



# Pharmacodynamic analysis of a fluid challenge with 4 ml kg<sup>-1</sup> over 10 or 20 min: a multicenter cross-over randomized clinical trial

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## Abstract

**Purpose** A number of studies performed in the operating room evaluated the hemodynamic effects of the fluid challenge (FC), solely considering the effect before and after the infusion. Few studies have investigated the pharmacodynamic effect of the FC on hemodynamic flow and pressure variables. We designed this trial aiming at describing the pharmacodynamic profile of two different FC infusion times, of a fixed dose of 4 ml kg<sup>-1</sup>.

**Methods** Forty-nine elective neurosurgical patients received two consecutive FCs of 4 ml kg<sup>-1</sup> of crystalloids in 10 (FC<sub>10</sub>) or 20 (FC<sub>20</sub>) minutes, in a random order. Fluid responsiveness was defined as stroke volume index increase  $\geq 10\%$ . We assessed the net area under the curve (AUC), the maximal percentage difference from baseline ( $d_{\max}$ ), time when the  $d_{\max}$  was observed ( $t_{\max}$ ), change from baseline at 1-min ( $d_1$ ) and 5-min ( $d_5$ ) after FC end.

**Results** After FC<sub>10</sub> and FC<sub>20</sub>, 25 (51%) and 14 (29%) of 49 patients were classified as fluid responders ( $p=0.001$ ). With the exception of the AUCs of SAP and MAP, the AUCs of all the considered hemodynamic variables were comparable. The  $d_{\max}$  and the  $t_{\max}$  were overall comparable. In both groups, the hemodynamic effects on flow variables were dissipated within 5 min after FC end.

**Conclusions** The infusion time of FC administration affects fluid responsiveness, being higher for FC<sub>10</sub> as compared to FC<sub>20</sub>. The effect on flow variables of either FCs fades 5 min after the end of infusion.

**Keywords** Fluid challenge · Pharmacodynamic · Neurosurgery · Fluids · Hemodynamics · Fluid responsiveness

## 1 Introduction

The appropriate fluid management in the perioperative period is an important, and still partially unclear, chapter of clinical practice for anesthesiologists [1–4]. Increasing evidence suggests that intraoperative fluid therapy should be tailored to individual patient's physiology to target fluid administration to specific stroke volume (SV) responses, or its surrogates [5–7]. For this reason, small repeated and fast boluses challenging the cardiovascular system should be preferred to continuous and prolonged infusions [8–10].

The fluid challenge (FC) is defined as a small amount of fluid given in a short period of time to assess whether the preload reserve of the patient can increase SV with further administration of fluids [11]. A number of studies performed in the operating room evaluated the hemodynamic effects of FC solely considering the effect before and after the infusion [12]. Recently, Aya demonstrated that at least 4 ml kg<sup>-1</sup>

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should be infused to effectively challenge the preload, additionally showing that the hemodynamic effect of the FC is dissipated within 10 min [13].

The approach of Aya et al. [13] considers the FC as a drug evoking a systemic response on flow (i.e. SV) and pressure variables [i.e. systolic arterial pressure (SAP)]. Accordingly, the pharmacodynamic effect is evaluated by considering the magnitude (i.e. the maximal changes from baseline obtained for a specific variable), the global effect [i.e. considering the area under the curve (AUC) obtained by plotting the changes overtime] and the persistence of the hemodynamic response after the end of FC administration. The infusion time of FC administration, which ranges in the literature between 5 and 30 min [12], may influence the magnitude of SV response and, in turn, the number of patients defined as fluid responders [5]. Since several intraoperative pathways of hemodynamic optimization are based on the response to repeated FCs [6, 10, 14–18], a prolonged infusion time may potentially affect fluid responsiveness and, in turn, wrongly drive intraoperative fluid management and eventually affect postoperative outcomes.

Since FC is a test embedding at least three variables (i.e., the amount of fluid; the time needed to complete the administration, and the SV change threshold used to define a positive response), the role of one single component on the final outcome can be addressed only by keeping the others fixed. Therefore, we designed this multicenter, in-patient randomized trial performed on elective patients scheduled for supine neurosurgery, hypothesizing that a FC of 4 ml kg<sup>-1</sup> infused over 10 min would be associated with a higher rate of fluid responders, as compared to a FC infused over 20 min. Furthermore, we described the pharmacodynamic profiles of the two different FC infusion times.

## 2 Materials and methods

### 2.1 Patients

This prospective multicenter randomized trial was carried out in the operating rooms of three Italian tertiary hospitals: the Humanitas Research Hospital (Rozzano, Milano), the University hospital “Maggiore della Carità” (Novara), and the San Bortolo Hospital (Vicenza). The protocol was designed in accordance with the principles outlined in the Declaration of Helsinki; the study was approved by all the local institutional ethics committees [Ethical Committee of the Coordinator Center—Humanitas Research Hospital, Rozzano (Milano; Italy); Protocol Number 92/19; 19 February 2019], and prospectively registered (NCT03810118). Informed consent was obtained from all the participants.

We enrolled adult patients with a body weight < 100 kg (for technical limitations regarding FC infusion, see

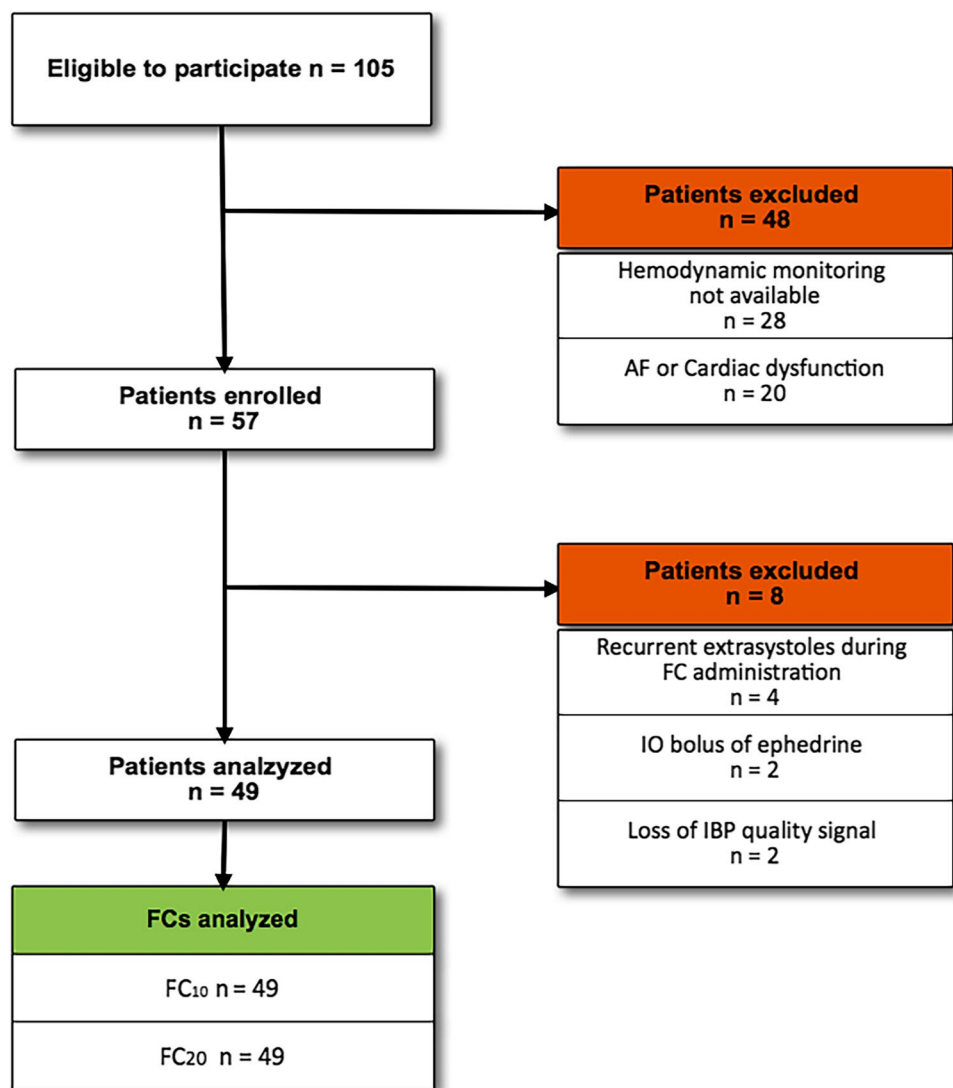
Supplemental Table 1 in the Supplementary Information), scheduled for elective supine neurosurgery and requiring a FC. The decision to administer a FC was at the discretion of the attending physician. The preoperative exclusion criteria were (1) any recurrent cardiac arrhythmia; (2) reduced left (ejection fraction < 30%) or right (systolic peak velocity of tricuspid annular motion < 0.17 m/s) ventricular systolic function. Once enrolled, the patient can be additionally excluded due to the occurrence of one of the following intraoperative conditions: (1) significant bleeding (more than 500 ml in ½ h); (2) recurrent extrasystoles; (3) persistent low quality of the arterial signal affecting hemodynamic monitoring measurements; (4) use of continuous infusion of vasopressors before the study protocol start (Fig. 1).

### 2.2 Perioperative management and hemodynamic monitoring

All patients received standard intraoperative monitoring including heart rate, peripheral oxygen saturation, continuous electrocardiography, invasive blood pressure monitoring. After pre-oxygenation, general anesthesia was induced with propofol, remifentanyl and rocuronium (0.6 mg kg<sup>-1</sup>), and maintained with propofol (1.5–3.0 mg kg<sup>-1</sup> h<sup>-1</sup>) plus remifentanyl (0.1–0.5 mcg kg<sup>-1</sup> min<sup>-1</sup>) to target the bispectral index (BIS monitor, Medtronic, Brooklyn Park, MN) between 40 and 60 throughout the surgical time. Neuromuscular transmission was monitored using train-of-four supramaximal stimulations. Patients were ventilated in volume-control mode with a Tidal Volume of 6–8 ml kg<sup>-1</sup> of predicted body weight and positive end-expiratory pressure between 3 and 5 cm H<sub>2</sub>O. Intraoperatively, all patients received Ringer’s solution, at 4 ml kg<sup>-1</sup> h<sup>-1</sup>, as maintenance fluid.

Invasive blood pressure monitoring was obtained by inserting a 20-G cannula into the radial artery and the pressure signal was then connected to the MostCare® device (Vytech Health, Padua, Italy). The arterial waveform was optimized to exclude under or over-damping and a square-wave test was used in all patients to check the quality of the pressure signal [19]. A comprehensive description of the analysis of the arterial waveform for SV calculation by MostCare® is reported elsewhere [20–22]. Arterial pressures [SAP, diastolic, mean (MAP), dicrotic] were directly measured from the arterial pressure waveform, while the indexed values, including SV index (SVI) and cardiac index (CI), by using the patient’s anthropometric characteristics. Finally, the system calculates the arterial elastance (Ea), as dicrotic pressure/SV.

**Fig. 1** Flow of patients in the study. *AF* atrial fibrillation, *FC* fluid challenge, *IO* intraoperative, *IBP* invasive blood pressure



### 2.3 Study protocol and measurements

Eligible patients consecutively received both FCs using a computer-generated random sequence of infusion. Each assignment was designated in a consecutively numbered, sealed, opaque envelope. The obtained envelopes were finally distributed to each enrolling center and serially opened before each enrolment. Each patient received both the FCs consecutively, according to the randomization sequence (FC<sub>10</sub>/FC<sub>20</sub> or FC<sub>20</sub>/FC<sub>10</sub>).

The study protocol start was triggered by the decision of the attending physician to administer the first FC, during a period of intraoperative hemodynamic stability after the induction of general anesthesia, defined as a change in mean arterial pressure < 10% over 5 min [23, 24]. Before the protocol start, an arterial blood gases analysis was obtained. We tested two

infusion times of FC administration (Ringer Acetate): FC<sub>10</sub> = 4 ml kg<sup>-1</sup> administered over 10 min; FC<sub>20</sub> = 4 ml kg<sup>-1</sup> administered over 20 min.

Each FC infusion was separated from the following by a 10-min period. For the patient's safety, interruption of the protocol was at the discretion of the attending anesthetist, by using a rescue bolus of 5 mg of ephedrine, whenever needed. A constant FC infusion was ensured by using a peripheral dedicated venous line (16 or 14 gauge), two volumetric infusion pumps (Alaris® GP Volumetric Pump, Cardinal Health, Switzerland or Terumo® -Terufusion TE-171, Tokyo, Japan) (Supplemental Table 1 and Supplemental Fig. 1 in the Supplementary Information).

The beginning of FC<sub>10</sub> and FC<sub>20</sub> infusions were recorded electronically on MostCare®. MostCare® was set to record a standard set of hemodynamic measurements by automatically averaging the recorded values every 30 s (i.e. two

values/min). Accordingly, baseline values of SAP, MAP, CI, SVI, Ea and HR were defined as the average of the two values recorded in minute before FC<sub>10</sub> or FC<sub>20</sub> administration.

The rough hemodynamic data recorded were finally exported into a dedicated EXCEL® (Microsoft, Redwood, MS, USA) spreadsheet for statistical elaboration and analysis.

## 2.4 Statistical analysis

The sample size calculation of this study was based on the expected proportions of responders after FC<sub>10</sub> and FC<sub>20</sub>, retrieved from a database of FCs administered with different infusion times. We predicted a rate of fluid responsiveness, after FC<sub>10</sub> and FC<sub>20</sub>, of 50% and 20%, respectively. An overall sample size of 48 FCs per single arm was estimated to find a difference of 30%, with an alpha and beta error of 5% and 10%, respectively [25].

Hemodynamic variables were summarised with median with interquartile (IQR 25th–75th) range or mean  $\pm$  standard deviation (SD) and compared as appropriate. For dichotomous or categorical variables, the McNemar's test for comparison of proportions of dependent variables was applied, whereas paired t test or Wilcoxon Signed-Rank test were used for continuous variables, as appropriate. Fluid responsiveness was defined as an SVI increase  $\geq$  10% after either FC<sub>10</sub> or FC<sub>20</sub>.

The pharmacodynamic effect of FC was assessed for the hemodynamic variables SAP, MAP, CI, SVI, Ea and HR by considering the percent change at each minute of the following variables, as compared to the baseline: the maximal percentage difference observed from baseline ( $d_{\max}$ ), time when the maximal value was observed ( $t_{\max}$ ), expressed as percentage of time over the whole FC administration period, and change from baseline at 1-min ( $d_1$ ) and 5-min ( $d_5$ ) after the end of the FC are also reported. Finally, the global effect has been quantified as the net AUC calculated using the trapezoidal rule [26] considering the overall percentage change from baseline to  $d_5$  (i.e. the percentage of increase of each single variables multiplied for the minutes of observation). The AUCs were then compared. The  $d_{\max}$  and the AUC defined the magnitude of hemodynamic response. One-way analysis of variance (ANOVA) for repeated measures was performed to compare hemodynamic changes of all the considered variables at baseline,  $d_1$  and  $d_5$ .

The effect of the duration of the FC and of the sequence of randomization on SVI changes was evaluated by means of a multilevel mixed-effects linear regression model, considering these two parameters as independent variables and the SVI changes from baseline of the entire population at the end of the FC and at  $d_5$ , as dependent variables. Finally, we analyzed both the period and carry-over effects for the AUC of the flow-related variables (see Supplemental

Methods section in the Supplementary Information for further details).

Statistical analyses were conducted using GraphPad PRISM V8 (GraphPad Software Inc., San Diego, CA, USA) and STATA version 16 (StatsCorp, Texas, USA). A p value of  $< 0.05$  was considered statistically significant.

## 3 Results

From April 2019 to February 2020, 152 consecutive patients were considered eligible to participate. However, 95 were excluded before and eight after the enrolment (Fig. 1). Finally, 49 patients receiving both the FCs were analysed (98 FCs overall) [Milano, 25 patients (51%); Vicenza, 14 patients (29%); Novara, ten patients (20%)]. Demographic characteristics, co-morbidities, surgical procedures, risk scores and ventilatory variables of the enrolled population are reported in Table 1. The protocol started  $42 \pm 9$  min after the induction of the general anesthesia in the FC<sub>10</sub> group and after  $45 \pm 11$  in the FC<sub>20</sub> group ( $p = 0.40$ ).

### 3.1 Assessment of baseline hemodynamic characteristics of the patients before FC<sub>10</sub> and FC<sub>20</sub>

As shown in the Supplemental Table 2 in the Supplementary Information, the baseline values before FC<sub>10</sub> and FC<sub>20</sub> administration of all the considered values in either the entire population or responders/non-responders were comparable. The analyses of either the period effect (mean difference (95% CI) 7.16 (– 8.51; 22.83); p-value: 0.36) or the carry-over effect (mean difference (95% CI) 7.16 (– 10.30; 24.62); p-value: 0.4) for the flow variables, considering the sequence of randomization, did not show a significant effect.

### 3.2 Fluid responsiveness

The FC of 4 ml kg<sup>-1</sup> was initially administered in 10 min (FC<sub>10</sub>) in 27 patients (55.1%) while in 20 min (FC<sub>20</sub>) in the other 22 patients (44.9%) ( $p = 0.42$ ). After FC<sub>10</sub>, 25 of 49 patients (51.0%) were classified as fluid responders, while after FC<sub>20</sub>, 14 were classified as responders (28.5%) [difference 95%CI – 22.45% (– 34.13 to – 10.77);  $p = 0.001$ ].

### 3.3 Pharmacodynamic effect of the FC<sub>10</sub> and FC<sub>20</sub>

#### 3.3.1 Magnitude of hemodynamic effect: AUC and $d_{\max}$

With the exception of the AUCs of SAP and MAP (both greater after FC<sub>10</sub> as compared to FC<sub>20</sub>) all the other AUCs were comparable (Table 2; see also Figs. 3 and 4).

**Table 1** Patients' characteristics at enrolment

Variables	Whole population
General characteristics	
Age (years)	55 (16)
Weight (kg)	71 ± 13
Sex (M, %)	21 (42.8%)
BMI, kg m <sup>-2</sup>	25 (22–27)
NSQIP score for serious complication, (%)	6.9 (5.2–9)
NSQIP score for all the complication, (%)	7.7 (5.5–10.1)
ASA score	
1 (%)	10 (20.4%)
2 (%)	33 (67.3%)
3 (%)	6 (12.2%)
Preoperative comorbidities (%)	
Hypertension	27%
Previous neoplasia	24%
Psychiatric diseases	15%
History of epilepsy	13%
Pulmonary diseases	6%
Endocrinological diseases	5%
Diabetes	5%
Gastrointestinal diseases	3%
Other metabolic diseases	2%
Duration of surgery, (min)	282 (150)
Preoperative hemoglobin, (mg dl <sup>-1</sup> )	14.1 (13.1–15.0)
Preoperative creatinine, (mg dl <sup>-1</sup> )	0.7 (0.3–0.8)
Intervention, n (%)	
Primitive cerebral neoplasia	86%
Cerebral metastasis	10%
Epilepsy surgery	2%
Vascular tumor	2%
Intraoperative ventilator settings and blood gases at T <sub>0</sub>	
V <sub>T</sub> , (ml)	480 (435–520)
Total PEEP, (cmH <sub>2</sub> O)	5 (4–5)
Driving pressure, (cmH <sub>2</sub> O)	11 (3)
RR, (breaths min <sup>-1</sup> )	12.7 (1.5)
PaO <sub>2</sub> /FiO <sub>2</sub> , (ratio)	368 (277–436)
C <sub>T</sub> , (ml cmH <sub>2</sub> O <sup>-1</sup> )	46 (40–52)
pH	7.42 (0.04)
PCO <sub>2</sub> , (mmHg)	38.7 ± 4.2
Lactate, (mmol l <sup>-1</sup> )	0.98 (0.75–1.74)
Base excess, (mEq l <sup>-1</sup> )	1.9 (0.9–3.3)

Values are presented as absolute (percentage); mean (standard deviation) or median (25th–75th interquartile range), as appropriate

NSQIP national surgical quality improvement program, ASA American society of anesthesiologists classification, V<sub>T</sub> tidal volume, PEEP positive end-expiratory pressure, RR respiratory rate, PaO<sub>2</sub>/FiO<sub>2</sub> arterial partial pressure of oxygen/fraction of inspired oxygen, C<sub>T</sub> total respiratory compliance, PaCO<sub>2</sub> arterial partial pressure of carbon dioxide

**Table 2** Pharmacodynamic effects of FC<sub>10</sub> (4 ml kg<sup>-1</sup> over 10 min) and FC<sub>20</sub> (4 ml kg<sup>-1</sup> over 20 min)

Hemodynamic variable	FC <sub>10</sub>	FC <sub>20</sub>	p-value
AUC SAP (%)	62 ± 32	31 ± 38	< 0.0001
AUC MAP (%)	59 ± 31	41 ± 35	0.009
AUC SVI (%)	47 ± 28	51 ± 32	0.49
AUC CI (%)	31 ± 25	26 ± 27	0.45
AUC Ea (%)	12 ± 24	22 ± 52	0.22
AUC HR (%)	9 ± 16	11 ± 20	0.46
d <sub>max</sub> SAP (%)	18 ± 18	16 ± 11	0.96
d <sub>max</sub> MAP (%)	15 ± 17	18 ± 11	0.15
d <sub>max</sub> SVI (%)	23 ± 14	26 ± 8	0.12
d <sub>max</sub> CI (%)	19 ± 14	22 ± 11	0.15
d <sub>max</sub> Ea (%)	- 14 ± 10	- 17 ± 6	0.36
d <sub>max</sub> HR (%)	10 ± 16	8 ± 12	0.80
t <sub>max</sub> SAP (%)	65 ± 30	68 ± 30	0.77
t <sub>max</sub> MAP (%)	64 ± 34	74 ± 24	0.33
t <sub>max</sub> SVI (%)	83 ± 31	76 ± 30	0.49
t <sub>max</sub> CI (%)	80 ± 32	77 ± 32	0.76
t <sub>max</sub> Ea (%)	70 ± 38	60 ± 41	0.51
t <sub>max</sub> HR (%)	43 ± 43	44 ± 45	0.96
d <sub>1</sub> SAP (%)	7 ± 17	2 ± 10	0.09
d <sub>1</sub> MAP (%)	6 ± 15	3 ± 10	0.45
d <sub>1</sub> SVI (%)	3 ± 14	3 ± 10	0.81
d <sub>1</sub> CI (%)	3 ± 13	2 ± 9	0.93
d <sub>1</sub> Ea (%)	0 ± 14	- 1 ± 18	0.94
d <sub>1</sub> HR (%)	0 ± 7	0 ± 6	0.52
d <sub>5</sub> SAP (%)	2 ± 10	1 ± 10	0.21
d <sub>5</sub> MAP (%)	4 ± 11	2 ± 9	0.22
d <sub>5</sub> SVI (%)	0 ± 10	0 ± 8	0.78
d <sub>5</sub> CI (%)	1 ± 8	2 ± 8	0.36
d <sub>5</sub> Ea (%)	1 ± 12	- 1 ± 19	0.55
d <sub>5</sub> HR (%)	3 ± 11	1 ± 8	0.65

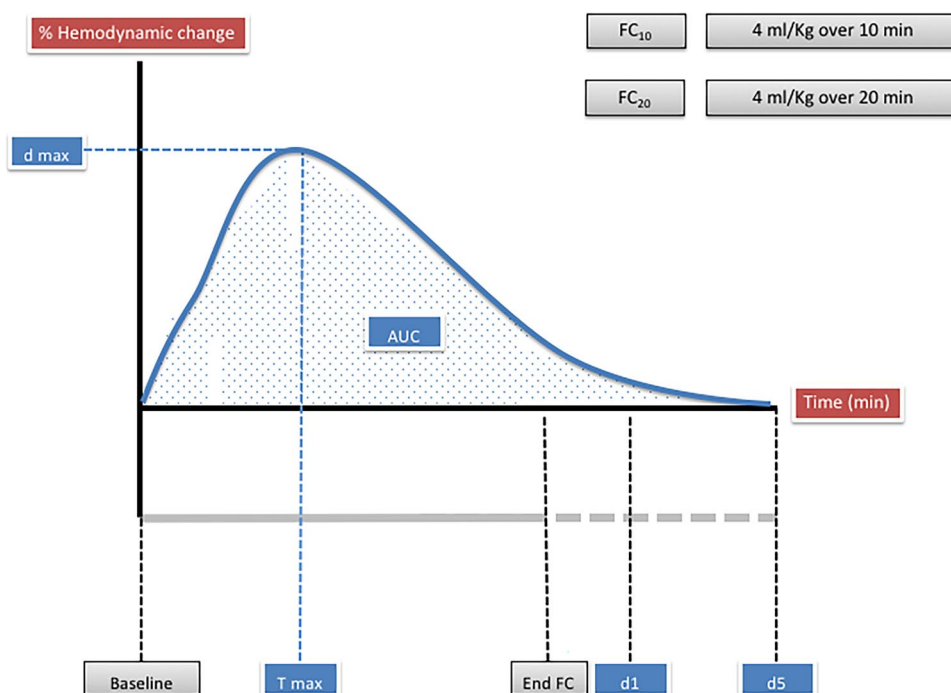
The area under the curve (AUC) has been quantified using the trapezoidal rule as the net overall percentage of increase (or reduction) of the considered variable from baseline to d<sub>5</sub>; d<sub>max</sub> is the maximal percentage difference from baseline; t<sub>max</sub> is the minutes when d<sub>max</sub> has been recorded (please note that this variable is expressed as percentage of time (from FC start to FC end) since the two tests have different durations—i.e. the 50% of t<sub>max</sub> is 5 min for FC<sub>10</sub> and 10 min for FC<sub>20</sub>); d<sub>1</sub> and d<sub>5</sub> the changes observed from baseline at 1-min time and 5-min after the end of the FC (see text and Fig. 2 for further explanations)

FC fluid challenge, SAP systolic arterial pressure, MAP mean arterial pressure, SVI stroke volume index, CI cardiac index, Ea arterial elastance, HR heart rate

The d<sub>max</sub> of pressure variables after FC<sub>10</sub> and FC<sub>20</sub> was comparable [SAP increase of 18% ± 18% vs. 16% ± 11%, respectively (p = 0.96); MAP increase of 15% ± 17% vs. 18% ± 11%, respectively (p = 0.15)]. Also, the d<sub>max</sub> of flow variables after FC<sub>10</sub> and FC<sub>20</sub> was comparable [SVI increase of 23% ± 14% vs. 26% ± 8%, respectively (p = 0.12);



**Fig. 2** Schematic representation of the pharmacodynamic assessment of the hemodynamic changes related to fluid challenge (FC) administration (FC<sub>10</sub> 4 ml kg<sup>-1</sup> over 10 min; FC<sub>20</sub> 4 ml kg<sup>-1</sup> over 20 min). The d<sub>max</sub> is the maximal percentage difference from baseline observed of the considered variable. The t<sub>max</sub> is the time when d<sub>max</sub> is observed. We also considered the changes from baseline at 1-min (d<sub>1</sub>) and 5-min (d<sub>5</sub>). The area under the curve (AUC), is calculated for each variable considering the percentage change from baseline to d<sub>5</sub>



CI increase of  $19\% \pm 14\%$  vs.  $22\% \pm 11\%$ , respectively ( $p=0.15$ ) (Table 2; see also Figs. 3 and 4). The maximal reduction of the Ea was  $-14\% \pm 10$  after the FC<sub>10</sub> and  $-17\% \pm 6$  after the FC<sub>20</sub> ( $p=0.36$ ). The d<sub>max</sub> of the HR was  $10\% \pm 16\%$  after the FC<sub>10</sub> and  $8\% \pm 12\%$  after the FC<sub>20</sub>.

### 3.4 Timing of maximal effect: t<sub>max</sub>

The t<sub>max</sub> was overall comparable after FC<sub>10</sub> and FC<sub>20</sub>. Specifically, the t<sub>max</sub> of pressure variables was reached after 64–74% of FC infusion, whereas the t<sub>max</sub> of flow variables after 76–83% (Table 2; see also Figs. 3 and 4). The t<sub>max</sub> of Ea and HR was reached after 60–70% and 43–44% of FC infusion, respectively.

### 3.5 Dissipation of FC infusion: d<sub>1</sub> and d<sub>5</sub>

The dissipation of the hemodynamic effect was overall comparable after FC<sub>10</sub> and FC<sub>20</sub>. In fact, with respect to the baseline, at d<sub>1</sub> the Ea and the HR were comparable, whereas all the other considered variables were significantly higher (Supplemental Table 3 in the Supplementary Information). On the contrary, at d<sub>5</sub> only the MAP was significantly higher, as compared to the baseline, after both after FC<sub>10</sub> and FC<sub>20</sub> (Supplemental Table 3 in the Supplementary Information). At d<sub>5</sub>, the percentage changes of all the considered variables were comparable after FC<sub>10</sub> and FC<sub>20</sub>, and, overall, below the 5% of increase, with respect to the baseline values (Table 2).

### 3.6 Effect of sequence of randomization and FC infusion time on SVI changes

As shown in the Supplemental Table 4 in the Supplementary Information, the sequence of randomization and the infusion time did not impact the SVI changes considered either at the end of FC<sub>10</sub> and FC<sub>20</sub> or at d<sub>5</sub>.

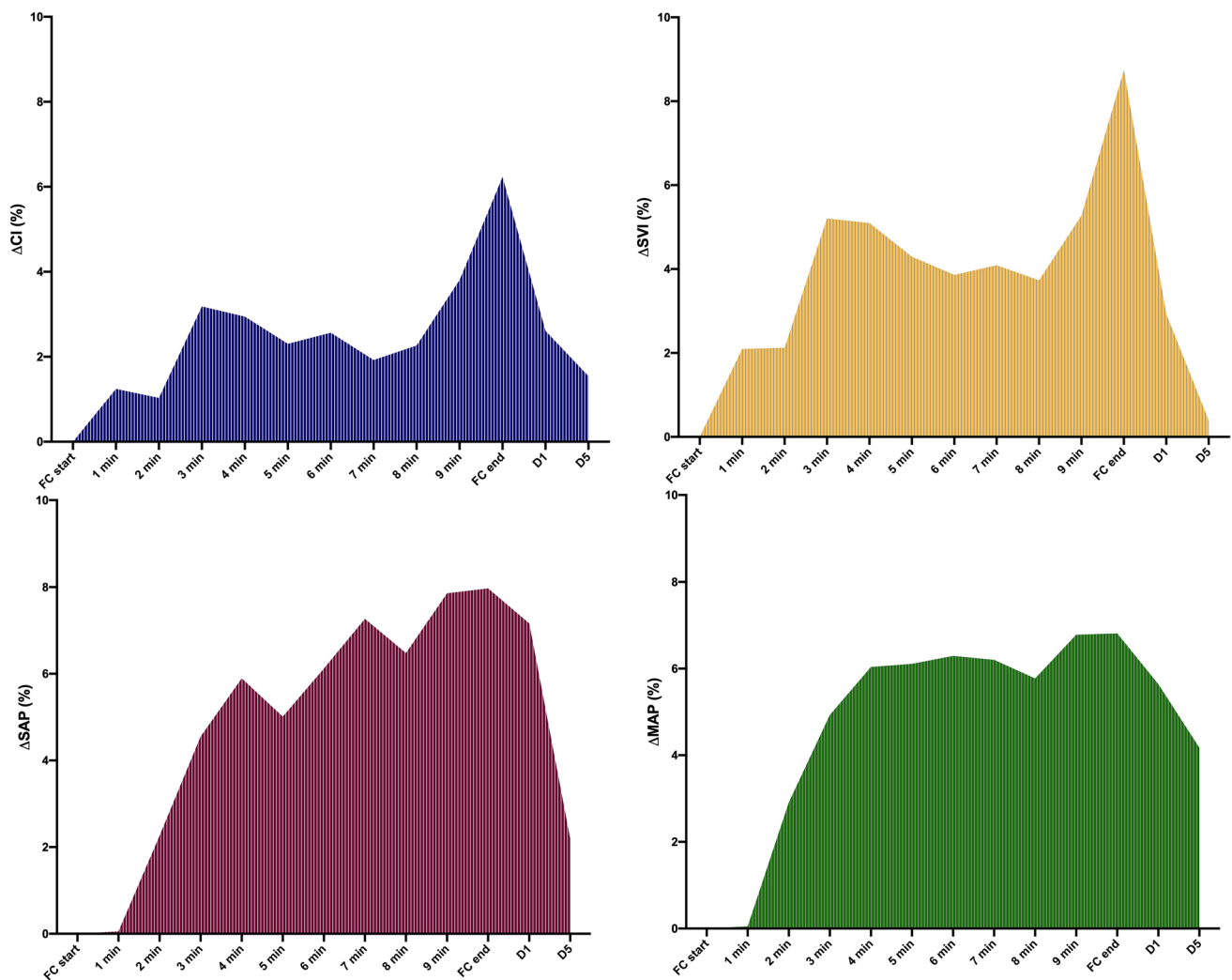
## 4 Discussion

To the best of our knowledge, this is the first trial exploring the pharmacodynamic effect of different infusion times of FC administration for a fixed dose of fluid. The main results of this trial performed in a selected population undergoing elective neurosurgery are: (1) the infusion times of FC administration affects the rate of fluid responsiveness, moving from 51.0% after FC<sub>10</sub> to 28.5% after FC<sub>20</sub>; (2) the magnitude of the hemodynamic effect on flow variables is overall dissipated within 5 min after FC end.

### 4.1 Pharmacodynamic data interpretation

The hemodynamic effect of the two FCs is depicted in the Figs. 3, 4 and 5.

During FC<sub>10</sub> infusion, the marked pressure response (more evident) and volume variables may be depicted as a “classic” bell-shaped pharmacodynamic curve, implying a sudden increase of the response until the peak is reached, and then a quick dissipation of the effect when the infusion



**Fig. 3** Area under the curve of cardiac index (CI; blue), stroke volume index (SVI; yellow); systolic arterial pressure (SAP; violet) and mean arterial pressure (MAP; green) calculated during FC<sub>10</sub> admin-

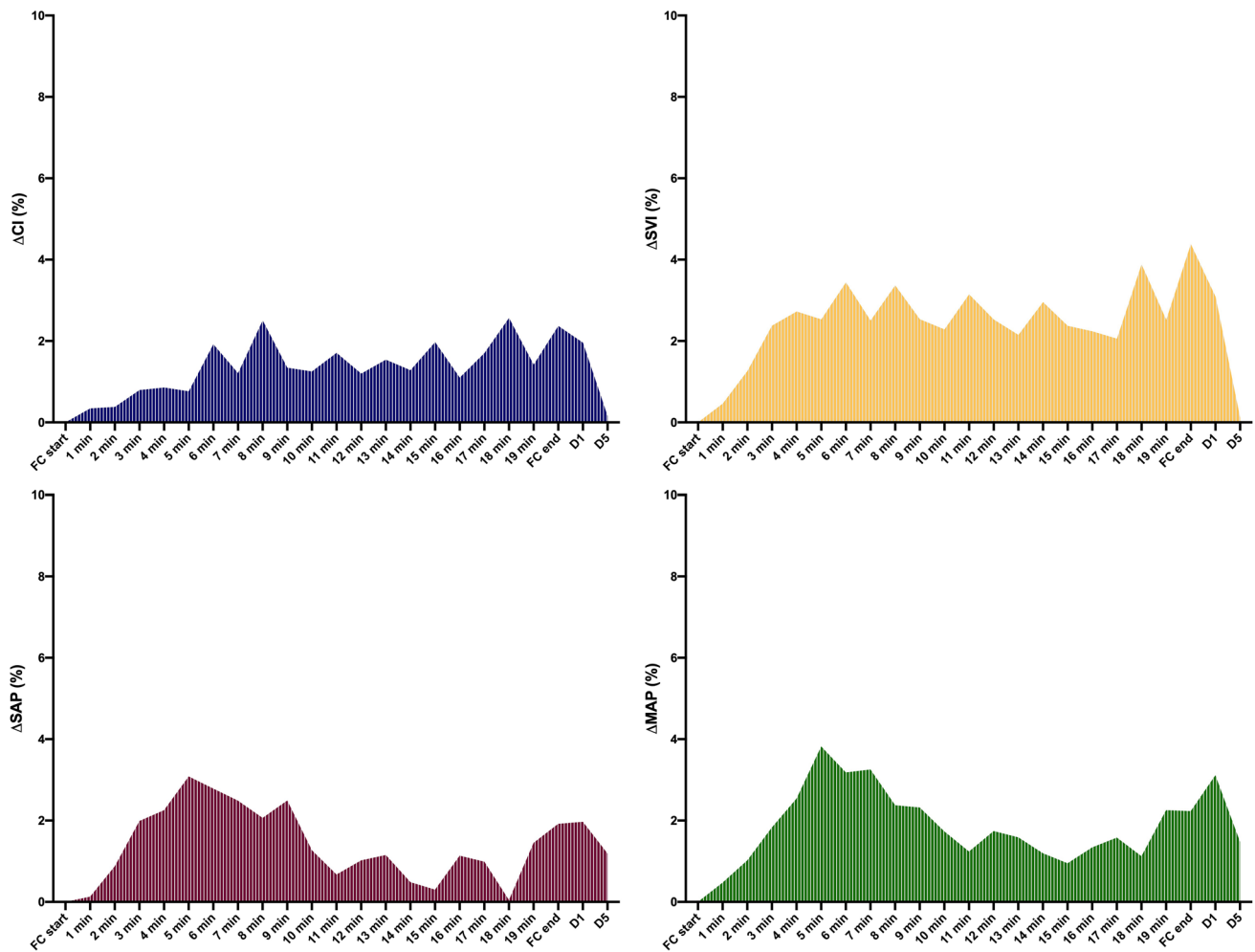
istration. FC<sub>10</sub>=fluid challenge of 4 ml kg<sup>-1</sup> over 10 min; FC, fluid challenge; d<sub>1</sub>, 1-min after FC<sub>20</sub> end; d<sub>5</sub>, 5-min after FC<sub>10</sub> end

is stopped. On the contrary, the hemodynamic response after FC<sub>20</sub> depicts roughly squared curves, implying a plateau of the response reached after about 3–4 min which is maintained until the end of the infusion.

The AUC is affected by the different duration of the infusion since this computation is performed employing a sum of the percentages of increase of the considered variable multiplied by the minutes of observation. For this reason, the AUC comparison between the two tests should be interpreted with caution. The AUC analysis, however, showed that the magnitude of the pressure changes after a FC<sub>10</sub> is significantly higher as compared to FC<sub>20</sub> (Fig. 5). This result suggests that the coupling between flow and pressure variables in hemodynamically stable surgical patients may also be influenced by the infusion times of the FC, a field of potential interest for future researches.

However, our study shows that this type computation is feasible and may be added to the “standard” analysis of a FC, to define the hemodynamic profile of the infusion.

On the contrary, the interpretation of the other pharmacodynamic variables is more intuitive. The effect in terms of peak and timing was overall comparable, and may be summarized as a maximal increase of 15–20% in pressure variables and of 20–25% of flow variables, reached after about 70–80% of the FC infusion. These data suggest that when the FC administered can challenge the system appropriately, the hemodynamic response is consistent, irrespective of the infusion time adopted. However, the maximum effect is reached close to the end of FC administration, or immediately after, as previously shown by Aya et al. (1 min after FC end) [13].



**Fig. 4** Area under the curve of cardiac index (CI; blue), stroke volume index (SVI; yellow); systolic arterial pressure (SAP; violet) and mean arterial pressure (MAP; green) calculated during FC<sub>20</sub> admin-

istration. FC<sub>20</sub>=fluid challenge of 4 ml kg<sup>-1</sup> over 20 min; FC, fluid challenge; d<sub>1</sub>, 1-min after FC<sub>20</sub> end; d<sub>5</sub>, 5-min after FC<sub>20</sub> end

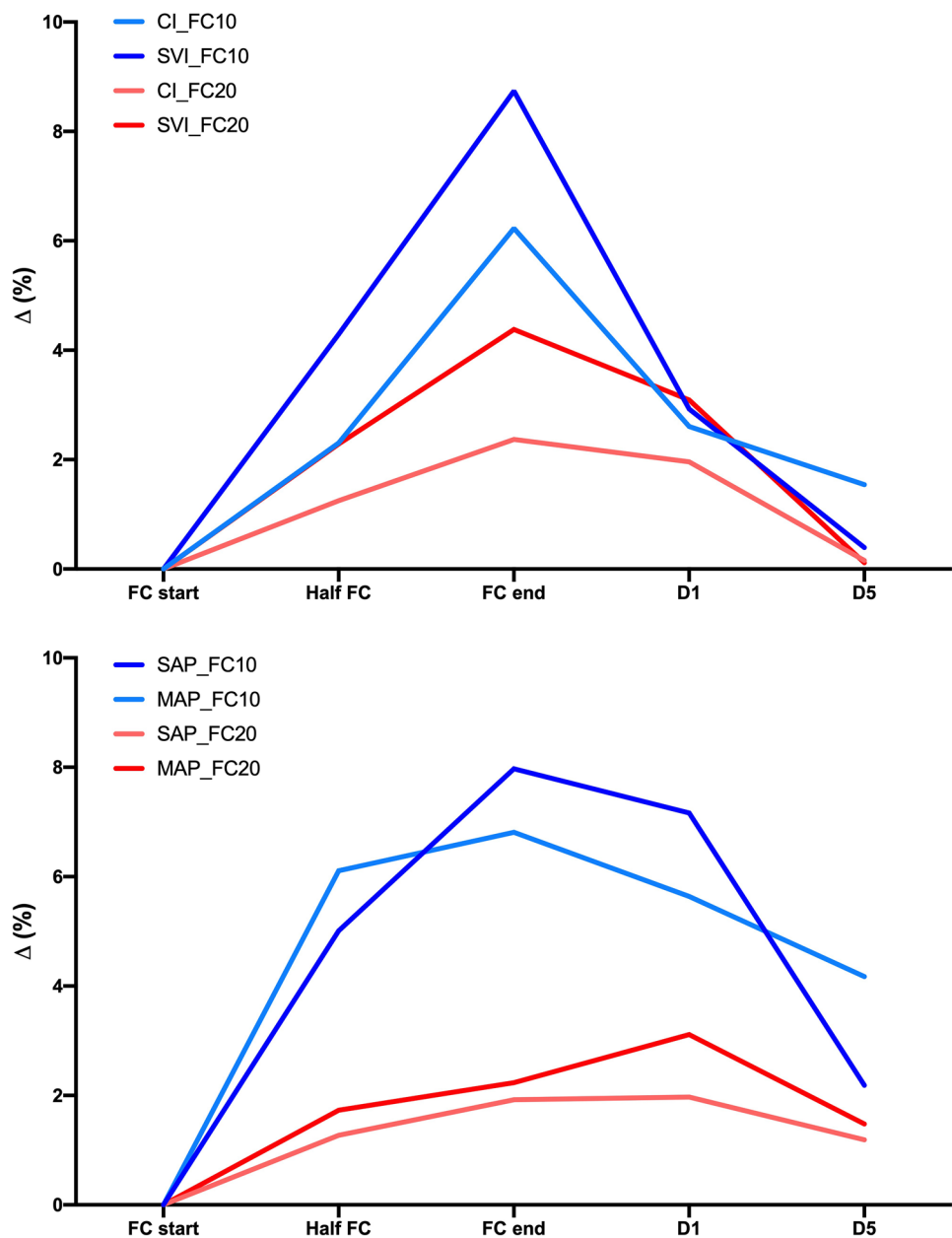
Finally, in line with the results of Aya et al. [13], the hemodynamic effect of both FC<sub>10</sub> and FC<sub>20</sub> was overall dissipated within 5 min after the end of the infusion. Several different mechanisms could be implied in the dissipation of the effect of FC. First of all, many years ago, Prather et al. described a stress-relaxation mechanism allowing a rapid return to intravascular pressure baseline in response to a rapid increase in intravascular volume [27]. Moreover, crystalloids are redistributed from the central circulation to the rest of the cardiovascular system, and particularly to the compliant veins [28]. On the contrary, the persistence of the MAP effect (Supplemental Table 3 in the Supplementary Information) may be related to the interplay between the heart and vessels after FC administration. Since flow and pressures variations are not precisely correlated in the cardiovascular system; the two system components would return to the steady-state at different timings. However, the MAP increase at the d<sub>5</sub> is below 5% of baseline values,

which should be considered clinically irrelevant. Also, it is important to underline that our results have been obtained by infusing crystalloids, and further studies in this field are warranted to assess the pharmacodynamic profile of colloids' infusion.

The overall analysis of MAP and SVI changes in our study may also be affected by the mathematical coupling between pressure and flow variables changes after the FCs, since the MostCare® system is based on the high sample rate analysis of the arterial waveform and is also very dependent on the quality of the arterial waveform signal [29]. The ability to track SVI changes by the hemodynamic monitoring adopted, which is usually uncalibrated in the operating room [30, 31], is crucial to assess the real effect of FC administration. However, very recently our group published a multicentric study showing that the least significant change of SVI detected by the MostCare® system (4.5%) is largely below the threshold used to define the responsiveness to each FC.



**Fig. 5** Flow and pressure variables' change (percentage of variation with respect to baseline values) at predefined time-point of FC administration.  $FC_{10}$  = 4 ml  $kg^{-1}$  over 10 min;  $FC_{20}$  = 4 ml  $kg^{-1}$  over 20 min; *SAP* systolic arterial pressure, *MAP* mean arterial pressure, *SVI* stroke volume index, *CI* cardiac index;  $d_1$ , 1-min after FC end;  $d_5$ , 5-min after FC end



## 4.2 Limitations of the study

This study has some limitations. First, the present study protocol did not exactly follow the trial registration, which reports the use of a “mini-FC” before administering the entire aliquot. This adjunctive test has been planned but never performed because, before the enrolment of the first participant, the authors recognized technical limitations in the described infusion pump systems to manage both the mini-FC and the fixed infusion times of two  $FC_{10}$  and  $FC_{20}$ . Data regarding the “mini-FC” have never been recorded, however, this discrepancy should be acknowledged.

Second, extrapolating pharmacodynamic evaluation from surgical patients is challenging. We deliberately aimed at selecting patients during a period of hemodynamic stability in neurosurgery, limiting the external validity of our results in different surgical settings or in critically ill patients. It is uncertain whether these results could also be applied in critically ill unstable patients, encouraging further researchers in this field, aiming at individualizing the modality of FC administration in different settings. Moreover, we adopted a standardized and reproducible electronic infusion set, ensuring a fixed infusion time and reducing the bias related to manual infusion

at the different steps of the protocol. Again, this setting is not always available.

Third, the insertion of a central line is not considered a standard clinical practice in the involved centers. We therefore could not obtain hemodynamic preload filling values related to “stressed volume” and venous compliance, according to Guyton’s physiology [32, 33], such as central venous pressure and mean filling pressure analogous. This bias may lead to false-negative FCs. We assumed a 4 ml kg<sup>-1</sup> FC volume to be adequate to challenge the system, only considering data from a single-center small-sized study, performed on postoperative cardiac patients [13].

Fourth, as shown in Fig. 1 the enrolment was limited by the availability in the operating room of the hemodynamic tool for the measurements since each center is equipped with only one MostCare®. This technical limitation could have partially biased the selection of those patients simultaneously eligible for the study, implying a choice that was at the discretion of the principal investigator of each center. Moreover, we excluded patients with cardiac dysfunctions. These two limitations may limit the external validity of our results.

Finally, we cannot exclude a carry-over hemodynamic effect of the first FC on the second, potentially biasing our results. In fact, the adopted protocol inevitably led to “clustered” observations, despite the adoption of a randomization of the FC sequence and comparable baseline hemodynamic values before FC administration.

## 5 Conclusions

In selected hemodynamically stable surgical patients, the number of fluid responders differs according to the infusion times of FC, being higher, for a fixed dose, after a 10-min infusion, as compared to a 20-min infusion. The effect on flow variables of either FCs fades 5 min after the end of infusion.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10877-021-00756-3>.

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**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Conflict of interest** *For the present study:* The authors declare that they have no conflict of interest. *Unrelated to the present study in the last 36 months:* Dr. Messina received travel expenses and registration for meetings, congresses, and courses and lecture fees from Vygon, Edwards and Philips. Dr. Monge Garcia has received Honoraria and/or Travel Expenses from Edwards Lifesciences and Deltex Medical. He also received supply medical equipment (Doppler probes) in return for carrying out research works for Deltex Medical. Prof. Cecconi is a consultant for Edwards Lifesciences, LiDCO and Cheetah Medical.

**Ethical approval and consent to participate** This prospective multi-center randomized trial was carried-out in the operating rooms of three Italian tertiary hospitals: the Humanitas Research Hospital (Rozzano, Milano), the University hospital “Maggiore della Carità” (Novara) and the San Bortolo Hospital (Vicenza). The protocol was designed in accordance with the principles outlined in the Declaration of Helsinki; the study was approved by all the local institutional ethics committees [Ethical Committee of the Coordinator Center—Humanitas Research Hospital, Rozzano (Milano; Italy); Protocol Number 92/19; 19 February 2019], and prospectively registered (NCT03810118).

**Informed consent** Informed consent was obtained from all the participants.

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