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META-ANALYSIS

Fluid Challenge During Anesthesia: A Systematic Review and Meta-analysis

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BACKGROUND: Assessing the volemic status of patients undergoing surgery is part of the routine management for the anesthesiologist. This assessment is commonly performed by means of dynamic indexes based on the cardiopulmonary interaction during mechanical ventilation (if available) or by administering a fluid challenge (FC). The FC is used during surgery to optimize predefined hemodynamic targets, the so-called Goal-Directed Therapy (GDT), or to correct hemodynamic instability (non-GDT).

METHODS: In this systematic review, we considered the FC components in studies adopting either GDT or non-GDT, to assess whether differences exist between the 2 approaches. In addition, we performed a meta-analysis to ascertain the effectiveness of dynamic indexes pulse pressure variation (PPV) and stroke volume (SV) variation (SVV), in predicting fluid responsiveness.

RESULTS: Thirty-five non-GDT and 33 GDT studies met inclusion criteria, including 5017 patients. In the vast majority of non-GDT and GDT studies, the FC consisted in the administration of colloids (85.7% and 90.9%, respectively). In 29 non-GDT studies, the colloid infused was the 6% hydroxyethyl starch (6% HES; 96.6% of this subgroup). In 20 GDT studies, the colloid infused was the 6% HES (66.7% of this subgroup), while in 5 studies was a gelatin (16.7% of this subgroup), in 3 studies an unspecified colloid (10.0% of this subgroup), and in 1 study albumin (3.3%) or, in another study, both HES 6% and gelatin (3.3%). In non-GDT studies, the median volume infused was 500 mL; the time of infusion and hemodynamic target to assess fluid responsiveness lacked standardization. In GDT studies, FC usually consisted in the administration of 250 mL of colloids (48.8%) in 10 minutes (45.4%) targeting an SV increase >10% (57.5%). Only in 60.6% of GDT studies, a safety limit was adopted. PPV pooled area under the curve (95% confidence interval [CI]) was 0.86 (0.80–0.92). The mean (standard deviation) PPV threshold predicting fluid responsiveness was 10.5% (3.2) (range, 8%–15%), while the pooled (95% CI) sensitivity and specificity were 0.80 (0.74–0.85) and 0.83 (0.73–0.91), respectively. SVV pooled area under the curve (95% CI) was 0.87 (0.81–0.93). The mean (standard deviation) SVV threshold predicting fluid responsiveness was 11.3% (3.1) (range, 7.5%–15.5%), while the pooled (95% CI) sensitivity and specificity were 0.82 (0.75–0.89) and 0.77 (0.71–0.82), respectively.

CONCLUSIONS: The key components of FC including type of fluid (colloids, often 6% HES), volume (500 and 250 mL in non-GDT studies and GDT studies, respectively), and time of infusion (10 minutes) are quite standardized in operating room. However, pooled sensitivity and specificity of both PPV and SVV are limited. (Anesth Analg 2018;127:1353–64)

KEY POINTS

- **Question:** Is the modality of fluid challenge (FC) administration consistent and the dynamic indexes of fluid responsiveness reliable in operating room?
- **Finding:** FC in operating room usually consists of a colloid bolus of 250 or 500 mL administered in about 10 minutes; the pooled sensitivity and specificity of pulse pressure variation and stroke volume variation are limited.
- **Meaning:** The FC is quite standardized in operating room, with the exception of volume used, and caution is needed when pulse pressure variation or stroke volume variation is used to assess fluid responsiveness.

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Perioperative fluid therapy is a key component of the management of surgical patients and dedicated algorithms and protocols are nowadays part of the included into routine intraoperative and perioperative care.[1,2] Conventional fluid administration, aimed at balancing fluid intake and output, should be distinguished from the acute treatment of hemodynamically unstable patients.[1,3] Several dynamic tests have been proposed to predict whether or not fluid infusion would increase the cardiac output (CO), such as the fluctuations of pulse pressure or stroke volume (SV) during mechanical ventilation or the increase in right preload by modifying the position of the patient[4] or interrupting positive pressure ventilation.[5]

The fluid challenge (FC) consists in assessing the hemodynamic effects of giving fluid in a limited period of time.[6] By allowing to restore fluid depletion when indicated, while minimizing the risk of overloading,[3] the FC is routinely used to assess fluid depletion in surgical patients.[6] In the operating room, fluids may be administered either to correct an unexpected episode of hypotension or hypovolemia[1,7–9] or in small aliquots protocolized to optimize hemodynamics, the so-called Goal-Directed Therapy (GDT).[10,11]

Type, amount and duration of the infusion, interval between FC administration and fluid responsiveness assessment, indices, and relative thresholds for determining the hemodynamic response are all important issues potentially affecting the outcome of the FC. A recent study considering adult critically ill patients, however, highlighted the lack of definite standards for FC administration and evaluation in intensive care unit (ICU).[12] It remains unclear, however, what the best approach to FC administration should be and, in fact, wide variability exists at this regard among studies performed both in the perioperative setting and in the ICU.[12]

Aim of this systematic review is to describe and compare the modality of FC administration in non-GDT and GDT studies performed in patients undergoing surgery, considering indications, hemodynamic targets and thresholds for fluid responsiveness assessment, use of safety limits, fluid type, dose, and time of infusion. In addition, we evaluated the use of 2 dynamic predictors of fluid responsiveness, pulse pressure variation (PPV) and SV variation (SVV), to guide FC administration and performed a meta-analysis to ascertain the reliability of both of these indexes in predicting fluid responsiveness.

METHODS

Study Selection and Inclusion Criteria

FC was considered as the infusion of a definite quantity of fluid of a specific quality in a period of time (expressed either as span or infusion rate), administered to assess variations of a hemodynamic variable. Studies in whom the FC was not defined or standardized were excluded.

All articles in English language, including adult patients, without restrictions related to type of surgery and surgical risk, and published in indexed scientific journals in the last 20 years were considered (January 1, 1997 to January 1, 2017). Reviews, case reports, and studies published in abstract form were excluded. Only 2-harm GDT studies (treatment–control subgroups) were included.

Search Strategy

Three authors (A.M., E.B., and C.P.) independently searched MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews using the following keywords and their related MeSh terms: "fluid challenge," "fluid responsiveness," "stroke volume variation," "pulse pressure variation," "dynamic indices OR indexes," "intraoperative fluid optimization," "surgery" "directed therapy," "goal-directed therapy," "fluid therapy," "goal oriented," "goal targeted," and "fluid optimization." References of included papers and review articles were also examined to identify additional studies missed during the primary search (Supplemental Digital Content, Document, http://links.lww.com/AA/C594).

Data Extraction

All articles were independently evaluated by couple of researchers who reported all collected data in an EXCEL (Microsoft, Redwood, MS) spreadsheet specifically designed for the study purposes. When data were not available, the corresponding authors were contacted. In case of disagreement for the article selection or variables to be retrieved, it was requested the intervention of a third, senior, expert (P.N., G.S.).

Whenever possible, the mean body surface area and weight of the enrolled samples were used to recalculate the nonindexed variables, reporting the corresponding indexed values (ie, from CO and SV to cardiac index and SV index [SVI]) and the volume/weight (mL/kg) reporting the absolute volume (mL). All the hemodynamic changes associated to FC administration were reported as percentage of variation with respect to baseline values.

Statistical Analysis

Statistical analyses were performed on the statistical figures reported in the selected articles. On this basis, the statistical unit of observation for the variables was the single study. The statistical software STATA13 (StataCorp, College Station, TX), StatsDirect version 3 (StatsDirect Ltd, Altrincham, UK), and Metadisc version 1.4 (http://www.hrc.es/investigacion/metadisc.html) were used to perform all the statistical analyses. Quantitative variables were summarized with means (standard deviations [SDs]) or medians (interquartile ranges [IQRs]) according to their distribution. Student t test or Mann-Whitney test was computed to find differences between non-GDT and GDT studies. Two-tailed P values <.05 were considered significant.

A meta-analysis of the PPV and SVV values before FC administration was performed, using data obtained from those studies evaluating PPV and SVV reliability in predicting fluid responsiveness by means of a receiving operating characteristics (ROCs) curve approach. Random effects models were used. In-between study heterogeneity was assessed through the I^2 indicator. Bias assessment graphs were plotted, and Egger regression analysis was used to evaluate the publication bias. The area under the curve (AUC) of pooled ROC curves was reported with 95% confidence interval (95% CI).

RESULTS

The electronic search identified 14,378 potentially relevant studies. Detailed description of the selection process flow is provided in the Figure. Two hundred five full-text articles

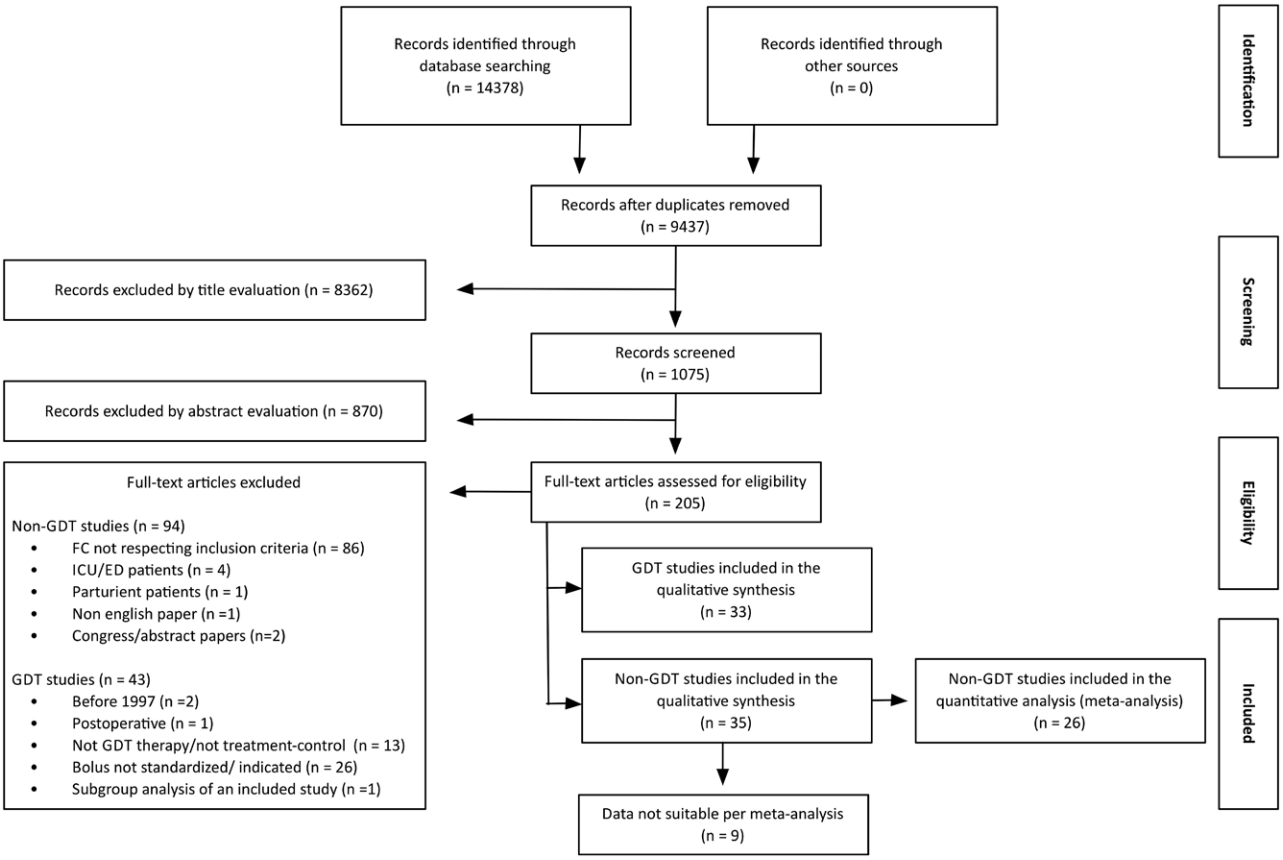

Figure. Flow of the studies. ED indicates emergency department; FC, fluid challenge; GDT, Goal-Directed Therapy; ICU, intensive care unit.

were selected, and only 35 non-GDT studies and 33 GDT studies met criteria for inclusion.

Epidemiological Design and Characteristics of the Population

Only studies published after 2001 met inclusion criteria (Tables 1–2). Overall, non-GDT studies recruited 1436 patients, with a median (IQR) of 38 (31–59) patients enrolled, 35 (21–50) of whom were analyzed. The median (IQR) number of FCs administered was 40 (30–52) for each study. Overall, the mean (SD) number of fluid responders was 57.7% (14.3%).

GDT studies were all randomized controlled trials and included 3581 patients with a higher median (IQR) number of enrolled [92 (49–125), $P < .0001$] and analyzed [81 (48–121), $P < .0001$] patients per study, as compared to non-GDT studies. Only 3 studies were not conducted in general anesthesia. Not 1 GDT study reported the number of fluid responders to the predefined FC (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C594).

Indications for FC Administration, Hemodynamic Targets, and Thresholds for Fluid Responsiveness Assessment and Use of Safety Limits

In 13 non-GDT (37.1%) studies, FC was infused "after induction" of the general anesthesia, while in 8 (22.8%) studies, FC was infused during a specific surgical timing; in 7 (20.0%), timing was not detailed; finally, in 5 (14.2%), FC was administered following the decision of the attending anesthetist, based on specific[16,39] (10%–20% drop in mean arterial pressure or cardiac index) or undefined criteria (Tables 3 and 4).[13,15,23]

In 24 (68.5%) non-GDT studies, either SVI or SV were used to assess fluid responsiveness; in 9 of these studies, a positive response was defined by an increase of ≥15%, in 7 of ≥10%, in 4 of ≥25%, in 2 of ≥20%, in one of ≥12%, and in another one of ≥5%. In the remaining 11 (31.5%) studies, the hemodynamic variables used to assess fluid responsiveness were either cardiac index or CO; in 7 of these studies, a positive response was defined by an increase of ≥15%, in 3 of >15%, and in 1 of ≥10%.

Three (9.1%) GDT studies administered the FC after the sequential evaluation of cardiac index, SVI, and SVV and one of cardiac index and SVI, while in 19 (57.5%), the GDT protocol was guided by a 10% increase of SV or SVI (in 5 of these studies the corrected systolic flow time [FTC] <0.35 seconds was also considered together with SV increase, and in 2 the SVV >10% or >13%); in 5 (15.1%) by SVV values ranging from 10% to 13%, in the remaining 6 (18.1%) by the variability index, PPV, mean arterial pressure, central venous oxygen saturation, or wedge pressure. In 12 of 19 GDT studies assessing an SV increase >10%,[50,52,55,56,59,60,63,65–67,73,74] the first bolus was administered regardless of predetermined cutoff hemodynamic values suggesting fluid depletion.

A safety limit indicating the absence of hemodynamic response to FC and risk of futile fluid administration was present in 60.6% and 0% of GDT and non-GDT studies, respectively.

Table 1. Characteristics of the Non-GDT Studies Included in the Systematic Review

	Year	Pt Enrolled	Pt Analyzed	Study Type	Intervention	Months	Type of Surgery
Blanié et al[13]	2016	46	43	Observational	None	ND	Mixed
Kang et al[14]	2016	107	76	Interventional	Lung recruitment maneuver	8	Thoracic
Jacquet-Lagrèze et al[15]	2016	40	40	Interventional	Mini-FC	2, 5	ND
Konur et al[16]	2016	25	25	Observational	None	ND	Abdominal
Zhang et al[17]	2016	40	40	Observational	None	ND	Abdominal (LPS)
Li et al[18]	2015	48	48	Observational	None	7	Neurosurgical
Berger et al[19]	2015	60	52	Observational	None	44	Neurosurgical
Tusman et al[20]	2016	52	51	Interventional	PEEP challenge	15	Cardiac
Guinot et al[8]	2015	77	73	Observational	None	6	Orthopedic (SB)
Siswojo et al[21]	2014	30	29	Observational	None	51	Mixed
Song et al[22]	2014	45	40	Observational	None	ND	Cardiac
Fu et al[23]	2014	33	30	Observational	None	46	Thoracic
Guinot et al[24]	2013	90	90	Observational	None	5	Mixed
Chin et al[25]	2013	45	42	Observational	None	ND	Robotic (LPS)
Kim et al[26]	2013	27	25	Observational	None	ND	Vascular
Guinot et al[27]	2014	61	59	Observational	None	ND	Mixed (LPS)
Yang et al[28]	2013	44	44	Observational	None	ND	Orthopedic
Lee et al[29]	2012	65	60	Prospective randomized	PCV/VCV groups	ND	Abdominal
Suehiro et al[30]	2011	73	73	Prospective randomized	Vt 8/Vt 6 groups	ND	Thoracic
Lee et al[31]	2011	38	35	Observational	None	11	Cardiac
Li et al[32]	2013	50	50	Observational	None	ND	Abdominal
Biais et al[33]	2011	35	35	Observational	None	ND	Vascular
Shin et al[34]	2011	35	33	Observational	None	ND	Abdominal
Biais et al[35]	2010	30	27	Observational	None	ND	Orthopedic
Zimmermann et al[36]	2010	20	20	Observational	None	ND	Abdominal
Suehiro and Okutani[37]	2010	30	30	Observational	None	4	Thoracic
de Waal et al[38]	2009	22	18	Observational	None	ND	Cardiac
Gouvêa et al[39]	2009	15	15	Observational	None	ND	Abdominal
Jørgensen et al[40]	2009	20	20	Observational	None	ND	Mixed
Belloni et al[41]	2008	19	19	Observational	None	11	Cardiac
Wiesenack et al[42]	2005	20	20	Observational	None	ND	Cardiac
Wiesenack et al[43]	2005	21	21	Observational	None	ND	Cardiac
Hofer et al[44]	2005	40	35	Observational	None	ND	Cardiac
Bennett-Guerrero et al[45]	2002	19	19	Observational	None	ND	Cardiac
Berkenstadt et al[46]	2001	15	15	Observational	None	ND	Neurosurgical

Abbreviations: GDT, Goal-Directed Therapy; FC, fluid challenge; LPS, laparoscopic surgery; ND, not defined; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; Pt, patients; SB, spontaneous breathing; VCV, volume-controlled ventilation; Vt, tidal volume.

Fluid Type, Dose, and Time of Infusion

Colloids were used in 30 non-GDT and GDT studies (85.7% vs 90.9%, respectively; $P = .80$) (Tables 3 and 4). In 29 non-GDT studies, the colloid infused was the 6% hydroxyethyl starch (HES 6%, 96.6% of this subgroup), while in 1 study the type of colloid was not specified. In 20 GDT studies, the colloid infused was the HES 6% (66.7% of this subgroup), while in 5 studies was a gelatin (16.7% of this subgroup), in 3 studies an unspecified colloid (10.0% of this subgroup), and in one study albumin (3.3%) or, in another study, both HES 6% and gelatin (3.3%). Overall, the use of HES 6% was not different between non-GDT and GDT studies (82.8% vs 63.6%, respectively; $P = .13$).

In 16 (45.7%) non-GDT studies, the volume administered was 7.5 mL/kg (7–10 mL/kg). In 11 of these studies reporting the mean body weight of the enrolled population, the median (IQR) volume was 619 mL (655–538 mL). In the remaining 19 non-GDT studies, 12 (34.2%) infused 500 mL.

In 16 (48.8%) GDT studies, FC consisted of 250 mL and the median (IQR) FC volume infused, while in 9 (27.2%), the FC volume administered was 3 mL/kg, but in 2 of these only the first bolus consisted of 7 mL/kg. Only 2 GDT studies reported the mean body weight and the mean (SD) calculated FC volume was 224 mL (24 mL). The median (IQR) volume infused was significantly higher in non-GDT as compared to GDT studies [500 mL (467–551 mL) vs 250 mL (150–250 mL); $P < .0001$].

Three (8.6%) non-GDT studies reported an infusion rate of 1 mL/kg/min. In the remaining 32, the FC was administered in 30 minutes in 7 (21.8%) studies, in 20 minutes in 2 (6.2%) studies, in 13 minutes in 1 (3.1%) study, in 10 minutes, in 15 studies (46.8%), in 5 minutes in 4 (12.5%) studies, in 3 minutes in 1 (3.1%) study, and in 2 minutes in 2 (6.2%) studies. The median (IQR) time of infusion was 10 minutes (5–20 minutes). In 15 (45.4%) GDT studies the FC was administered in a median (IQR) time of 10 minutes (5–15 minutes), while in the others as "bolus". Mean (SD) infusion time was not significantly different between non-GDT and GDT (14 minutes [9 minutes] vs 9 minutes [5 minutes], respectively; $P = .07$).

The rate of infusion was calculated in 28 (80.0%) non-GDT studies and in 12 (36.3%) GDT studies reporting both volume and time of FC administration. In non-GDT studies, the mean (SD) rate of infusion was 49.2 mL/min (29.1

Table 2. Characteristics of the GDT Studies Included in the Systematic Review

Authors	Year	Pt Enrolled	Pt Analyzed	Study Type	Intervention Group	Control Group	Months	Type of Surgery
Osawa et al[47]	2016	126	126	RCT	62	64	26	Cardiac
Funk et al[48]	2015	40	40	RCT	20	20	ND	Vascular
Colantonio et al[49]	2015	80	80	RCT	38	42	28	Abdominal
Moppett et al[50]	2015	130	114	RCT	51	63	41	Orthopedic (SB)
Fellahi et al[51]	2015	100	92	RCT	43	49	13	Cardiac
Pearse et al[52]	2014	734	730	RCT	366	364	30	Abdominal
Pestaña et al[53]	2014	205	142	RCT	72	70	19	Abdominal
Zeng et al[54]	2014	60	60	RCT	30	30	21	Abdominal
McKenny et al[55]	2013	102	101	RCT	51	50	ND	Gynecological
Bundgaard-Nielsen et al[56]	2013	44	42	RCT	21	21	12	Urological
Zhang et al[57]	2013	80	60	RCT	30	30	ND	Thoracic
Scheeren et al[58]	2013	64	52	RCT	26	26	12	Mixed
Bisgaard et al[59]	2013	40	40	RCT	20	20	29	Vascular
Bisgaard et al[60]	2013	85	64	RCT	32	32	20	Vascular
Ramsingh et al[61]	2013	46	36	RCT	18	20	ND	Mixed
Srinivasa et al[62]	2013	98	74	RCT	37	37	ND	Abdominal (LPT or LPS)
Bartha et al[63]	2013	282	149	RCT	74	75	12	Orthopedic (SB)
Forget et al[64]	2013	21	21	RCT	11	10	ND	Abdominal
Challand et al[65]	2012	292	179	RCT	89	90	13	Abdominal
Brandstrup et al[66]	2012	151	150	RCT	71	79	15	Abdominal (LPT or LPS)
Cecconi et al[67]	2011	40	40	RCT	20	20	13	Orthopedic (SB)
Jammer et al[68]	2010	241	241	RCT	121	120	26	Abdominal
Forget et al[69]	2010	86	82	RCT	41	41	6	Abdominal
Mayer et al[4]	2010	60	60	RCT	30	30	14	Abdominal
Benes et al[70]	2010	120	105	RCT	51	54	23	Mixed
Harten et al[71]	2008	30	29	RCT	14	15	18	Abdominal
Noblett et al[72]	2006	108	103	RCT	51	52	ND	Abdominal
Pearse et al[73]	2005	122	122	RCT	62	60	22	Mixed
Wakeling et al[74]	2005	134	128	RCT	64	64	22	Abdominal
Gan et al[75]	2002	100	100	RCT	50	50	ND	Mixed
Conway et al[76]	2002	57	57	RCT	29	28	ND	Abdominal
Valentine et al[77]	1998	120	120	RCT	60	60	37	Vascular
Sinclair et al[78]	1997	40	40	RCT	20	20	ND	Orthopedic

Abbreviations: GDT, Goal-Directed Therapy; LPS, laparoscopic surgery; LPT, laparotomy surgery; ND, not defined; Pt, patients; RCT, randomized controlled trial; SB, spontaneous breathing.

mL/min), while in GDT studies was 36.5 mL/min (31.4 mL/min) (P = .07).

Meta-analysis: Pooled ROC Curve of PPV and SVV

PPV and SVV were tested as dynamic indexes of fluid responsiveness only in non-GDT studies. The reported values of the ROC curve analysis fitted the criteria for meta-analysis in 10 non-GDT studies for PPV, including 366 patients and infusing 390 FCs,[15,16,22,25,26,28,31,33,35,38,44] and in 16 non-GDT studies for SVV, including 816 patients and infusing 1020 FCs[16–19,25–27,29,30,34–38,44,46] (see Table 5).

For the PPV, the pooled AUC (95% CI) was 0.86 (0.80–0.92). The mean (SD) threshold of PPV predicting fluid responsiveness was 10.5% (3.2%), ranging from 8%[16] to 15%.[28] The pooled (95% CI) sensitivity and specificity were 0.80 (0.74–0.85) and 0.83 (0.73–0.91), respectively. Heterogeneity (I^2 [95% CI]) for PPV sensitivity was 0.0% (0.0–52.7), while for PPV specificity (I^2 [95% CI]) was 43.5% (0.0–71.4) (Supplemental Digital Content, Figures 1 and 3, http://links.lww.com/AA/C594).

For the SVV, the pooled AUC (95% CI) was 0.87 (0.81–0.93). The mean (SD) threshold of SVV predicting fluid responsiveness was 11.3% (3.1%), ranging from 7.5%[26] to 15.5%.[17] The pooled (95% CI) sensitivity and specificity were 0.82 (0.75–0.89) and 0.77 (0.71–0.82), respectively. Heterogeneity (I^2 (95% CI]) for SVV sensitivity was 68.3% (40.9–79.9), while for SVV specificity (I^2 (95% CI]) was 22.0% (0.0–56.8) (Supplemental Digital Content, Figures 2–3, http://links.lww.com/AA/C594). Funnel plots, and associated Egger tests, aimed at assessing publication bias/small study effects show asymmetries (Supplemental Digital Content, Figures 1–2, http://links.lww.com/AA/C594).

DISCUSSION

The present study shows that in surgical patients FC consists, in the majority of the cases, in the administration of colloids, more frequently in aliquots of 500 mL (single bolus, non-GDT studies) or 250 mL (multiple boluses, GDT studies) administered in about 10 minutes. SVI or SV changes are used to assess fluid responsiveness, but the threshold of >10% is standardized only in GDT studies. The reliability of PPV and SVV in predicting fluid responsiveness is limited.

There is increasing evidence that fluid management affects the outcome of critically ill and surgical patients,[80] and the debate regarding the correct fluid management in operating room is still open.[7,10,11,81,82] Irrespectively to the applied fluid therapy policy (GDT, zero balance, or fluid restriction), however, intraoperative fluid administration should be titrated on hemodynamic parameters to prevent fluid overload,[80] while the absolute volume of

Table 3. Modalities of FC Administration in Non-GDT Studies

Authors	Clinical Judgment	FC Administration Timing	Volume Infused (mL)	Time of Infusion (min)	Reference Variable	Type of Fluid	Hemodynamic Monitoring	Responders (%)
Blanié et al[13]	Yes (clinical signs and/or hemodynamic parameters)	ND; based on clinical signs and/or hemodynamic parameters	250	10	CI > 15%	Colloids	CardioQ/ Nexfin	ND
Kang et al[14]	No	End of surgical procedure, supine	10/kg	30	SVI ≥ 25%	HES 6%	FloTrac	NA
Jacquet-Lagrèze et al[15]	Yes, not defined	After induction; attending anesthetist's decision	500	13	ND	HES 6%	HemoSonic	38
Konur et al[16]	Yes (10%–20% drop in MAP or CI)	After ascites aspiration; attending anesthetist's decision based on hemodynamic parameters	10/kg	10	CI ≥ 15%	HES 6%	PiCCO2	65.5
Zhang et al[17]	ND	ND	7/kg	30	SVI ≥ 15%	HES 6%	FloTrac/PAC	65
Li et al[18]	No	After 5 min of hemodynamic stability	200	3	SV ≥ 10%	RL	FloTrac	69
Berger et al[19]	No	After prone/supine position	250	30	SVI ≥ 20%	HES 6%	FloTrac	42.3
Tusman et al[20]	No	PEEP challenge	500	10	CI ≥ 15%	Saline 0.9%	PiCCO2	40
Guinot et al[8]	No	ND	500	10	SV > 15%	RL	NICCOMO	37
Siswojo et al[21]	No	ND	500	5	SVI ≥ 10%	HES 6%	CardioQ	59
Song et al[22]	No	After induction	6/kg	10	SVI ≥ 15%	HES 6%	PCWP	57.5
Fu et al[23]	Yes, not defined	ND; Attending anesthetist's decision	8/kg	30	CI ≥ 10%	HES 6%	FloTrac	53
Guinot et al[24]	No	After 5 min of hemodynamic stability	500	10	SV ≥ 15%	Crystalloids	CardioQ	58.9
Chin et al[25]	No	After trendelenburg + pneumoperitoneum	500	10	SV ≥ 15%	HES 6%	FloTrac + TEE	52
Kim et al[26]	No	ND	500	10	CO ≥ 15%	HES 6%	FloTrac	56
Guinot et al[27]	No	After intra-abdominal insufflation (LPS)	500	10	SV ≥ 15%	RL	CardioQ	64
Yang et al[28]	No	After induction	6/kg	10	SVI ≥ 10%	HES 6%	CardioQ	59
Lee et al[29]	No	After induction	10/kg	20	SVI ≥ 15%	HES 6%	FloTrac	43.3
Suehiro and Okutani[30]	No	30 min after one-lung ventilation	500	30	CI ≥ 15%	HES 6%	FloTrac	60.5
Lee et al[31]	No	ND	10/kg	10	CI ≥ 15%	HES 6%	PAC	82.8
Li et al[32]	No	After induction	7/kg	30	SV ≥ 25%	HES 6%	FloTrac	77.5
Biais et al[33]	No	After induction	500	10	SV ≥ 15%	HES 6%	FloTrac	57
Shin et al[34]	No	Anhepatic phase (liver transplant)	10/kg	5	CI ≥ 15%	HES 6%	FloTrac	54.5
Biais et al[35]	No	After supine/prone position	500	10	CO ≥ 15%	HES 6%	FloTrac	61.1
Zimmermann et al[36]	No	ND	7/kg	1 mL/kg/min	SVI ≥ 15%	HES 6%	FloTrac	75
Suehiro and Okutani[37]	No	30 min after incision	500	30	SV ≥ 25%	HES 6%	FloTrac	50
de Waal et al[38]	No	During operation (open chest)	10/kg	10	SVI ≥ 12%	HES 6%	PiCCOplus	83.3
Gouvêa et al[39]	Yes (10%–20% drop in MAP or CI)	One FC for each of 5 specific surgical times (liver transplant); attending anesthetist's decision based on hemodynamic parameters	350	10	SVI > 10%	HES 6%	PAC	34
Jørgensen et al[40]	No	After induction	200	2	SV ≥ 10%	HES 6%	CardioQ	70
Belloni et al[41]	No	After induction	7/kg	5	CI > 15%	HES 6%	PAC, LiDCOplus, TEE	57.9
Wiesenack et al[42]	No	After induction	7/kg	1 mL/kg/min	SVI ≥ 20%	HES 6%	PiCCOplus	65
Wiesenack et al[43]	No	After induction	7/kg	1 mL/kg/min	SVI ≥ 10%	HES 6%	PAC	90.5
Hofer et al[44]	No	After induction	10/kg	20	SV ≥ 25%	HES 6%	PiCCOplus, PAC	60
Bennett-Guerrero et al[45]	No	After induction	250	5	SV ≥ 10%	HES 6%	PAC, TEE	47.2
Berkenstadt et al[46]	No	After induction	100	2	SV ≥ 5%	HES 6%	PiCCOplus	50

CardioQ, Deltex Medical Ltd, Chichester, United Kingdom; FloTrac, Edwards Lifesciences, Irvine, CA; HemoSonic, Imedex, France; Arrow Critical Care Products; LiDCOplus, LiDCOltg, Cambridge, United Kingdom; Nexfin, BMEYE, Amsterdam, the Netherlands; NICCOMO, Non-Invasive Continuous Cardiac Output (Imedex, France); PiCCO2/PiCCOplus, PULSION Medical Systems, Munich, Germany.

Abbreviations: CI, cardiac index; CO, cardiac output; FC, fluid challenge; GDT, Goal-Directed Therapy; HES 6%, hydroxyethyl starch 6%; MAP, mean arterial pressure; NA, not applicable; ND, not defined; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; PEEP, positive end-expiratory pressure; RL, Ringer Lactate; SV, stroke volume; SVI, stroke volume index; TEE, transesophageal echocardiography.

Table 4. Modalities of FC Administration in GDT Studies

	Hemodynamic Goals	Safety Limit	Volume Infused (mL; mL/kg)	Time of Infusion (min)	Type of Fluid	Hemodynamic Monitoring
Osawa et al[47]	CI <3 L/min/m^2 → SVI < 35 mL/m^2 (sequence)	SVI ≥ 35 mL/m^2 or CVP rise ≥4 mm Hg	250	ND	Ringer Lactate	LiDCOrapid
Funk et al[48]	SVV > 13%	55 cm^3/kg 6%, SVV < 13%	250	ND	HES 6%	FloTrac-Vigileo
Colantonio et al[49]	CI <2.5 L/min/m^2 → SVI < 35 mL/m^2 → SVV > 15% (sequence)	ND	250	15	HES 6%	FloTrac-Vigileo
Moppett et al[50]	SV > 10% or 10% fall in SV	ND	250	ND	Gelofusine	LiDCO
Fellahi et al[51]	SVV > 11%	ND	100	ND	HES 6%	ECOM
Pearse et al[52]	SV > 10% for ≥20 min	ND	250	5	Colloid (unspecified)	LiDCOplus
Pestaña et al[53]	MAP ≥ 65 mm Hg and CI ≥ 2.5 L/min/m^2	ND	250	10	HES 6% or gelatine	NICOM
Zeng et al[54]	SVV > 13% for >5 min or SV > 10%	ND	200	15	HES 6%	FloTrac-Vigileo
McKenny et al[55]	SV > 10%	SV increase <10%	3	5	HES 6%	ODM
Bundgaard-Nielsen et al[56]	SV ≥ 10%	SV increase < 10%; new FC if SV drop > 10%	3	ND	HES 6%	CardioQ
Zhang et al[57]	SVV > 11%	SVV < 9% and CI ≥ 2.5 L/min/m^2	50	1	HES 6%	FloTrac-Vigileo
Scheeren et al[58]	SVV > 10% or SV > 10%	SVV < 8%	200	10	HES 6%	FloTrac-Vigileo
Bisgaard et al[59]	SVI ≥ 10% for 20 min	ND	250	ND	Colloid (unspecified)	LiDCOplus
Bisgaard et al[60]	SVI ≥ 10% for 20 min	ND	250	ND	HES 6%	LiDCOplus
Ramsingh et al[61]	SVV ≥ 12% for 2 min	Max 20 mL/kg of albumin	250	ND	Albumin	FloTrac-Vigileo
Srinivasa et al[62]	SV > 10% and FTc < 0.35 s	FTc > 0.4 s	7 (first), 3 (others)	ND	Gelofusine	CardioQ
Bartha et al[63]	SV > 10% or 10% fall in SV	ND	3	ND	Colloid (unspecified)	LiDCO
Forget et al[64]	PVI ≥ 13% for 5 min	ND	250	ND	HES 6%	MasimoSET
Challand et al[65]	SV > 10%	SV increase <10%	200	5	HES 6%	CardioQ
Brandstrup et al[66]	SV > 10% or 10% fall in SV	ND	250	ND	HES 6%	CardioQ
Cecconi et al[67]	SV > 10%, SV stable 20 min	After 25 mL/kg of HES 6%, FCs performed with Ringer Lactate	250	ND	HES 6%	FloTrac-Vigileo
Jammer et al[68]	$Scvo_2$ < 75%	$Scvo_2$ increase ≤1% after 5 min	3	10–15	HES 6%	Central Venous Line, ABL700
Forget et al[69]	PVI ≥ 13% for 5 min	Repeated until PVI < 13%	250	ND	HES 6%	MasimoSET
Mayer et al[79]	CI < 2.5 L/min/m^2 → SVI < 35 mL/m^2 → SVV > 12% (sequence)	ND	500	ND	Crystalloids (unspecified)	FloTrac-Vigileo
Benes et al[70]	SVV ≥ 10% and CVP < 15	CVP changes >3 mm Hg	3	5	HES 6%	FloTrac-Vigileo
Harten et al[71]	PPV changed >10%	ND	250	15	HES 6%	LiDCOplus
Noblett et al[72]	SV > 10% and FTc < 0.35 s	FTc > 0.4 s	7 (first), 3 (others)	ND	Succinyl Gelatine 4%	CardioQ
Pearse et al[73]	SV > 10% for 20 min; repeated if falls	SV increase <10%	250	ND	Gelofusine	LiDCOplus
Wakeling et al[74]	SV > 10% or 10% fall in SV	CVP rise >3 mm Hg	250	2	Hemagel or Gelofusine	CardioQ
Gan et al[75]	FTc < 0.35 s and SV > 10%	FTc > 0.4 s and no change in SV	200	10	HES 6%	ODM
Conway et al[76]	SV > 10% and FTc < 0.35 s	FTc > 0.35 s and no change in SV	3	15	HES 6%	TECO 2
Valentine et al[77]	PCWP < 15 mm Hg	PCWP >12 mm Hg or 3000 mL of fluids administered	9	ND	Ringer Lactate	PAC
Sinclair et al[78]	FTc < 0.35 s, SV > 10%	FTc > 0.4 s and no change in SV	3	5–10	HES 6%	ODM

ABL700, Diamond Diagnostics, Holliston, MA; CardioQ, Deltex Medical Ltd, Chichester, United Kingdom; ECOM, endotracheal cardiac output monitor, Medical, Inc, San Juan Capistrano, CA; FloTrac-Vigileo, Edwards Lifesciences, Irvine, CA; Gelofusine, B Braun Medical Ltd, Sheffield, United Kingdom; LiDCO/LiDCOrapid/LiDCOplus, LiDCOltg, Cambridge, United Kingdom; MasimoSET, Masimo, Irvine, CA; Nicom, Cheetah Medical, Tel-Aviv, Israel; ODM, oesophageal Doppler monitor; TECO 2, Medicina, Oak House, Cookham, Berkshire, United Kingdom.

Abbreviations: CI, cardiac index; CVP, central venous pressure; FC, fluid challenge; FTc, corrected systolic flow time; GDT, Goal-Directed Therapy; HES 6%, hydroxyethyl starch 6%; MAP, mean arterial pressure; ND, not defined; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; PPV, pulse pressure variation; PVI, pleth variability index; $Scvo_2$, central venous oxygen saturation; SV, stroke volume; SVI, stroke volume index; SVV, stroke volume variation.

Table 5. Reported Sensitivity and Specificity of PPV and SVV in Non-GDT Studies Included in the Meta-analysis

Authors	Year of Publication	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Best Cutoff (%)	AUC-ROC
PPV-ROC characteristics									
Biais et al[35] (prone)	2010	17	2	0	8	100	80	15	0.96
Biais et al. (supine)[35]	2010	14	2	2	9	88	82	11	0.95
de Waal et al[38]	2009	10	0	5	3	64	100	10	0.55
Konur et al[16] (Dissection)	2016	11	4	3	7	80	66	8	0.74
Konur et al[16] (Anhepatic)	2016	19	4	0	2	100	33	4	0.51
Chin et al[25]	2013	17	2	5	18	77	90	9.5	0.87
Kim et al[26]	2013	10	1	4	10	71	91	9.5	0.85
Lee et al[31]	2011	25	1	4	5	86	83	7.7	0.84
Song et al[22]	2014	16	5	6	13	74	71	13	0.75
Hofer et al[44]	2005	15	4	6	10	72	72	13.5	0.81
Biais et al[33]	2011	17	0	3	15	85	100	11	0.94
Yang et al[28] (prone)	2013	25	2	1	16	97	90	14	0.97
Yang et al[28] (supine)	2013	19	1	7	17	73	94	15	0.93
SVV-ROC characteristics									
Biais et al[35] (prone)	2010	16	2	1	8	94	80	14	0.94
Biais et al[35] (supine)	2010	14	1	2	10	88	91	9	0.93
Zimmermann et al[36]	2010	15	1	0	4	100	80	11	0.99
Lee et al[29] (VCV)	2012	21	14	5	20	80	60	11	0.72
Lee et al[29] (PCV)	2012	20	5	6	29	75	85	14	0.80
de Waal et al[38]	2009	15	1	0	2	100	78	8	0.49
Konur et al[16] (Dissection)	2016	13	5	1	6	92	54	9	0.77
Konur et al[16] (Anhepatic)	2016	14	1	5	5	72	83	21	0.85
Li et al[18]	2012	27	2	6	13	81	83	11.5	0.89
Suehiro et al[30] (6 mL/kg)	2011	24	17	18	14	58	44	10.5	0.65
Suehiro et al[30] (8 mL/kg)	2011	40	9	7	17	86	66	10.5	0.77
Chin et al[25]	2013	17	5	5	15	15	75	9.5	0.81
Berger et al[19] (supine)	2015	20	11	23	29	29	62	12	0.76
Berger et al[19] (prone)[a]	2015	NA	NA	NA	NA	NA	NA	NA	0.53
Kim et al[26]	2014	13	4	1	7	7	64	7.5	0.84
Guinot et al[27]	2013	35	3	3	18	18	87	14	0.92
Hofer et al[44]	2005	16	4	5	10	10	71	12.5	0.82
Suehiro et al[37]	2010	12	1	3	14	14	92	10.5	0.90
Zhang et al[17]	2016	22	1	4	13	13	93	15.5	0.93
Shin et al[34]	2011	16	3	2	12	12	80	8	0.89
Berkenstadt et al[46]	2001	6	0	2	7	7	93	9.5	0.87

Abbreviations: AUC, area under the curve; GDT, Goal-Directed Therapy; FN, false negatives; FP, false positives; NA, not available; PCV, pressure-controlled ventilation; PPV, pulse pressure variation, ROC, receiving operating characteristics; SVV, stroke volume variation; TN, true negatives; TP, true positives; VCV, volume-controlled ventilation.

[a]The AUC of the study was not statistically significant, and the optimal cutoff value, the sensitivity, and the specificity were not reported.

fluids administered is less important than the modality of administration.[10]

Colloids were overall used in the 86% of the studies included in the review. This is somewhat surprising, considering that several studies showed, in critically ill patients, the use of colloids being associated with an increased risk of renal failure and death.[83–85] Worth mentioning, however, recent meta-analysis do not confirm these caveats in surgical patients.[86,87] In principle, the infusion of colloids should be associated with a long-lasting hemodynamic effect on SV, reducing intraoperative fluid administration,[88] and increasing microcirculatory blood flow.[89,90] While the hemodynamic effect of 250 mL crystalloids is dissipated within 10 minutes,[91] the macromolecules of colloids are retained in the intravascular compartment with a phase of distribution dependent on patient's volemic status.[92] Indeed, a number of GDT studies show that intraoperative SV optimization through colloids, predominantly starch solutions suspended in crystalloids, associated with background crystalloid infusions or inotropes infusion, results in improved postoperative outcomes.[88]

In 36.3% of the GDT trials,[50,52,55,56,59,60,63,65–67,73,74] the first FC was administered regardless of the values of dynamic or static indexes of fluid responsiveness and, then, was repeated according to SV response. The number of fluid responders to the first bolus was not assessed in any GDT trial. However, Bartha et al,[93] in a subanalysis of a GDT aimed to SV and oxygen delivery optimization and performed in patients with hip fracture,[63] reported a 38.5% and a 8.5% of responders to the first and the second FC (3 mL/kg of colloids) respectively, while only 13.8% of controls responded to clinician-guided FC, consisting of Ringer acetate or colloids, before spinal anesthesia.

A range of SVV from 10% to 13% and safety limits between 8% and 13% have been used in 15.1% of the studies (Table 4). The hemodynamic targets and thresholds adopted are variable among studies. Despite 63.3% of the studies evaluated SVV variations after FC administration, a 10% target threshold was adopted in 38.2% of the studies. Indeed, the choice of a predefined threshold could be inaccurate, the "gray zone" of inaccuracy of the dynamic indexes ranging between 9% and 13%.

The lack of a definitive threshold might influence the number of fluid responders because the ROC curve approach is constructed using a reference gold standard test to define the positive or negative result. For example, the definition of fluid responsiveness could be affected by the threshold adopted because a patient considered responder for a >10% increase in SV may not be responder if the threshold is raised up to >15%.[94]

Regarding the meta-analysis of the dynamic index of fluid responsiveness, in the literature, the reliability of PPV and SVV in operating room has been investigated only in few systematic reviews and, to our knowledge, the present review is the largest ever conducted. Marik et al[95] report for PPV an AUC of 0.93 (95% CI, 0.92–0.94) in a subgroup of studies where a mean intraoperative tidal volume >8 mL/kg was delivered. In this meta-analysis, only 5 studies after induction of anesthesia were included, while 10 after surgery. In 2011, Zhang et al[96] reported an AUC of 0.94 (95% CI, 0.907–0.945) for SVV in 8 surgical studies. However, as pointed out by the authors, because of the small number of included studies, the cumulative AUC of SVV would drop down to 0.84 by excluding only 1 study reporting an AUC of 0.99.[36] Furthermore, as suggested by our findings, publication bias/small study effects should be also considered.

Interestingly, despite most of the validity criteria affecting dynamic indexes reliability, such as tidal volume, heart rate-to-respiratory rate ratio, presence of spontaneous breathing activity, pulmonary and chest wall compliance, and right ventricle function, should be more frequently respected in the operating room rather than in ICU,[97] pooled sensitivity and specificity of both PPV (0.79 and 0.84, respectively) and SVV (0.80 and 0.77, respectively) are quite limited. A more recent approach to fluid responsiveness introduced the flexible gray-zone concept[98] instead of the simplistic ROC curve application to define fixed cutoffs to discriminate responders and nonresponders. This gray-zone approach identifies a range of inaccuracy, in which up to 25% of PPV values of surgical patients are included.[98] The results of this meta-analysis suggest caution in relying on baseline PPV and SVV to assess fluid responsiveness, encouraging the use in operating room of recently introduced hemodynamic tests, such as the end-expiratory occlusion and the mini-FC tests.[9,99]

CONCLUSIONS

In surgical patients, much more than in ICU patients, some FC key components, such as type of fluid (colloids, often 6% HES), volume (500 and 250 mL in non-GDT and GDT studies, respectively), and time of infusion (10 minutes) are quite standardized. In non-GDT studies, thresholds for assessment of fluid responsiveness are not standardized and safety limits are not used, while GDT studies frequently adopt a >10% increase of SV or SVI with safety limits. The pooled sensitivity and specificity of PPV and SVV are limited, suggesting caution when using these indexes of fluid responsiveness in the operating room.

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