Intensive Care Med (2013) 39:1299–1305
DOI 10.1007/s00134-013-2928-6

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Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients

Received: 25 December 2012
Accepted: 4 April 2013
Published online: 8 May 2013

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-013-2928-6) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* The difference between mean systemic filling (Pmsf) and central venous pressure (CVP) is the venous return gradient (dVR). The aim of this study is to assess the significance of the Pmsf analogue (Pmsa) and the dVR during a fluid challenge. *Methods:* We performed a prospective observational study in postsurgical patients. Patients were monitored with a central venous catheter, a LiDCO^{TM}plus and the Navigator^{TM}. A 250-ml intravenous fluid challenge was given over 5 min. A positive response to the fluid challenge was defined as either a stroke volume (SV) or cardiac output increase of greater than 10 %. *Results:* A total of 101 fluid challenges were observed in 39 patients. In 43 events (42.6 %) the SV and CO increased by more than 10 %. Pmsa increased similarly during a fluid challenge in responders and non-responders (3.1 ± 1.9 vs. 3.1 ± 1.8, $p = 0.9$), whereas the dVR increased in responders (1.16 ± 0.8 vs. 0.2 ± 1, $p < 0.001$) as among non-responders CVP increased along with Pmsa (2.9 ± 1.7 vs. 3.1 ± 1.8, $p = 0.15$). Resistance to venous return did not change immediately after a fluid challenge. Heart performance (Eh) decreased significantly among non-responders (0.41 ± 0.15 vs. 0.34 ± 0.13, $p < 0.001$) whereas among responders it did not change when compared with baseline value (0.35 ± 0.15 vs. 0.34 ± 0.12, $p = 0.15$). *Conclusions:* The changes in Pmsa and dVR measured at the bedside during a fluid challenge are consistent with the cardiovascular model described by Guyton.

Keywords Fluid challenge · Goal-directed therapy · Preload · Mean filling pressure · Venous return

Introduction

The gold standard for testing fluid responsiveness is a fluid challenge. The technique consists of infusing a small quantity of fluid in a short period of time, enough to increase the preload and test the response of the ventricle according to the Frank–Starling principle [1]. The infusion of intravenous fluids can re-establish intravascular filling, increase cardiac output and eventually restore tissue perfusion. However, this therapy is not exempt from undesirable effects, particularly in patients with acute lung injury [2, 3], head injury [4] and acute renal failure [5]. Thus, a measurable monitoring of intravascular volume status in critically ill patients would be very valuable for evaluating the causes of cardiovascular instability and targeting the adequate therapy.

The mean systemic filling pressure (Pmsf) is a quantitative measure of intravascular filling. It is defined as the pressure in the whole cardiovascular system when the heart is stopped and there is no fluid motion and it was first described by Bayliss and Starling [6] in a dog model during cardiac arrest. The Pmsf depends basically on two

variables: the "stressed volume", which is the blood that stretches the blood vessels and causes intravascular pressure, and the compliance of the cardiovascular system.

Under steady conditions, the cardiac output (CO) and venous return (VR) are equal, and any parameter that determines VR will therefore also determine CO [7]. Guyton [8] stated that VR is defined by three parameters: the Pmsf, the right atrial pressure (RAP) and the resistance to venous return (RVR). The difference between the Pmsf and RAP or central venous pressure (CVP) is the pressure gradient of venous return (dVR) where the Pmsf is the pressure that promotes the return of blood to the heart. Under steady resistances, the VR is approximately proportional to this dVR [9]. In addition, Guyton noticed that an increase in blood volume increases the Pmsf and also decreases the RVR because of distension of vessels wall [10].

The main problem is that Pmsf is not an easy variable to monitor in patients with an intact circulation. As far as we know, two methods have been proposed to calculate the Pmsf [11, 12]. Recently, a non-invasive, software algorithm based on Guyton's physiology has been developed [13] to estimate a Pmsf analogue (Pmsa) using the mean arterial pressure (MAP), RAP, CO and patient's anthropometric data. In essence, the system (Navigator™, Applied Physiology, Pty Ltd, Sydney, Australia) employs a mathematical algorithm to run a cardiovascular model that uses real measured variables to adjust the model parameters. Afterwards, the model heart is stopped, rather than stopping the patient's heart, and the Pmsa is estimated. In addition, the software calculates the global pumping efficiency of the heart (Eh), defined as

$$\mathrm{Eh} = \mathrm{Pmsa} - \mathrm{CVP}/\mathrm{Pmsa}$$

Therefore, if the heart stops, the CVP will approach Pmsa and Eh approaches zero, and if the CO increases, the CVP will tend to zero and Eh will tend to one.

The aims of the present study are firstly to test the hypothesis that the Pmsa behaves as a quantitative indicator of intravascular volume status during a fluid challenge, secondly to investigate if the gradient of venous return (dVR) obtained with Navigator™ is proportional to CO values in patients with an intact circulation, thirdly to observe if the estimated RVR decreases after a fluid challenge and finally to study the changes of Eh in response to a fluid challenge.

Patients and methods

The institutional review board for research (National Research Ethics Service Committee) considered this study a service evaluation and therefore no written informed consent was required.

Patients

Patients admitted to general or cardiothoracic intensive care unit (ICU) requiring a fluid challenge either as part of the early goal-directed therapy protocol or according to the clinical needs were prospectively enrolled. Patients without a central venous catheter or with previous known aortic regurgitation, tachyarrhythmia, presence of an intra-aortic balloon pump, pregnancy or body weight less than 50 kg were excluded from the study.

Measurements

Patients were treated according to standard clinical protocols and no extra interventions were performed for the purposes of this study. All patients were monitored using a multi-parameter monitor with invasive arterial blood pressure and CVP. Both of them were referenced to the intersection of the anterior axillar line and the 5th intercostal space. Beat-to-beat CO was obtained by pulse contour analysis with LiDCO™plus (LiDCO Ltd, Cambridge, UK). Pulse contour measurements were calibrated with three lithium-dilution CO measurements. This calibration was not repeated after the fluid infusion.

Navigator™ software (Applied Physiology, Sydney, Australia) was connected to the multi-parameter monitor and to the LiDCO™plus. The estimation of Pmsa is based on the equation

$$\mathrm{Pmsa} = a(\mathrm{RAP}) + b(\mathrm{MAP}) + c(\mathrm{CO})$$

where a and b are dimensionless constants ($a + b = 1$); typically $a = 0.96$ and $b = 0.04$. c Has the dimensions of resistance and is a function of the patient's anthropometric measures (height, weight and age).

$$c = \frac{0.038(94.17 + 0.193 \times \mathrm{age})}{4.5(0.99^{\mathrm{age}-15})\ 0.007184\ (\mathrm{height}^{0.725})\ (\mathrm{weight}^{0.425})}$$

RVR was calculated dividing dVR by CO.

The type of fluid depended on the clinical requirements of the patients. In some cases the fluid challenge was performed with blood products such as fresh frozen plasma (FFP) or red blood cells concentrate (RBC).

Haemodynamic values were recorded electronically during the whole study period. The average of the values recorded during the minute before and after the fluid challenge was used for the analysis. The fluid challenge consisted of an infusion of 250 ml of fluid in less than 10 min. According to the unit protocol, an increase in stroke volume and CO immediately after the fluid challenge of more than 10 % was considered as a positive response.

Statistical analysis

The normality of the variables was tested using the Kolmogorov–Smirnov test. All haemodynamic variables were analysed as continuous variables and expressed as mean ± SD when normally distributed or as median [IQR]. The comparison of means was performed using Student's *t* test. A linear regression analysis was used to evaluate the relationship between CO and dVR. Correlation coefficient (R^2) and slope (b1) were obtained. To assess the ability of the value of Pmsa, Eh and dVR before the fluid challenge to distinguish between positive and negative responses, we first compared the values of each variable between responders and non-responders. Receiver-operating characteristics (ROC) curves were then generated by varying the discriminating threshold of each variable. Statistical analysis was performed using SPSS software (IBM SPSS Statistics 19) and GraphPad Prism 5.0. For all comparisons, a p value of less than 0.05 was considered significant.

Results

A total of 101 fluid challenges were performed in 39 patients. Demographic data are summarised in Table 1. Most of the patients received between one and two fluid challenges (Electronic Supplementary Material, Table 1). In no case was the dose of vasopressor changed during the fluid challenge.

The mean volume infused during the fluid challenge was 252 ± 8.9 ml and the duration of the fluid challenge was 3.9 ± 2.7 min. The type of fluid used was Hartmann's solution in 52.5 %, Volplex® in 37.6 %, FFP in 5 %, RBC in 3.8 % and normal saline in 1.3 % of the cases. In 43 of 101 (42.6 %) events the fluid challenge resulted in an increase in SV and CO equal to or greater than 10 % (responders). Table 2 summarizes the values of haemodynamic variables in both groups at baseline and after a fluid challenge. The CO, MAP and dVR were significantly lower in responders at baseline.

Table 1 Main characteristics of the patients at inclusion

Demographics	Mean ± SD
Age (years)	68.3 ± 12
Females (*n*)	13 (33 %)
Height (m)	1.67 ± 0.1
Weight (kg)	74.3 ± 19.2
BSA (m^2)	1.8 ± 0.3
ICNARC score	19.2 ± 9.5
Main diagnosis	*n* (%)
CABG	10 (25)
Valve replacement/repair	10 (25)
Cardiogenic shock	5 (12.8)
Abdominal surgery	4 (10.2)
CABG and valve replacement	2 (5.1)
Orthopaedic surgery	2 (5.1)
Distributive shock	3 (7.6)
Other	3 (7.6)
Vasoactive therapy	*n* (%)
Noradrenaline	2 (6.3)
Dopamine	5 (15.7)
Milrinone	4 (12.5)
Respiratory support	*n* (%)
SIMV-PC	20 (51)
SV	10 (26)
PCV	5 (13)
PSV	3 (8)
CPAP	1 (3)

BSA body surface area, *ICNARC* intensive care national audit & research centre, *CABG* coronary artery by-pass graft, *SIMV-PC* synchronised intermittent mandatory ventilation with pressure control, *SV* stroke volume, *PCV* pressure control ventilation, *PSV* pressure support ventilation, *CPAP* continuous positive airway pressure

Pmsa

The Pmsa at baseline before each fluid challenge was similar in both groups with mean value around 18 mmHg. A fluid challenge increased Pmsa similarly in responders and non-responders ($p = 0.9$). Figure 1 shows the Pmsa changes in response to a fluid challenge in those patients that received one and two fluid challenges. Figure 1 in the Electronic Supplementary Material shows the evolution of Pmsa in a patient after cardiac surgery, during an episode of haemorrhagic shock and following a surgical review in theatre over a period of 5 h.

dVR

After a fluid challenge, dVR increased significantly in responders from 5.7 ± 1.1 to 6.9 ± 1.2 ($p < 0.001$), whereas among non-responders there was no significant change (6.7 ± 1.5 to 6.9 ± 1.8, $p = 0.15$, Fig. 2). Observing the components of dVR (Pmsa-CVP), the CVP increased in both groups although significantly more in non-responders ($p = 0.008$). No difference was found between the increment of CVP (ΔCVP) and the increment of Pmsa (ΔPmsa) among non-responders (2.9 ± 1.7 vs. 3.1 ± 1.8, $p = 0.15$), whereas among responders these two values were significantly different (2 ± 1.9 vs. 3.1 ± 1.9, $p < 0.001$; Table 2).

CO and dVR correlated at baseline (constant −0.6, b1 0.8, R^2 0.575, $p < 0.001$; Fig. 3). Correlation between changes in CO (ΔCO) and changes in dVR [Δ(dVR)] showed a constant 0.2, b1 0.2, R^2 0.236 ($p < 0.001$).

RVR

There were no differences in RVR at baseline between responders and non-responders, nor after a fluid challenge in both groups (Table 2).

Table 2 Comparison of the effect of a fluid challenge on haemodynamic parameters among responders and non-responders

	Responders ($n = 43$)				Non-Responders ($n = 58$)			
	Pre-infusion	Post-infusion	Δ	p	Pre-infusion	Post-infusion	Δ	p
HR, bpm	88.8 ± 10.3	88.5 ± 10.3	0.2	0.5	88.3 ± 15.5	87.9 ± 14.7	0.4	0.3
MAP, mmHg	66 ± 7.3*	77.1 ± 9.8	11.1 ± 6.5*	<0.001	72.8 ± 12.7	76.6 ± 14.4	3.8 ± 4.8	<0.001
CO, L min^{-1}	3.8 ± 1.1*	4.4 ± 1.3	0.7 ± 0.3*	<0.001	4.9 ± 1.6	5 ± 1.7	0.1 ± 0.3	0.003
CVP, mmHg	12.1 ± 5.7	14.1 ± 5.5	2 ± 1.9*	<0.001	11.1 ± 5.3	14.1 ± 5.4	2.9 ± 1.7	<0.001
Pmsa, mmHg	17.8 ± 5.1	20.9 ± 5.1	3.1 ± 1.9	<0.001	17.9 ± 4.9	21 ± 4.9	3.1 ± 1.8	<0.001
dVR, mmHg	5.7 ± 1.1*	6.9 ± 1.2	1.16 ± 0.8*	<0.001	6.7 ± 1.5	6.9 ± 1.8	0.2 ± 1	0.15
Eh	0.35 ± 0.15	0.34 ± 0.12	−0.01 ± 0.04*	0.15	0.41 ± 0.15	0.34 ± 0.13	−0.06 ± 0.05	<0.001
RVR	1.5 ± 0.3	1.6 ± 0.3	0.0 ± 0.2	0.4	1.4 ± 0.3	1.4 ± 0.3	0.0 ± 0.2	0.9

Values are mean ± SD

CO cardiac output, *HR* heart rate, *MAP* mean arterial pressure, *Pmsa* mean systemic pressure analogue, *CVP* central venous pressure, *dVR* pressure gradient of venous return, *Eh* heart efficiency, *RVR* resistance to venous return

* $p < 0.05$ when compared with non-responders

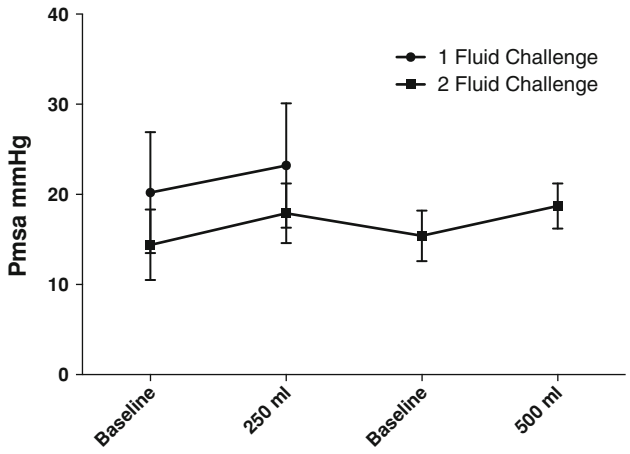

Fig. 1 Values of mean filling pressure analogue (*Pmsa*) in patients that received 1 and 2 fluid challenges. GraphPad Prism software 5.0

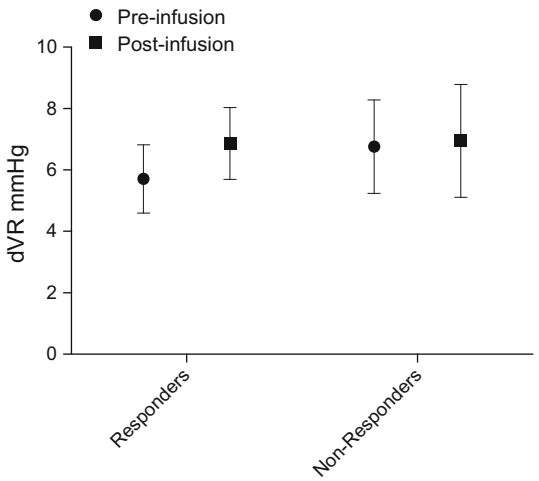

Fig. 2 Variation of pressure gradient of venous return (*dVR*) before (*pre-infusion*) and after (*post-infusion*) a fluid challenge in responders and non-responders. Significant increase of dVR in reponders. GraphPad Prism software 5.0

Eh

Eh decreased significantly among non-responders whereas among responders it did not change when compared with baseline value ($p = 0.15$).

Fluid responsiveness

Table 3 and Fig. 2 of the Electronic Supplementary Material summarise the ROC curve analysis for the prediction of fluid responsiveness at the baseline. A value of dVR pre-infusion greater than or equal to 6.1 discriminates a non-responder with a sensitivity 69 % and specificity of 69.8 % (positive predictive value (PPV) 75.5 %, negative predictive value (NPV) 62.5 %).

Discussion

This study confirms that the computerised approach to the circulation using the Guytonian physiology provided by Navigator™ allows us to better understand the changes generated by a fluid challenge in the arterial and venous side of the circulation. In summary we have found several important points confirming the Guytonian model of the circulation at the bedside. Changes in the gradient of VR are associated with changes in CO after a fluid challenge. Changes in the Pmsa reflect the changes in circulating blood volume, being a good indicator of changes in volume status. The RVR does not change immediately after a fluid challenge. The Eh decreases in non-responders. Changes in CVP reflect the changes in the Pmsa in the majority of non-responders.

Pmsa

Changes of the Pmsa behave as a good indicator of the changes in circulating blood volume, increasing in both groups similarly in response to fluid infusion. This finding

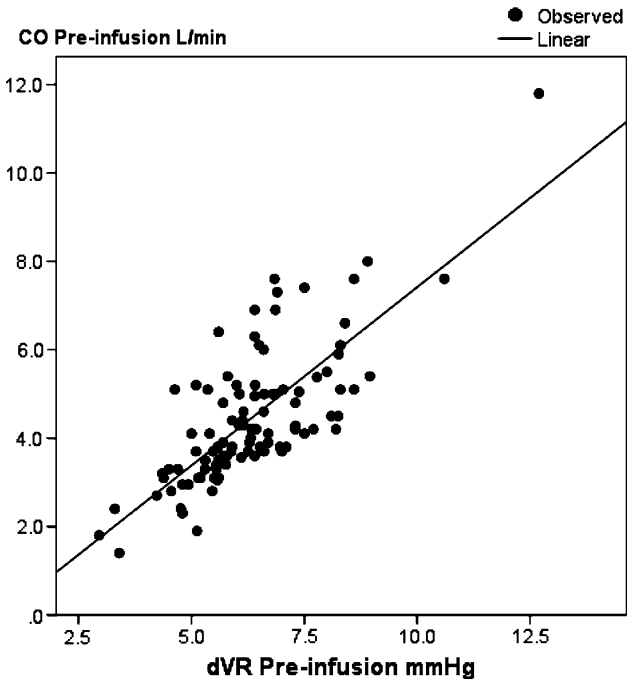

Fig. 3 Correlation between cardiac output (*CO*) and pressure gradient of venous return (*dVR*) at baseline (constant −0.6, B1 0.8, R^2 0.575, $p < 0.001$). IBM SPSS 19

is in agreement with the data published by Parkin et al. [14] in patients on continuous haemofiltration, and recently by Maas and colleagues [15] in an study comparing the equilibrium pressure in the arm during stop-flow (Parm), the inspiratory-hold manoeuvre-derived Pmsf and the Pmsa in patients after cardiac surgery. Although the value of Pmsa underestimates the Pmsf, the Pmsa has proved to be a trustable method to follow the changes in the effective circulating blood volume, compared to the other methods for measuring the Pmsf.

dVR

Changes in dVR estimated by Navigator™ behave as it was described by Guyton [8] in response to a blood transfusion (fluid challenge) in a dog model. During the ascending part of the Frank–Starling curve, the heart is able to regulate the CVP by increasing the end-diastolic volume. Once this part of the curve is exceeded, the heart is no longer able to compensate for increments in Pmsa, allowing the CVP to increase and preventing any further increment in the gradient of venous return (dVR). In other words, in non-responders the CVP increases along with Pmsa. Guyton [9] already pointed out that the RAP (CVP as its surrogate) acts as a reverse force to retard VR. Similarly, some authors [16–18] have suggested that CVP could be considered as an indicator of cardiac performance in response to an increment of preload and others have proposed monitoring the changes in CVP to limit the infusion of fluids during a fluid challenge [19, 20] which might have important practical implications in clinical settings where CO monitoring is not easily available. In responders, CVP can increase, remain static or even decrease after a fluid challenge as a consequence of the compensatory effects on the venous circulation or concomitant vasodilatation.

Interestingly, we have found no difference in RVR after a fluid challenge. There are several explanations for this observation. First, the volume in Guyton's experiments is proportionally greater than in our study. Guyton [10] transfused 200 ml in dogs with a mean weight of 14.25 kg. This volume would be equivalent to almost 1 L in an adult of 70 kg. Second, we observe the effect of the fluid challenge immediately after the end of the infusion. As the increase of resistance is theoretically related to the distension of the vessels, possibly we need to observe the effect of the volume longer to detect the change of resistance.

Table 3 Receiver-operating characteristic curve analysis for the haemodynamic parameters at baseline of a fluid challenge

Variable	AUC	*p*	95 % CI
Pmsa	0.5	0.9	0.38–0.62
Eh	0.6	0.1	0.48–0.71
dVR	0.7	0.001	0.6–0.8

AUC area under the curve, *CI* confidence interval, *Pmsa* mean filling pressure analogue, *Eh* heart efficiency, *MAP* mean arterial pressure, *CO* cardiac output, *dVR* pressure gradient of venous return

Eh

The change of Eh (ΔEh) indicates in which part of the Frank–Starling curve we are. A decrease in Eh after a fluid challenge (250 ml in <10 min) reveals that the heart is approaching the flat part of the Frank–Starling curve, and thereby CVP starts to increase. In non-responders, Eh decreases because dVR remains invariable despite the increase in Pmsa. On the other hand, the lack of change in Eh after a fluid challenge means that the heart is able to increase the end diastolic volume to avoid almost any change in CVP. A minimal decrease in responders can be observed, as the dVR can increase after a fluid challenge, despite an increase of CVP. Actually, 83 % of fluid challenge with a decrease of −0.01 or an increase in Eh corresponds to responders. However, this decrease in Eh suggests that in spite of the SV response (>10 %), we are moving near the flat part of the Frank–Starling curve.

Prediction of fluid responsiveness

None of the parameters studied (Pmsa, Eh or dVR) exhibited a good predictable relationship to fluid

responsiveness. As pointed out in previous studies [21, 22], even the most perfect measure of cardiac preload will never be a reliable predictor of volume responsiveness given that the slope of the Frank–Starling curve depends on ventricular function, so that a given value of preload can be associated with the steep part of the curve and fluid responsiveness (in normal heart) or with the flat part of the curve and absence of preload reserve (in failing heart).

Limitations

Pmsa is a value estimated on the basis of three real measures: CVP, MAP and CO. Any alteration in the measure of these variables has an impact on the value of Pmsa, in particular the CVP. As it has been noted by other authors [23], an accurate measure of the CVP is not always so simple, and can be easily altered by the wrong position of the transducer in relation to the midpoint of the right atrium.

Secondly, another possible limitation is the population of our study. It is a mixed surgical population with patients from orthopaedic, general and cardiac surgery. It is possible that focusing only on one type of patients the haemodynamic variables obtained with Navigator™ may be different. Further studies are needed to elucidate whether the changes observed in these variables (dVR, dPmsa, dCVP) repeat the same pattern in other populations, such as septic patients.

Finally, almost all the fluid challenges were performed with 250 ml of fluid within 5–10 min. This is the standard technique used in our unit and could limit the applicability of some of our findings somewhere else. In addition, we have observed several types of fluids, including colloids, crystalloids and blood products. We cannot exclude that the type of fluid given might affect some of our findings.

In summary, the changes in Pmsa and dVR observed with Navigator™ during a fluid challenge are consistent with the physiology described by Guyton.

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