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ORIGINAL ARTICLE

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Autologous red blood cell transfusion does not result in a more profound increase in pulmonary capillary wedge pressure compared to saline in critically ill patients: A randomized crossover trial

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Abstract

Background and Objectives: Transfusion-associated circulatory overload (TACO) is a major cause of severe transfusion-related morbidity. Transfusion of red blood cells (RBCs) has been shown to induce hydrostatic pressure overload. It is unclear which product-specific factors contribute. We set out to determine the effect of autologous RBC transfusion versus saline on pulmonary capillary wedge pressure (PCWP) change.

Materials and Methods: In a randomized crossover trial, patients who had undergone coronary bypass surgery were allocated to treatment post-operatively in the intensive care unit with either an initial 300 ml autologous RBC transfusion (salvaged during surgery) or 300 ml saline infusion first, followed by the other. Primary outcome was the difference in PCWP change. Secondary outcome measures were the difference in extra-vascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI).

Results: Change in PCWP was not higher after autologous RBC transfusion compared to saline (ΔPCWP 0.3 ± 0.4 vs. 0.1 ± 0.4 mmHg). ΔEVLWI and ΔPVPI were significantly decreased after autologous RBC transfusion compared to saline (ΔEVLWI -1.6 ± 0.6 vs. 0.2 ± 0.4, $p = 0.02$; ΔPVPI -0.3 ± 0.1 vs. 0.0 ± 0.1, $p = 0.01$). Haemodynamic variables and colloid osmotic pressure were not different for autologous RBC transfusion versus saline.

Conclusion: Transfusion of autologous RBCs did not result in a more profound increase in PCWP compared to saline. RBC transfusion resulted in a decrease of EVLWI and PVPI compared to saline. Our data suggest that transfusing autologous RBCs may lead to less pulmonary oedema compared to saline. Future studies with

allogeneic RBCs are needed to investigate other factors that may mediate the increase of PCWP, resulting in TACO.

KEYWORDS
autologous blood transfusion, volume overload

Highlights

- Transfusion-associated circulatory overload (TACO) is the leading cause of transfusion-related morbidity and mortality. The onset mechanism has long been hypothesized as due to the capacity of red blood cells (RBCs) to increase hydrostatic pressure in the pulmonary vascular system.
- Transfusion of autologous RBCs does not result in a more profound increase in pulmonary capillary wedge pressure than transfusion of an equal volume of saline.
- Future studies should focus on other factors, including allogeneic RBC transfusion, and their role in the onset of TACO.

INTRODUCTION

Physicians consider blood transfusion a life-saving treatment, but transfusion has been associated with adverse events [1]. Transfusion-associated circulatory overload (TACO) is one of the major causes of severe transfusion-related morbidity and mortality [2], with an incidence of up to 6% in a critical care population [3]. Volume overload has a central role in the poorly understood pathophysiology of this clinical diagnosis [2, 4]. Hydrostatic pressure is a crucial component in the aetiology of the extravascular fluid accumulation in TACO [5], and an inflammatory process may contribute to this [6–8].

Multiple studies indicate that transfusion may lead to TACO through pathways other than hydrostatic pressure alone. Half of the reported TACO cases are diagnosed after transfusing only a single unit of red blood cells (RBCs), so volume overload is not to be expected [9]. The incidence of TACO is specific to the transfusion product [10, 11]. In a case–control study of critically ill patients, TACO patients received significantly less volume than patients diagnosed with circulatory overload in the absence of transfusion [3]. Furthermore, pro-inflammatory aspects of blood transfusion have gained more and more importance. One-third of TACO patients present with fever [8], and if leukocytes were reduced, this was associated with a decrease in the incidence of TACO [6]. Combined evidence suggests a transfusion-related acute lung injury (TRALI)-like inflammatory response, and enhanced vascular permeability, leading to pulmonary oedema [5, 6].

Previous studies assessing the effect of allogeneic RBC transfusion on hydrostatic pressure have found a pulmonary capillary wedge pressure (PCWP) rise of 3 mmHg in chronic anaemic patients following transfusion [12, 13], and suggested pulmonary artery pressure (PAP) increases after standard-issue versus fresh RBCs in critically ill patients [14]. A volunteer study showed an increase in the mean PAP following autologous transfusion of 1 unit of stored RBCs [15]. It remains to be determined whether hydrostatic pulmonary oedema is caused by the characteristics of the RBC product or by the allogeneic aspect of RBC transfusion. To exclude allogeneic aspects of RBC transfusion, a clinical study on the effects of autologous RBC transfusion versus crystalloid infusion on hydrostatic pulmonary pressure may help in identifying pulmonary oedema formation mechanisms after transfusion. In this randomized trial, we studied the effect of fresh autologous RBC transfusion versus saline infusion on PCWP change in cardiac surgery patients scheduled for bypass grafting with cardiopulmonary bypass (CPB) support. Systemic inflammation during extracorporeal circulation can lead to endothelial dysfunction. Therefore, these patients represent critically ill patients with endothelial dysfunction [16], at risk for TACO [11, 17, 18]. We hypothesized that transfusion of autologous RBCs would result in a more profound increase in PCWP and pulmonary oedema formation compared to transfusion of an equal volume of saline.

MATERIALS AND METHODS

The TACO crossover trial was an investigator-initiated, single-centre, prospective, crossover, randomized clinical trial. The study was performed at the Amsterdam University Medical Center, Location AMC, in the Netherlands. The local institutional review board approved the trial (NL59191.018.16), which was also registered at clinicaltrials.gov (NTC03135457) on 1 May 2017 and performed according to the CONSORT guidelines [19]. Written informed consent was obtained from all patients. Patient enrolment started in August 2017, and inclusion was completed in March 2020.

Study population

Patients (≥18 years old) scheduled to undergo elective non-redo on-pump coronary artery bypass graft surgery were eligible for enrolment. Patients undergoing emergency cardiac surgery, with severe arrhythmias, pulmonary hypertension, congenital heart disease, or

severe mitral or tricuspid valve disease, were excluded because of possible interference with pulmonary artery catheter (PAC) measurements. Patients with contraindications for PAC placement were excluded. Patients with chronic kidney disease ≥stage 4, those requiring massive transfusion during surgery or CPB duration of ≥2 h, or those on a high dose of corticosteroid infusion were not considered eligible because of the possible interaction with vascular permeability. Included patients with post-operative haemodynamic instability (defined as a mean arterial pressure <60 mmHg, central venous pressure >20 mmHg and noradrenaline dosage of >0.3 mcg/kg/min) were excluded before randomization.

Randomization intervention

A crossover design was used, in which patients were allocated to either infusion of 300 ml saline with a subsequent transfusion of 300 ml RBCs (from now on referred to as saline:RBCs) or the same in the reversed order (RBCs:saline), with a standardized wash-out period of 10 min. After admission to the intensive care unit (ICU), the patients were randomized by independent investigators in a 1:1 allocation ratio with the sealed-envelope method. Patients and care providers (with the exception of ICU nurses) were blinded to the treatment order. Blinding of the investigators was not possible because of the different aspects of the fluids given.

Intervention

According to local protocol, patients underwent coronary artery bypass graft surgery under general anaesthesia provided by anaesthesiologists who were not involved in the study. Induction of anaesthesia was achieved with midazolam, sufentanil, propofol, ketamine and rocuronium, followed by tracheal intubation. Maintenance of anaesthesia was achieved with sevoflurane, propofol and sufentanil. A PiCCO arterial line (Pulsion Medical Systems, Munich, Germany) and a PAC (Edwards LifeSciences, Irvine, CA) were placed under ultrasound guidance. Correct PAC placement was verified by transesophageal echocardiography intra-operatively and chest radiograph post-operatively and allowed the measurement of PCWP, which correlates closely with left atrial pressure, the gold standard to determine hydrostatic pulmonary pressure [20]. CPB was performed under mild hypothermia with a minimum temperature of 35°C employing a membrane oxygenator. A standard operating procedure during cardiac surgery is to use a blood salvaging device, a Fresenius Continuous Auto Transfusion System (Fresenius Kabi AG, Bad Homburg, Germany), whereby post-operative autologous transfusion was used as a non-investigational product. This autotransfusion system allows blood collection and washing with saline for transfusion. A high-quality wash was done to ensure a haematocrit of ≥60%. After surgery, patients were transferred to the ICU and sedated with propofol for the study duration. Patient in whom <300 ml of RBCs was obtained were excluded, and another patient was enrolled in their place.

The products were infused at a rate of 10 ml/min. This rate was based on previous studies that revealed an effect on hydrostatic pressure but not activation of mechanotransduction [13, 21]. Furthermore, this rate is representative of clinical practice and as advised in the British Society for Haematology Guideline on the administration of blood components. Haemodynamic measurements, including a passive leg raise (PLR) test, were performed before and after saline infusion and RBC transfusion to assess fluid responsiveness and volume status [22]. Hypovolemia may result in less increase in PCWP, although absolute haemodynamic values correlate poorly with volume status. A positive PLR test was defined as a cardiac output (CO) increase of >10%. Patients were prospectively screened for TACO criteria, according to the 2011 ISBT TACO definition, until 6 h post transfusion and for 12 h retrospectively using the 2018 revised surveillance case definition [23]. Patients who dropped out before the start of the second intervention, triggering exclusion criteria after randomization, were excluded, and another patient was enrolled in their place.

Patient data collection

Pre-operative patient characteristics were obtained from the electronic patient data system. PCWP was obtained through balloon inflation and wedging of the PAC, at the end of expiration, under positive end-expiratory pressure. Wedging was performed immediately before and directly following infusion at fixed time points. The PiCCO device uses transpulmonary thermodilution to measure CO, cardiac index (CI), extravascular lung water index (EVLWI), pulmonary vascular permeability index (PVPI), global end-diastolic volume index (GEDVI) and the systemic vascular resistance index (SVRI) [24]. Pulmonary vascular resistance index (PVRI) was calculated using standard formulas. Transpulmonary thermodilution was performed randomly throughout the respiratory cycle by three consecutive injections of 20 ml cold saline. All pressures were obtained after calibration conformed to standard ICU practice. Haemodynamic values were recorded in the electronic patient data system. Laboratory methods are described in Appendix S1. All data were collected using an electronic clinical report form built in Castor EDC, a Good Clinical Practice-compliant data capture system (Castor EDC, Amsterdam, the Netherlands).

Outcomes

The primary outcome was the difference in PCWP before and after transfusion (ΔPCWP). We compared RBC transfusion against saline infusion. Secondary outcomes included ΔEVLWI as a measure of pulmonary oedema, ΔPVPI as a measure of vascular permeability, as well as ΔSVRI, ΔPVRI and other haemodynamic variables. Furthermore, predefined secondary outcomes included colloid osmotic pressure (COP).

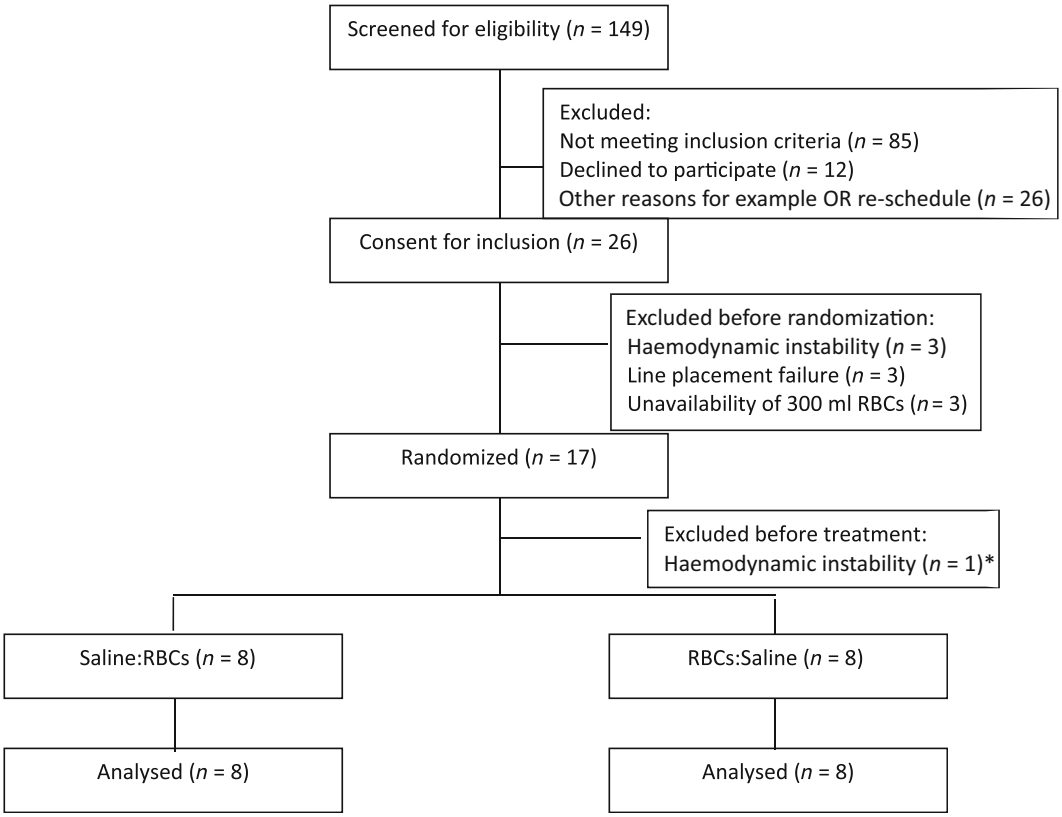

FIGURE 1 Flow-chart. *Measurements were not possible due to re-thoracotomy.

Sample size calculation

A sample size calculation was performed, indicating 8 patients per group, and a total of 16 patients were required to detect a difference in delta (Δ)PCWP of 4 mmHg, which is a clinically relevant difference with $\alpha = 0.05$ and a power of 95% (two-sided 2 × 2 ANOVA) [25]. ΔPCWP and variance were based on previous studies showing haemodynamic responses to RBC transfusion and saline loading [12, 13, 26].

Statistical analysis

Baseline assessments and outcome parameters were summarized using descriptive statistics. Data were analysed for normality. Wilcoxon signed rank tests were used for non-parametric related samples. Two-sample *t*-tests were used for testing the treatment effect in the presence of a period effect [25]. Wilcoxon rank sum statistics was used for non-parametric data in a crossover design [27]. Fisher's exact tests were used for binary outcomes with counts <5. Pearson's correlation coefficient was used to assess the linearity between ΔPCWP and PLR to assess the effect of volume status on ΔPCWP. A *p*-value of <0.05 was regarded as statistically significant. Analyses were performed with the SPSS software package (IBM SPSS Statistics, version 26; IBM Corporation).

RESULTS

Twenty-six patients were included between August 2017 and March 2020 (Figure 1). One-hundred and forty-nine patients were screened for eligibility. There was no screening for patients between March 2018 and March 2019 because of the unavailability of investigators. Nine patients were excluded before randomization. Seventeen patients were randomized, of whom one was excluded before initiation of treatment because of haemodynamic instability leading to re-thoracotomy. Sixteen patients completed the study and were included in the analysis. None of the included patients received an RBC transfusion during surgery. Three patients received platelet transfusion intra-operatively, one in treatment order saline:RBCs and two in treatment order RBCs:saline.

Demographic and baseline characteristics are shown in Table 1. Baseline differences were not assessed [19].

Primary endpoints

PCWP was not different before and after saline infusion or RBCs transfusion (PCWP before and after saline 13.0 ± 1.3 and 13.3 ± 1.3 mmHg vs. before and after RBC 12.9 ± 1.2 vs. 13.6 ± 1.5 mmHg, Table 2). Infusion of saline or RBCs did not increase ΔPCWP differently (ΔPCWP 0.3 ± 0.4 vs. 0.1 ± 0.4 mmHg, $p = 0.74$, Table 2, Figure S1). Crossover differences for the first

TABLE 1 Demographic and baseline characteristics of the study population

Parameter	Saline:RBC	RBC:Saline
Demographic data		
Patients (*n*)	8	8
Female/male (*n*)	0/8	2/6
Age (years)	68 ± 9	65 ± 11
Weight (kg)	87 ± 15	88 ± 22
Body mass index (kg/m^2)	27 ± 3	28 ± 6
Comorbidities		
Heart failure (*n*)	1	0
Diabetes (*n*)	2	2
Kidney disease (*n*)	0	0
COPD GOLD class ≤2 (*n*)	1	2
Medication		
Beta-blocker (*n*)	5	7
Acetylsalicylic acid (y/n)	8	8
Clopidogrel (y/n)	3	3
Vitals before surgery		
Heart rate (beats/min)	69 ± 11	64 ± 15
Systolic arterial pressure (mmHg)	134 ± 17	136 ± 19
Diastolic arterial pressure (mmHg)	80 ± 15	82 ± 15
Respiratory rate (breaths/min)	14 ± 1	15 ± 1
Post-operative data at ICU arrival		
Fluid balance (ml)	2810 ± 1218	2893 ± 961
Noradrenaline dosage (mcg/h)	390 ± 340	440 ± 270
Temperature (°C)	36.4 ± 0.2	36.4 ± 0.3
PEEP (cmH_2O)	5 ± 1	7 ± 2
Haemoglobin (mmol/L)	7.7 ± 1.1	6.4 ± 0.7
Positive PLR test 1	2	2
Positive PLR test 2	2	1

Note: Data are displayed as absolute numbers or mean ± standard deviation. Noradrenaline dosage is at time of intensive care unit (ICU) arrival.
Abbreviations: COPD, chronic obstructive lung disease; PEEP, positive end expiratory pressure; PLR, passive leg raise test; RBC, red blood cell.

allocation period did not differ compared to differences for the second allocation period (difference in PCWP per period −0.9 ± 0.6 vs. 0.2 ± 0.3, $p = 0.18$, Wilcoxon rank sum test).

Secondary endpoints

EVLWI and PVPI were significantly lower following RBC transfusion (EVLWI 7.0 ± 0.7 vs. 8.5 ± 0.6, $p = 0.02$ resp. PVPI 1.5 ± 0.2 vs. 1.8 ± 0.1, $p = 0.02$, before vs. after RBCs, Wilcoxon signed rank test). ΔEVLWI and ΔPVPI were significantly different following RBC transfusion compared to saline (ΔEVLWI −1.6 ± 0.6 vs. 0.2 ± 0.4, $p = 0.02$, and ΔPVPI −0.3 ± 0.1 vs. 0.0 ± 0.1, $p = 0.01$, ΔRBCs vs. Δsaline, Wilcoxon signed rank test Table 2, Figure S2). ΔSVRI and ΔPVRI were not different for infusion of saline or RBC transfusion (ΔSVRI 180 ± 85 vs. 0 ± 123, and ΔPVRI vs. 54 ± 37 vs. 25 ± 39, ΔRBCs vs. Δsaline, Wilcoxon signed rank test Table 2, Figure S2). Crossover differences for the first allocation period did not differ from the second allocation period for EVLWI, PVPI, SVRI and PVRI (EVLWI, $p = 0.25$; PVPI, $p = 0.59$; SVRI, $p = 0.9$; PVRI, $p = 0.19$, Wilcoxon rank sum test). Other haemodynamic variables, including SVRI, PVRI, MAP, CO, GEDVI and IBTVI, were the same before and after saline infusion or RBC transfusion (Table 2).

Passive leg raise test

Two patients in each treatment order had a positive PLR test before any transfusion or saline infusion. There was a poor correlation between PLR test and ΔPCWP after both saline infusion and RBC transfusion ($r = 0.14$, $p = 0.69$ and $r = -0.19$, $p = 0.57$).

Laboratory results

ΔCOP did not significantly differ after the intervention (ΔCOP 0.0 ± 0.7 vs. −0.5 ± 0.6 mmHg, $p = 0.25$, Table 2). ΔPV was significantly larger after saline infusion (−80 ± 30 vs. 40 ± 30 ml, $p = 0.02$, Table 2). Absolute COP and PV did not differ between before and after the intervention.

TACO criteria

The number of TACO diagnoses according to the 2011 ISBT TACO definition, as well as according to the 2018 revised surveillance case definition, was not different for the groups allocated to saline infusion first and RBCs transfusion second, versus the reversed order (Tables S1 and S2, TACO diagnosis 1 out of 8 vs. 0 out of 8, $p = 0.5$).

DISCUSSION

This study investigated pulmonary hydrostatic pressure after transfusing autologous RBC versus crystalloid infusion. Furthermore, we explored pulmonary oedema formation in coronary artery bypass graft surgery patients in the ICU. The main finding of this randomized clinical trial is that we found the same PCWP following transfusion of 1 unit RBC compared to saline infusion in these patients. Secondary findings are that RBC transfusion may decrease EVLWI and PVPI compared to saline infusion.

This study focused on pulmonary hydrostatic pressure following transfusion. We found no PCWP increase following autologous RBC transfusion compared to saline infusion. Previous observational and retrospective studies assessing the effect of allogeneic RBC transfusion on hydrostatic pressure had shown an increase in PCWP in chronic anaemic and critically ill patients [12, 13, 28]. These studies

TABLE 2 Haemodynamic variables before and after saline infusion and RBC transfusion

Parameter	Before saline	After saline	Δsaline	Before RBCs	After RBCs	ΔRBCs	*p*-Value
PCWP (mmHg)	13.0 ± 1.3	13.3 ± 1.3	0.3 ± 0.4	12.9 ± 1.2	13.6 ± 1.5	0.1 ± 0.4	0.74
EVLWI (ml/kg)	8.7 ± 1.3	7.9 ± 0.6	0.2. ± 0.4	8.5 ± 0.6	7.0 ± 0.7*	−1.6 ± 0.6***	0.02
PVPI	1.6 ± 0.1	1.7 ± 0.1	0.0 ± 0.1	1.8 ± 0.1	1.5 ± 0.2**	−0.3 ± 0.1****	0.01
CI (L/min/m^2)	2.4 ± 0.2	2.6 ± 0.2	0.1 ± 0.1	2.5 ± 0.2	2.5 ± 0.2	0.0 ± 0.1	0.44
GEDVI (ml/m^2)	713 ± 45	725 ± 41	11 ± 21	710 ± 37	741 ± 61	21 ± 23	0.57
MAP (mmHg)	71 ± 2	72 ± 3	2 ± 2	68 ± 3	72 ± 3	4 ± 3	0.31
SVRI (DS/cm^{-5}/m^2)	2025 ± 125	1903 ± 119	0 ± 123	1783 ± 150	2023 ± 157	180 ± 85	0.19
PVRI (DS/cm^{-5}/m^2)	277 ± 47	330 ± 68	25 ± 39	310 ± 68	298 ± 49	54 ± 37	0.56
ITBVI (ml/m^2)	840 ± 95	904 ± 56	78 ± 72	927 ± 48	926 ± 129	−24 ± 135	0.65
COP (mmHg)	19.9 ± 0.7	19.7 ± 0.7	0.0 ± 0.6	19.8 ± 0.7	19.5 ± 0.8	−0.5 ± 0.6	0.25
CBV (L)	5.4 ± 0.8	5.4 ± 0.8	–	5.4 ± 0.8	5.4 ± 0.8	–	–
PV (ml)	3760 ± 20	3670 ± 20	−80 ± 30	3700 ± 20	3710 ± 20	40 ± 30	0.02

Note: Δ = delta; data are displayed as mean ± SE.

Abbreviations: CBV, circulating blood volume; CI, cardiac index; COP, colloid osmotic pressure; EVLWI, extra vascular lung water index; GEDVI, global end-diastolic volume index; ITBVI, intra thoracic blood volume index; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; PV, plasma volume; PVPI, pulmonary vascular permeability index; RBCs, red blood cells; SVRI, systemic vascular resistance index.

*$p = 0.02$ before versus after RBCs, Wilcoxon signed rank test; **$p = 0.02$ before versus after RBCs, Wilcoxon signed rank test; ***$p = 0.02$ ΔRBCs versus Δsaline, Wilcoxon signed rank test; ****$p = 0.01$ ΔRBCs versus Δsaline, Wilcoxon signed rank test.

were before the introduction of leukoreduction and were therefore performed with whole blood. There is emerging evidence that pulmonary oedema formation following transfusion may be explained by other mechanisms than solely an RBC transfusion effect [6–8]. These results may be important, as autologous RBC transfusion did not result in a more profound increase in PCWP compared to saline. However, the absence of change in the current study does not imply that in the setting of clinical TACO, an increase in hydrostatic pressure is present. However, our results suggest that factors other than just the volume of an RBC transfusion are needed to induce clinical TACO.

Storage lesion may be an alternative pathway leading to hydrostatic pulmonary oedema after transfusion. Baron-Stefaniak et al. compared fresh versus standard-issued RBCs and suggested PAP increase in the latter [14]. We transfused fresh RBCs and confirmed their finding that RBCs stored for 3 days did not alter PVRI. On the other hand, Berra et al. found a significant increase in PAP by estimating the mean PAP non-invasively during autologous transfusion of RBCs stored for 40 days in 14 volunteers with endothelial dysfunction [15]. The transfused products had increased levels of storage lesions such as cell-free haemoglobin. Increased levels of storage lesions, combined with ongoing haemolysis after transfusion, might have resulted in increased plasma nitric oxide (NO) consumption. In general, increased capillary pressure leads to enhanced NO release through mechanotransduction [21]. Reduced NO bioavailability may have led to vasoconstriction and PAP increase in a patient cohort with known decreased availability of endothelial NO before transfusion [15]. However, PVRI was not measured, and PAP is not a direct measure of hydrostatic pressure overload, as is PCWP. In our study, the absence of increased PCWP following autologous RBC transfusion was confirmed by PVRI, which was not different after the transfusion. Furthermore, increased PAP is not directly correlated to pulmonary oedema formation [29].

We found a decrease in pulmonary oedema measured by EVLWI and vascular permeability measured by PVPI after RBC transfusion compared to saline infusion. Various factors may explain these findings. First, the calculation of EVLWI includes GEDVI [24]. PVPI is calculated as the ratio of extravascular lung water (EVLW) over the pulmonary blood volume, so a decrease in EVLW will lead to a decrease in PVPI. Increasing preload and GEDVI should theoretically decrease EVLWI and PVPI. However, CO and GEDVI are the same before and after transfusion (Table 2). Second, the calculation of EVLWI and PVPI includes the downslope time of the thermodilution curve. Intrinsic specific density properties of an RBC transfusion and saline will affect the specific heat capacity differently. However, the manufacturer-recommended blood temperature differences were met during the thermodilution measurements; therefore, the algorithm calculating the haemodynamic variables from the downslope time should apply. Third, altered rheology by RBC transfusion versus saline infusion may affect the mean transit time of the cold fluid bolus [30]. Therefore, EVLWI and PVPI calculations may be affected. Last, COP differences may facilitate decreased vascular extravasation for RBCs compared to saline [31]. However, our study (not powered for COP differences) shows similar COP before and after RBC and saline infusion. Furthermore, COP measurement of RBCs in a previous study showed a pressure of 1.9 mmHg compared to a theoretical COP of 0 for saline [32]. Therefore, a large impact on plasma COP in vivo is not expected.

Several limitations apply to our study. First, our study included only one clinical TACO case. We cannot exclude that in clinical TACO other mechanisms may imply. However, this study focused on the effect of autologous RBC transfusion versus saline on the change in PCWP, which helps us to understand the factors involved in the onset of TACO. Second, this is a single-centre study with a small sample

size. Third, we cannot rule out a carry-over effect due to the nature of the crossover design [25]. However, since a standardized protocol was followed with a standardized wash-out period, PCWP did not change after RBC transfusion or saline infusion, and there was no correlation between PLR and PCWP, so carry-over effects should be minimal. Fourth, because autologous RBCs are not readily available for every patient, extrapolation to clinical practice is limited. Fifth, we performed measurements in anaesthetised patients in contrast to previous studies, which may affect volume compliance for saline and RBCs. Sixth, our study design lacks an allogeneic control group, which is due to ethical considerations. A lack of a representative study population is demonstrated by the preliminary termination of a recent study investigating fresh versus standard-issue allogeneic RBC transfusion [14]. Furthermore, allogeneic RBC transfusion for patients without any transfusion indication constitutes an ethical dilemma.

In conclusion, in this randomized clinical trial, we found the same PCWP following transfusion of 1 unit RBCs compared to saline infusion in critically ill patients. Our data suggest that transfusing fresh autologous RBCs may lead to less pulmonary oedema, and less vascular permeability than infusing saline. Future research should focus on other factors that may mediate the increase of PCWP resulting in pulmonary oedema, including allogeneic transfusion.

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CONFLICT OF INTEREST

Dr. Denise P. Veelo reported receipt of grants and consultancy fees from Edwards Lifesciences, and research grants from Philips and Hemologic. Dr. Markus W. Hollmann reported serving as executive section editor of pharmacology for *Anaesthesia & Analgesia* and as section editor of anaesthesiology for the *Journal of Clinical Medicine* and receipt of speakers fees from CSL Behring and Eurocept BV and consultancy fees from Eurocept BV. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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