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

Short Running Title: Minimal volume for a fluid challenge.

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Conflict of Interest:

- Hollmann D. Aya: Applied Physiology. LiDCO
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- Michael Grounds: no conflict of interest
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Abstract

Objective: The objectives of this study are to determine what is the minimal volume required to perform an effective fluid challenge (FC) and to investigate how different doses of intravenous fluids in a FC affect the changes in cardiac output and the proportion of responders and non-responders.

Design: quasi-randomised controlled trial.

Setting: Cardiothoracic intensive care unit, tertiary university hospital

Patients: 80 Post-cardiac surgery patients.

Intervention: intravenous infusion of 1, 2, 3 or 4 mL/Kg (body weight) of crystalloid over 5 minutes.

Measurements: Mean systemic filling pressure measured using the transient stop-flow arm arterial-venous equilibrium pressure (Pmsf-arm), arterial and central venous pressure (CVP), cardiac output (CO; LiDCO*plus*, LiDCO, Cambridge, UK) and heart rate.

Results: The groups were well matched with respect to demographic and baseline physiological variables. The proportion of responders increased from 20% in the group of 1mL/kg to 65% in the group of 4 mL/kg (p = 0.04). The predicted minimal volume required for a FC was between 321 to 509 mL. Only 4 mL/Kg increase Pmsf-arm beyond the limits of precision and was significantly associated with a positive response (OR 7.73, 95% CI 1.78 to 31.04).

Conclusion: The doses of fluids used for a FC modify the proportions of responders in postoperative patients. A dose of 4 ml/Kg increases Pmsf-arm and reliably detects responders and non-responders.

Key Words

- Fluid challenge
- Mean systemic filling pressure
- Crystalloids
- Haemodynamics
- Fluid responders
- Fluidtherapy

Introduction

One of the commonest interventions performed in critical care is a fluid challenge (FC). A FC is the administration of a "small" amount of intravenous (IV) fluids, in order to assess the cardiac response to an increase in intravascular volume [1,2]. Despite the simplicity of this test, it is unclear how much volume should be used to perform a FC. Volumes from 100 mL up to 3 litres have been reported in the literature [3] and similar results are observed in clinical practice as reported recently in a large multicentre study about the FC technique with a median volume of 500 mL (500 – 999 mL)[4].

The mean systemic filling pressure (Pmsf) is a quantitative measure of the intravascular volume. It is the pressure in the cardiovascular system when there is no blood flow, and it is defined by the relationship between intravascular stress volume and mean vascular capacitance. Guyton observed that acute expansion of intravascular volume increases venous return insofar as the increase in volume increases Pmsf [5]. As under steady conditions, venous return equals CO, an effective FC should be able to increase the Pmsf in order to challenge the cardiac response, otherwise, the volume given may have no haemodynamic effect and it would be possible that a number of non-responders might be actually non-challenged.

Cecconi et al[6] reported that a FC of 250 ml increased the Pmsf analogue by 3.1 ± 1.9 mmHg. Recently, a study [7] about the precision of the measurement of the Pmsf-arm reported a least significant change (LSC) of 14 % of baseline value for a single measurement, which is the minimal change that should be observed in order to believe that a real change occurs beyond the limits of precision. We hypothesise that the volume of fluids may affect not only the change in Pmsf but also the change in CO and the proportion of responders to a FC. Thus, the objectives of the present study are, first, to determine what is the minimal volume of intravenous fluids required to increase the Pmsf-arm by the LSC to perform an effective FC and, second, to determine how different doses of fluids in a FC affect the changes in CO and the proportion of responders.

Methods

This study was approved by the Camden & Islington Research Ethic Committee (13/LO/1307, December 2013). Written informed consent was obtained from all patients.

Study design

This is a quasi-randomised [8,9], single–blinded, controlled study with an allocation ratio of 1:1. The different arms consisted of doses of 1, 2, 3 and 4 ml/kg (actual body weight) of Compound Sodium Lactate (Hartmann's Solution, Baxter, Thetford, UK) as a FC infused over 5 minutes manually using a syringe of 60 mL and a timer in the multi-parameter monitor. Patients were approached when admitted to hospital before cardiac surgery. The first 20 patients were allocated to receive 1mL/kg (total body weight), the following 20 to 2 mL/Kg and so on. Pmsf-arm, mean arterial pressure (MAP), CO, SV, heart rate (HR) and CVP were recorded at baseline and after the FC. After the second measurement, the dose of fluids was completed according to the clinical prescription. Clinical indication for a FC was according to the standard clinical post-operative protocol [10] (Supplemental Digital Content (SDC) Figure 1).

Participants

Patients admitted to cardiothoracic intensive care unit (ICU) following cardiac surgery were prospectively enrolled. Patients with occlusive peripheral vascular disease, post-operative valve regurgitation, presence of an intra-aortic balloon pump, pregnancy, body weight below 50 kg, absence of radial arterial catheter, evidence or strong suspicious of active bleeding or sepsis and patients requiring fluid resuscitation or changes in vasoactive therapy were excluded from the study. All patients were studied during the initial period in the ICU, once they achieved a hemodynamic and respiratory steady state, defined by changes no greater than 10 % in heart rate, respiratory rate, CO, stroke volume, arterial pressure and arterial saturation of oxygen for at least ten minutes.

Measurements

Invasive arterial pressure and CVP were used for the study. Pressure transducers were referenced to the intersection of fifth intercostal space and anterior axillar line and connected to the multi-parameter monitor (IntelliVue MX800, Philips Healthcare, Best, Netherlands) with patients lying fully supine in bed. Pmsf-arm was measured using the transient stop-flow arterial venous equilibrium method [11] by stopping the blood flow in the arm using a pneumatic tourniquet (AT4 pneumatic tourniquet, AneticAid, Leeds, UK) to pressures 50-60

mmHg above systolic pressure and held for 60 seconds. Pmsf-arm is defined as the arterial pressure at 60 seconds of cuff-inflation [7]. CO was monitored with a non-calibrated LiDCO*plus* monitor (version 4.02.92) or with a pulmonary artery catheter (Edwards Lifesciences, Irvine, USA). Responders are defined as an increase in CO equal or greater than 10% from baseline.

Statistical analysis

Sample size calculation is described in detail in the SDC. Descriptive statistics and graphics were used to understand the data structure and the variables nature. Continuous variables are summarized by their means, medians, standard deviations and/or inter-quartiles. Categorical or binary variables are summarized in terms of proportions stratified by patients' groups.

Differences between dose groups

The analyses consist of a series of regression models for differences in changes of haemodynamics (i.e. ΔPmsf-arm) on dose of fluids (1, 2, 3, and 4 ml/kg), CO response groups (responders and non-responders) and adjusted for the haemodynamic of interest at baseline (i.e. Pmsf-arm baseline). The predicted means of the changes in each group adjusted for the mean values of the corresponding baseline are reported after fitting the most parsimonious model. Proportions are compared with a chi-square test.

Determination of minimal volume

To determine the minimal volume required to increase Pmsf-arm by 14%, step-wise multiple linear regression was used with change of Pmsf-arm as dependent variable. The set of independent predictors explored included Pmsf-arm baseline, volume (mL), weight (Kg), concomitant use of vasodilators (Morphine, Alfentanil, Milrinone and/or Nitroglycerin), Diabetes Mellitus status, use of extracorporeal circulation (pump) intra-operatively, concomitant use of vasoconstrictors (Dopamine, Noradrenaline, Adrenaline), baseline arterial pressure (MAP) and temperature. To estimate the minimal volume, the model was run to predict the values of ΔPmsf-arm for all the baseline values, and we choose the volume values (mL) for which the outcome would achieve a 14 % increase in the lower bound of the 95% CI. The presence of missing values have been assessed (cardiac echocardiographic parameters) and the data have been analysed using multiple imputation techniques under missing at random assumption [12]. Fluid responsiveness was also considered as a binary outcome (responders vs non-responder). A logistic regression was employed to estimate the odds ratio (OR) of responders vs. non-responders by dose of crystalloids infused. Hosmer Lemeshow statistic tested the goodness

of fit of the model. *P*-values of less than 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS for Macintosh software (IBM, version 21.0.0) and STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

119 patients were screened between September 2014 and January 2015. Out of those, 39 did not satisfy the eligibility criteria (SDC – Figure 2). Baseline demographic and clinical characteristics of participants by group are presented in the SDC – Table 1. Except for heart rate, there were not significant differences between groups at baseline.

33 patients (41.3 %) were responders to the FC. The proportion of responders is significantly different across the four groups (χ^2 (3) 8.82, $p = 0.038$; Figure 1). This difference is attributable to responders of group 1 (20%) and group 4 (65%). Proportions of responders between groups 1, 2 and 3 mL/kg were not significantly different.

Descriptive statistics of changes in haemodynamics by dose of crystalloids and CO response are presented in Table 1 and estimated differences by dose of crystalloids and CO response adjusted by baseline values are reported in Table 2. Predicted changes of haemodynamics adjusted by baseline values are presented in SDC – Table 2. ΔPmsf-arm was significantly greater with 2, 3 and 4 ml/kg compared to 1 mL/kg ($p = 0.007$, 0.01 and < 0.001 respectively, Figure 2). The changes on other haemodynamic parameter are explained in detail in the SDC.

The regression model of ΔPmsf-arm (%) revealed as significant predictors Pmsf-arm at baseline and the absolute volume (mL) infused. There is not enough evidence to support a strong effect of the concomitant use of vasodilators on ΔPmsf-arm (%), however, it was considered clinically relevant and was maintained into the model (Table 3). Weight was neither a significant predictor (B -0.01 (95% CI -0.19, 0.16), p =0.88) nor the interaction with volume (mL) ($p = 0.42$). An increase of 1 mL of crystalloids increases the ΔPmsf-arm by 0.05% holding the Pmsf-arm at baseline and the use of vasodilators constant. The estimated volume required to achieve a change in Pmsf-arm of at least 14% in the lower limit of the 95% confidence interval, adjusted by the Pmsf-arm at baseline is between 321 to 393 mL without vasodilators and between 446 to 509 mL in those patients where vasodilators were being used (SDC – Table 3).

There is only some marginal evidence ($p = 0.07$) to support some differences between patients with severe diastolic dysfunction and those with normal diastolic function of left ventricle (SDC – Table 4).

In the logistic regression model, only the dose of 4 mL/Kg was significantly associated with the probability of a positive response to the FC compared to 1 mL/Kg. (O.R. 7.43, 95% C.I. 1.78 to 31.04; SDC – Table 5).

Discussion

The findings of this study demonstrate the importance of the volume used for a FC on the effectiveness of this cardiovascular test. Small volumes seem to be less likely to increase the Pmsf-arm and this affects the ability to identify responders in terms of CO: up to 45% of responders may possibly be misclassified as non-responders. The change in CO is strongly affected by the dose used and very little affected by the systolic or diastolic function at baseline. The Pmsf-arm at baseline and the volume infused are the major determinants of the change in Pmsf: volumes between 320 to 510 mL, which are fairly equivalent to 4 mL/Kg, seem to be sufficient for an effective FC. When an effective FC is performed, MAP increases along with the CO, and CVP increases in both responders and non-responders.

The effect of blood volume on Pmsf was already demonstrated by Guyton's experiments [5]. The ΔPmsf depends on the change of stressed volume and the capacitance of the vascular system [13], which in turns depends on several factors such as the sympathetic tone, hypercapnea, hypoxia and aortic and cardiopulmonary chemoreceptors [14]. The Pmsf values reported in this study are similar to previous studies in similar populations [6,7,11], and the baseline values are very similar in the four groups, which reassure that the haemodynamic effect of the intravascular volume was fairly similar on the four groups. Noradrenaline can increase Pmsf and reduce vascular capacitance [15,16] but in our study the infusion of vasoconstrictors did not show a significant effect on ΔPmsf-arm. Conversely, the infusion of vasodilators, although not reaching statistical significance, has a clinical impact on the dose required for a fluid challenge, which is explain by the increase in unstressed volume. The volume infused and the Pmsf-arm at baseline explains only 28% of the total variability of the change in Pmsf-arm, which point out the complexity of the regulation of the vascular capacitance: in 24.7% of cases the Pmsf-arm did not change (only in the group of 1 mL/Kg) after the FC. Capacitance vessels tone, interstitial pressure and trans-capillary fluid flow are some of the relevant factors that could possibly explain the great variability associated to the change of Pmsf.

Pmsf at baseline is a significant predictor, inversely related to the change of Pmsf-arm: for one mmHg of increase of Pmsf-arm at baseline, the ΔPmsf-arm will decrease by 0.35 mmHg. This may suggest that there is a physiological upper limit for Pmsf regardless the volume given, so that part of the volume is redistributed between stressed and non-stressed compartments or distributed between the intravascular and extravascular space.

In some cases the CO increases despite an increase of Pmsf below the LSC. This can be explained by the gradient generated between the intravenous pressure and the mechanical force used to infuse the fluids into the venous system. Small volumes infused at a high rate may push enough blood into the right ventricle, emulating an increase in venous return and testing the preload reserve of the right heart. In addition, other factors associated with the cardiac sensitivity to the change in preload must be taken into consideration: our results suggest that severe diastolic dysfunction may reduce this sensitivity, but these results should be taken with caution as this study was not specifically design to answer this question. The results of our analysis of the changes of CO according to the LV or RV function only highlights that fact that the main factor that explain the differences is the dose of crystalloids used.

The changes observed in CVP suggest that this variable cannot be used as a safety limit, as there is no evidence to support the assertion that changes on CVP differ between responders and non-responders. This is in agreement with a recent study that showed that the overall impact of a fluid challenge on the CVP is greater in non-responders, but not the change at any particular time point after the fluid infusion[17]. However, CVP could be possibly used as indicator of effectiveness of the test: it only increases in the group of 4 mL/Kg, where the changes in CO and Pmsf were clear. The increase of CVP in responders can be explained by a physiological increase in right atrial pressure and right ventricle (RV) end-diastolic pressure in response to an increase in venous return that transitory overcomes the RV capacity.

Our results may bring into question the negative predictive value of small volumes to reliably assess fluid responsiveness. Muller et al [18] proposed a mini-FC using an infusion of 100 ml of colloids over 1 minute in patients with acute cardiovascular failure. The response was assessed measuring the variation of sub-aortic variation time index (VTI) using Doppler echocardiography after 100 ml and then after the infusion of 400 mL of colloids over 14 minutes. The authors proposed a dVTI cut-off of 10 %, which had a sensitivity of 95 % and specificity of 78% with a negative predictive value of 93 %. In contrast with our study, Muller et al. chose colloids, which are known to increase CO more than crystalloids [19,20], the VTI may also be more sensitive and less dependent on accuracy of arterial catheters and, much more importantly, Muller and colleagues studied patients with acute circulatory failure where all the normal cardiac reflexes may not work properly. Guinot and colleagues [21] reported a similar study using crystalloids and measuring the change in SV by thoracic impedance cardiography. A dSV of 7% after 100 mL of crystalloids showed a sensitivity of 89 %, specificity of 89 % with a negative predictive value of 93%. Another important difference with our study is the method use to assess fluid responsiveness, as we use continuous CO based on pulse-power analysis. Mallat et al [22] carried out a

similar study in 49 fully sedated patients using the PiCCO device (PiCCO, Pulsion Medical System, Munich) to measure continuous cardiac index (CCI). The area under the receiver operating characteristic curves (AUC) for the dCCI after 100 mL of colloid infusion over 1 minute was 0.78 with a large grey zone that included 67 % of the subjects. For a cut-off value of 5.2% for dCCI after 100 mL, sensitivity was 77% and specificity 74%.

Limitations

There are some limitations in this study that need to be acknowledged. First, there is a different rate of fluid infusion, which probably has an important effect on the changes of haemodynamics. A minimum period of 5 minutes was required between 2 inflations of the tourniquet to measure Pmsf-arm without triggering local ischaemic mediators that can affect the precision of the technique [7]. Thus, to maintain a constant rate, it would have been necessary to administer the FC over 25 minutes or longer (15 mL/min) in the 4 mL/Kg group, which was considered too long for a FC. Second, arm occlusion method is a non-invasive method to measure Pmsf-arm in patients with intact circulation, but its accuracy remains uncertain giving the difficulties to measure the real Pmsf. Pmsf-arm was compared with other minimally invasive methods showing good correlation with other values[11], but none of those methods can be considered as a gold-standard to measure Pmsf, and all of them have limitations and potential pitfalls. In a dog model the Pmsf is between 7 and 12 mmHg while the CVP is between 2-3 mmHg[23]. It is likely that Pmsf in normal humans is similar to dogs. The baseline Pmsf in this study was 23.6 mmHg. This higher Pmsf may partly be explained by the higher CVP as the Pmsf must be higher than the CVP to ensure venous return. Nevertheless, the precision of the Pmsf-arm, which is the relevant concept in this study, was studied and reported in a previous study[7]. Third, we used a non-calibrated LiDCO*plus* monitor, which clearly affects the accuracy of CO measurements. However, this device incorporates two independent systems: the LiDCO™ lithium dilution technique and the PulseCO™ pulse power algorithm, which can reliably track changes of CO [24]. Fourth, we selected a fairly homogeneous sample of post-operative cardiac surgery patients that were in a stable haemodynamic state. This was necessary to obtain good quality data and to avoid further variability in the results as cardiovascular compliance can vary significantly in other sub-populations of critically ill patients. This may bias our sample to a relatively healthy subpopulation of critically ill patients. Therefore, our results may not be extrapolated to other subgroups such as septic or trauma patients, where the unstressed volume might be substantially reduced, and the compliance substantially modified. Those patients may require a greater dose for an effective test. Fifth, patients were allocated to each group using a quasi-randomisation approach, as defined by the Cochrane handbook[9]. This method of allocation increases the risk of

systematic errors related to the environment that may interfere with the measurement process and selection bias. For that reason a comparison of the baseline values and demographic characteristics was conducted, and it demonstrates a reasonable equality between groups. Nevertheless, a strict randomisation would have added further robustness to this study.

Conclusion

The dose of fluids used for a FC can modify the proportions of responders in a cohort of postoperative patients. A dose of 4 ml/Kg increases Pmsf-arm beyond the limits of precision and reliably detects responders and non-responders.

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Figure Legends

Fig 1 Proportion of responders and non-responders by dose of crystalloids used for a fluid challenge. Proportions are compared across different doses of crystalloids with a chi-square statistic.

Fig 2 Predicted mean of changes of Pmsf-arm (%) adjusted by the mean baseline value of Pmsf-arm, by dose of crystalloids used for a fluid challenge. Error bars represent 95% confidence interval. Horizontal line represents the threshold for the least significant change of Pmsf-arm.