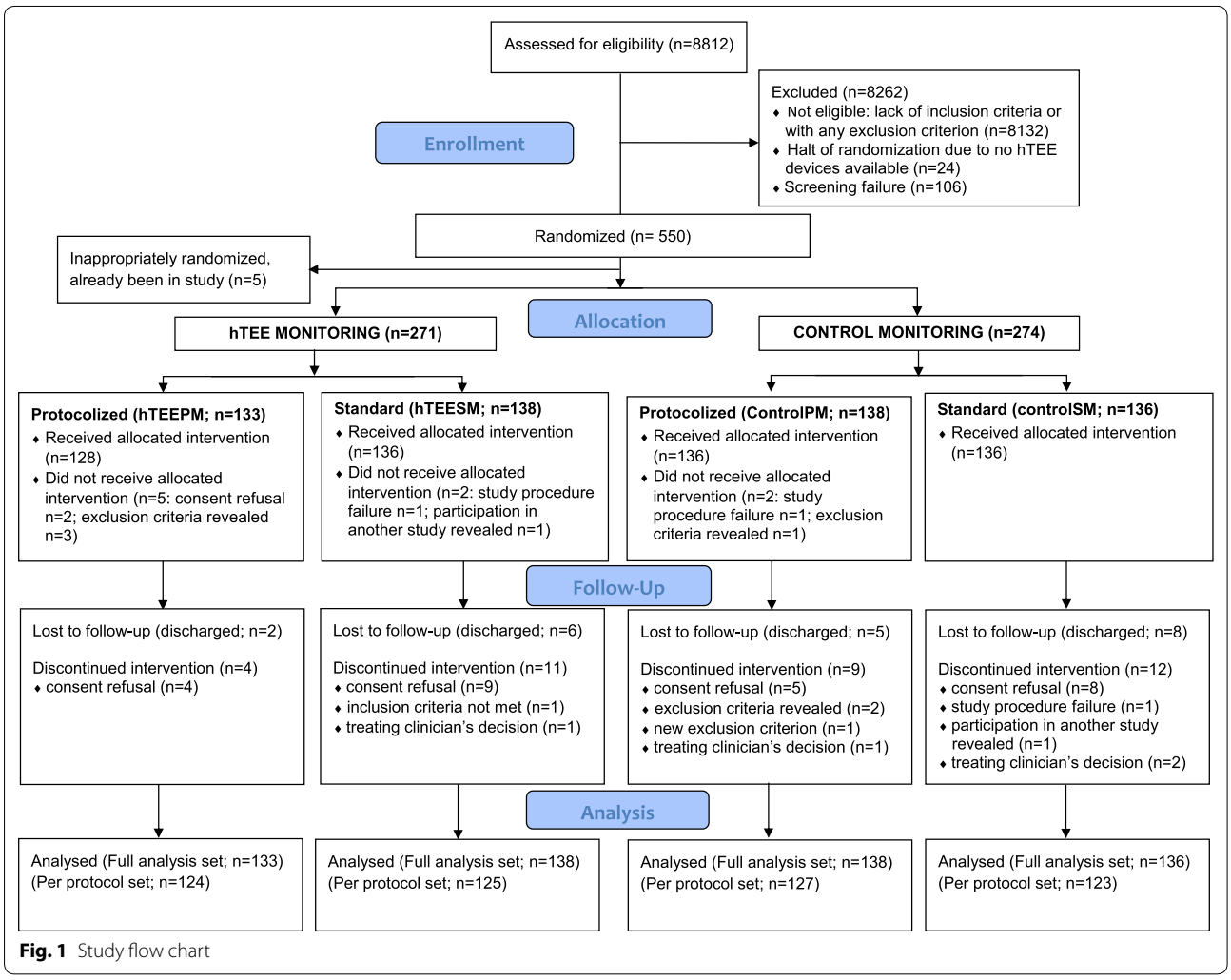

Fig. 1 Study flow chart

Table 1 Patient characteristics at randomization

Values	All (*n*=545)	hTEE (n=271)	Control (*n*= 274)
Age, median (IQR), years	70 (60–77)	70 (60–77)	70 (60–77)
Female sex, no. (%)	181 (33)	96 (35)	85 (31)
BMI, median (IQR), kg/m2	27 (24–31)	27 (25–29)	28 (24–31)
Admission from, no. (%)			
Emergency department	113 (21)	53 (20)	60 (22)
Ward	100 (18)	52 (19)	48 (18)
External	56 (10)	31 (11)	25 (9)
Coronary angiogram suite	84 (15)	40 (15)	44 (16)
Operating theater	177 (33)	82 (30)	95 (35)
Other	15 (3)	13 (5)	2 (1)
Admission diagnosis, no. (%)			
Cardiovascular	320 (59)	158 (59)	162 (59)
Gastrointestinal	38 (7)	19 (7)	19 (7)
Metabolic	7 (1)	1 (0)	6 (2)
Neurologic	17 (3)	10 (4)	7 (3)
Renal or urinary	6 (1)	3 (1)	3 (1)
Respiration	53 (10)	24 (9)	29 (11)
Trauma	17 (3)	7 (3)	10 (4)
Infectious	85 (16)	48 (18)	37 (14)
Other	2 (0)	1 (0)	1 (0)
Comorbidities, no (%)			
Chronic lung disease	101 (19)	45 (17)	56 (20)
Chronic cardiovascular	357 (66)	163 (60)	194 (71)
Chronic liver disease	31 (6)	12 (4)	19 (7)
Chronic renal failure	119 (22)	58 (21)	61 (22)
Immunosuppression	20 (4)	11 (4)	9 (3)
Lymphoma	3 (1)	1 (0)	2 (1)
Metastatic cancer	27 (5)	18 (7)	9 (3)
Leukemia or myeloma	4 (1)	3 (1)	1 (0)
APACHE II score, median (IQR)	26 (20–32)	26 (21–32)	27 (20–32)
SOFA score, median (IQR)	11 (9–13)	10 (8–13)	11 (9–13)

APACHE II Acute Physiology, Age, Chronic Health Evaluation II score, *BMI* body mass index, *IQR* interquartile range, *SOFA* sequential organ failure assessment score

Secondary and further outcomes of interest (Table 2)

Time to death and post hoc analyses of ICU, hospital and 28 day mortality did not differ between hTEE and standard monitoring. No difference between groups in LOS in ICU and hospital, duration of mechanical ventilation or duration of renal replacement therapy, volume

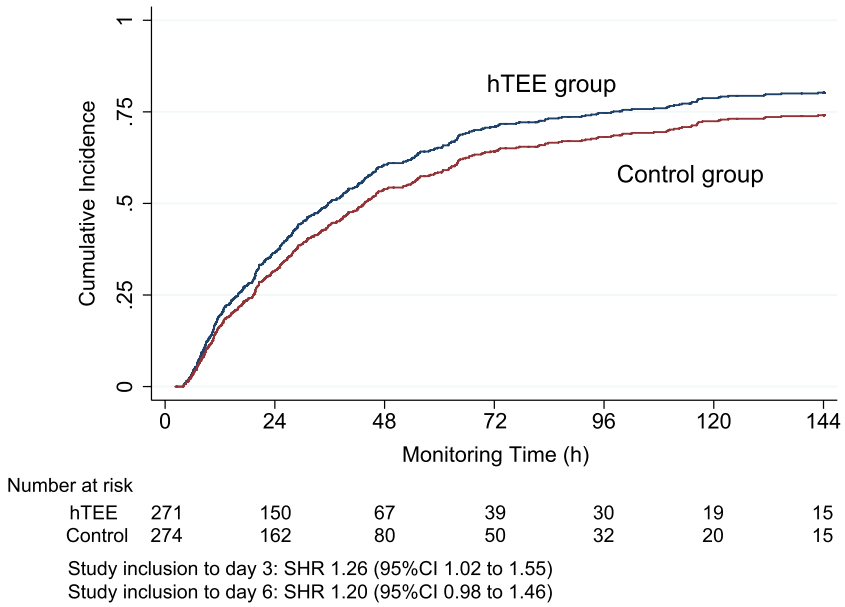

Fig. 2 Proportion of patients who reached resolution of hemodynamic instability (intention-to-treat analysis)

administration during the 72 h of monitoring and time to resolution of signs of hypoperfusion (Supplementary Fig. 2a/b) was observed. Post hoc analysis indicated fewer changes in hemodynamic management in hTEE patients [hTEE median 2, interquartile range (IQR) 1–3; control median 2, IQR 1–4, $p < 0.001$].

Exploratory analyses

The clinical assessment of hemodynamic status using all available information at the first assessment after study inclusion indicated insufficient cardiac output, impaired left ventricular systolic function, and hypovolemia as the most common causes of circulatory shock. Adrenaline and noradrenaline were the most used vasoactive drugs (Supplementary Table 2). The incidence of adverse events attributable to prolonged circulatory shock and treatment with vasopressors and inotropes was low (Supplementary Table 3). Oropharyngeal bleeding was observed in one hTEE patient, and additional sedation and muscle relaxants for hTEE examinations were given in 186 (68.6%) and 20 (7.4%) of patients, respectively.

Discussion

The main finding was that adding hTEE to standard hemodynamic monitoring for up to 72 h in patients with circulatory shock did not shorten the time to resolution of hemodynamic instability at 6 days, the primary outcome. However, when examining the first 72 h of hTEE monitoring in a sensitivity analysis, a clinically and statistically significant reduction could be observed. In addition, the per-protocol analysis indicated enhanced resolution of hemodynamic instability over 72 h and 6 days. Adding protocolized intervals of assessment of hemodynamics to hTEE or standard monitoring did not influence resolution of hemodynamic instability, i.e., we observed neither an effect of more frequent assessments nor an interaction between the use of hTEE and protocol-defined minimum frequency of assessments. Although earlier resolution of shock is conceivably beneficial, our study was not powered to show an outcome benefit, and no differences in mortality or ICU or hospital LOS were observed.

Several issues need to be considered. This was a single center study, and blinding was not feasible. The study center has a trained ICU specialist in charge of patient care 24/7, and advanced hemodynamic monitoring was available for all study groups. More frequent assessment might per se enhance resolution of hemodynamic instability. To avoid such bias, we mandated structured assessment of hemodynamic disorders at minimum intervals. Conventional monitoring was used as often in control as in hTEE groups, except for more frequent use of TTE in the control groups. The low mortality for patients with shock supports the view of high-quality care in all patients. Additional sedation was often necessary to be able to perform hTEE and may have prolonged hypotension and attenuated potential benefits of hTEE. The more frequent treatment changes in the control groups also suggest that the control groups did not receive fewer efforts to treat shock. Since the study was powered for

Table 2 Secondary outcomes and further outcomes of interest

Secondary outcomes	hTTE (n=271)	Control (n=274)		*p* value
Hazard of death within 3 days, HR (95% CI)	1.01 (0.65–1.54)	1 (reference)		0.981
Hazard of death within 6 days, HR (95% CI)	0.95 (0.67–1.34)	1 (reference)		0.778
Resolution of clinical signs of hypoperfusion within 3 days, SHR (95% CI)	1.24 (0.97–1.58)	1 (reference)		0.08
Resolution of clinical signs of hypoperfusion within 6 days, SHR (95% CI)	1.20 (0.95–1.50)	1 (reference)		0.13
Use of conventional hemodynamic monitoring, no. (%)			**Odds ratio (95% CI)**	
Pulmonary artery catheter	168 (62)	181 (66)	0.82 (0.55–1.2)	0.31
Central venous catheter	239 (88.2)	246 (89.8)	0.85 (0.5–1.45)	0.56
Conventional TTE	71 (26.2)	97 (35.4)	0.65 (0.45–0.94)	0.02
Conventional TEE	59 (21.8)	63 (23)	0.93 (0.62–1.4)	0.74
Further outcomes of interest (post hoc analysis)			**Risk difference (95% CI)**	
ICU mortality, no. (%)	63 (23.3)	68 (24.8)	– 0.02 (– 0.09 to 0.06)	0.67
Hospital mortality, no. (%)	80/271 (29.5)	87/272 (32.0)	– 0.02 (– 0.1 to 0.05)	0.53
28 day mortality, no. (%)[a]	87/270 (32.2)	95/273 (34.8)	– 0.03 (– 0.1 to 0.05)	0.52
Duration of any organ support (n = 498), median (IQR), h	42.8 (16.2–109.7)	38.3 (15.3–111.2)		0.73
Duration of MV (n = 498), median (IQR), h	42.1 (15.3–97.1)	35.6 (13.5–100.2)		0.73
Duration of RRT (n = 102), mean (SD), h	161.2 (36.9–309.2)	122.3 (38.6–404)		0.68
LOS in ICU (n = 499), median (IQR), h	60 (32.2–120.4)	55.1 (29.3–121.3)		0.87
LOS in hospital (n = 499), median (IQR), h	237.5 (94.1–454.8)	248.5 (88.8–478.1)		0.91
Cumulative amount of resuscitation fluids (n = 498), median (IQR), ml[a]	3200 (1425–5400)	3325 (1490–6500)		0.46

CI confidence interval, *HR* hazard ratio, *hTEE* hemodynamic transesophageal echocardiography, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *MV* mechanical ventilation, *RRT* renal replacement therapy, *TEE* transesophageal echocardiography, *TTE* transthoracic echocardiography, *VT* ventricular tachycardia, *SVT* supraventricular tachycardia

[a] Variables not in the statistical analysis plan

the main effect of hTEE and not for an interaction of protocolized assessment of hemodynamics, the lack of such interaction should be interpreted with caution. However, the lack of effect of assessment frequency on the primary outcome indicates that our findings are not caused by a more frequent or thorough assessment

of the intervention patients. The study ICU is the only adult ICU in this large academic medical center. The case mix with more than 50% of the patients with primary cardiovascular cause for the hemodynamic instability and almost 20% with infectious condition likely reflect the general ICU population and may deviate from case mix of specialized ICUs. Our findings should therefore be confirmed in a larger multicenter trial to improve generalizability.

The time to reach hemodynamic stability was longer than the one used for sample size calculations. In the study, 4 h of hemodynamic stability without vasopressors was required based on arterial pressure measurements every 2 min. For sample size calculation, time of stopping vasopressors was used to define stable hemodynamics and the competing risk of death was not included potentially leading to underpowering the study for the main outcome. We considered 25% reduction in time to resolution of hemodynamic instability as clinically relevant. Despite the longer time to stabilization as expected, the rate of reaching hemodynamic stability during active monitoring over 72 h was approximately 25% higher in patients with hTEE monitoring. This study was not designed to evaluate the potential benefits of earlier shock resolution. Reduced exposure to catecholamines and their side effects may be beneficial per se and earlier shock resolution may reduce the risk and severity of organ dysfunction [24–26].

The results should not be interpreted to indicate that hTEE could replace other hemodynamic monitoring. In all study groups, the patient care was guided by comprehensive assessment of all hemodynamic and clinical information, not by a single technology. Echocardiography has become an essential tool for assessment of hemodynamics in the ICU patient, but its impact on outcomes has not been assessed. Conventional echocardiography is clearly a diagnostic tool, whereas hTEE facilitates continual monitoring and assessment of response to treatment. Conventional echocardiography was available for all study patients, and still, hTEE seems to have offered a benefit. Conventional echocardiography was used more often in the patients without hTEE, attenuating potential benefits in the hTEE group and suggesting that hTEE provided information relevant to the treatment. This is supported by the fact that fewer changes in treatment were done in patients with hTEE. The lack of improvement in time to resolution of hemodynamic instability on day 6 in the ITT set and the improvement until 72 h, the maximal duration of hTEE use, as well as the consistent reduction in time to resolution of hemodynamic instability in the per-protocol analysis support the view that use of hTEE helped to optimize the treatment.

We are not aware of any previous randomized, controlled trial to show that specific monitoring technologies, whether or not coupled with treatment protocols [7–10, 27–29], would impact the clinical course of acute circulatory failure. Most recently, protocol-based hemodynamic management, with or without combination with central venous oxygen saturation monitoring failed to improve outcome as compared to usual care in sepsis [7–10]. Earlier, adding pulmonary artery catheter to usual care in a heterogeneous ICU patient cohort [27], or adding minimally invasive cardiac output to usual care in hemodynamically unstable patients [28] did not improve outcome. In acute lung injury, care using either central venous or pulmonary artery catheter-driven protocols resulted in no difference in outcomes [29]. A monitoring strategy can only influence the process of care and patient-oriented outcomes, if coupled with the right treatment. Protocolized hemodynamic treatments in ICU patients have so far failed to show any benefit [7–10, 27–29]. This has been attributed at least in part to failure of treatment protocols to individualize patient care. Our study mandated regular patient assessments and definition of the hemodynamic status but specifically did not stipulate how the findings should influence the hemodynamic management. Similarly, the study procedures did not mandate how to deal with diverging information from different monitoring modalities. Accordingly, the clinicians based their decisions on the comprehensive evaluation of all information available in each individual patient, i.e., individualized the treatment instead of one-size-fits-all treatment protocols. Conceivably, in the present study, adding hTEE to standard monitoring helped the clinicians to optimize care in individual patients, which resulted in faster resolution of hemodynamic instability during the monitoring and fading of this effect after hTEE was discontinued. The hTEE probes are approved to be used for a maximum of 72 h, and the study protocol did not include an option to continue the monitoring by replacing the probe.

In conclusion, we found no evidence that the use of hTEE monitoring for up to 72 h in the initial resuscitation of patients with shock influenced the resolution of hemodynamic instability over 6 and 28 days. However, in a sensitivity analysis focusing on the first 72 h when hTEE was used, we observed a significant increase in the rate of resolution of hemodynamic instability. The results of this single center trial and the potential benefits from earlier shock resolution for patient-centered outcomes should be confirmed in a larger multicenter trial.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05670-6) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
Dr Takala has, after his retirement from the Department of Intensive Care Medicine in August 2018, provided paid consultancy services for the Medical Director and the Director of Technology and Innovation of the Inselspital, Bern University Hospital, and to Nestec SA. The Department of Intensive Care Medicine has, or has had in the past, research contracts with Orion Corporation, Abbott Nutrition International, B. Braun Medical AG, CSEM SA, Edwards Lifesciences Services GmbH, Kenta Biotech Ltd, Maquet Critical Care AB, Omnicare Clinical Research AG and research & development/consulting contracts with Edwards Lifesciences SA, Maquet Critical Care AB, and Nestlé. The money was paid into a departmental fund, and nine of the authors received financial gain. The Department of Intensive Care Medicine has received unrestricted educational grants from the following organizations for organizing a quarterly postgraduate educational Symposium, the Berner Forum for Intensive Care (until 2015): Fresenius Kabi, GSK, MSD, Lilly, Baxter, Astellas, AstraZeneca, B | Braun, CSL Behring, Maquet, Novartis, Covidien, Nycomed, Pierre Fabre Pharma AG (formerly known as RobaPharm), Pfizer, Orion Pharma, Bard Medica S.A., Abbott AG, Anandic Medical Systems. The Department of Intensive Care Medicine has received unrestricted educational grants from the following organizations for organizing bi-annual postgraduate courses in the fields of critical care ultrasound, management of ECMO and mechanical ventilation: Pierre Fabre Pharma AG (formerly known as RobaPharm), Pfizer AG, Bard Medica S.A., Abbott AG, Anandic Medical Systems, PanGas AG Healthcare, Orion Pharma, Bracco, Edwards Lifesciences AG, Hamilton Medical AG, Fresenius Kabi (Schweiz) AG, Getinge Group Maquet AG, Dräger Schweiz AG, Teleflex Medical GmbH.

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