Use of the Fluid Challenge in Critically Ill Adult Patients: A Systematic Review

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The fluid challenge (FC) aims at identifying patients in whom fluid administration improves hemodynamics. Although the FC has been extensively studied, the implementation and definition of improvement are not standardized. This systematic review of studies published between January 1, 1994 and December 31, 2014 characterizes these key components of the FC for critically ill adult patients, as described in the medical literature in the last 20 years. A literature search was performed using MEDLINE, Embase, and Cochrane. For each study, data were collected on study design, study size, study setting, patient population, and how the FC was administered. Eligibility criteria for FC were (1) the infusion of a definite quantity of fluid, (2) of a specific type, (3) in a fixed time period (expressed as either span or infusion rate), (4) with a defined hemodynamic variable as the target, and (5) for a predetermined threshold. One hundred fifty-seven full-text manuscripts were extracted from 870 potentially relevant studies. The inclusion criteria were met by 71 studies including 3617 patients. Sixty-six studies were from a single center and 45 were prospective observational in format. The most common amount infused was 500 cc, used by 55 (77.5%) studies. The most commonly infused fluids were colloids (62.0%). In 43 (60.5%) studies, the FC was administered between 20 and 30 minutes. A positive response to fluid administration was defined as an increase ≥15% of cardiac index or cardiac output in 44 (62.6%) studies. Static or dynamic physiologic indices were utilized in a minority of studies (16.9%) and safety limits for interrupting the FC are adopted in 4 (5.6%) studies only. This systematic review indicates that the FC most commonly consists in infusing 500 mL of crystalloids or colloids in 20–30 minutes, and considered an increase in cardiac index ≥15% as a positive response. However, definite standards for FC administration and evaluation remain undefined. (Anesth Analg 2017;125:1532–43)

Critically ill patients often receive fluids to increase blood pressure or cardiac output (CO) by increasing the cardiac stroke volume (SV).[1,2] The fluid challenge (FC) is a diagnostic approach to hemodynamic management which aims at identifying the patients who respond to fluid administration with an increase in blood pressure or CO.[3] In this way, the FC can identify patients for whom use of inotropes or vasopressors is the appropriate strategy. Therapeutically, a positive FC suggests that fluid administration should be continued as long as the response to FC is positive.[4] The decision to stop fluid administration occurs when a negative response to FC occurs.

A patient is considered responsive to FC when hemodynamic improvement is observed after volemic expansion. While consensus exists on the use of FC to assess preload responsiveness,[1,5] the type of fluid, extent and rate of administration, and hemodynamic targets (either variable and thresholds) are not standardized in clinical practice. Cecconi et al,[1] after reviewing the key components of the FC and its clinical use in the intensive care unit (ICU), proposed the infusion of a standard volume of 200 mL (or 3 mL/kg) in 5 minutes, while guidelines for ICU management of patients with severe sepsis and septic shock propose 500–1000 mL of crystalloids or 300–500 mL of colloids in 30 minutes.[6] By affecting the extent of fluid responsiveness and hence the rate of responders, varying criteria for performing the FC and assessing the result FC may limit comparability among studies.

Two large observational studies indicate that both the mode of administration and assessment of the FC in the current clinical practice vary considerably between countries and over time.[7,8] In particular, the 2015 FENICE trial, a recent prospective observational study performed in 311 ICUs located in 46 countries, found significant variability with respect to the amount and type of fluid and the rate of administration.[8] To address this issue, we systematically reviewed existing literature to evaluate whether the FC in

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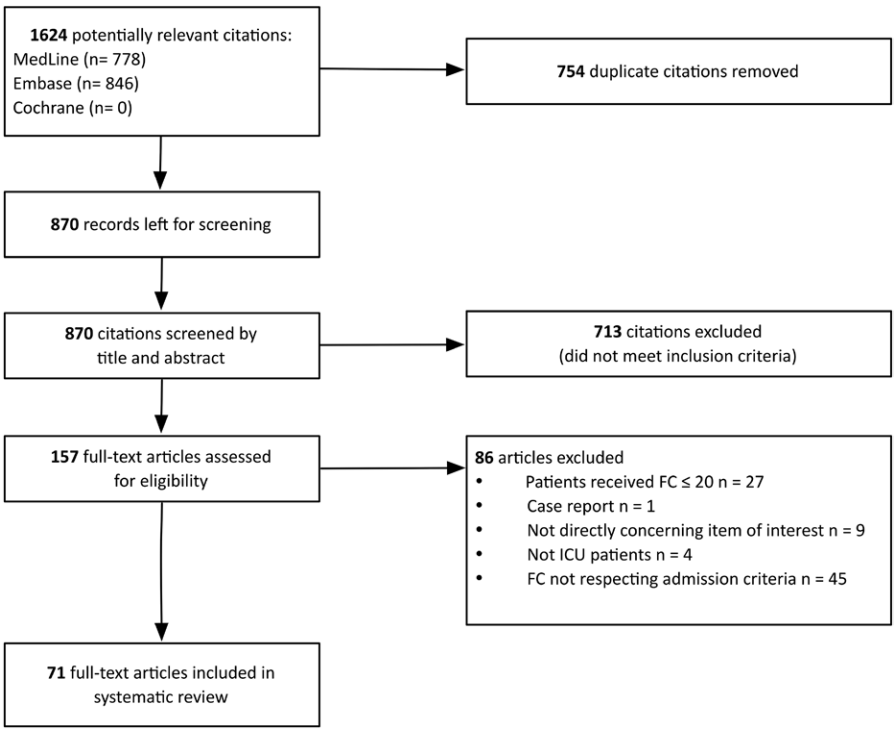

Figure 1. Flow of the studies. FC indicates fluid challenge; ICU, intensive care unit.

critically ill patients is consistent among studies along the last 2 decades with respect to (a) amount and kind of fluid administration, (b) time of infusion, (c) hemodynamic variables and thresholds for fluid responsiveness, and (d) safety limits.

METHODS

Study Selection and Inclusion Criteria

For the purposes of this review, we defined FC as the infusion of a definite quantity of fluid of a specific quality in a fixed time (expressed as either span or infusion rate), and defined the outcome of the FC as a change in a defined hemodynamic variable for a predetermined threshold.

We included the following hemodynamic variables as potential indicators of a positive FC: CO, cardiac index (CI), SV, SV index (SVI), or surrogate SV estimations, ie, aortic velocity-time integrals and aortic blood flow, as assessed by either transthoracic or transoesophageal echocardiography. Only articles published in indexed scientific journals between January 1, 1994 and December 31, 2014 in the English language were considered. We selected studies enrolling more than 20 ICU patients receiving at least one FC. Reviews, case reports, and studies published in abstract form were not considered.

Search Strategy

Two authors (A.M. and F.L.) independently searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews using the following key words and their related MeSh terms: "fluid challenge," "fluid responsiveness," "stroke volume variation," "pulse pressure variation," "dynamic indices OR indexes," "passive leg raising," "inferior cava vein collapsibility," "systolic pressure variation." Included papers were also examined to identify other studies of interest missed during the primary search.

Data Extraction

Pairs of examiners evaluated sets of 15–16 articles. The 2 members of each pair, who performed the evaluation independently from each other, extracted from the selected articles the following information using an ad hoc standardized form: study setting (type of study, geographical area and time period where and when the study was performed, and sample size), patient sample characteristics (gender, age, reason for admission, underlying diseases, ICU scores of gravity, mode of ventilation, and inotropic/vasopressor support), and criteria for hemodynamic instability.

When data from specific studies were not available, the corresponding authors were contacted to obtain missing information. In case of disagreement between the 2 examiners, the opinion of a third, senior, examiner was requested for a conclusive decision (P.N. or G.S.). The list of excluded articles was reported in Supplemental Digital Content, http://links.lww.com/AA/B745. Results were overall summarized qualitatively, owing to the between-study clinical and methodological heterogeneity.

Patients were divided into subgroups for analysis according to the primary cause of hemodynamic instability. We divided patients into 4 groups defined as: (1) septic, ie, systemic inflammatory response syndrome, sepsis, and septic shock, or conditions determining systemic inflammation (ie, pneumonia, pancreatitis, and abdominal infections), (2) postsurgical (postoperative patients without additional complications), (3) cardiac (patients with cardiogenic shock or recovering after cardiac arrest), (4) hypovolemic (trauma, nontraumatic hemorrhagic conditions, dehydration).

Table 1. Characteristics of the Studies Included in the Systematic Review

Authors	Year of Publication	Patients	Study	Centers	Months	Intervention
Michard et al[38]	2000	40	Prospective observational study	1	nd	None
Michard et al[37]	2003	36	Prospective observational study	1	nd	None
Feissel et al[20]	2004	39	Prospective observational study	1	nd	None
Vieillard-Baron et al[54]	2004	66	Prospective observational study	1	nd	None
Silva et al[50]	2004	24	Prospective observational study	1	nd	None
Kramer et al[30]	2004	21	Prospective observational study	1	nd	None
Vallée et al[52]	2005	51	Prospective observational study	1	nd	None
Monnet et al[45]	2005	38	Prospective observational study	1	nd	None
Monnet et al[59]	2006	71	Prospective interventional study	1	nd	PLR
Natalini et al[48]	2006	22	Prospective observational study	1	8	None
Perner et al[49]	2006	30	Prospective observational study	1	nd	None
Feissel et al[21]	2007	23	Prospective observational study	1	nd	None
Auler et al[16]	2007	59	Prospective observational study	1	nd	None
Soubrier et al[76]	2007	32	Prospective interventional study	1	6	Forced respiratory maneuver
Osman et al[78]	2007	96	Retrospective study	1	36	None
Monnet et al[40]	2007	76	Prospective observational study	1	nd	None
Lamia et al[60]	2007	24	Prospective interventional study	1	nd	PLR
Maizel et al[9]	2007	34	Multicentre interventional study	4	nd	PLR
Wyffels et al[56]	2007	32	Prospective observational study	1	8	None
Huang et al[27]	2008	22	Prospective observational study	1	nd	None
Jabot et al[62]	2009	35	Prospective interventional study	1	nd	PLR
Monge Garcia et al[61]	2008	30	Prospective interventional study	1	6	Valsalva maneuver
Vallée et al[53]	2009	84	Prospective observational study	1	24	None
Vistisen et al[55]	2009	23	Prospective observational study	1	5	None
Monge Garcia et al[39]	2009	38	Prospective observational study	1	nd	None
Biais et al[63]	2009	30	Prospective interventional study	1	nd	PLR
Mahjoub et al[35]	2009	35	Prospective observational study	1	6	None
Moretti et al[46]	2010	29	Prospective observational study	1	12	None
Heijmans et al[26]	2010	92	Prospective observational study	1	nd	None
Preau et al[64]	2010	34	Prospective interventional study	1	19	PLR
Lakhal et al[11]	2010	102	Multicentre interventional study	3	nd	PLR
Mahjoub et al[65]	2010	31	Prospective interventional study	1	6	PLR
Wyler von Ballmoos et al[57]	2010	22	Prospective observational study	1	nd	None
Loupec et al[31]	2011	40	Prospective observational study	1	nd	None
Giraud et al[25]	2011	30	Prospective observational study	1	nd	None
Monnet et al[43]	2011	373	Prospective observational study	1	nd	None
Machare-Delgado et al[33]	2011	25	Prospective observational study	1	8	None
Lakhal et al[12]	2011	65	Multicenter observational study	3	18	None
Muller et al[66]	2011	39	Prospective interventional study	1	11	100 mL FC test
Yazigi et al[58]	2012	60	Prospective observational study	1	14	None
Lakhal et al[10]	2012	112	Multicentre interventional study	3	18	PLR
Khwannimit et al[29]	2012	42	Prospective observational study	1	nd	None
Monnet et al[44]	2012	38	Prospective observational study	1	nd	None
Monnet et al[71]	2012	54	Prospective interventional study	1	nd	PLR; EEO
Muller et al[47]	2012	40	Prospective observational study	1	24	None
Preau et al[68]	2012	23	Prospective interventional study	1	12	Deep inspiration maneuver
Mahjoub et al[34]	2012	83	Prospective observational study	1	24	None
Monnet et al[74]	2012	47	Prospective interventional study	1	nd	PLR; EEO
Monge Garcia et al[69]	2012	37	Prospective interventional study	1	5	PLR
Biais et al[17]	2012	35	Prospective observational study	1	nd	None
Dong et al[70]	2012	32	Prospective interventional study	1	18	PLR
Fellahi et al[67]	2012	25	Prospective interventional study	1	6	PLR
Fellahi et al[22]	2012	25	Prospective observational study	1	4	None
Suehiro et al[14]	2012	80	Prospective observational study	1	8	None
Cecconi et al[18]	2012	31	Prospective observational study	1	6	None
Freitas et al[15]	2013	40	Prospective observational study	1	19	None
Saugel et al[75]	2013	31	Prospective interventional study	1	10	PLR
Fischer et al[24]	2013	87	Prospective observational study	1	8	None
Lakhal et al[13]	2013	130	Multicenter observational study	3	18	None
Monnet et al[41]	2013	35	Prospective observational study	1	nd	None
Monnet et al[42]	2013	51	Prospective observational study	1	nd	None
Kupersztych-Hagege et al[72]	2013	48	Prospective interventional study	1	nd	PLR
Monnet et al[73]	2013	65	Prospective interventional study	1	nd	PLR

(*Continued*)

Table 1. Continued

Authors	Year of Publication	Patients	Study	Centers	Months	Intervention
Luzi et al[32]	2013	52	Prospective observational study	1	4	None
Fischer et al[23]	2013	45	Prospective observational study	1	6	None
Marik et al[36]	2013	34	Prospective observational study	1	9	PLR
Smorenberg et al[51]	2013	32	Prospective observational study	1	nd	None
Hu et al[79]	2013	63	Retrospective study	1	24	None
Ishihara et al[28]	2013	43	Prospective observational study	1	nd	None
Charbonneau et al[19]	2014	44	Prospective observational study	1	11	None
Wu et al[77]	2014	50	Prospective interventional study	1	8	10 second FC test

Abbreviations: EEO, end-expiratory occlusion test; FC, fluid challenge; nd, not defined; PLR, passive leg raising.

We also assessed the relationship between rates of FC that exceeded the average response of the overall studies and primary reason for hemodynamic instability (see above); the 2 most common criteria for indicating FC administration; and modalities of FC delivery (type of fluid and rate of administration).

Statistical Analysis

Statistical analysis was conducted on the summary statistics described in the selected articles (eg, means, medians, proportions) and, therefore, the statistical unit of observation for all the selected variables was the single study and not the patient. No meta-analyses on summary findings or on individual patient data were performed.

Descriptive statistics of individual studies used different statistical indicators for central tendency and variability, such as means and standard deviations (SD; ie, age, tidal volume, fluid responders, severity scores), whereas absolute and relative frequencies were adopted for qualitative variables. To show 1 single indicator for the quantitative variables we collected, means with SD or medians and interquartile ranges (IQR) were used, as appropriate.

Student *t* test or Mann-Whitney *U* test in case of parametric or nonparametric distributions, respectively, were used to assess a difference of mean values between responders and nonresponders.

A logistic regression was performed using summary statistics displayed in the selected articles with the scope of assessing the relationship between a proportion of responders higher than 52% (ie, average proportion of responders; we dichotomized the variable for the logistic regression purposes) and several independent covariates (ie, hemodynamic instability, oliguria, hypotension, type of fluid, and rate of administration).

The statistical software STATA13 (StataCorp, College Station, TX) was used to perform all the computations.

RESULTS

The electronic search identified 870 potentially relevant studies. Detailed description of the selection process flow is provided in Figure 1. After evaluating 157 full-text manuscripts, the inclusion criteria were met by 71 studies, none published before 2000. Five of the 157 (3.1%) studies required revision by senior examiners because of disagreement between the coupled examiners. We did not find any further relevant publications by reviewing the bibliography of the selected studies.

Study Design

Of the 71 studies included, 5 were multicentered (3 interventional[9–11] and 2 observational[12,13]), while 64 were single-centered (45 prospective observational,[14–58] 19 prospective interventional,[59–77] and 2 retrospective[78,79] (Table 1). The median (IQR) of the mean duration of the studies was 9.0 (6.0–18.0) months; 60 of them (83.1%) were performed in a university hospital and 59 (81.7%) in European countries.

Characteristics of the Population Enrolled

Overall, the 71 studies include 3617 patients, with a median (IQR) of 38 (31–59) per study. The median (IQR) of the mean patient age across studies was 61.0 (58.5–65.0) years overall, 25 (7–40) for patients with septic shock, 26 (16–32) for surgical 14 (7–18) for patients with cardiogenic shock, 6 (5–12) for patients with hypovolemic shock, 6 (4–11) for trauma patients, and 3 (2–5) for patients with hemorrhagic shock. The median (IQR) of the mean number of FCs administered was 39 (32–68).

Ten studies did not report gender.[21,26,33,41,47,48,55,57,65,74] Thirty-two studies[16–18,20–28,30,36–41,45,46,51,55,56,58–60,63,67,75,76,78] did not report any severity of illness scores at ICU admission. Of the remaining 39 studies, in 9 studies the median (IQR) of the mean reported sepsis-related organ failure assessment score was 10.5 (9.0–12.0),[14,15,29,31,33,48–50,57] in 10 the median (IQR) of the mean reported acute physiology and chronic health evaluation score was 19.0 (17.0–23.0),[15,29,47,50,61,66,69,70,77,79] and in 27 the median (IQR) of the mean a simplified acute physiology score was 55.0 (47.0–57.5).[9–13,19,31,32,34,35,42–44,48,52–54,57,62,64–66,68,71–74,76]

Twenty-four studies (33.8%) did not report the use of vasopressors or inotropes.[9,15,16,18,20,26–28,32,36,47,48,55–58,63–65,68,70,76,77,79] In the remaining studies, norepinephrine was the most common (44/47, 93.6%), at a dose of 0.4 (0.2–0.7) μg/kg/min, followed by dobutamine (26/47, 55.3%), at 7.1 (6.0–8.0) μg/kg/min, dopamine (13/47, 27.7%) at 7.5 (5.0–10.0) μg/kg/min, and epinephrine (10/47, 21.3%) at 0.4 (0.15–0.55) μg/kg/min (median of the mean dose of drug reported across the studies).

The mode of ventilation was not specified in 10 (14.1%) studies,[10,13,18,21,37,44,50,52,77,79] while 6 (8.5%) enrolled only spontaneously breathing patie nts.[9,47,61,64,68,76] Thirty-nine (55.0%) studies included patients receiving volume-targeted controlled ventilation,[11,12,15–17,19,20,22–26,28–31,34–36,38,41,45–48,51,53,54,56–58,65,67,69,70,72–74,78] with the median (IQR) of the mean tidal volume across studies of 7.4 (6.5–8.1) mL/kg. One (1.4%) included patients receiving pressure-targeted controlled ventilation.[27] Two (2.8%) studies enrolled patients undergoing volume-targeted assist/control,[33,71] 1 (1.4%) pressure support,[49] and 1 (1.4%) airway pressure release ventilation.[14] The remaining studies enrolled a mixed population of patients spontaneously breathing or mechanically ventilated.[32,40,42,43,59,60,62,63,75]

Table 2. Indications for Fluid Challenge Administration

	Indications for FC								
Authors	Hypotension	Oliguria	Skin Mottling	Tachycardia	Physician Judgment	Need or Reduction of Inotropes or Vasopressors	Lactate Increase	Diagnosis of Sepsis or Septic Shock	Renal or Hepatic Dysfunction
Michard et al[38]	Yes	No	No	No	No	Yes	No	Yes	No
Michard et al[37]	No	No	No	No	Yes	No	No	No	No
Feissel et al[20]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Vieillard-Baron et al[54]	Yes	No	No	No	No	Yes	No	Yes	No
Silva et al[50]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
Kramer et al[30]	No	No	No	No	No	No	No	No	No
Vallée et al[52]	Yes	No	No	No	No	Yes	No	No	No
Monnet et al[45]	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Monnet et al[59]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Natalini et al[48]	Yes	No	No	No	No	No	No	No	No
Perner et al[49]	No	No	No	No	No	Yes	Yes	No	No
Feissel et al[21]	No	No	No	No	Yes	No	No	Yes	No
Auler et al[16]	No	No	No	No	Yes	No	No	No	No
Soubrier et al[76]	Yes	Yes	Yes	Yes	No	No	No	No	No
Osman et al[78]	g	nd	nd	nd	nd	nd	nd	nd	nd
Monnet et al[40]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Lamia et al[60]	Yes	Yes	Yes	Yes	No	No	No	No	No
Maizel et al[9]	Yes	Yes	No	No	Yes	No	No	No	Yes
Wyffels et al[56]	Yes	No	No	No	Yes	no	no	No	No
Huang et al[27]	nd	nd	Nd	nd	nd	nd	nd	nd	nd
Jabot et al[62]	No	No	No	No	No	No	No	Yes	No
Monge Garcia et al[61]	Yes	Yes	No	Yes	nd	No	No	no	No
Vallée et al[53]	Yes	Yes	No	Yes	No	No	No	No	No
Vistisen et al[55]	nd	nd	Nd	nd	nd	nd	nd	nd	nd
Monge Garcia et al[39]	Yes	Yes	Yes	Yes	No	Yes	No	no	No
Biais et al[63]	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Mahjoub et al[35]	Yes	No	No	No	Yes	Yes	No	No	No
Moretti et al[46]	No	No	No	No	No	No	No	No	No
Heijmans et al[26]	No	No	No	No	Yes	No	No	No	No
Preau et al[64]	Yes	Yes	Yes	yes	No	No	No	Yes	No
Lakhal et al[11]	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Mahjoub et al[65]	Yes	No	No	No	No	Yes	Yes	No	No
Wyler von Ballmoos et al[57]	No	No	No	No	Yes	No	No	No	No
Loupec et al[31]	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Giraud et al[25]	Yes	No	No	No	Yes	No	No	No	No
Monnet et al[43]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Machare-Delgado et al[33]	Yes	No	No	No	Yes	Yes	No	No	No
Lakhal et al[12]	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Muller et al[66]	No	Yes	No	No	No	Yes	No	No	No
Yazigi et al[58]	nd	nd	nd	nd	nd	nd	nd	nd	nd
Lakhal et al[10]	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Khwannimit et al[29]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Monnet et al[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Monnet et al[71]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Muller et al[47]	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Preau et al[68]	Yes	Yes	Yes	Yes	No	No	No	No	No
Mahjoub et al[34]	Yes	No	No	No	Yes	Yes	Yes	No	No
Monnet et al[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Monge Garcia et al[69]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Biais et al[17]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Dong et al[70]	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Fellahi et al[67]	No	No	No	No	Yes	No	No	No	No
Fellahi et al[22]	No	No	No	No	Yes	No	No	No	No
Suehiro et al[14]	No	No	No	No	No	No	No	No	No
Cecconi et al[18]	No	No	No	No	No	No	No	Yes	Yes
Freitas et al[15]	No	No	No	No	Yes	No	No	Yes	No
Saugel et al[75]	No	No	No	No	Yes	No	No	No	No
Fischer et al[24]	No	No	No	No	Yes	No	No	No	No
Lakhal et al[13]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
Monnet et al[41]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Monnet et al[42]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Kupersztych-Hagege et al[72]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Monnet et al[73]	nd	nd	Nd	nd	yes	nd	nd	no	No

(*Continued*)

Table 2. Continued

	Indications for FC								
Authors	Hypotension	Oliguria	Skin Mottling	Tachycardia	Physician Judgment	Need or Reduction of Inotropes or Vasopressors	Lactate Increase	Diagnosis of Sepsis or Septic Shock	Renal or Hepatic Dysfunction
Luzi et al[32]	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Fischer et al[23]	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Marik et al[36]	nd	nd	nd	nd	nd	nd	nd	nd	nd
Smorenberg et al[51]	Yes	No	No	No	No	Yes	No	No	No
Hu et al[79]	Yes	Yes	Yes	No	No	No	Yes	No	No
Ishihara et al[28]	Yes	No	No	No	No	No	No	No	No
Charbonneau et al[19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Wu et al[77]	Yes	Yes	Yes	Yes	Yes	No	No	No	No

Hypotension is defined as systolic or mean arterial pressure either below an absolute value, or expressed as percentage of reduction from baseline, or indicated as a generic reduction of blood pressure; oliguria corresponds to a drop in urine output below 0.5 mL/h for at least 2 consecutive hours; tachycardia is characterized by an increase in heart rate above 100 beats/min. Lactate indicates the presence of either generic lactate acidosis or an increase above a predefined cutoff level. The diagnosis of sepsis/septic shock, renal and hepatic dysfunction is done according to the international guidelines available at the time the study was performed. The diagnosis of sepsis/septic shock as inclusion criteria in the study was not considered as indication for FC administration. The "physician judgment" in some studies was just based on subjective decision of the attending physician while in other studies it was based on predefined criteria of hemodynamic instability.

Abbreviations: FC, fluid challenge; nd, not defined.

Indication for the Fluid Challenge

Several clinical, pharmacological, or laboratory indicators of fluid depletion were used to trigger a FC. Hypotension (systolic or mean arterial pressure either below a fixed value or expressed as percent reduction from baseline or a generic reduction of the blood pressure) was used in 48 (67.6%),[9–13,17,19,20,23,25,28,29,31–36,38–45,47,48,50–54,56,59–61,63–65,68–72,74,76,77,79] oliguria (a drop in urine output below 0.5 mL/h for 2 or 3 consecutive hours) in 37 (52.1%),[9–13,17,19,20,23,29,31,32,34,39–45,47,50,53,59–61,63,64,66,68–72,74,76,77,79] physician judgment in 35 (49.3%),[9,13,15–17,19–26,29,31,33–35,37,40–44,56,57,59,67,69,71–75,77] clinical evidence of skin mottling in 33 (46.4%),[10,12,13,17,19,20,23,29,31,32,39–45,47,50,59–61,63,64,68–72,74,76,77,79] tachycardia, as defined by an increase in heart rate above 100 to 110 beats/min, in 29 (40.8%),[17,19,20,23,29,32,39–45,47,50,53,59–61,63,64,68–72,74,76,77] need for initiating or reducing administration of vasoactive drugs in 23 (32.3%),[10–13,31,33–35,38–40,44,45,49,51,52,54,59,65,66,69,70,74] lactate increase in 17 (23.9%),[10–13,19,20,32,34,41,44,47,49,50,65,72,74,79] diagnosis of sepsis/septic shock in 9 (12.7%),[15,18,19,21,38,50,54,62,64] and renal or hepatic dysfunction in 5 (7.0%) studies (see Table 2).[9,18–20,63]

A safety limit interrupt the FC was used in 4 (5.6%) studies by the same authors.[10–13]

Quantity of Fluid Challenge

In 12 (17%) studies,[15,16,19–21,26,46,52–54,58,75] the median (IQR) of the mean volume administered was 7 (7–9) mL/kg. Of the remaining 59 (83.1%) studies, 55 (77.5%) infused 500 mL,[9–14,17,22–25,27,29–45,47–51,55,56,59–74,76–78] 2 (2.8%) 250 mL,[18,28] 1 (1.4%) 200 mL,[57] and 1 (1.4%) 300 mL (see Table 3).[79]

Type of Fluid Administered

Colloids were used in 44 (62.0%) studies, where 34 (77.3%) infused 6% hydroxyethylstarch,[15,19–24,26,27,29,31,37–39,46–48,50,53–58,61,64,66–70,76,78,79] 3 (6.7%) 4% succinyl-gelatine,[35,51,52] and 2 (4.5%) 6%[49] or 10% Dextran.[28] In 5 (11.3%) studies, the type of colloid was unspecified.[10–13,18] Twenty-six (36.5%) studies[9,14,16,17,25,32–34,36,40–45,59,60,62,63,65,71–75,77] used crystalloids and 1 (1.5%) study utilized blood (Table 3).[30]

Of 6 studies identified in the 2000 to 2004 period, 5 (83.3%) infused colloids and another one (12.5%) blood. Of 27 studies in the 2005–2010 period, 18 (66.6%) used colloids and 9 (33.4%) crystalloids. Of 38 studies in the 2011 to 2014 period, 20 (52.5%) use colloids and 18 (47.5%) crystalloids (Figure 2).

Duration of Fluid Administration

The duration of fluids administration was 30 minutes in 32 studies (45.1%),[10–15,21,29,32,35,37–39,41,42,44,46,48–51,53,54,61,64,65,68–70,73–75] 15 minutes in 15 studies (21.1%),[9,17,19,22–24,26,30,47,52,60,63,66,67,77] 20 minutes in 11 studies (15.5%),[16,20,28,34,43,56,58,71,76,78,79] 10 minutes in 9 studies (12.7%),[25,31,33,36,45,57,59,62,72] and in 5,[18] 7.5,[40] and 90[55] minutes in one single study (1.4%). Only one study (1.4%) reported the infusion rate (10 mL/kg/h).[27] The median (IQR) of the mean rate of infusion, across 58 studies indicating volume and duration of infusion, was 18 (6–67) mL/min (see Table 3).

Hemodynamic Response

Overall, the mean (SD) of the mean rate of fluid responders across the studies was 52.0% (13.0%). Forty-four studies (62.0%) assessed fluid responsiveness considering the rate of increase in CI or CO. The positive response was defined by an increase ≥15% in 34 studies[14–16,19–25,27,28,31,38,41–44,46,48,53,55,56,62,67,69,71–78]; ≥10% in 7 studies[10–13,49,50,79]; ≥12% in 2 studies,[44,59] and ≥11% in 1 investigation.[46] Twenty-two (31.0%) studies utilized either SVI or SV for assessing fluid responsiveness; 15 of these studies considered positive response an increase ≥15%,[17,18,29,32,34,35,37,39,58,60,61,63,64,68,70] 5 studies ≥10%,[33,36,51,52,57] and 2 single studies ≥12%[65] and ≥ 5%.[26] Five studies (7.0%) used aortic blood flow or aortic velocity-time integrals increase ≥15% to identify fluid responsiveness (see Table 3).[40,45,47,59,66]

Forty-five studies reported the variation of mean (SD) arterial pressure before and after FC, which was higher in responders than in nonresponders (11.5 ± 5.4% vs 6.1 ± 3.9%, respectively; $P < .001$).

Subgroup Analysis

Only 2 subgroups of studies enrolled at least 75% of patients with one specific cause of hemodynamic instability, septic (31 studies[12,15,19–21,27,29,33–35,37,38,41–44,49,50,54,60,62,64–66,68,70–73,76,78]) and

Table 3. Modalities of Fluid Challenge in the Studies Included

Authors	Volume (mL)	Fluid	Time of Infusion (min)	Rate of infusion (mL/min)	Hemodynamic Variable	Measuring Device	Responders (%)	FC Infusion Triggered by Static or Dynamic Indexes	Safety Limit
Michard et al[38]	500	6% HES	30	16.7	CI ≥ 15%	PAC	40	No	No
Michard et al[37]	500	6% HES	30	16.7	SVI >15%	PiCCO	49	No	No
Feissel et al[20]	8/kg	6% HES	20	nd	CO ≥ 15%	ECO-TTE	41	No	No
Vieillard-Baron et al[54]	10/kg	6% HES	30	nd	CI ≥ 11%	ECO-TEE	30	No	No
Silva et al[50]	500	6% HES	30	16.7	CI > 10%	PAC	63	PVC low (IC) PAOP < 12 mm Hg (IC)	No
Kramer et al[30]	500	blood	15	33.3	CO ≥ 12%	PAC	28.6	PAOP>24 mm Hg (EC)	No
Vallée et al[52]	4/kg	4% Succ.	15	nd	SVI > 10%	CardioQ	39.2	No	No
Monnet et al[45]	500	Saline	10	50.0	ABF >15%	ECO-TEE	53	No	No
Monnet et al[59]	500	Saline	10	50.0	ABF ≥ 15%	ECO-TEE	52	No	No
Natalini et al[48]	500	6% HES	30	16.7	CI ≥ 15%	PAC	59	No	No
Perner et al[49]	500	6% Dextran 70	30	16.7	CI > 10%	PiCCO	47	No	No
Feissel et al[21]	8/kg	6% HES	30	nd	CI ≥ 15%	ECO-TTE	64	No	No
Auler et al[16]	20/kg	Lactated Ringer solution	20	nd	CI ≥ 15%	PAC	66	No	No
Soubrier et al[76]	500	6% HES	20	25.0	CI ≥ 15%	ECO-TTE	59	No	No
Osman et al[78]	500	6% HES	20	25.0	CI ≥ 15%	PAC	43	No	No
Monnet et al[40]	500	Saline	7.5	66.7	ABF ≥ 15%	ECO-TEE	54	No	No
Lamia et al[60]	500	Saline	15	33.3	SV ≥ 15%	ECO-TTE	59	No	No
Maizel et al[9]	500	Saline	15	33.3	CO ≥ 12%	ECO-TTE	50	No	No
Wyffels et al[56]	500	6% HES	20	25.0	CI ≥ 15%	PAC	62	PAOP > 18 mm Hg (EC)	No
Huang et al[27]	500	6% HES	10 mL/kg/h	nd	CI ≥ 15%	PiCCO/PAC	46	No	No
Jabot et al[62]	500	Saline	10	50.0	CI > 15%	PiCCO	100	No	No
Monge Garcia et al[61]	500	6% HES	30	16.7	SVI ≥ 15%	FloTrac	37	No	No
Vallée et al[53]	6/kg	6% HES	30	nd	CI > 15%	PiCCO	46	No	No
Vistisen et al[55]	500	6% HES	90	5.6	CI > 15%	PAC	74	No	No
Monge Garcia et al[39]	500	6% HES	30	16.7	SVI ≥ 15%	Vigileo	50	No	No
Biais et al[63]	500	Saline	15	33.3	SV ≥ 15%	ECO-TTE / Vigileo	66.6	No	No
Mahjoub et al[35]	500	4% Succ.	30	16.7	SV > 15%	ECO-TTE	66	PPV>12% (IC)	No
Moretti et al[46]	7/kg	6% HES	30	nd	CI >15%	PiCCO2	59	EVLWi >14 mL/kg,	No
Heijmans et al[26]	10 *BMI	6% HES	15	nd	SVI ≥ 5%	LiDCO plus / PAC	51	no	No
Preau et al[64]	500	6% HES	30	16.7	SV ≥ 15%	ECO-TTE	41	no	No
Lakhal et al[11]	500	Gelatine	30	16.7	CO > 10%	PiCCO	42	EVLWi >22 mL/kg (EC) PAOP >18 mm Hg (EC)	Yes
Mahjoub et al[65]	500	Saline	30	16.7	SVI > 12%	CARDIOQ	51.5	PPV >12 mm Hg (IC)	No
Wyler von Ballmoos et al[57]	200	6% HES	10	20.0	SV >10%	PAC	28	No	No
Loupec et al[31]	500	6% HES	10	50.0	CO ≥ 15%	ECO-TTE/TEE	52.5	No	No
Giraud et al[25]	500	Saline	10	50.0	CI ≥ 15%	PAC	47	CI <2.2 L/min/m^2 (IC) PAOP >18 mm Hg (IC)	No
Monnet et al[43]	500	Saline	20	25.0	CI ≥ 15%	PiCCO	62	No	No
Machare-Delgado et al[33]	500	Saline	10	50.0	SVI ≥ 10%	ECO-TTE	32	No	No
Lakhal et al[12]	500	Gelatine	30	16.7	CO ≥ 10%	PAC/PiCCO	40	No	Yes
Muller et al[66]	500	6% HES	15	33.3	VTI ≥ 15%	ECO-TTE	54	No	No
Yazigi et al[58]	7/kg	6% HES	20	nd	SVI ≥ 15%	PAC	68	PAOP ≥ 18 mm Hg (EC)	No
Lakhal et al[10]	500	Gelatine	30	16.7	CO ≥ 10%	PiCCO/PAC	39	EVLWi >22 mL/kg (EC) PAOP>18 mm Hg (EC)	Yes
Khwannimit et al[29]	500	6% HES	30	16.7	SVI ≥ 15%	FloTrac	57	No	No
Monnet et al[44]	500	Saline	30	16.7	CI > 15%	PiCCO/Nexfin	42	No	No
Monnet et al[71]	500	Saline	20	25.0	CI ≥ 15%	PiCCO	55	No	No
Muller et al[47]	500	6% HES	15	33.3	VTI ≥ 15%	ECO-TTE	50	No	No
Preau et al[68]	500	6% HES	30	16.7	SV > 15%	ECO-TTE	43.5	No	No
Mahjoub et al[34]	500	Saline	20	25.0	SV >15%	ECO-TTE	71	No	No
Monnet et al[74]	500	Saline	30	16.7	CI > 15%	PiCCO	46	No	No
Monge Garcia et al[69]	500	6% HES	30	16.7	CO ≥ 15%	CardioQ	57	No	No

(*Continued*)

Table 3. Continued

Authors	Volume (mL)	Fluid	Time of Infusion (min)	Rate of infusion (mL/min)	Hemodynamic Variable	Measuring Device	Responders (%)	FC Infusion Triggered by Static or Dynamic Indexes	Safety Limit
Biais et al[17]	500	Saline	15	33.3	SV ≥ 15%	ECO-TTE/PRAM	54	No	No
Dong et al[70]	500	6% HES	30	16.7	SVI ≥ 15%	PiCCO	68	No	No
Fellahi et al[67]	500	6% HES	15	33.3	CI > 15%	PiCCO/ECOM	56	No	No
Fellahi et al[22]	500	6% HES	15	33.3	CI ≥ 15%	PiCCO/ECOM	84	No	No
Suehiro et al[14]	500	Ringer lactate	30	16.7	CI ≥ 15%	VIGILEO	47.5	No	No
Cecconi et al[18]	250	COLLOIDS	5	50.0	SV >15%	LidCO plus	39	No	No
Freitas et al[15]	7/kg	6% HES	30	nd	CO >15%	PAC	48	No	No
Saugel et al[75]	7/kg	Crystalloids	30	nd	CI ≥15%	PiCCO	29	No	No
Fischer et al[24]	500	6% HES	15	33.3	CI>15%	PiCCO	71	No	No
Lakhal et al[13]	500	Gelatine	30	16.7	CO > 10% (regular rhythm) CO > 15 % (arrhythmia)	PiCCO/PAC	37	EVLWi >22 mL/kg (EC) PAOP>18 mm Hg (EC)	Yes
Monnet et al[41]	500	Saline	30	16.7	CI ≥ 15%	PiCCO	43	No	No
Monnet et al[42]	500	Saline	30	16.7	CI >15%	PiCCO2	49	No	No
Kupersztych-Hagege et al[72]	500	Saline	10	50.0	CI ≥ 15%	NICOM / PiCCO	39.6	No	No
Monnet et al[73]	500	Saline	30	16.7	CI > 15%	PiCCO	52	No	No
Luzi et al[32]	500	Saline	30	16.7	SV ≥ 15%	ECO-TTE	59	No	No
Fischer et al[23]	500	6% HES	15	33.3	CI ≥ 15%	PiCCO / Nexfin	73	No	No
Marik et al[36]	500	Saline	10	50.0	SVI > 10%	NICOM	53	No	No
Smorenberg et al[51]	500	4% Succ.	30	16.7	SVI > 10%	PAC	44	PVC < 10 mm Hg (IC) PAOP < 12 mm Hg (IC)	No
Hu et al[79]	300	6% HES	20	15.0	CI ≥ 10%	PiCCO	52	No	No
Ishihara et al[28]	250	10 % Dextran	20	12.5	CI >15%	PiCCO	53	No	No
Charbonneau et al[19]	7/kg	6% HES	15	nd	CI ≥ 15%	ECO-TEE	59	No	No
Wu et al[77]	500	Crystalloids	15	33.3	CO ≥ 15%	ECO-TTE	54	No	No

PiCCO/PiCCO2; PULSION Medical Systems, Munich, Germany. LidCO plus; LidCO Group PLC, London, UK. NICOM; Cheetah Medical, Portand, OR. Nexfin; BMEYE, Amsterdam, the Netherlands. CardioQ; Deltex Medical Ltd, Chichester, UK. PRAM; Vygon Health, Padua, Italy. FlowTrac; Edwards Lifesciences, Irvine, CA.

Abbreviations: ABF, aortic blood flow; BMI, body mass index; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; EC, exclusion criteria; ECO-TTE, transthoracic echocardiography; ECO-TEE, transesophageal echocardiography; EVLWi, Extravascular Lung Water Index; 4% Succ, Succinylated gelatine 4%; 6% HES, 6% Hydroxyethylstarch; IC, inclusion criteria; nd, not defined; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; PPV, pulse pressure variation; SV, stroke volume; SVI, stroke volume index; VTI, Velocity Time Integral.

postsurgery (16 studies[16,18,22–24,26,28,30,51,55–58,61,63,67]). The median (IQR) of the mean rate of fluid responders did not differ between the 2 subgroups, 49% (42–49) and 59% (42–70) for septic and postsurgery, respectively (P = .27). Hypotension was the most common criteria for FC administration in both groups, (71.0% and 43.8% of septic and postsurgery subgroups, respectively). Oliguria was the second most used criteria for indicating FC, representing 58.1% and 12.5% of septic and postsurgery subgroup, respectively. Colloids were used in 19 (61.3%) of the 31 studies including predominantly septic patients, and in 13 (86.7%) of 16 studies of the postsurgery subgroup. The mean (SD) of the mean rate of fluid administration was 23.6 (11.2) mL/min in septic and 26.6 (11.9) mL/min in postsurgery. The median (IQR) of the mean duration of FC administration was 30 minutes (20–30) in septic and 15 minutes (15–20) in postsurgery (P = .02) subgroups.

Assessment of Variables Affecting FC Outcome

Table 4 summarizes the logistic regression analysis assessing the relationship between the primary reasons determining hemodynamic instability (sepsis or postsurgical), presence of oliguria and hypotension (the 2 most common criteria for FC), rate of administration and a positive response rate exceeding the average rate (52%) of responders of the overall studies. We found no correlation between a higher rate of fluid responsiveness and any of these variables.

DISCUSSION

In a systematic review of studies published in the last 20 years on the FC in critically ill adult patients, we found marked variability in the definition, implementation, and assessment of the FC. In the majority of the studies, a 500 cc bolus (most often of colloid) was infused over 30 minutes, without predetermined stopping rules, and ≥15% increases in CI or CO were used to assess the result. We also observed that the median time of FC administration and use of oliguria as a criterion for FC, were both more likely in the septic subgroup.

Indication for the Fluid Challenge

The most common criteria for attempting a FC clinical signs such as hypotension (67.6% of studies) and oliguria (52.1% of studies) may not exclusively be the result of fluid depletion. For instance, ICU sedation affects both tachycardia and hypotension.[80] Also, reduction in urinary output may result from renal dysfunction and thus not necessarily respond to a FC.[81] Importantly, our subgroup analysis found oliguria to be more commonly used as an indication for FC in studies enrolling predominantly septic patients.

About half the patients in the studies we reviewed did not respond to fluid administration, which suggests that using these signs to identify potential fluid responders may not be successful.

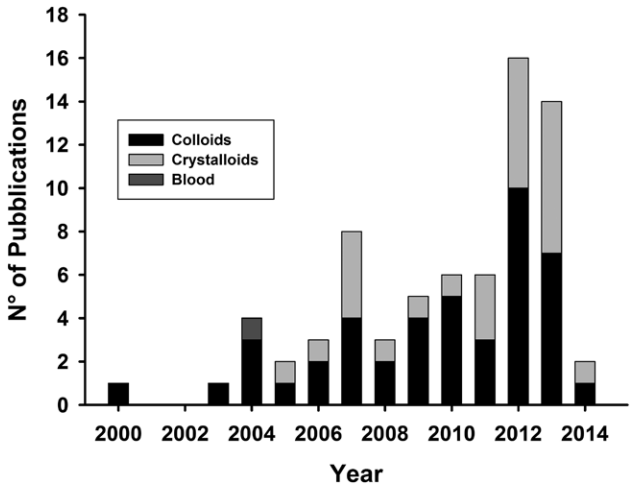

Figure 2. Quality of fluid challenge over the years.

Table 4. Relationship Between Rates of Rates of Responders and Patients' Characteristics

Variables	Studies With Responders ≥ 52%	Studies With Responders < 52%	*P* Value
Septic patients, n (%)	10/24 (41.7)	6/23 (26.1)	.26
Postsurgery patients, n (%)	10/34 (29.4)	6/35 (17.1)	.23
Hypotension, n (%)	24/36 (66.7)	24/36 (66.7)	.80
Oliguria, n (%)	18/36 (50.0)	19/36 (52.7)	1.00
Colloids, n (%)	21/36 (58.3)	23/35 (68.6)	.37
Time of FC administration (min)	20 (15–30)	30 (15–30)	.07

See text for further explanations.
Abbreviation: FC, fluid challenge.

Static or dynamic physiologic indices were utilized in a minority of studies (16.9%). This frequency is considerably less than the 57.3% reported by the FENICE study.[8] The association between these indices and clinical signs may improve the selection of patients for FC. However, static indices, particularly central venous pressure are unreliable for fluid response assessment in ICU patients[82] and pulse pressure variation, the most reliable dynamic index,[83] can be properly used only in a small portion of ICU patients in whom all the validity criteria of this dynamic index are satisfied.[84]

Quantity and Duration of Fluid Challenge

In 77.5% of the studies, the FC consisted of 500 mL fluid boluses. Five hundred milliliters was also the median volume FC used in the FENICE study.[8] In 60.5% of studies, the infusion was administered in 20 or 30 minutes, with a median infusion rate of 18 mL/min, similar to the median 24 minutes and 17 mL/min recently reported by the FENICE study.[8] Interestingly, the duration of volume administration was shorter in studies with a rate of FC responders ≥52%, suggesting that a more rapid FC may affect responsiveness. The phase of distribution among different tissue compartments for crystalloids normally takes 25–30 minutes, and the fraction remaining in the plasma is related to both duration and rate of infusion.[85] Aya et al[86] recently suggested an even shorter duration, finding that the hemodynamic effect of 250 mL of crystalloids infused over 5 minutes, is dissipated within 10 minutes, in both responders and nonresponders. The hemodynamic effect of colloids is likewise complex, as infusion of the same volume causes a greater plasma expansion in hypovolemic than in nonhypovolemic patients.[87]

Type of Fluid Challenge

Figure 2 lists the type of fluids utilized for the FC throughout between 2000 and 2014. Overall, colloids were used more often than crystalloids. When grouping studies in 3 epochs, however, the ratio between colloids and crystalloids decreased from 5:0 in the 2000–2004 period, to approximately 3:1 in the 2005–2010 period, to approximately 1:1 in the 2011 to 2014 period. In keeping with this trend, a large 2007 cross-sectional study found colloids used more frequently than crystalloids,[7] whereas in the 2013, FENICE survey crystalloids are more commonly used (74%).[8]

Hemodynamic Response

While in 62.6% of the studies an increase of ≥15% of CI or CO immediately after FC completion defined a positive response, in current clinical practice fluid responsiveness is often assessed by an rise in arterial blood pressure.[8] This metric only reflects an increase in CO in patients with high arterial elastance[8] and is not reliable when used for passive leg raising test evaluation.[88] The threshold value of the variable used to assess fluid responsiveness may thus influence the result of a FC for some patients, who may be responders when the threshold for responsiveness is 10% but nonresponders when the threshold is increased to 15%.

CONCLUSIONS

The FC is not well standardized and lacks of consistency among the published studies. The most common form of administration, whose appropriateness remains to be clarified, consists in infusing 500 mL of crystalloid or colloids in 20 or 30 minutes, and assessing whether or not this infusion determines an increase in CI or CO ≥15%. Defining strict criteria for FC administration and response assessment is deemed necessary for meaningful comparisons of data among studies.

DISCLOSURES

Name: Antonio Messina, MD, PhD.
Contribution: This author designed the study, collected the data, performed the data analysis, and wrote the manuscript.
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Contribution: This author helped with data collection, manuscript preparation, and data interpretation.
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Name: Paolo Navalesi, MD, FERS.
Contribution: This author designed the study, collected the data, performed the data analysis, and wrote the manuscript.
All authors listed on the title page have read the draft, confirmed the validity and legitimacy of the data and its interpretation, approved the final version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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