Critical Care

RESEARCH

Open Access

Effects of rapid fluid infusion on hemoglobin concentration: a systematic review and meta-analysis

Armin A. Quispe-Cornejo[1,5], Ana L. Alves da Cunha[2,5], Hassane Njimi[1], Wasineenart Mongkolpun[1], Ana L. Valle-Martins[3], Mónica Arébalo-López[4,5], Jacques Creteur[1] and Jean-Louis Vincent[1*]

Abstract

Background: Rapid fluid administration may decrease hemoglobin concentration (Hb) by a diluting effect, which could limit the increase in oxygen delivery (DO_2) expected with a positive response to fluid challenge in critically ill patients. Our aim was to quantify the decrease in Hb after rapid fluid administration.

Methods: Our protocol was registered in PROSPERO (CRD42020165146). We searched PubMed, the Cochrane Database, and Embase from inception until February 15, 2022. We selected studies that reported Hb before and after rapid fluid administration (bolus fluid given over less than 120 min) with crystalloids and/or colloids in adults. Exclusion criteria were studies that included bleeding patients, or used transfusions or extracorporeal circulation procedures. Studies were divided according to whether they involved non-acutely ill or acutely ill (surgical/trauma, sepsis, circulatory shock or severe hypovolemia, and mixed conditions) subjects. The mean Hb difference and, where reported, the DO_2 difference before and after fluid administration were extracted. Meta-analyses were conducted to assess differences in Hb before and after rapid fluid administration in all subjects and across subgroups. Random-effect models, meta-regressions and subgroup analyses were performed for meta-analyses. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I^2 statistic.

Results: Sixty-five studies met our inclusion criteria (40 in non-acutely ill and 25 in acutely ill subjects), with a total of 2794 participants. Risk of bias was assessed as "low" for randomized controlled trials (RCTs) and 'low to moderate' for non-RCTs. Across 63 studies suitable for meta-analysis, the Hb decreased significantly by a mean of 1.33 g/dL [95% CI − 1.45 to − 1.12; $p < 0.001$; $I^2 = 96.88$] after fluid administration: in non-acutely ill subjects, the mean decrease was 1.56 g/dL [95% CI − 1.69 to − 1.42; $p < 0.001$; $I^2 = 96.71$] and in acutely ill patients 0.84 g/dL [95% CI − 1.03 to − 0.64; $p = 0.033$; $I^2 = 92.91$]. The decrease in Hb was less marked in patients with sepsis than in other acutely ill patients. The DO_2 decreased significantly in fluid non-responders with a significant decrease in Hb.

Conclusions: Hb decreased consistently after rapid fluid administration with moderate certainty of evidence. This effect may limit the positive effects of fluid challenges on DO_2 and thus on tissue oxygenation.

Keywords: Hematocrit, Fluid resuscitation, Oxygen delivery, Hemodilution, Fluid challenge

Introduction

The main objectives of fluid administration in acutely ill patients are to correct hypovolemia and increase cardiac output and oxygen delivery (DO_2), to restore adequate tissue perfusion [1–3]. However, rapid administration

*Correspondence: jlvincent@intensive.org

[1] Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium
Full list of author information is available at the end of the article

of crystalloids and/or colloids may have a hemodiluting effect, resulting in a decrease in hemoglobin concentration (Hb). As a consequence, even when cardiac output increases, DO_2 may not increase as much as anticipated. For example, from the DO_2 equation ($DO_2 = CO \times (1.39 \times [Hb] \times SaO_2 + (0.003 \times PaO_2)$, at an SaO_2 of 100%, when Hb decreases from 10 to 9 g/dL cardiac output needs to increase by about 11% to keep DO_2 steady (and more when the hemoglobin is lower). Additionally, a decrease in Hb after a fluid bolus might be (mis) interpreted as anemia, resulting in an unnecessary blood transfusion [2].

Several studies have reported that fluid administration is associated with a transient decrease in Hb [1–3], which sometimes [3–5], but not always [6, 7], returns rapidly to baseline values after urination. Patients with circulatory shock may show a larger and more persistent hemodiluting effect [1, 2], especially when they are oliguric [8]. However, despite these reports and a clinical perception of Hb reduction after fluid administration, the magnitude of hemodilution in different clinical scenarios has not been objectively assessed.

We therefore conducted a systematic review with meta-analysis to quantify the decrease in Hb after rapid fluid administration in various adult populations.

Methods

This study was performed according to the PRISMA guidelines and registered on the PROSPERO database on the 28th of April 2020 (CRD42020165146). The protocol is available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=165146.

Search strategy and selection criteria

We searched PubMed, the Cochrane Database of Systematic Reviews, and Embase from inception until February 15, 2022, to identify all clinical studies in adults (> 18 years) that reported an Hb value before and after rapid fluid administration or fluid challenge with crystalloids and/or colloids of any kind. The full search strings for the three databases, selection strategy, and exclusion criteria are given in Additional file 1. There was no standardized definition of rapid fluid administration, but we excluded studies in which fluid was given over more than 120 min.

The titles and abstracts of the retrieved references were screened independently by three authors (AAQC, ALAC, WM) to assess eligibility for full-text review. The selected full-text articles were then screened independently by the same authors. Any disagreement was resolved by consensus with a fourth author (JLV).

Data extraction

Information extracted from each study included (full details in Additional file 1):

(1) Characteristics of the study.
(2) Type of study population: non-acutely ill (healthy volunteers, pre-surgical patients and those with chronic medical conditions) or acutely ill (divided into four subgroups: surgical or trauma, sepsis, circulatory shock and/or severe hypovolemia, and 'mixed conditions').
(3) Type of interven(tion (type, amount, and duration of fluid administered).
(4) Outcome measure (baseline and post-fluid Hb and DO_2).
(5) Information about fluid responsiveness when available, using the definition in the original article.

Data analysis

The primary analysis was the mean difference with 95% confidence interval (95% CI) in Hb before and after rapid fluid administration (ΔHb). A secondary analysis was the mean difference in DO_2. Anticipating a high degree of heterogeneity inherent to the differences between different protocols, we used a random-effects model according to the Hartung-Knapp method. We assessed heterogeneity across studies using the I^2 statistic. We analyzed the differences in ΔHb according to the type of population (non-acutely ill, acutely ill), type of fluid (colloid vs. crystalloid), quantity administered (≤ 250 mL, 250–500 mL, 500–1000 mL, and > 1000 mL during ≤ 1 h; 1000–1500 mL and > 1500 mL during > 1 h), duration of administration (≤ 1 vs. > 1 h), baseline Hb (< 12 g/dL, 12–14 g/dL, > 14 g/dL) and the presence of fluid responsiveness (fluid responder and fluid non-responder). We made no adjustment for multiple comparisons.

For each trial, the risk of bias was evaluated independently by three authors (AAQC, ALAC, WM) using the Cochrane risk of bias tools to evaluate the quality of included randomized controlled trials (RCTs) (Cochrane RoB 2 tool) and non-RCTs (ROBINS-I tool). A fourth author (JLV) resolved any disagreements. Certainty of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

Studies in which the mean ΔHb with its standard deviation was reported or could be calculated were included in the meta-analysis. If a study presented data in different subgroups of patients each cohort was considered separately for the meta-analysis [9].

The results of studies grouped according to pre-specified study-level characteristics (type of population, subgroups of patients, type of fluid, duration of fluid administration, quantity of fluid administered, different ranges of baseline Hb (8 to 12 g/dL, > 12 to ≤ 14 g/dL, and > 14 g/dL) and presence of fluid responsiveness (fluid responders vs. fluid non-responders as defined in the original studies) were compared using a stratified meta-analysis or random-effects meta-regression.

All analyses were conducted using Stata software, version 17 (StataCorp) with meta command. Statistical significance was considered at the 5% level.

Results

Description of included studies

The search yielded 8605 studies, 1011 of which underwent full-text screening (Fig. 1). A total of 65 studies, with 157 study sets (subgroups of the included studies) and 2794 subjects met our inclusion criteria for the systematic review; 63 of the 65 studies were eligible for the meta-analysis, with 154 study sets and 2774 subjects. A general visual inspection of the degree of bias detailed in Additional file 1: Table E1 shows 'low risk' for RoB 2 and 'low to moderate risk' for ROBINS-I [10]. The certainty of evidence was judged as moderate due to minor concerns across (1) imprecision, (2) a considerable amount of heterogeneity, and (3) some risk of publication bias in the acutely ill population.

Forty of the 65 studies included in the systematic review were conducted in non-acutely ill subjects [6, 7, 11–48] and 25 in acutely ill patients, of which 10 were in patients with circulatory shock and/or severe hypovolemia [1, 49–57], 8 were in surgical or trauma patients [58–65], 6 in patients with sepsis [66–71], and 1 in the 'mixed conditions' subgroup [72] (Additional file 1: Tables E2 and E3).

For the meta-analysis, 38 of the 63 studies were conducted in non-acutely ill subjects [7, 11–23, 25–27, 29–35, 37–48] and 25 in acutely ill patients, of which 10 were in patients with circulatory shock and/or severe hypovolemia [1, 49, 51–57], 8 in surgical or trauma patients [58–61, 63–65], 6 in patients with sepsis [66–71], and 1 in patients with mixed conditions [72] (Additional file 1: Table E3).

Primary outcome

Across all 63 studies included in the meta-analysis, there was a significant decrease in Hb after rapid fluid administration by a mean of 1.33 g/dL [95% CI − 1.45 to − 1.12] (Fig. 2, Additional file 1: Fig. E1).

The decrease in Hb was less marked in the acutely ill (ΔHb − 0.84 g/dL [95% CI − 1.03 to − 0.64]) than in the non-acutely ill (ΔHb − 1.56 g/dL [95% CI − 1.69 to − 1.42]) ($p < 0.001$) (Additional file 1: Table E4, Fig. 2). There was considerable heterogeneity across studies ($I^2 = 96.88$ overall; 96.71 for the non-acutely ill group and 92.91 for the acutely ill). The effect of small studies was significant for the acutely ill population ($p < 0.001$) but not for the non-acutely ill population ($p = 0.125$).

In the meta-regression analysis, the larger effect size of ΔHb in the non-acutely ill was associated with longer duration (min) (Additional file 1: Fig. E2) and larger amount (ml) of fluid administration (Additional file 1: Fig. E3).

Subgroup analyses

The results of the subgroup analyses related to change in Hb according to type of fluid, rate of fluid administration, baseline Hb, and fluid responsiveness in the acutely ill population subgroups are shown in Figs. 2, 3, Additional file 1: Figs. E4–E6 and Tables E5–9. The largest decrease in Hb was in the surgery/trauma subgroup (ΔHb − 1.23 g/dL [95% CI − 1.64 to − 0.82]) (Additional file 1: Table E4).

Across all the 157 study sets included in the systematic review, 52 reported more than one measurement after fluid administration. In these patients, the Hb returned to baseline within 8 h in the non-acutely ill and within 5 h in the acutely ill (Fig. 4, Additional file 1: Figs. E6 and E7).

Fluid type

In the studies included in the meta-analysis, 63 study sets concerned crystalloids, 82 colloids, and 9 a mix of both fluid types (these were not included in the 'type of fluid' analysis) (Additional file 1: Table E3). The decrease in Hb was greater with colloids than with crystalloids overall (ΔHb − 1.57 g/dL [95% CI − 1.74 to − 1.40] vs. − 1.07 g/dL [95% CI − 1.21 to − 0.92], $p < 0.001$) and in non-acutely ill and acutely ill groups (Fig. 3 and Additional file 1: Fig. E4 and Table E5). When either crystalloids or colloids were administered, the decrease in Hb in the acutely ill was significantly lower than that in the non-acutely ill (Fig. 3, Additional file 1: Table E5). The decrease in Hb was greater with colloids than with crystalloids in the surgery/trauma subgroup and in patients with mixed conditions (Additional file 1: Table E5 and Fig. E4).

Duration and amount of fluid

The median duration of infusion was 30 [20–44] minutes in non-acutely ill and acutely ill populations (Additional file 1: Tables E2 and E3). In non-acutely ill subjects, the ΔHb increased with increasing volume of fluid administered over ≤ 1 h, up to 1000 mL (Additional file 1: Table E6 and Figs. E4 and E5); the ΔHb for amounts of fluid > 1000 mL given over > 1 h was − 1.4 g/dL [95%CI − 1.97 to − 0.84] (Additional file 1: Table E7 and Fig. E5).

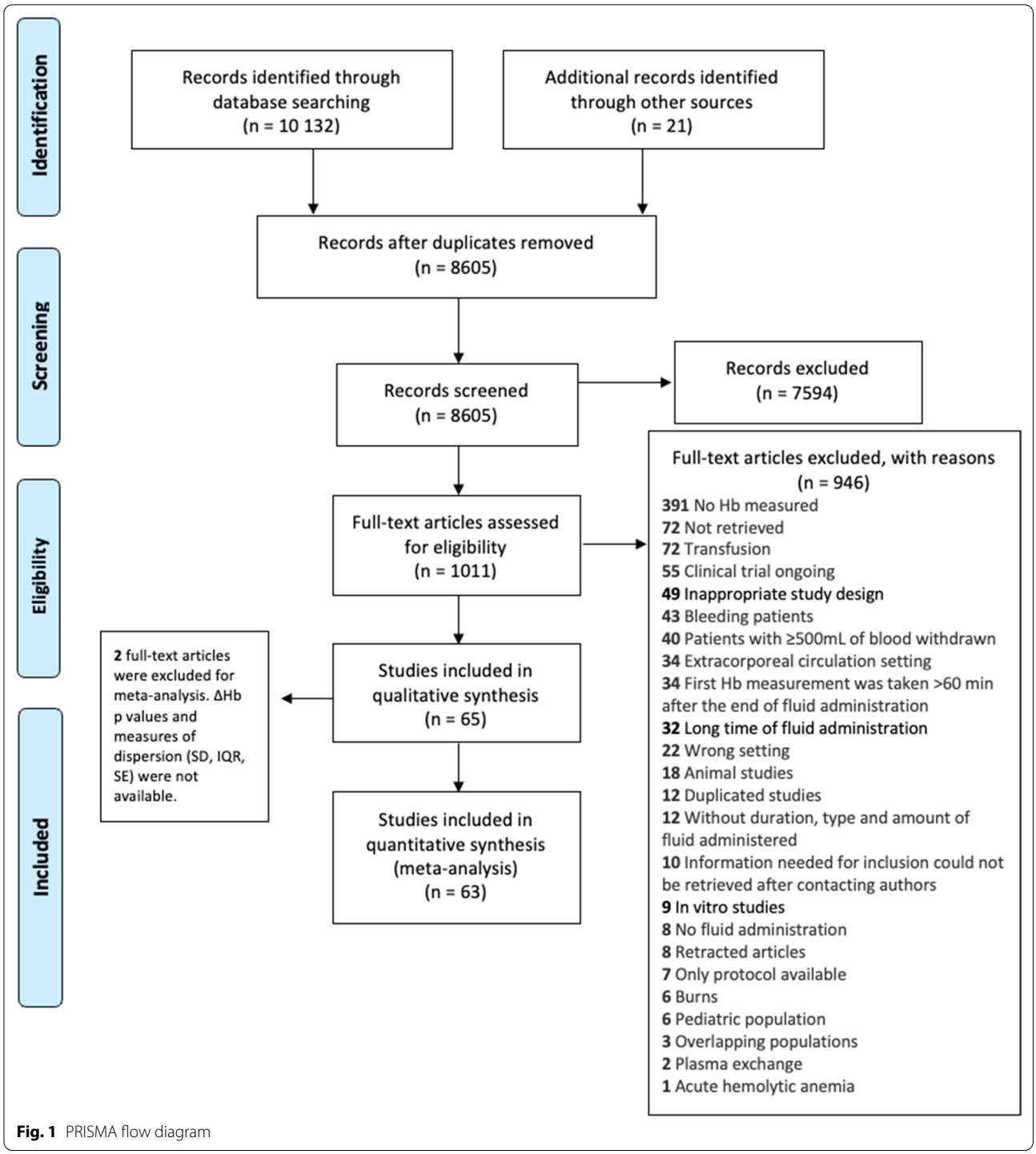

Fig. 1 PRISMA flow diagram

In acutely ill patients, the ΔHb was not directly related to the amount of fluid given (Additional file 1: Tables E6 and E7 and Fig. E5). The decrease in Hb was significantly lower in acutely ill than in non-acutely ill subjects only when an amount of 251–500 mL was administered (Additional file 1: Table E6 and Fig. E5).

Effect of baseline Hb

The Hb decreased significantly in acutely and non-acutely ill groups regardless of its baseline value but the decrease was greater when the baseline Hb was > 14 g/dL than at lower values (decrease of 17% in acutely ill and 11% in non-acutely ill patients). When the baseline

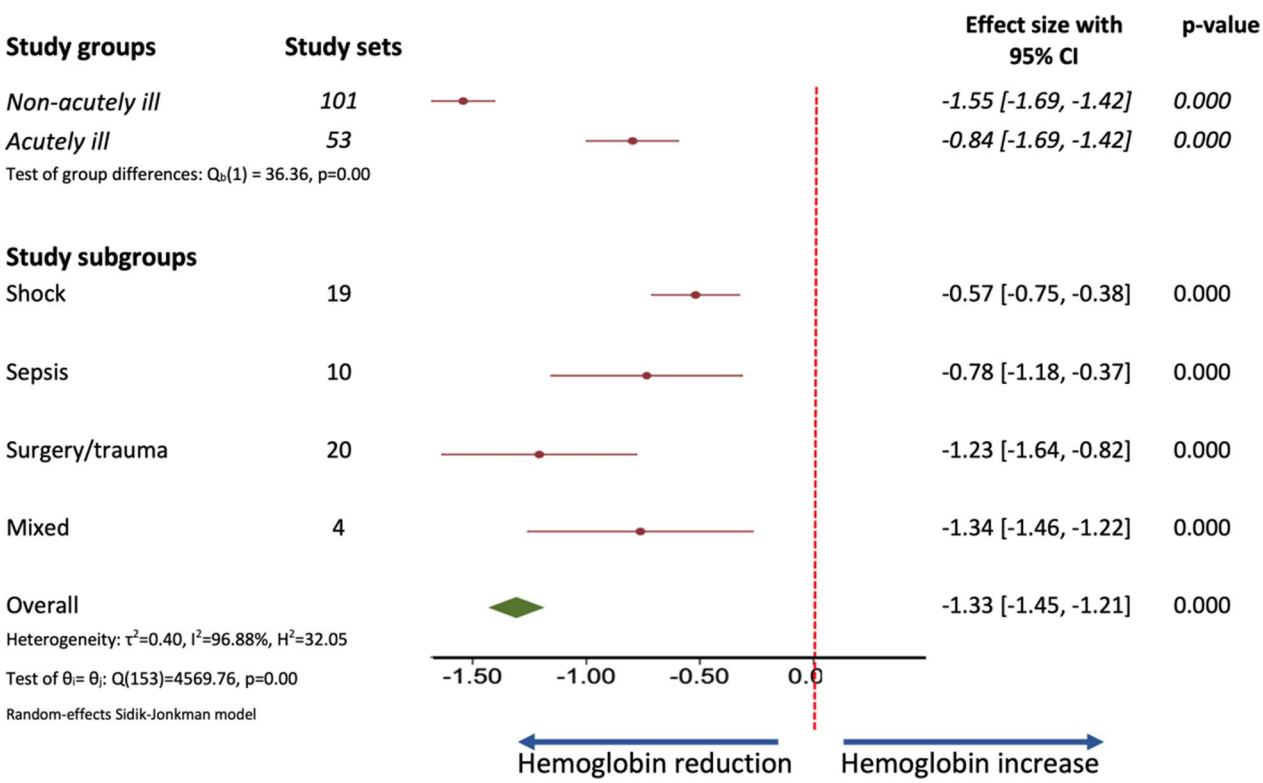

Fig. 2 Forest plot of all groups and subgroups

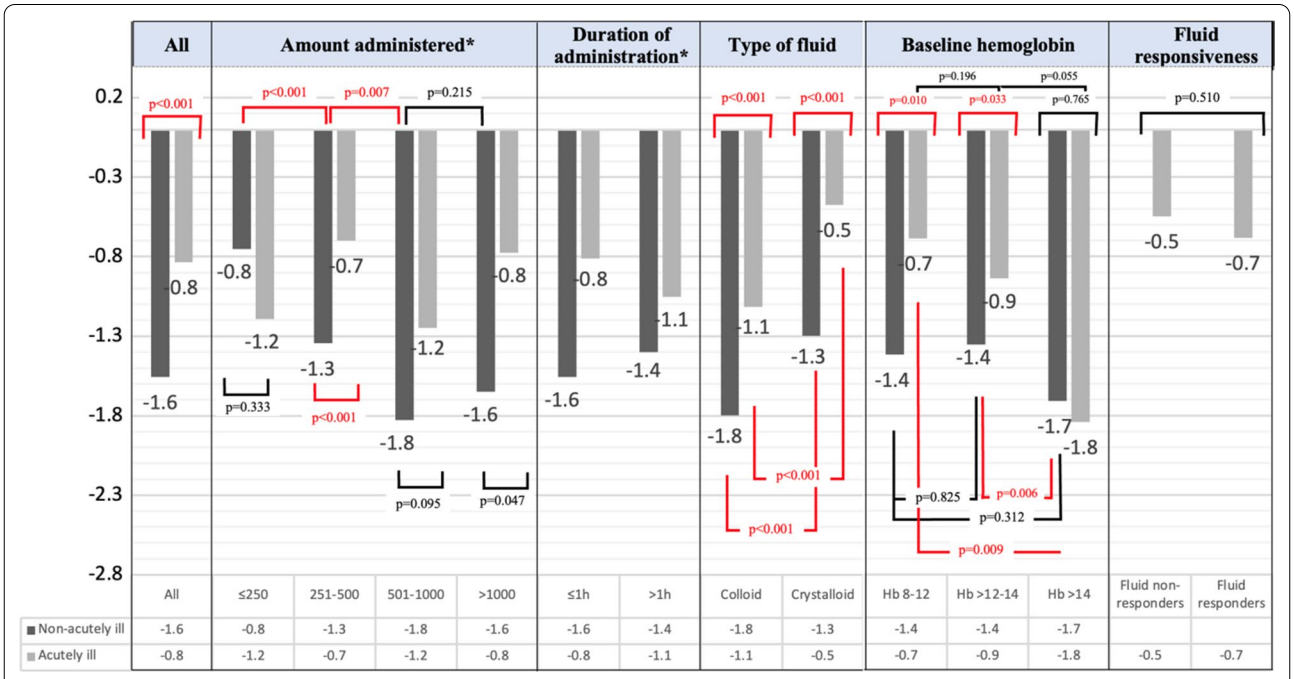

Fig. 3 Decrease in hemoglobin concentration (Hb) in non-acutely ill and acutely ill patients according to amount of fluid administered, duration of fluid administration, type of fluid, baseline hemoglobin, and fluid responsiveness

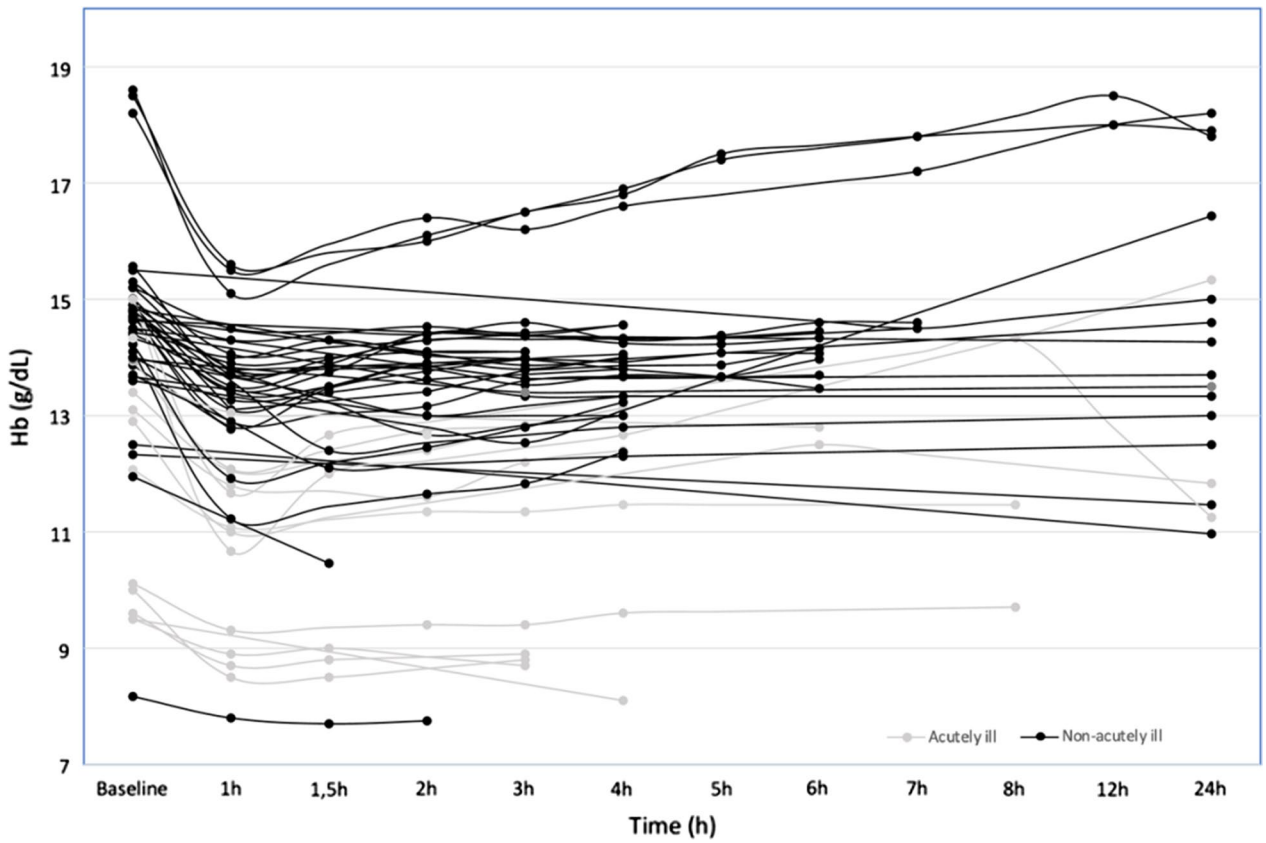

Fig. 4 Change in hemoglobin concentration (Hb) from baseline in non-acutely ill (black lines) and acutely ill (gray lines) subjects at different time points

Hb was < 14 g/dL, the decrease in Hb was less marked in acutely ill than in non-acutely ill patients, but similar in acutely ill patients and in non-acutely ill when the baseline Hb was > 14 g/dL (ΔHb − 1.84 g/dL vs. − 1.71 g/dL, $p = 0.765$) (Fig. 3, Additional file 1: Table E8).

Fluid responsiveness and change in DO_2

Twenty-eight study sets from 15 studies that reported fluid responsiveness were included in the meta-analysis [1, 49, 53–57, 60, 62, 64–67, 69, 71] (Additional file 1: Table E10). All the studies defined fluid responsiveness as an increase in cardiac index of more than 10 or 15% after fluid administration, except one [71] in which fluid responsiveness was defined as a 5% increase in end-tidal carbon dioxide (EtCO2). In every setting analyzed, there was a significant decrease in Hb, which was of a similar magnitude in fluid responders and non-responders (Fig. 3, Additional file 1: Table E9), except in the sepsis subgroup due to a single study that reported an increase in Hb after fluid administration [71]

Twenty-four study sets from 13 studies that reported changes in DO_2 before and after fluid administration were included in the meta-analysis [1, 49, 54–57, 60, 62, 64–67, 69] (Additional file 1: Table E10). In 11 of the studies, DO_2 was calculated using the standard formula ($DO_2 = CO \times (1.39 \times [Hb] \times SaO_2 + (0.003 \times PaO_2))$; 2 studies [49, 66] did not report how DO_2 was calculated. There was an overall increase in DO_2 of 35.8 ml/min/m^2 [95% CI 13.4–58.2; range − 39 to 120 ml/min/m^2]. There was a significant difference in the change in DO_2 between fluid responders (67.76 [95% CI 46.11–89.40]) and non-responders (− 16.30 [95% CI − 31.52 to − 1.09]) ($p < 0.001$) (Additional file 1: Table E11). DO_2 decreased in the studies in which cardiac index did not increase significantly only when there was a significant decrease in Hb [1, 60] (Additional file 1: Table E12).

Discussion

Our results show a significant reduction in Hb (a mean of 1.33 g/dL) after fluid administration in all groups of acutely and non-acutely ill subjects, despite marked heterogeneity across studies as evidenced by the high I^2 statistic. This reduction was larger with colloids than

with crystalloids. Across the acutely ill population, the largest decrease in Hb was seen in the surgery/trauma subgroup.

Under physiological conditions, a decrease in Hb after rapid fluid administration is both intuitive, through a hemodiluting effect, and counterintuitive, as the kidneys should eliminate the excessive fluid and there may be a fluid shift toward the extravascular space. Interest in this concept was initially raised with the observations by Greenfield and colleagues [73] that rapid crystalloid administration in healthy volunteers was followed by a transient decrease in Hb that started to return toward baseline after 20 min. Studies examining fluid resuscitation in healthy volunteers are, however, different from those in more complex critically ill patients, in whom various dynamic factors act to influence physiological behavior.

The effects of fluid administration vary according to a number of factors, including type and amount of fluid [74–76], renal clearance [14, 23, 24, 77, 78], endothelial integrity [79–82], electrolyte cotransporters, metabolic channels, and aspects associated with a relative shift toward the extravascular space [4]. Colloids are at least one and a half times more effective at volume expansion than crystalloids [83]. As they are expected to remain longer in the bloodstream than crystalloids [84], they may potentially induce a greater reduction in Hb [28], as we observed. Meyer et al. reported that 6% HES (130/0.4) induced sustained hemodilution in critically ill patients with or without sepsis [51]. In patients with sepsis, the decrease in Hb was similar with colloids and crystalloids, suggesting that some capillary leakage may have abolished the differences between the two types of fluids. Moreover, sepsis and circulatory shock are characterized by diffuse endothelial injury and capillary hyperpermeability [14, 23, 79, 81, 82, 85], resulting in greater extravasation of fluid. Studies have shown that 5% or less of a crystalloid infusion remains in the intravascular volume after 1 h in septic patients [80, 86]. In our review, the reduction in Hb was less pronounced in patients with sepsis and shock than in surgery/trauma patients, compatible with greater egress of fluids outside the vascular space in these patients [51, 53].

The amount of fluid given is an important factor in the likely degree of hemodilution induced. The degree by which the Hb decreased was directly related to the amount of fluid given, up to 1000 mL, during the first hour in the non-acutely ill population. However, this trend was not evident in acutely ill patients, likely because of the altered physiological mechanisms in acute illness described previously, notably the fluid extravasation.

In acutely and non-acutely ill populations, the Hb decrease was greatest when the baseline Hb was > 14 g/dL; this may have been due to initial hemoconcentration in some patients [70]. In some groups, the decrease in Hb was as large as 20% (surgery/trauma subgroup) when the baseline Hb was > 14 g/dL. In septic patients, the decrease was more limited, consistent with the expected extravasation phenomenon in patients with sepsis.

In the surgery/trauma subgroup, the type and duration of the procedure [22, 87], the influence of anesthesia on different factors, such as vasodilation and increase in vascular compliance, and a potential reduction in glomerular filtration rate may influence the effect of fluid administration on Hb [88], but we have no data on these aspects. The greater reduction in Hb in the surgical subgroup in our analysis may be explained by the stable and previously healthy condition of many of the patients (elective surgery, interventions performed during induction of anesthesia), physiologically similar to that of non-acutely ill subjects [2, 89].

In the presence of hypovolemia, fluid administration may result in an increase in cardiac output via the Frank-Starling mechanism [90], although this effect may be transient [7, 53], whereas the reduction in Hb may last up to 72 h [91]. This persistent reduction in Hb may limit the ability of fluid administration to achieve the desired objective, i.e., to increase DO_2 and tissue oxygenation. In subjects in whom Hb decreased, DO_2 either increased [1, 54–56, 60, 64, 65] or remained stable [62, 66] when cardiac index increased, but decreased [1, 60] when cardiac index did not increase, suggesting that it may be deleterious to administer fluids if cardiac index does not increase.

Of note, hemodilution may also have beneficial effects. For example, hemodilution has been shown to promote cerebral blood flow in preclinical cardiac arrest studies [92, 93]. The decrease in blood viscosity associated with hemodilution can increase red blood cell velocity, facilitating red blood cell influx into the capillaries and therefore improving oxygen transfer to the tissues [94, 95].

Limitations and strengths

Strengths of this study are the exhaustive review of clinical studies in different settings. We excluded major confounders, such as acute bleeding and transfusion, and classified the risk of bias [96–98].

However, we acknowledge that there was considerable heterogeneity in the included patient populations, in terms of the underlying fluid status of the patients, the fluid tonicity, the timing of the fluid bolus in relation to resuscitation status, the type, amount, and duration of fluid administration, and the timing of observations, which might create bias and limit the interpretation and application of any aggregate quantification. Moreover, there may have been some overlap among groups;

for example, some of the patients in the sepsis studies may have had septic shock. Despite our exclusion criteria, in some cases (especially in surgical settings) unrecognized bleeding may have influenced the results. We were also unable to investigate the longer-term effects of rapid fluid administration. None of the studies was specifically designed to evaluate hemoglobin decrease, so we were unable to assess patient-centered outcomes. We extracted some data from graphs, which may have reduced the accuracy of these values, although the participation of two reviewers in this process reduced any observation bias. When needed, we assigned a standard weight and height to calculate fluid amounts and indexes. Finally, the clinical implications of the magnitude of pooled decrease in hemoglobin are not clear, as our study was not designed for this purpose.

Conclusion

Notwithstanding the study heterogeneity and moderate certainty of evidence, our observations were consistent across studies, showing a systematic decrease in Hb after rapid fluid administration and raising uncertainty about the effects of fluid on DO_2 in fluid non-responders, i.e., when cardiac index does not increase during the fluid challenge. These observations add a cautious note to the enthusiastic performance of fluid challenges and remind us how important it is to stop the test when cardiac output does not increase.

Abbreviations

CO: Cardiac output; DO_2: Oxygen delivery; $ETCO_2$: End-tidal carbon dioxide; Hb: Hemoglobin; RCT: Randomized controlled trial.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-022-04191-x.

Additional file 1. Online supplementary data.

Acknowledgement

We acknowledge the help of Drs Ana Sofia Valente, Javier Quispe Blanco, Anahy Fernandez Cruz, and Ing. Carolina Alves da Cunha in data organization and logistics.

Author contributions

AAQC, ALAC, and JLV designed the study; AAQC, ALAC, WM, ALVM, and MAL performed the literature search and extracted the data; AAQC and ALAC wrote the first draft of the manuscript; HN performed the statistical analyses; HN, WM, ALVM, MAL, JC, and JLV reviewed the article for critical content; all authors read and approved the final text.

Funding

No external funding.

Availability of data and materials

Data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

JLV is Editor-in-Chief of Critical Care. He has no other conflicts of interest. The other authors have no conflicts of interest.

Author details

[1]Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium. [2]Department of Intensive Care, Hospital da Senhora da Oliveira, Guimarães, Portugal. [3]Department of Intensive Care, Hospital Mater Dei, Belo Horizonte, Brazil. [4]Department of Intensive Care, Hospital Univalle Norte, Cochabamba, Bolivia. [5]Instituto Académico Científico Quispe Cornejo, La Paz, Bolivia.

Received: 7 August 2022 Accepted: 4 October 2022
Published online: 23 October 2022

References

1. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med. 2013;41:1412–20.
2. Perel A. Iatrogenic hemodilution: A possible cause for avoidable blood transfusions? Crit Care. 2017;21:291.
3. Hahn RG, Drobin D, Ståhle L. Volume kinetics of Ringer's solution in female volunteers. Br J Anaesth. 1997;78:144–8.
4. Hahn RG, Svensén C. Plasma dilution and the rate of infusion of Ringer's solution. Br J Anaesth. 1997;79:64–7.
5. Hahn RG. Influences of red blood cell and platelet counts on the distribution and elimination of crystalloid fluid. Medicina (Kaunas). 2017;53:233–41.
6. Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci (Lond). 2001;101:173–9.
7. Lobo DN, Stanga Z, Aloysius MM, Wicks C, Nunes QM, Ingram KL, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. Crit Care Med. 2010;38:464–70.
8. Haupt MT, Gilbert EM, Carlson RW. Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis. 1985;131:912–6.
9. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH et al: Handling continuous outcomes in quantitative synthesis. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. edn. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
10. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12:55–61.
11. Ehrly AM, Landgraf H. Influence of intravenous infusions of hydroxyethylstarch (HES) (MW 40,000 and 450,000) on the blood flow properties of healthy volunteers. Angiology. 1985;36:41–4.
12. Murray AM, Morgan M, Whitwam JG. Crystalloid versus colloid for circulatory preload for epidural caesarean section. Anaesthesia. 1989;44:463–6.
13. Stamler KD. Effect of crystalloid infusion on hematocrit in nonbleeding patients, with applications to clinical traumatology. Ann Emerg Med. 1989;18:747–9.
14. Berg S, Engman A, Hesselvik JF, Laurent TC. Crystalloid infusion increases plasma hyaluronan. Crit Care Med. 1994;22:1563–7.

15. Jung F, Meier C, Koscielny J, Pindur G, Moll A, Schimetta W, et al. Effects of a hypervolemic hemodilution with HES 100/0.5 10% in patients with PAOD stage II: elimination kinetics and blood fluidity. Clin Hemorheol Microcirc. 1996;16:631–43.
16. Kass LE, Tien IY, Ushkow BS, Snyder HS. Prospective crossover study of the effect of phlebotomy and intravenous crystalloid on hematocrit. Acad Emerg Med. 1997;4:198–201.
17. Levin JM, Frederick Bde B, Ross MH, Fox JF, von Rosenberg HL, Kaufman MJ, et al. Influence of baseline hematocrit and hemodilution on BOLD fMRI activation. Magn Reson Imaging. 2001;19:1055–62.
18. Yamauchi H, Fukuyama H, Ogawa M, Ouchi Y, Kimura J. Hemodilution improves cerebral hemodynamics in internal carotid artery occlusion. Stroke. 1993;24:1885–90.
19. Treib J, Haass A, Pindur G, Grauer MT, Wenzel E, Schimrigk K. Decrease of fibronectin following repeated infusion of highly substituted hydroxyethyl starch. Infusionsther Transfusionsmed. 1996;23:71–5.
20. Ueyama H, He YL, Tanigami H, Mashimo T, Yoshiya I. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective Cesarean section. Anesthesiology. 1999;91:1571–6.
21. Waters JH, Bernstein CA. Dilutional acidosis following hetastarch or albumin in healthy volunteers. Anesthesiology. 2000;93:1184–7.
22. Rehm M, Haller M, Orth V, Kreimeier U, Jacob M, Dressel H, et al. Changes in blood volume and hematocrit during acute preoperative volume loading with 5% albumin or 6% hetastarch solutions in patients before radical hysterectomy. Anesthesiology. 2001;95:849–56.
23. Berg S, Golster M, Lisander B. Albumin extravasation and tissue washout of hyaluronan after plasma volume expansion with crystalloid or hypooncotic colloid solutions. Acta Anaesthesiol Scand. 2002;46:166–72.
24. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP. (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond). 2003;104:17–24.
25. Kuipers H, Brouwer T, Dubravcic-Simunjak S, Moran J, Mitchel D, Shobe J, et al. Hemoglobin and hematocrit values after saline infusion and tourniquet. Int J Sports Med. 2005;26:405–8.
26. Lehmann G, Marx G, Förster H. Bioequivalence comparison between hydroxyethyl starch 130/0.42/6: 1 and hydroxyethyl starch 130/0.4/9: 1. Drugs R D. 2007;8:229–40.
27. Ruttmann TG, Montoya-Pelaez LF, James MF. The coagulation changes induced by rapid in vivo crystalloid infusion are attenuated when magnesium is kept at the upper limit of normal. Anesth Analg. 2007;104:1475–780.
28. Borup T, Hahn RG, Holte K, Ravn L, Kehlet H. Intra-operative colloid administration increases the clearance of a post-operative fluid load. Acta Anaesthesiol Scand. 2009;53:311–7.
29. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256:18–24.
30. Yamakage M, Bepperling F, Wargenau M, Miyao H. Pharmacokinetics and safety of 6 % hydroxyethyl starch 130/0.4 in healthy male volunteers of Japanese ethnicity after single infusion of 500 ml solution. J Anesth. 2012;26:851–7.
31. Andrijauskas A, Ivaškevičius J, Porvaneckas N, Stankevičius E, Svensen CH, Uvarovas V, et al. A mini volume loading test for indication of preoperative dehydration in surgical patients. Medicina (Kaunas). 2015;51:81–91.
32. Bihari S, Wiersema UF, Perry R, Schembri D, Bouchier T, Dixon D, et al. Efficacy and safety of 20% albumin fluid loading in healthy subjects: a comparison of four resuscitation fluids. J Appl Physiol. 1985;2019(126):1646–60.
33. Bihari S, Wiersema UF, Schembri D, De Pasquale CG, Dixon DL, Prakash S, et al. Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes interstitial pulmonary edema in healthy subjects. J Appl Physiol. 1985;2015(119):783–92.
34. Andrijauskas A, Svensen CH, Porvaneckas N, Šipylaitė J, Stankevičius E, Činčikas D, et al. A mini volume loading test (mVLT) using 2.5-mLkg(-1) boluses of crystalloid for indication of perioperative changes in hydration status. Medicina (Kaunas). 2016;52:354–65.
35. Li Y, Shan Y, Lin X. Effect of acute hypervolemic hemodilution of 6% hydroxyethyl starch 130/0.4 on the EC(50) of propofol at two clinical endpoints in patients. Exp Ther Med. 2016;11:110–6.
36. Lee JH, Choo YJ, Lee YH, Rhim JH, Lee SH, Choi BM, et al. Population-based volume kinetics of Ringer's lactate solution in patients undergoing open gastrectomy. Acta Pharmacol Sin. 2019;40:710–6.
37. Zdolsek M, Hahn RG, Zdolsek JH. Recruitment of extravascular fluid by hyperoncotic albumin. Acta Anaesthesiol Scand. 2018;62:1255–60.
38. Bradley CR, Bragg DD, Cox EF, El-Sharkawy AM, Buchanan CE, Chowdhury AH, et al. A randomized, controlled, double-blind crossover study on the effects of isoeffective and isovolumetric intravenous crystalloid and gelatin on blood volume, and renal and cardiac hemodynamics. Clin Nutr. 2020;39:2070–9.
39. Yi JM, Bang JY, Choi B, Cho C, Lee YH, Lee EK, et al. Population-based volume kinetics of crystalloids and colloids in healthy volunteers. Sci Rep. 2019;9:18638.
40. Dewachter P, Laxenaire MC, Donner M, Kurtz M. Stoltz JF [In vivo rheologic studies of plasma substitutes]. Ann Fr Anesth Reanim. 1992;11:516–25.
41. Molter GP, Soltész S, Larsen R, Baumann-Noss S, Biedler A. Silomon M [Haemodynamic effects following preoperative hypervolemic haemodilution with hypertonic hyperoncotic colloid solutions in coronary artery bypass graft surgery]. Anaesthesist. 2003;52:905–18.
42. Ehrly AM, Seebens H. Saeger-Lorenz K [Effect of a 10% and 6% hydroxyethyl starch solution (molecular weight 200,000/0.62) in comparison with a 10% dextran solution (molecular weight 40,000) on flow properties of blood and tissue oxygen pressure in patients with intermittent claudication]. Infusionstherapie. 1988;15:181–7.
43. van den Broek WG, Trouwborst A, Bakker WH. The effect of iso-oncotic plasma substitutes: gelatine, dextran 40 (50 g/l) and the effect of Ringer's lactate on the plasma volume in healthy subjects. Acta Anaesthesiol Belg. 1989;40:275–80.
44. Comes L, Mureşan A, Costin Z. Observations on isovolemic hemodilution in acute ischemic stroke. Rom J Intern Med. 1996;34:43–7.
45. Sefrin P, Rauch S, Zieglmeyer C. Changes in blood coagulation in treatment with hydroxyethyl starch]. Anaesthesiol Reanim. 1998;23:149–56.
46. Bubenek-Turconi Şl, Văleanu L, Popescu M, Panaitescu E, Tomescu D, Cacoveanu MC, et al. Continuous noninvasive hemoglobin monitoring reflects the development of acute hemodilution after consecutive fluid challenges. Anesth Analg. 2020;130:696–703.
47. Hahn RG, Nemme J. Volume kinetic analysis of fluid retention after induction of general anesthesia. BMC Anesthesiol. 2020;20:95.
48. Li H, Bersten A, Wiersema U, Schembri D, Cavallaro E, Dixon DL, et al. Bolus intravenous 0.9% saline leads to interstitial permeability pulmonary edema in healthy volunteers. Eur J Appl Physiol. 2021;121:3409–19.
49. Edwards JD, Nightingale P, Wilkins RG, Faragher EB. Hemodynamic and oxygen transport response to modified fluid gelatin in critically ill patients. Crit Care Med. 1989;17:996–8.
50. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation. 2003;56:9–13.
51. Meyer P, Pernet P, Hejblum G, Baudel JL, Maury E, Offenstadt G, et al. Haemodilution induced by hydroxyethyl starches 130/0.4 is similar in septic and non-septic patients. Acta Anaesthesiol Scand. 2008;52:229–35.
52. Spiel AO, Kliegel A, Janata A, Uray T, Mayr FB, Laggner AN, et al. Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids. Resuscitation. 2009;80:762–5.
53. Nunes TS, Ladeira RT, Bafi AT, de Azevedo LC, Machado FR, Freitas FG. Duration of hemodynamic effects of crystalloids in patients with circulatory shock after initial resuscitation. Ann Intensive Care. 2014;4:25.
54. Guinot PG, Guilbart M, Hchikat AH, Trujillo M, Huette P, Bar S, et al. Association between end-tidal carbon dioxide pressure and cardiac output during fluid expansion in operative patients depend on the change of oxygen extraction. Medicine (Baltimore). 2016;95: e3287.
55. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Ann Intensive Care. 2016;6:10.
56. Xu B, Yang X, Wang C, Jiang W, Weng L, Hu X, et al. Changes of central venous oxygen saturation define fluid responsiveness in patients with septic shock: a prospective observational study. J Crit Care. 2017;38:13–9.
57. Mongkolpun W, Gardette M, Orbegozo D, Vincent JL, Creteur J. An increase in skin blood flow induced by fluid challenge is associated with

an increase in oxygen consumption in patients with circulatory shock. J Crit Care. 2022;69: 153984.
58. Omar MN, Shouk TA, Khaleq MA. Activity of blood coagulation and fibrinolysis during and after hydroxyethyl starch (HES) colloidal volume replacement. Clin Biochem. 1999;32:269–74.
59. Awad S, Dharmavaram S, Wearn CS, Dube MG, Lobo DN. Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine(R)) and 6% hydroxyethyl starch (Voluven(R)) on blood volume. Br J Anaesth. 2012;109(2):168–76.
60. Fellahi JL, Fischer MO, Rebet O, Dalbera A, Massetti M, Gérard JL, et al. Cerebral and somatic near-infrared spectroscopy measurements during fluid challenge in cardiac surgery patients: a descriptive pilot study. J Cardiothorac Vasc Anesth. 2013;27:266–72.
61. Paydar S, Bazrafkan H, Golestani N, Roozbeh J, Akrami A, Moradi AM. Effects of intravenous fluid therapy on clinical and biochemical parameters of trauma patients. Emerg (Tehran). 2014;2:90–5.
62. Rebet O, Fischer MO, Zamparini G, Gérard JL, Fellahi JL, Hanouz JL. Near-infrared spectroscopy hemoglobin index measurement during fluid challenge: a prospective study in cardiac surgery patients. J Cardiothorac Vasc Anesth. 2015;29:924–9.
63. Skytte Larsson J, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten SE. Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: a randomized study on crystalloid vs colloid. Br J Anaesth. 2015;115:736–42.
64. Fischer MO, Bonnet V, Lorne E, Lefrant JY, Rebet O, Courteille B, et al. Assessment of macro- and micro-oxygenation parameters during fractional fluid infusion: a pilot study. J Crit Care. 2017;40:91–8.
65. Abou-Arab O, Braik R, Huette P, Bouhemad B, Lorne E, Guinot PG. The ratios of central venous to arterial carbon dioxide content and tension to arteriovenous oxygen content are not associated with overall anaerobic metabolism in postoperative cardiac surgery patients. PLoS ONE. 2018;13: e0205950.
66. Asfar P, Kerkeni N, Labadie F, Gouëllo JP, Brenet O, Alquier P. Assessment of hemodynamic and gastric mucosal acidosis with modified fluid versus 6% hydroxyethyl starch: a prospective, randomized study. Intensive Care Med. 2000;26:1282–7.
67. Fernandes CJ Jr, Akamine N, De Marco FV, De Souza JA, Lagudis S, Knobel E. Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. Crit Care. 2001;5:362–7.
68. Matejovic M, Krouzecky A, Rokyta R Jr, Novak I. Fluid challenge in patients at risk for fluid loading-induced pulmonary edema. Acta Anaesthesiol Scand. 2004;48:69–73.
69. Friedman G, Jankowski S, Shahla M, Gomez J, Vincent JL. Hemodynamic effects of 6% and 10% hydroxyethyl starch solutions versus 4% albumin solution in septic patients. J Clin Anesth. 2008;20:528–33.
70. Smart L, Macdonald SPJ, Bosio E, Fatovich D, Neil C, Arendts G. Bolus therapy with 3% hypertonic saline or 0.9% saline in emergency department patients with suspected sepsis: a pilot randomised controlled trial. J Crit Care. 2019;52:33–9.
71. Robba C, Messina A, Battaglini D, Ball L, Brunetti I, Bassetti M, et al. Early effects of passive leg-raising test, fluid challenge, and norepinephrine on cerebral autoregulation and oxygenation in COVID-19 critically ill patients. Front Neurol. 2021;12: 674466.
72. Spoelstra-de Man AM, Smorenberg A, Groeneveld AB. Different effects of fluid loading with saline, gelatine, hydroxyethyl starch or albumin solutions on acid-base status in the critically ill. PLoS ONE. 2017;12: e0174507.
73. Greenfield RH, Bessen HA, Henneman PL. Effect of crystalloid infusion on hematocrit and intravascular volume in healthy, nonbleeding subjects. Ann Emerg Med. 1989;18:51–5.
74. Manning RD Jr, Guyton AC. Dynamics of fluid distribution between the blood and interstitium during overhydration. Am J Physiol. 1980;238:H645–51.
75. Renkin EM, Rew K, Wong M, O'Loughlin D, Sibley L. Influence of saline infusion on blood-tissue albumin transport. Am J Physiol. 1989;257:H525–33.
76. Ståhle L, Nilsson A, Hahn RG. Modelling the volume of expandable body fluid spaces during i.v. fluid therapy. Br J Anaesth. 1997;78:138–43.
77. Hahn RG. Renal water conservation determines the increase in body weight after surgery: a randomized, controlled trial. Saudi J Anaesth. 2017;11:144–51.
78. Hahn RG, Nyberg Isacson M, Fagerström T, Rosvall J, Nyman CR. Isotonic saline in elderly men: an open-labelled controlled infusion study of electrolyte balance, urine flow and kidney function. Anaesthesia. 2016;71:155–62.
79. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. N Engl J Med. 2015;373:1350–60.
80. Ueyama H, Kiyonaka S. Predicting the need for fluid therapy-does fluid responsiveness work? J Intensive Care. 2017;5:34.
81. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care. 2014;18:696.
82. Grathwohl KW, Bruns BJ, LeBrun CJ, Ohno AK, Dillard TA, Cushner HM. Does hemodilution exist? Effects of saline infusion on hematologic parameters in euvolemic subjects. South Med J. 1996;89:51–5.
83. Orbegozo Cortés D, Gamarano Barros T, Njimi H, Vincent JL. Crystalloids versus colloids: exploring differences in fluid requirements by systematic review and meta-regression. Anesth Analg. 2015;120:389–402.
84. Huskisson L. Intravenous volume replacement: which fluid and why? Arch Dis Child. 1992;67:649–53.
85. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth. 2012;108:384–94.
86. Sánchez M, Jiménez-Lendínez M, Cidoncha M, Asensio MJ, Herrerot E, Collado A, et al. Comparison of fluid compartments and fluid responsiveness in septic and non-septic patients. Anaesth Intensive Care. 2011;39:1022–9.
87. Rehm M, Haller M, Brechtelsbauer H, Akbulut C, Finsterer U. Extra protein loss not caused by surgical bleeding in patients with ovarian cancer. Acta Anaesthesiol Scand. 1998;42:39–46.
88. Lahsaee SM, Ghaffaripour S, Hejr H. The effect of routine maintenance intravenous therapy on hemoglobin concentration and hematocrit during anesthesia in adults. Bull Emerg Trauma. 2013;1:102–7.
89. Shander A, Lobel GP, Javidroozi M. Anesthesia for patients with anemia. Anesthesiol Clin. 2016;34:711–30.
90. Vincent JL, Cecconi M, De Backer D. The fluid challenge. Crit Care. 2020;24(1):703.
91. Maiden MJ, Finnis ME, Peake S, McRae S, Delaney A, Bailey M, et al. Haemoglobin concentration and volume of intravenous fluids in septic shock in the ARISE trial. Crit Care. 2018;22:118.
92. Safar P, Xiao F, Radovsky A, Tanigawa K, Ebmeyer U, Bircher N, et al. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke. 1996;27:105–13.
93. Leonov Y, Sterz F, Safar P, Johnson DW, Tisherman SA, Oku K. Hypertension with hemodilution prevents multifocal cerebral hypoperfusion after cardiac arrest in dogs. Stroke. 1992;23:45–53.
94. Tu YK, Liu HM. Effects of isovolemic hemodilution on hemodynamics, cerebral perfusion, and cerebral vascular reactivity. Stroke. 1996;27:441–5.
95. Hudetz AG, Wood JD, Biswal BB, Krolo I, Kampine JP. Effect of hemodilution on RBC velocity, supply rate, and hematocrit in the cerebral capillary network. J Appl Physiol. 1985;1999(87):505–9.
96. Berkow L. Factors affecting hemoglobin measurement. J Clin Monit Comput. 2013;27:499–508.
97. Tombridge TL. Effect of posture on hematology results. Am J Clin Pathol. 1968;49:3.
98. Mayer GA. Diurnal, postural and postprandial variations of hematocrit. Can Med Assoc J. 1965;93:1006–8.

Publisher's Note