Haemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomised controlled study.

Supplemental Digital Content

Table of Contents

Methods

Sample size calculation

Sample size calculations have been made as for testing the dose group effect on Pmsf change as the main outcome. This is equivalent to testing the association between this outcome and a 4-category variable (3 degrees of freedom) controlled for other covariates including the baseline Pmsf. Apart from the usual setting of power (0.8) and type one error (0.05) the necessary input for a minimum sample size calculation requires the specification of the value of R-squared explained by the groups variable (set to 0.05, towards the worst case scenario spectrum) and the value of R-squared explained by the rest of the independent variables of interest altogether (that includes the baseline Pmsf). A sensitivity analysis has been carried out to the latter value and, given that the baseline Pmsf is expected to explain some of the variability of the change - that has been set to 0.15. This scenario would result in a minimum 63 patients necessary for this experiment. A 25% increase has been applied to allow for missing information and a final number of 80 have been recruited. PASS software has been used for the calculation (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA)

Results

Changes in haemodynamics

There is no significant effect of CO response on the ΔPmsf-arm ($p = 0.82$, Table 2, SDC – Figure 3). ΔCO was only significantly greater with 4 mL/Kg compared to 1 mL/Kg ($p = 0.002$, Table 2, SDC – Figure 4). ΔSV was significantly greater with 2 and 4 mL/Kg compared with 1 ml/Kg, and significantly greater in responders than in non-responders (Table 2, SDC – Figure 5). ΔHR was significantly greater with 2, 3 and 4 mL/Kg compared with 1 mL/Kg, and significantly greater in responders compared with non-responders (Table 2, SDC – Figure 6). ΔCVP was significantly greater only with 4 mL/Kg compared with 1mL/Kg and no difference was observed between responders and no-responders (Table 2, SDC – Figure 7). ΔMAP was significantly greater only with 4 mL/Kg compared with 1 mL/Kg and was significantly greater in responders than in non-responders (Table 2, SDC – Figure 8)

Tables

SDC – Table 1 Baseline characteristics of participants by group of dose of crystalloids.

	1 ml/Kg	2 ml/kg	3 ml/kg	4 ml/kg	p
Females, n (%)	6 (30)	6 (30)	3 (15)	3 (15)	0.5
Age (years)	66.5 (51.5 – 74.5)	70.5 (64.4 – 76-5)	72.0 (63.5 – 79.5)	69.0 (61.5 – 71.5)	0.7
Height (cm)	166 (162.2 – 170)	171.5 (158.0 – 177.0)	172.5 (168.0 – 178.0)	171.0 (167.0 – 179.0)	0.08
Weight (Kg)	76.5 (67.0 – 89.0)	81.0 (73.0 – 91.0)	86.0 (72.8 – 100.8)	91.0 (73.3 – 105.8)	0.15
DM, n (%)	8 (40)	3 (15)	3 (15)	3 (15)	0.2
APACHE II score	15.5 (11.3 – 18.8)	12.5 (11.0 – 16.8)	15.0 (10.0 – 17.0)	12.0 (10.0 – 16.0)	0.5
ICNARC score	14.0 (10.0 – 19.8)	13.0 (11.0 – 18.5)	14.0 (10.0 – 16.0)	13.0 (9.0 – 15.0)	0.5
Temperature (ºC)	36.1 (35.4 – 36.4)	36.1 (35.6 – 36.5)	36.1 (35.4 – 36.3)	36.2 (35.4 – 36.4)	0.95
Type of surgery					
CABG, n (%)	8 (40)	7 (35)	12 (60)	9 (45)	0.3
AVR ± CABG, n (%)	6 (30)	8 (40)	6 (30)	7 (35)	0.3
MVR ± CABG, n (%)	6 (30)	4 (20)	1 (5)	1 (5)	0.3
Other, n (%)	0 (0)	1 (5)	1 (5)	3 (15)	0.3
Off-pump, n (%)	0 (0)	1 (5)	2 (10)	1 (5)	0.9
LV systolic function					
Normal, n (%)	15 (75)	14 (70)	11 (55)	11 (55)	0.6
Mild – Moderate impairment, n (%)	5 (25)	4 (20)	4 (20)	5 (25)	0.6
Severe impairment, n (%)	0 (0)	0 (0)	1 (5)	1 (5)	0.6
No information, n (%)	0 (0)	2 (10)	4 (20)	3 (15)	0.6
LV diastolic function					
Normal, n (%)	2 (10)	4 (20)	2 (10)	1 (5)	0.5
Mild – Moderate impairment, n (%)	8 (40)	10 (50)	9 (45)	11 (55)	0.5
Severe impairment, n (%)	1 (5)	0 (0)	0 (0)	1 (1)	0.5
Not determinated, n (%)	8 (40)	3 (15)	4 (20)	3 (15)	0.5
No information, n (%)	1 (5)	3 (15)	5 (25)	4 (20)	0.5
RV systolic function					
Normal, n (%)	18 (90)	18 (90)	14 (70)	13 (65)	0.2
Mild – Moderate impaired, n (%)	1 (5)	0 (0)	1 (5)	3 (15)	0.2
No information, n (%)	1 (5)	2 (10)	5 (25)	4 (20)	0.2
Rhythm					
Sinus Rhythm, n (%)	12 (60)	13 (65)	14 (70)	14 (70)	0.7
Atrial Fibrilation, n (%)	2 (10)	0 (0)	0 (0)	0 (0)	0.7
Pace Maker, n (%)	6 (30)	7 (35)	6 (30)	6 (30)	0.7
Respiratory Mode					
Pressure controlled ventilation, n (%)	12 (60)	16 (80)	14 (70)	13 (65)	0.9
Pressure support ventilation, n (%)	6 (30)	3 (15)	5 (25)	5(25)	0.9
Spontaneous ventilation, n(%)	2 (10)	1 (5)	1 (5)	2 (10)	0.9
Respiratory Rate (bpm)	14.5 (12.0 – 18.0)	12.0 (12.0 – 14.8)	13.5 (12.0 – 16.0)	12.0 (12.0 – 14.0)	0.2
FiO2	0.48 (0.40 – 0.59)	0.50 (0.40 – 0.50)	0.45 (0.40 – 0.60)	0.50 (0.40 – 0.60)	0.9
Inspiratory Pressure (cmH2O)	18.0 (15.0 – 22.0)	18.0 (16.0 – 20.0)	18.0 (16.0 – 20.0)	17.5 (15.8 – 20.3)	0.9

Positive End-Expiratory Pressure (cmH2O)	5.0 (5.0 – 6.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	0.6
Tidal Volume (mL)	498.5 (455.3 – 633.8)	522.0 (440.5 – 654.5)	498.0 (441.5 – 605.0)	577.0 (499.0 – 634.0)	0.7
Vasoconstrictors used, n (%)	14 (70)	10 (50)	9 (45)	10 (50)	0.4
Noradrenaline (μg/Kg/min)	0.00 (0.00 – 0.06)	0.00 (0.00 – 0.06)	0.00 (0.00 – 0.09)	0.00 (0.00 – 0.05)	0.7
Dopamine (μg/Kg/min)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 2.50)	0.7
Vasodilators used, n (%)	8 (40)	6 (30)	4 (20)	8 (40)	0.5
Milrinone (ng/kg/min)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.98
Nitroglycerin (mg/h)	0.00 (0.00 – 0.88)	0.00 (0.00 – 0.38)	0.00 (0.00 – 0.00)	0.00 (0.00 – 1.88)	0.07
Propofol (mg/h)	100.0 (72.5 – 100.0)	100 (57.5 – 115.0)	100.0 (100.0 – 145.0)	100.0 (20.0 – 137.5)	0.5
Alfentanyl (mg/h)	0.00 (0.00 – 0.75)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.8
Morphine (mg/h)	1.00 (0.00 – 2.00)	0.00 (0.00 – 2.00)	0.00 (0.00 – 1.75)	0.50 (0.00 – 2.00)	0.9
Cardiac Output Monitor					
LiDCO, n (%)	12 (60)	17 (85)	15 (75)	17 (85)	0.2
Pulmonary Arterial Catheter, n (%)	8 (40)	3 (15)	5 (25)	3 (15)	0.2
Baseline Haemodynamics					
Pmsf-arm (mmHg)	21.5 (17.3 – 27.5)	23.0 (20.0 – 26.8)	24.0 (19.5 – 25.7)	23.5 (20.3 – 29.8)	0.5
Mean arterial pressure (mmHg)	79.5 (71.3 – 85.5)	74.0 (69.3 – 89.5)	71.0 (67.0 – 78.5)	72.5 (67.3 – 80.5)	0.1
Cardiac Output (L/Min)	5.6 (4.4 – 7.2)	5.5 (4.6 – 7.5)	5.2 (4.5 – 7.1)	5.6 (3.9 – 6.4)	0.9
Stroke Volume (mL)	67.0 (56.5 – 86.5)	68.5 (54.8 – 83.0)	71.0 (65.0 – 92.8)	64.0 (51.8 – 82.5)	0.4
Heart Rate (bpm)	81.0 (76.2 – 107.0)	82.2 (79.6 – 91.3)	74.4 (66.1 – 80.0)	81.8 (75.4 – 88.3)	0.004
Central venous pressure (mmHg)	11.0 (7.3 – 14.0)	9.0 (8.3 – 11.8)	9.0 (8.0 – 13.8)	10.0 (8.0 – 15.0)	0.7
Fluid challenge volume (ml)	76.6 ± 14.3	162.5 ± 28.9	257.6 ± 51.8	352.6 ± 79.9	

DM diabetes mellitus; ICNARC intensive care national audit and research centre; APACHE Acute physiology and chronic health evaluation; CABG Coronary Artery by-pass graft; AVR Aortic Valve replacement; MVR mitral valve replacement; LV left ventricle; RV right ventricle; FiO2 Fraction inspired of oxygen; Pmsf-arm Mean systemic filling pressure measured in the arm. Categorical data are expressed as count (percentage) and compared using Fisher's Exact Test. Continuous data are compared using one-way ANOVA *F* statistic, with Welch correction when appropriate.

SDC - Table 2 Predicted changes in haemodynamics adjusted by mean baseline values by dose of crystalloids and CO response groups.

	1 mL/Kg	2 mL/Kg	3 mL/Kg	4 mL/Kg
ΔPmsf-arm (mmHg)	0.10 (-1.26, 1.47)	2.91 (1.77, 4.05)*	2.48 (1.38, 3.57)*	4.15 (2.99, 5.31)*
NR	0.74 (-0.48, 1.96)	2.08 (0.74, 3.43)	3.33 (1.86, 4.80)	3.86 (1.96, 5.76)
R	-0.53 (-2.96, 1.90)	3.74 (1.91, 5.58)	1.63 (0.01, 3.25)	4.44 (3.10, 5.79)
ΔPmsf-arm (%)	0.85 (-6.37, 4.67)	14.81 (10.19, 19.43)*	10.84 (6.41, 15.28)*	18.28 (13.57, 22.99)*
NR	1.62 (-3.34, 6.57)	9.09 (3.63, 14.56)	14.31 (8.37, 20.25)	16.96 (9.25, 24.67)
R	-3.31 (-13.17, 6.53)	20.53 (13.09, 27.98)	7.37 (0.80, 13.94)	19.61 (14.14, 25.07)
ΔCO (L/min)	0.21 (-0.02, 0.44)	0.43 (0.20, 0.66)	0.43 (0.20, 0.66)	0.75 (0.52, 0.98)*
NR	0.05 (-0.09, 1.20)	0.22 (0.06, 0.38)	0.16 (-0.02, 0.34)	0.02 (-0.20, 0.24)
R	0.79 (0.37, 1.21)	0.81 (0.51, 1.12)	0.80 (0.52, 1.07)	1.13 (0.91, 1.35)
ΔSV (mL)	2.48 (0.01, 4.96)	7.24 (5.16, 9.31)*	6.37 (4.37, 8.38)	10.51 (8.43, 12.60)*
NR	1.41 (-0.80, 3.62)	3.39 (0.94, 5.84)	2.89 (0.07, 5.71)	4.33 (0.99, 7.68)
R†	3.56 (-0.86, 7.98)	11.08 (7.74, 14.42)	9.86 (6.89, 12.82)	16.69 (14.23, 19.16)
ΔMAP (mmHg)	4.44 (1.73, 7.14)	7.11 (4.85, 9.37)	3.47 (1.28, 5.66)	9.21 (6.96, 11.47)*
NR	1.33 (-1.08. 3.74)†	3.56 (0.87, 6.24)	3.07 (0.16, 5.98)	7.08 (3.46, 10.70)
R†	7.54 (2.73, 12.36)	10.66 (7.04, 14.29)	3.87 (0.65, 7.09)	11.35 (8.67, 14.02)
ΔHR (bpm)	4.70 (2.68, 6.72)	-0.70 (-2.35, 0.95)*	-1.37 (-3.03, 0.30)*	-3.70 (-5.36, -2.05)*
NR	1.05 (-0.73, 2.82)	-0.66 (-2.63, 1.31)	-2.15 (-4.37, 0.08)	-4.76 (-7.43, -2.09)
R†	8.36 (4.77, 11.94)†	-0.73 (-3.40, 1.93)	-0.59 (-2.96, 1.78)	-2.65 (-4.60, -0.70)
ΔCVP (mmHg)	0.80 (0.05, 1.55)	0.89 (0.28, 1.50)	1.26 (0.64, 1.88)	2.49 (1.88, 3.11)*
NR	0.32 (-0.34, 0.98)	0.94 (0.20, 1.67)	1.43 (0.60, 2.25)	2.30 (1.31, 3.29)
R	1.28 (-0.05, 2.61)	0.85 (-0.14, 1.84)	1.10 (0.22, 1.98)	2.69 (1.97, 3.42)

Adjusted estimated means presented with 95% confidence interval. Pmsf-arm mean systemic filling pressure measured with the stop-flow arterial-venous equilibrium method on the arm; CO cardiac output; SV stroke volume; HR heart rate; CVP central venous pressure; MAP mean arterial pressure. R responders according to change in CO greater than 10%; NR non-responders.* $p < 0.05$ when compared with the reference category (1 ml/Kg) adjusted by the mean baseline of each variable and the CO response. † $p < 0.05$ for the effect of the response of CO (R vs NR).

SDC - Table 3. Estimated volume (mL) required for a fluid challenge to achieve an estimated change in Pmsf-arm of at least 14%, for several values of Pmsf-arm at base line and the use of vasodilators

Pmsf-arm Base line (mmHg)	Volumen (mL) with no vasodilators	Volume (mL) with Vasodilators
20	321	446
21	327	452
22	334	458
23	341	465
24	350	473
25	359	481
26	369	490
27	381	499
28	393	509

SDC - Table 4 Multivariable regression models of the changes in cardiac output after a fluid challenge according to perioperative echocardiographic information adjusted by CO at baseline

	B	**S. E.**	***p***	**(95% C.I)**
Model 1				
Constant	0.45	0.06	<0.001	(0.33, 0.57)
CO Baseline	0.03	0.03	0.42	(-0.04, 0.10)
Model 2: Left-ventricle systolic dysfunction				
Constant	0.49	0.12	<0.001	(0.24, 0.74)
CO Baseline	0.03	0.03	0.43	(-0.04, 0.09)
Normal *vs* Mild-Moderate LVSD	-0.05	0.15	0.73	(-0.34, 0.24)
Normal LVSF *vs* Severe S.D.	-0.12	0.40	0.76	(-0.92, 0.68)
Mild-Moderate vs Severe S.D.	-0.07	0.39	0.86	(-0.85, 0.71)
Model 3: Left-ventricle diastolic dysfunction				
Constant	0.52	0.07	<0.001	(-0.38, 0.67)
CO Baseline	0.03	0.03	0.33	(-0.03, 0.10)
Normal *vs* Mild-Moderate LVDD	-0.20	0.19	0.30	(-0.59, 0.18)
Normal *vs* Severe LVDD	-0.69	0.37	0.07	(-1.44, 0.04)
Mild-Moderate *vs* Severe LVDD	-0.50	0.40	0.22	(-1.30, 0.31)
Model 4: Right-ventricle systolic dysfunction				
Constant	0.35	0.24	0.15	(-0.13, 0.84)
CO Baseline	0.02	0.03	0.46	(-0.04, 0.09)
Normal *vs* Mild-Moderate RVSD	0.11	0.25	0.66	(-0.39, 0.61)

CI confidence interval; S.E. standard error; LVSD left-ventricle systolic dysfunction; LVDD left-ventricle diastolic dysfunction; RVSD right-ventricle diastolic dysfunction.

SDC - Table 5. Univariate logistic regression model across the categorical variable represented by the groups of dose of fluids to predict a positive response to a fluid challenge.

Dose	OR	*p*	95% CI
2 vs 1 ml/Kg	2.15	0.293	(0.52, 9.00)
3 vs 1 ml/Kg	3.27	0.098	(0.80, 13.35)
4 vs 1 ml/Kg	7.43	0.006	(1.78, 31.04)
Intercept	0.25	0.13	

Figures

SDC Figure 1 Protocol used as standard clinical practice. The dose of the fluids was modified according to the allocation group and then completed after the second measurement.

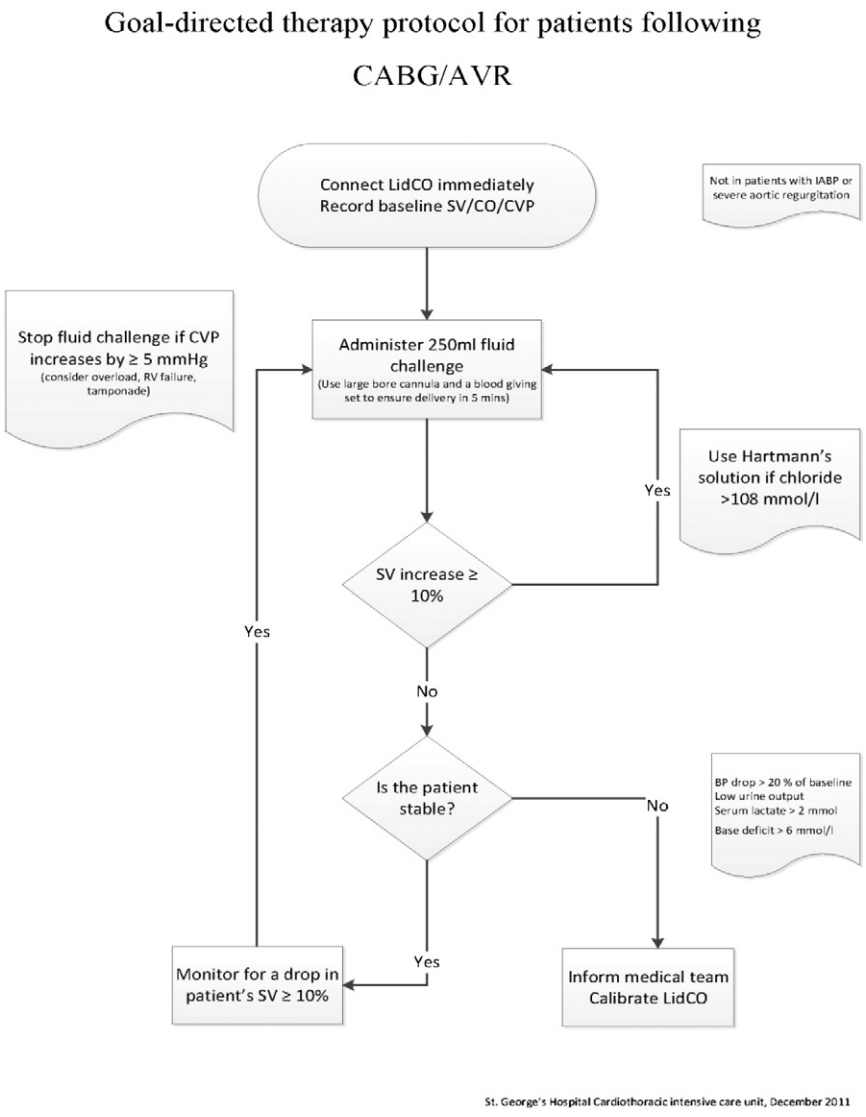
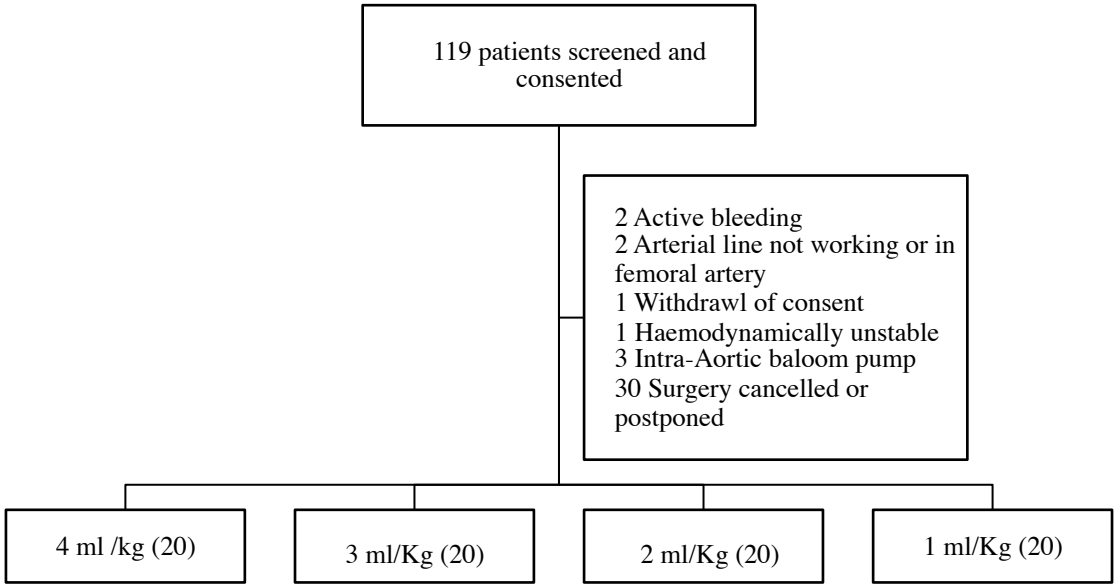
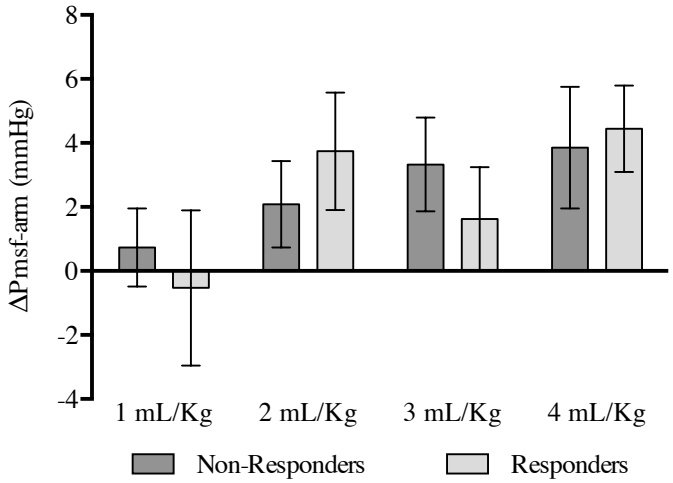


Fig. 1. Algorithm for SV maximization.

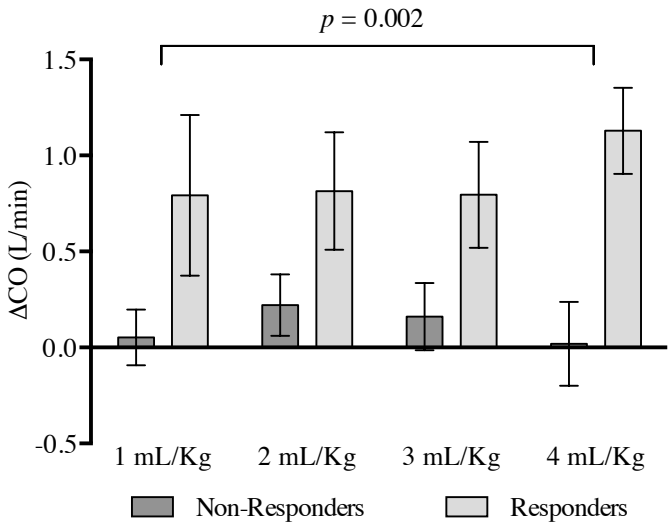
SDC – Figure 2 Flow-chart of the participants screening and finally enrolled into the study.



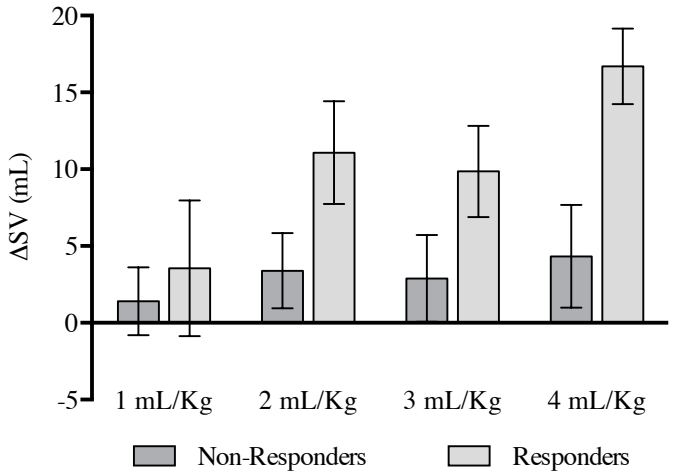
SDC – Figure 3. Predicted means of change in mean systemic filling pressure-arm (∆Pmsf-arm) adjusted by mean Pmsf-arm at baseline. Values presented by dose of crystalloids and CO response with 95% confidence interval.



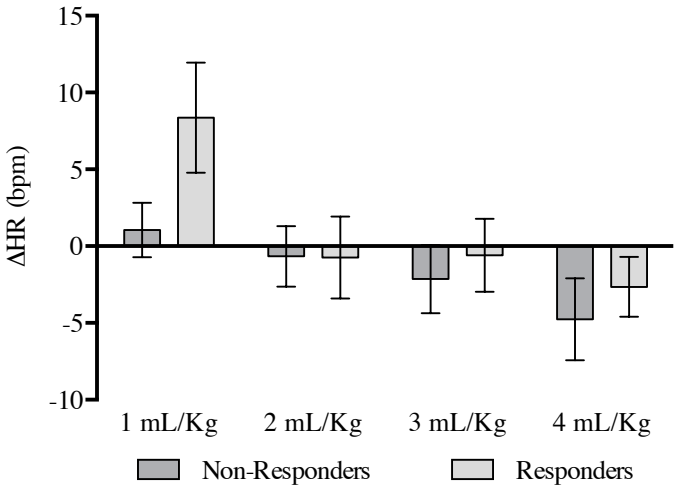
SDC – Figure 4 Predicted mean of changes of cardiac output (CO, L/min) adjusted by the mean baseline value of CO. Data presented by dose of crystalloids used for a fluid challenge and CO response. Error bars represent 95% confidence interval.



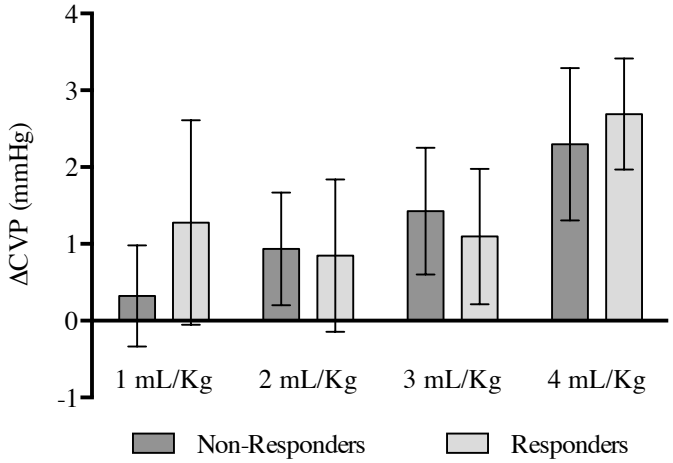
SDC - Figure 5. Predicted means of change in stroke volume (∆SV) adjusted by mean SV at baseline. Values presented by dose of crystalloids and CO response with 95% confidence interval.



SDC – Figure 6. Predicted means of change in heart rate (∆HR) adjusted by mean baseline value of HR. Values presented by dose of crystalloids and CO response with 95% confidence interval.



SDC – Figure 7. Predicted means of change in central venous pressure (∆CVP) adjusted by mean baseline value of CVP. Values presented by dose of crystalloids and CO response with 95% confidence interval.



SDC – Figure 8. Predicted means of change in mean arterial pressure (∆MAP) adjusted by mean baseline value of MAP. Values presented by dose of crystalloids and CO response with 95% confidence interval.