Intensive Care Med
DOI 10.1007/s00134-014-3637-5

EDITORIAL

Xavier Monnet
Michael R. Pinsky

Predicting the determinants of volume responsiveness

Received: 24 December 2014
Accepted: 26 December 2014

© Springer-Verlag Berlin Heidelberg and ESICM 2015

X. Monnet
Medical Intensive Care Unit, EA4533, Service de réanimation médicale, Paris-Sud University Hospitals, Paris-Sud University, 78 rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France

M. R. Pinsky (✉)
Department of Critical Care Medicine, University of Pittsburgh, 606 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 1526, USA
e-mail: pinskymr@upmc.edu
Tel.: 412-647-7766

Resuscitation from circulatory shock and stabilization of patients following major surgery are important and common problems faced by practicing acute care physicians. In mechanically ventilated patients without significant arrhythmias a pulse pressure variation (PPV) or stroke volume variation (SVV) greater than 15 % is highly predictive of volume responsiveness, defined as greater than 15 % increase in cardiac output (CO) in response to a fluid bolus of 250–500 ml [1, 2]. Similarly, measures of inferior or superior vena caval diameter change during ventilation and the step increase in arterial pressure or CO during transient end-expiratory hold all are also good predictors [3]. Finally, the dynamic change in CO in response to a passive leg raising maneuver is an excellent predictor under most commonly seen clinical scenarios [4]. Although one can easily predict volume responsiveness at the bedside using these and other functional hemodynamic monitoring approaches, none of these parameters explain why a patient is or is not volume responsive.

Cardiovascular state is characterized by performance parameters that encompass cardiac contractility, circulating blood volume, and vascular tone. These, in turn, as originally described by Guyton [5], can be assessed functionally as the effective circulating blood volume, resistance to venous return, and cardiac performance curve. Effective circulating blood volume, which itself is a function of total blood volume, blood flow distribution, and peripheral vasomotor tone, can be approximated as mean systemic pressure (Pms), the upstream pressure driving blood back to the heart from the circulation. That flow, also known as venous return, determines cardiac output, since in steady state conditions the heart must pump all the blood it receives back out and cannot pump any more than it receives. The downstream pressure for venous return is right atrial pressure (Pra). Thus, cardiac output is determined by both this pressure gradient and the resistance to venous return. Maas et al. [6] and Persichini et al. [7] examined at the bedside the effects of changes in norepinephrine infusion rates on cardiovascular state. Both groups showed that both Pms and Pra, their pressure difference (dVR), and the slope of the (Pms − Pra)/CO were altered. Decreasing vasomotor tone not only decreased Pms and dVR but decreased the resistance to venous return, minimizing the expected decline in venous return that would have otherwise occurred if only Pms had decreased. Similarly, increasing vasomotor tone not only increased Pms but also increased the resistance to venous return, minimizing any increase in flow expected by such increased dVR. Importantly, in the Maas et al. study, the ultimate increase or decrease in CO observed in response to the increase in vasomotor tone was the baseline cardiac performance. Thus non-volume-responsive patients decreased their CO, presumably because the increase in arterial pressure-induced left ventricular afterload was a more important determinant of CO than was the increase in Pms. Importantly, in their study, dVR did not increase in the non-responders and

Published online: 27 January 2015

presumably cardiac performance deteriorated in the face of increasing afterload. Thus, the final cardiovascular state created in response to either fluid loading or changes in vasomotor tone is a complex relationship between changes in effective circulating blood volume and cardiac performance.

The classical method for estimating Pms and the resistance to venous return is to measure arterial blood pressure during cardiac arrest. Maas et al. and Persichini et al. used different methods, both based on an estimation of the venous return curve from a beat-to-beat measure of Pra and stroke volume during inspiratory and expiratory holds under positive pressure ventilation [6, 7]. Nevertheless, these later methods are not easy to use in routine practice. If one could assess both effective circulating blood volume and cardiac performance continuously at the bedside then it would be relatively easy to predict a patient's response to specific cardiovascular interventions. Importantly, Parkin and Leaning used a mathematical modeling technique to develop an algorithm for estimating an analogous value of Pms from commonly measured hemodynamic variables without stopping the heart. With this technique, one can accurately and continuously measure Pms, as an analogue construct, referred to as Pmsa [8]. By knowing both Pmsa and Pra, one can define cardiac performance (heart efficiency, Eh) as the ratio dVR/Pms, with a perfect heart having an Eh of 1. Mass et al. [9] reported a poor agreement between Pmsa and Pms but showed that changes in Pmsa could reflect changes in Pms measured by an independent technique. Then Lee et al. [10] subsequently validated, in an animal model, that this dynamic estimate of Pmsa was accurate under conditions of changing intravascular volume and endotoxin-induced changes in vasomotor tone. Finally, using the same algorithm, Cecconi et al. [11] showed that changes in dVR explained the changes in CO seen in postoperative patients in response to fluid bolus challenges.

So can we put these concepts together into a single analysis? The study by Gupta et al. [12] in a recent issue of *Intensive Care Medicine* attempts to do just that. Using the Parkin and Leaning Pmsa and Eh calculations, they described the CO changes of 61 cardiac postsurgical patients in response to 107 fluid boluses. They showed that patients with volume responsiveness, defined by an increase in CO of at least 10 %, were characterized by higher Eh than non-responders. The authors confirmed the results of Cecconi et al. [11] by showing that the increase in CO during volume expansion was accompanied by an increase in dVR that could be evidenced by the mathematical modeling algorithm. Note that this is not surprising since, with this algorithm, Pmsa is computed from CO itself. Furthermore, when traditional measures of cardiac performance, like cardiac power (CPvol), defined as the product of stroke volume and developed pressure divided by Pmsa [13], was also measured, lower CPvol, describing an under-filled heart, predicted volume responsiveness. Nevertheless and again, this result is marred by the fact that CPvol was estimated from CO. Since CO was lower in responders than in non-responders before fluid bolus, the fact that it was also the case for CPvol is not surprising. Thus, the findings of Gupta et al. should be compared with a technique estimating Pms by a method independent of CO measurement. Nevertheless, this new study supports the findings of Mass et al. [6] and is consistent with those of Persichini et al. [7] and Cecconi et al. [11].

So where do we go from here? Is it enough to show that bedside assessments of cardiovascular state can be made, should we incorporate these assessments into routine bedside care, or incorporate such "advanced" analytics only in those difficult to diagnose or manage patients who do not respond as predicted? There really is no right answer. The main interest of assessing venous return in critically ill patients, as illustrated in the study by Gupta et al. [12], is to provide us with a comprehensive understanding of the individual patient's pathophysiology during circulatory failure and its response to treatments. Although knowing that patient responses follow measurable physiological parameters in a predictable fashion may be comforting to the novice clinician and useful to illustrate patient responses during bedside teaching, will it affect patient outcome? If the results of the two recent early goal-directed therapy in sepsis trials are any indication, probably not. Presently, the usefulness of these measures could reside in the province of the difficult to manage patient whose responses behave in an unpredictable fashion or in whom the cardiac and peripheral vascular components of their instability remain unclear but opposite treatments need to be given if the diagnosis is either one or the other. Still, considering the relative ease in continuous bedside measures of Pmsa, Eh, and CPvol, it would be interesting for critical care professionals to be cognizant of the techniques that allow their calculation and how they change in response to disease progression and treatment. The way in which it could modify a patient's evaluation and management is to be defined.

Acknowledgments This work was supported in part by NIH grant HL67181.

Conflicts of interest XM is a member of the Medical Advisory Board of Pulsion Medical Systems. MRP is a member of the Medical Advisory Board of LiDCO Ltd, Masimo Inc, received honoraria for lectures from Masimo Inc, and an institutional grant from Edwards LifeSciences.

References

1. Pinsky MR (2014) Functional haemodynamic monitoring. Curr Opin Crit Care 20:288–293
2. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37:2642–2647
3. Monnet X, Teboul JL (2013) Assessment of volume responsiveness during mechanical ventilation: recent advances. Crit Care 17:217
4. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL (2006) Response to leg raising predicts fluid responsiveness in critically ill. Crit Care Med 34(1402–1407):4
5. Guyton AC (1955) Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 35:123–129
6. Maas JJ, Pinsky MR, de Wilde RB, de Jonge E, Jansen JR (2013) Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves. Crit Care Med 41:143–150
7. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, Monnet X (2012) Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med 40:3146–3153
8. Parkin WG, Leaning MS (2008) Therapeutic control of the circulation. J Clin Monit Comput 22:391–400
9. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR (2012) Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. Intensive Care Med 38:1452–1460
10. Lee JM, Ogundele O, Pike F, Pinsky MR (2013) Effect of acute endotoxemia on analog estimates of mean systemic pressure. J Crit Care 28:880.e9–e15
11. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Grounds RM, Rhodes A (2013) Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med 39:1299–1305
12. Gupta K, Sondergaard S, Parkin G, Leaning M, Aneman A (2015) Applying mean systemic filling pressure to assess the response to fluid boluses in cardiac post-surgical patients. Intensive Care Med. doi: 10.1007/s00134-014-3611-2
13. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, LeJemtel TH, Cotter G, Investigators S (2004) Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 44:340–348

Intensive Care Med
DOI 10.1007/s00134-014-3611-2

ORIGINAL

Kapil Gupta
Soren Sondergaard
Geoffrey Parkin
Mark Leaning
Anders Aneman

Applying mean systemic filling pressure to assess the response to fluid boluses in cardiac post-surgical patients

Received: 18 August 2014
Accepted: 10 December 2014

© Springer-Verlag Berlin Heidelberg and ESICM 2014

Take home message: Cardiac power scaled to the mean systemic filling pressure and dynamic assessments of the venous return pressure gradient relative to the change in mean systemic filling pressure provided quantitative assessments of the efficiency of volume expansion to increase cardiac output.

K. Gupta · A. Aneman (✉)
Intensive Care Unit, Liverpool Hospital, South West Sydney Clinical School, UNSW, Sydney, Australia
e-mail: anders.aneman@swsahs.nsw.gov.au
Tel.: +61 2 8738 3400

S. Sondergaard
Department of Anaesthesiology and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden

G. Parkin
Intensive Care Unit, Monash Medical Centre, Clayton, Australia

M. Leaning
CHIME, University College London, London, UK

Present Address:
K. Gupta
Department of Anaesthesia, Safdarjung Hospital, New Delhi, India

Abstract *Purpose:* To evaluate an analogue of mean systemic filling pressure (P_{msa}) and derived variables to quantitatively assess the effectiveness of volume expansion in increasing cardiac output.
Methods: Sixty-one cardiac post-surgical patients were studied and 107 fluid boluses were captured. Cardiac output, mean arterial pressure and right atrial pressure were recorded with P_{msa} before and after a bolus fluid. An increase in cardiac output greater than 10 % following a fluid bolus defined a patient as a responder. Cardiac power (i.e. the product of arterial pressure and cardiac output) and P_{msa} to right atrial pressure gradient (i.e. the driving pressure for venous return and hence cardiac output) were evaluated to assess the efficiency of volume expansion to increase cardiac output. Cardiac power relative to P_{msa} (CP_{vol}), its dynamic changes and the dynamic changes in P_{msa}–right atrial pressure gradient relative to the P_{msa} change (E_{vol}) were investigated.
Results: CP_{vol} was lower and E_{vol} was higher in responders vs. non-responders. Furthermore, in patients receiving a second fluid bolus, E_{vol} correlated with the degree of increase in cardiac output. Multivariate regression analysis identified both CP_{vol} and E_{vol} as independent variables associated with volume responsiveness.
Conclusions: Using an algorithm to derive a mean systemic filling pressure analogue, cardiac power and dynamic measures of the venous return pressure gradient relative to the mean systemic filling pressure provided an assessment of the efficiency of volume expansion in post-surgical cardiac patients.

Keywords Cardiovascular system · Methods · Hemodynamics · Cardiac output · Blood volume

Introduction

While intravascular fluid loading is common in treating haemodynamic insufficiency, there is a paucity of evidence-based, scalar measures based on cardiovascular variables and determinants to assess such therapy. The conventional way of assessing volume responsiveness is by the infusion of a fluid bolus or by a passive leg-raising manoeuvre [1]. An increase in cardiac output (CO) by 10–15 % has been used to define patients as responders or

non-responders. The response to volume is, however, more complex and should be described on the basis of efficiency of the administered volume to increase the power of the heart. Thus both mean arterial pressure (MAP) and CO, encompassing vascular tone and contractility, and any potential expense of increased right atrial pressure (P_{ra}), should be included.

The commonly applied evaluation of pulse pressure or stroke volume variation during positive pressure ventilation [2] provides information on the volume state as it is influenced by changes in intrathoracic pressure. While simple (i.e. giving the dichotomous result volume responsive vs. non-responsive) and hence in wide use, not all cardiovascular determinants as described above are considered. The validity criteria for cardiorespiratory interactions may furthermore not always be met in the intensive care unit [3]. Additional methods to gain continuous quantitation of the volume state irrespective of heart rhythm and respiratory pattern would be expedient to guide the optimisation of cardiac output.

The mean systemic filling pressure (P_{ms}) is the physiologically precise variable to gauge the systemic volume state. The difference between P_{ms} and right atrial pressure (P_{ra}) determines the pressure gradient for the venous return (VR) and hence, together with the resistance to venous return (RVR), the CO, i.e.

$$\mathrm{CO} = \mathrm{VR} = (P_{ms} - \mathrm{RAP})/\mathrm{RVR} \quad (1)$$

An analogue of P_{ms} (P_{msa}) can be derived using a mathematical model based on anthropometric variables (age, height, weight) and direct measures of CO, P_{ra} and MAP [4]:

$$P_{msa} = a \times P_{ra} + b \times \mathrm{MAP} + c \times \mathrm{CO} \quad (2)$$

From Eq. (2) it is evident that any increase in the volume state (P_{msa}) may be variably partitioned between P_{ra}, MAP and CO, and assessing volume responsiveness should consequently include all. If the entire rise is in P_{ra} and none in MAP or CO the patient is not volume responsive. Conversely, if the entire rise is in MAP and CO the patient is maximally volume responsive. The usual response of course is between these limits. The product of MAP and CO is referred to as cardiac power and provides an integrative measure of cardiac hydraulic pumping ability that correlates with clinical outcomes in cardiac patients [5–7].

The aim of this study was to explore the clinical applicability of P_{msa} together with a set of P_{msa}-derived measures to quantitatively assess the response to fluid boluses in patients admitted to ICU following cardiac surgery. It was hypothesised first, that the pressure gradient for VR (derived using P_{msa}) would correlate with changes in CO; second, that dynamic changes in P_{msa} could provide a clinically valid adjunct to changes in CO in assessing volume responsiveness; third, that baseline cardiac power scaled to P_{msa} could indicate its potential increase by volume expansion. Hence, this study was designed to provide a comprehensive assessment of the response to volume expansion. It was not primarily designed to a priori predict volume responsiveness. This distinction is important, particularly as a quantitative volume assessment may still provide valuable information to guide subsequent therapy in case of no significant response to volume expansion, beyond that of the 'non-responsive' result of predictive methods in current use.

Materials and methods

This study was approved by the South Western Sydney Local Health District Research and Ethics Office (LNR/14/LPOOL/150). Patients admitted to Liverpool ICU following elective cardiac surgery during a 3-month period were consecutively enrolled in the study to minimize selection bias.

Patients

All patients had radial arterial (measuring MAP), central venous (measuring P_{ra}) and pulmonary arterial (measuring CO) catheters inserted as per institutional protocol. Patient and surgical demographics are shown in Table 1. Patients were initially ventilated in volume-controlled mode (PEEP of 5 cmH_2O, respiratory rate 12–16/min, tidal volume 6–8 mL/kg) and sedated using propofol and fentanyl or morphine. Ventilation was weaned and patients were evaluated for extubation within 6 h of admission. A MAP greater than 70 mmHg and a cardiac index (CI) greater than 2.5 L/min/m^2 were targeted unless the surgeon's post-operative orders specified other values.

Measurements and calculations

All pressure transducers were referenced to the mid-axillary line and haemodynamic variables determined with the patient supine, including CO by thermodilution randomly in the respiratory cycle. The mean of triplicate cold bolus injections within a ±10 % variation was recorded to ensure that a minimal change by 10 % could be detected [8]. Haemodynamic variables were serially transmitted from the Philips Intellivue MP70 intensive care monitor to the navigator Clinical Decision Support System (CDSS) (supplied as NaviCorder by CPL Innovations Pty Ltd, Sydney, NSW, Australia) to record CO, MAP, P_{ra} and P_{msa}. Haemodynamic variables and details of any interventions were entered in real time at the bedside by the same investigator (KG) into a clinical data form and later transferred to a desktop computer for further analysis.

Table 1 Patient demographics, surgical procedures and use of vasopressors/inotropes

Demographics	Mean ± SD
Age, years	63 ± 11
Weight, kg	86 ± 19
Height, cm	170 ± 8.8
Women, *n* (%)	15 (25 %)
Body surface area, m^2	1.97 ± 0.22
Surgery	***n*** **(%)**
CABG alone	40 (66)
CABG + valve replacement	8 (13)
Valve replacement	8 (13)
Bentall's procedure	5 (8)
DDD pacing	7 (11)
Vasopressors/inotropes	***n*** **(%)**
Noradrenaline	27 (44)
Dobutamine	6 (10)
Milrinone	10 (16)
Sodium nitroprusside	9 (15)
Glyceryl trinitrate	6 (10)

CABG coronary artery bypass graft

The operating CO is determined by the point at which the venous return and cardiac function curves intersect (Fig. 1). When the heart is functioning on the steep portion of the cardiac output curve, volume expansion will increase P_{ms} more than P_{ra} [ΔP_{ms} ($P_{ms2} - P_{ms1}$) > ΔP_{ra} ($P_{ra2} - P_{ra1}$)], generating a greater driving pressure for VR and hence CO (see Eq. 1). This is in contrast to the result when the heart is functioning on the flat part of the cardiac output curve, where ΔP_{ms} is approximately the same as ΔP_{ra}, thus with no or minimal change in CO. These changes are based on the assumption that RVR remains almost constant, which is reasonable when the volume load is small [9].

The ratio of change in driving pressure for VR to the change in P_{msa} represents a measure of the heart's ability to respond to a volume bolus or alternatively the efficiency of the volume to accomplish an increase in MAP and/or CO under prevailing conditions. Thus, volume efficiency is described by

$$E_{vol} = \Delta(P_{msa} - P_{ra})/\Delta P_{msa} \quad (3)$$

The non-dimensional variable E_{vol} provides a quantitative assessment of the response to volume expansion that changes depending on what portion of the cardiac function curve intersects with the venous return curve. The individual's vascular compliance and the size of the volume bolus are incorporated in P_{msa}. E_{vol} is a dynamic measure based on consecutive calculations of heart efficiency, E_h:

$$E_h = (P_{msa} - P_{ra})/P_{msa} \quad (4)$$

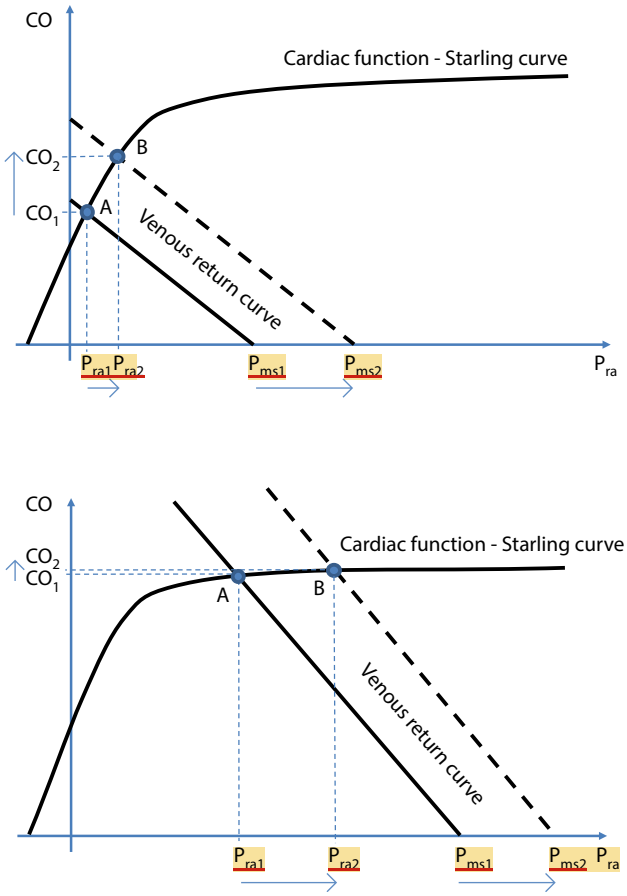

Fig. 1 The operating cardiac ouput is determined by the point at which the venous return and cardiac output curves intersect. The heart is volume responsive when P_{ms} increases more than P_{ra} (fluid bolus moves patient from point *A* to *B*, *upper panel*) in contrast to the non-responsive state when the change in P_{ms} approximately equals the change in P_{ra} (fluid bolus moves patient from point *A* to *B*, *lower panel*)

The E_h equation clarifies that increasing heart efficiency as a global measure is dependent on an unchanged P_{ra} following volume expansion while CO and/or MAP changes. Finally, cardiac power was calculated as described previously [5] and scaled to the volume state:

$$CP_{vol} = ([MAP \times CO]/451)/P_{msa} \quad (5)$$

Its dynamic relation to the volume state was investigated as a measure of power efficiency, E_{power}, describing how the heart converts added power (ΔP_{msa}) to increased MAP × CO [Δ(MAP × CO)]:

$$E_{power} = \Delta([MAP \times CO]/451)/\Delta P_{msa} \quad (6)$$

Protocol

This was an observational study and all interventions were at the discretion of the treating intensivist, who remained blinded to the Navigator CDSS. The Navigator

CDSS data were captured immediately before any intervention and repeated 10 min following the end of a fluid bolus (250 mL) to ensure steady state and to allow time for stress relaxation of the vasculature to minimize changes in RVR. Measurements were performed irrespective of spontaneous breathing efforts and respiratory rate, irregular atrial/ventricular rhythms, paced rhythms, or amounts of vasopressor/inotropic support to ensure that the proposed measures to assess volume expansion were investigated under pragmatic conditions.

An increase in CO by more than 10 % was used to define the response to volume as a binary outcome (responsive vs. non-responsive), consistent with previous studies [2].

Statistical analysis

Normally distributed data (D'Agostino and Pearson omnibus normality test) were described by mean and standard deviation and differences analysed by Student's *t* test. Non-normally distributed data were described by median and interquartile range and differences analysed by the Mann–Whitney test. A multiple regression analysis (enter if $p < 0.1$) was used to identify haemodynamic variables (before volume expansion and dynamic changes after) independently associated with volume and were subsequently evaluated in a logistic regression model. Independent variables were further explored using receiver operating characteristics (ROC) to determine their overall association (area under the curve, AUC), sensitivity, specificity and threshold criterion with volume responsiveness. Finally, linear regression analysis was used to determine the correlation between any assessment of volume expansion and the change in cardiac output as a continuous outcome. A p value less than 0.05 was used to denote statistical significance.

All analyses were performed using MedCalc version 12.3 (MedCalc Software, Ostend, Belgium).

Results

Sixty-one patients were studied and 107 episodes of fluid resuscitation were captured (in about half of patients using 0.9 % NaCl, and otherwise using 4 % albumin, packed red blood cells, return of pump blood, fresh frozen plasma, or pooled platelets). Overall, a fluid bolus had a volume of 264 ± 16 mL and was administered over 14 ± 4 min. There were 12 instances when the treating intensivist prescribed a bolus larger than 250 mL of fluid (843 ± 168 mL) for immediate resuscitation. These episodes were still included in continuous analyses, but excluded from binary analyses of volume responsiveness. Twenty-five patients had a second fluid bolus following the first one.

Haemodynamic variables split by responders vs. non-responders to volume expansion are summarized in Table 2. Overall, responders had lower ($P_{msa} - P_{ra}$), CO, CP_{vol} before a bolus and initially higher systemic vascular resistance (SVR) compared to non-responders. P_{msa} increased in both responders and non-responders capturing all fluid boluses, whereas this change did not reach statistical significance in the subset of patients with a second fluid bolus. Both ($P_{msa} - P_{ra}$) and CP_{vol} increased in responders while E_h remained unchanged. The ($P_{msa} - P_{ra}$) gradient correlated with CO at baseline ($r^2 = 0.57$, $p < 0.001$) and the change in ($P_{msa} - P_{ra}$) correlated with the change in CO ($r^2 = 0.71$, $p < 0.001$).

The E_{vol} was higher in responders vs. non-responders [0.32 (0.15–1.0) vs. 0.07 (0.1–0.28), difference 0.24 (0.11–0.44), $p < 0.001$]. Similarly, E_{power} was higher in responders [0.33 (0.26–0.40)] vs. non-responders [0.02 (0.01–0.05)], difference 0.31 (0.24–0.38), $p < 0.001$.

In the multivariate regression analysis the pre-bolus E_h, the pre-bolus ($P_{msa} - P_{ra}$), the pre-bolus CP_{vol}, the $\Delta(P_{msa} - P_{ra})$, the ΔP_{msa}, the E_{vol} and the E_{power} were all identified as independent variables associated with volume responsiveness. A logistic regression incorporating all P_{msa}-derived assessments of responses to volume expansion for all episodes ($n = 107$) correctly identified 74 % of responders with an AUC of 0.81 (0.73–0.88). As single variables, $\Delta(P_{msa} - P_{ra})$ and E_{power} were equally, with an AUC of 0.90 (0.83–0.95) and 0.90 (0.84–0.96) respectively, associated with volume responsiveness followed by E_{vol} [AUC 0.86 (0.77–0.92)] and pre-bolus CP_{vol} [AUC 0.74 (0.68–0.81)]. These AUCs were all greater than for CO alone [0.65 (0.54–0.75), $p = 0.01$]. Table 3 summarizes the performance of the independent variables at baseline, excluding variables dependent on dynamic changes, to assess volume responsiveness for the first ($n = 61$) and second ($n = 25$) fluid boluses.

E_{vol} correlated with the increase in CO assessing all episodes ($r^2 = 0.72$, $p < 0.001$). In the 25 patients with a second fluid bolus, the E_{vol} for the first bolus correlated with the increase in CO for the second bolus ($r^2 = 0.35$, $p = 0.002$) whereas $\Delta(P_{msa} - P_{ra})$ and ΔP_{msa} for the first bolus did not correlate with the increase in CO for the second bolus ($r^2 = 0.13$, $p = 0.07$ and $r^2 = 0.04$, $p = 0.33$, respectively).

Discussion

This study demonstrated that the P_{msa} generated by the Navigator CDSS when used together with P_{ra} to describe the venous return pressure gradient correlated well with changes in CO as expected by cardiovascular dictum. The response to volume expansion could be quantitatively

Table 2 Haemodynamic variables in responders and non-responders to a fluid bolus for all episodes captured (top, $n = 107$) and in the subset of patients receiving a second fluid bolus (bottom, $n = 25$)

All boluses	Responders ($n = 34$)				Non-responders ($n = 73$)			
	Pre-bolus	Post-bolus	Δ (95 % CI)	p	Pre-bolus	Post-bolus	Δ (95 % CI)	p
MAP (mmHg)	74 ± 11	76 ± 7.9	1.6 (−3.0 to 6.1)	0.49	73 ± 8.5	75 ± 8.2	2.7 (−0.02 to 5.4)	0.05
P_{ra} (mmHg)	11 ± 4	13 ± 5	1.6 (−0.58 to 3.7)	0.15	11 ± 4	12 ± 4	1.5 (0.19 to 2.8)	0.03
P_{msa} (mmHg)	17 ± 3.7	19 ± 4.3	2.2 (1.5 to 2.9)	0.02	17 ± 3.6	19 ± 4.1	1.4 (0.9 to 1.9)	0.03
$P_{msa} - P_{ra}$ (mmHg)	5.7 ± 0.82*	6.6 ± 0.99	0.86 (0.42 to 1.3)	<0.001	6.6 ± 1.1	6.5 ± 1.1	−0.098 (−0.45 to 0.26)	0.59
CO (L/min)	4.4 ± 0.85*	5.7 ± 1.1	1.2 (0.74 to 1.7)	<0.001	5.6 ± 1.6	5.4 ± 1.5	−0.19 (−0.69 to 0.30)	0.44
CP_{vol} (W/mmHg)	0.042 ± 0.01*	0.048 ± 0.01	0.006 (0.001 to 0.013)	0.04	0.053 ± 0.02	0.049 ± 0.02	0.004 (−0.009 to 0.002)	0.17
E_h	0.36 ± 0.13	0.36 ± 0.13	0.0023 (−0.059 to 0.064)	0.94	0.39 ± 0.11	0.36 ± 0.10	−0.034 (−0.069 to 0.001)	0.06
SVR (dyn s/cm^5)	1,171 ± 288*	920 ± 200	−251 (−371 to −132)	<0.001	945 ± 257	993 ± 267	49 (−37 to 134)	0.26
RVR (dyn s/cm^5)	105 ± 18	95 ± 16	−10 (−18 to −1.8)	0.02	98 ± 18	100 ± 19	1.9 (−4.1 to 8.0)	0.53
Second bolus	Responders ($n = 10$)				Non-responders ($n = 15$)			
	Pre-bolus	Post-bolus	Δ (95 % CI)	p	Pre-bolus	Post-bolus	Δ (95 % CI)	p
MAP (mmHg)	71 ± 8	73 ± 7	2 (−5.4 to 9.5)	0.58	76 ± 12	79 ± 10	3 (−4.8 to 10)	0.47
P_{ra} (mmHg)	12 ± 4	14 ± 6	2.1 (−2.8 to 7.1)	0.39	11 ± 3	12 ± 4	1.6 (−0.9 to 4.3)	0.20
P_{msa} (mmHg)	18 ± 4.3	19 ± 5.5	1.9 (−2.7 to 6.6)	0.39	17 ± 3.1	19 ± 4.3	2.0 (−0.6 to 4.5)	0.12
$P_{msa} - P_{ra}$ (mmHg)	5.5 ± 1.0*	6.6 ± 1.0	1.1 (0.12 to 2.0)	0.03	6.6 ± 1.1	6.9 ± 1.1	0.30 (−0.45 to 1.1)	0.42
CO (L/min)	4.4 ± 0.9*	5.4 ± 0.4	0.9 (0.1 to 2.0)	0.03	5.9 ± 1.5	5.6 ± 1.7	−0.3 (−1.4 to 0.8)	0.55
CP_{vol} (W/mmHg)	0.033 ± 0.01*	0.044 ± 0.02	0.011 (0.001 to 0.021)	0.04	0.053 ± 0.01	0.054 ± 0.02	0.001 (−0.01 to 0.01)	0.98
E_h	0.35 ± 0.13	0.32 ± 0.14	0.032 (−0.09 to 0.16)	0.60	0.39 ± 0.09	0.37 ± 0.10	−0.02 (−0.08 to 0.05)	0.61
SVR (dyn s/cm^5)	1,124 ± 229	1,093 ± 271	31 (−204 to 267)	0.78	1,034 ± 362	963 ± 278	−71 (−289 to 148)	0.52
RVR (dyn s/cm^5)	103 ± 18	104 ± 17	1.2 (−14 to 17)	0.87	101 ± 20	98 ± 18	−2.8 (−16 to 10)	0.66

Changes pre- and post-bolus are listed with the 95 % confidence intervals [Δ(95 % CI)] and the corresponding p values

MAP mean arterial pressure, P_{ra} right atrial pressure, P_{msa} analogue mean systemic filling pressure, *CO* cardiac output, CP_{vol} cardiac power relative to the volume state as measured by P_{msa}, E_h heart efficiency, *SVR* systemic vascular resistance, *RVR* resistance to venous return

* $p < 0.05$ between responders and non-responders before administration of a fluid bolus

Table 3 Receiver operating characteristics of variables associated with an increase in cardiac output following a fluid bolus including the area under the curve (AUC), p value, and cut-off value to define responders vs. non-responders

	AUC (95 % CI)	p value	Criterion	Sensitivity (%)	Specificity (%)
1st bolus $n = 61$					
Pre CP_{vol}	0.83 (0.75–0.91)	<0.001	<0.047	97.1	57.5
Pre ($P_{msa} - P_{ra}$)	0.72 (0.63–0.82)	<0.001	<6.2	79.4	56.2
Pre E_h	0.60 (0.51–0.70)	0.08	N/A	N/A	N/A
2nd bolus $n = 25$					
Pre CP_{vol}	0.97 (0.94–1.02)	<0.001	<0.040	90.0	94.7
Pre ($P_{msa} - P_{ra}$)	0.76 (0.56–0.96)	0.03	<6.0	60.0	86.7
Pre E_h	0.68 (0.45–0.92)	0.12	N/A	N/A	N/A

N/A not applicable

assessed on the basis of cardiac power relative to the P_{msa} at baseline as well as by its dynamic changes following a volume bolus. The dynamic changes in venous return pressure gradient ($P_{msa} - P_{ra}$) for a given change in P_{msa} provided a quantitative measure of the efficiency of a volume bolus to increase CO.

The assessment of systemic filling pressure is central to this study but can only be directly measured at no-flow conditions with arterial and venous pressures at equilibrium and is hence only an estimative pressure in humans [9]. The P_{msa} provided by the Navigator CDSS circumvents this limitation using a mathematical model of circulatory cessation. The P_{msa} has previously been reported to accurately guide volume replacement during dialysis [10], and to correlate with changes in the intravascular volume state [11, 12] also using alternative methods to assess mean systemic filling pressure [13]. It has furthermore been demonstrated to accurately reflect the volume state during acute endotoxaemia [14]. A key finding of this study is the applicability of P_{msa} and the related assessment of the venous return gradient to explain changes in CO that were well aligned with the physiological principles described by Guyton [15, 16]. This corroborates the Navigator CDSS algorithm to derive P_{msa} that can be obtained in all patients with concurrent monitoring of MAP, P_{ra} and CO without further manipulation.

The concept of energy and power encompassed in cardiac power was already discussed in Starling's Linacre Lecture on the law of the heart [17]. In the present study, the cardiac power was assessed relative to the volume state (CP_{vol}) before volume expansion to evaluate this derived variable's ability to assess volume responsiveness. The AUCs for CP_{vol} both for the first and second fluid bolus demonstrated high sensitivity albeit lower specificity to assess volume responsiveness. Furthermore, in terms of dynamic changes, the power efficiency (E_{power}) was closely associated with volume responsiveness while heart efficiency (E_h) was unchanged. The usefulness of P_{msa} has been debated [18, 19] since it is dependent on the measurement of CO that ultimately is the variable of interest when giving fluid to improve tissue perfusion. This study demonstrated that cardiac power scaled to the volume state, including its dynamic measure, was superior to assess the efficiency of volume expansion compared to CO alone. This is not surprising considering that the cardiac power scaled to the volume state in addition incorporates vascular tone and contractility. The CP_{vol} variable can be obtained regardless of mode of breathing and heart rhythms. The deleterious effects of volume overloading [20] as well as the importance of early optimization of the intravascular volume [21] are well established, particularly in septic patients, but also post-operatively for cardiac surgical patients [22]. Fluid management might be rationalized by combining the haemodynamic information used to derive P_{msa} by the Navigator CDSS.

The venous return pressure gradient ($P_{msa} - P_{ra}$) correlated with CO and identified responders to a fluid bolus in a previous study [12]. This study, based on a larger cohort of patients, demonstrated an even better correlation ($r^2 = 0.71$ vs. 0.58) with a similar threshold value for ($P_{msa} - P_{ra}$) to identify fluid responsiveness (6.0–6.2 vs. 6.1 mmHg) [12]. The original study by Guyton demonstrated a reduced RVR following an increase in intravascular volume [23] that was not observed in a previous evaluation of P_{msa} and volume expansion [12], while it was demonstrated in this study, albeit with a minimal (less than 10 %) decrease compared to baseline. The slightly larger volumes of fluid and delayed measurements of haemodynamic changes in this study might explain the differences in results since vessel distention and hence reduced RVR are not instantaneous following acute volume expansion.

The quantitative assessment of volume expansion in this study, E_{vol}, derived from the intersection of the venous return curve with the heart performance curve, was significantly higher in responders compared to non-responders. It was an independent variable associated with fluid responsiveness in the multiple regression analysis and demonstrated an AUC greater than 0.8 for the receiver operating characteristic. Static filling pressures, such as P_{msa}, P_{ra} or ($P_{msa} - P_{ra}$), are unlikely to reflect volume responsiveness [24] since they do not take into account the slope of the cardiac function curve where the

venous return curve intersects. This limitation is avoided by assessing dynamic changes in ($P_{msa} - P_{ra}$) as incorporated into the E_{vol} calculation. The results of this study support this approach to quantitatively assess interactions between venous return and cardiac function. The significant correlation between the E_{vol} established from the response to the first fluid bolus and the change in CO following a second bolus demonstrates the utility of those scalar, continuous and dimensionless measures to assess the response to volume expansion. Notably, the change in ($P_{msa} - P_{ra}$), while useful for identifying fluid responders, did not correlate with the change in CO for the subsequent bolus. The risk of an overzealous expansion of the intravascular compartment can thus tentatively be reduced using CP_{vol} and E_{vol} since both the presence and magnitude of the response to volume expansion can be assessed.

The strengths of this study include its pragmatic design which is conducive to a high external validity of results. It also has important limitations. It was observational without prescriptive fluid therapy and investigated a single patient cohort of post-cardiac surgery patients with a limited number of repeat fluid boluses compared to the total given. No comparisons were made to other methods to gauge volume responsiveness, such as pulse pressure/stroke volume variation. The validity of the results should be further tested in other categories of patients, not least septic patients, using a prospective design to guide and assess the efficacy CP_{vol}, and E_{vol} in fluid optimization. The use of continuous CO measurements (together with MAP and P_{ra}) could allow for ongoing determination of CP_{vol} and E_{vol} based on spontaneous haemodynamic variability in critically ill patients. The efficiency measures presented in this study could have particular value when incorporated into real-time bedside systems such as monitors and decision support systems.

In conclusion, using an algorithm to derive a mean systemic filling pressure analogue, the cardiac power and dynamic assessments of the venous return pressure gradient relative to the mean systemic filling pressure provided a quantitative assessment of the haemodynamic response to volume expansion in post-surgical cardiac patients.

Conflicts of interest Geoffrey Parkin and Mark Leaning are directors of CPL Innovations, a software company in the area of cardiovascular decision support systems. The other authors have no conflicts of interest to declare.

References

1. Pinsky MR (2014) Functional haemodynamic monitoring. Curr Opin Crit Care 20:288–293
2. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37:2642–2647
3. Mahjoub Y, Lejeune V, Muller L, Perbet S, Zieleskiewicz L, Bart F, Veber B, Paugam-Burtz C, Jaber S, Ayham A, Zogheib E, Lasocki S, Vieillard-Baron A, Quintard H, Joannes-Boyau O, Plantefeve G, Montravers P, Duperret S, Lakhdari M, Ammenouche N, Lorne E, Slama M, Dupont H (2014) Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. Br J Anaesth 112:681–685
4. Parkin WG, Leaning MS (2008) Therapeutic control of the circulation. J Clin Comput Monit 22:391–400
5. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, LeJemtel TH, Cotter G, Investigators S (2004) Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 44:340–348
6. Mendoza DD, Cooper HA, Panza JA (2007) Cardiac power output predicts mortality across a broad spectrum of patients with acute cardiac disease. Am Heart J 153:366–370
7. Popovic B, Fay R, Cravoisy-Popovic A, Levy B (2014) Cardiac power index, mean arterial pressure, and Simplified Acute Physiology Score II are strong predictors of survival and response to revascularization in cardiogenic shock. Shock 42:22–26
8. Nilsson LB, Nilsson JC, Skovgaard LT, Berthelsen PG (2004) Thermodilution cardiac output—are three injections enough? Acta Anaesthesiol Scand 48:1322–1327
9. Schipke JD, Heusch G, Sanii AP, Gams E, Winter J (2003) Static filling pressure in patients during induced ventricular fibrillation. Am J Physiol 285:H2510–H2515
10. Parkin G, Wright C, Bellomo R, Boyce N (1994) Use of a mean systemic filling pressure analogue during the closed-loop control of fluid replacement in continuous hemodiafiltration. J Crit Care 9:124–133
11. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR (2012) Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. Intensive Care Med 38:1452–1460
12. Cecconi M, Aya HD, Geisen M, Ebm C, Fletcher N, Grounds RM, Rhodes A (2013) Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients. Intensive Care Med 39:1299–1305
13. Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, Jansen JR (2009) Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. Crit Care Med 37:912–918
14. Lee JM, Ogundele O, Pike F, Pinsky MR (2013) Effect of acute endotoxemia on analog estimates of mean systemic pressure. J Crit Care 28:880.e9–e15
15. Guyton AC (1968) Regulation of cardiac output. Anesthesiology 29:314–326

16. Guyton AC (1955) Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 35:123–129
17. Starling E (1918) The Linacre Lecture on the law of the heart. Longmans, Green, London
18. Teboul JL (2013) Mean systemic pressure: we can now estimate it, but for what? Intensive Care Med 39:1487–1488
19. Teboul JL (2014) Mean systemic filling pressure: we can now estimate it, but for what? Response to comment by Parkin. Intensive Care Med 40:140
20. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D, Sepsis Occurrence in Acutely Ill Patients Investigators (2006) Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 34:344–353
21. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
22. Searl CP, Perrino A (2012) Fluid management in thoracic surgery. Anesthesiol Clin 30:641–655
23. Guyton AC, Lindsey AW, Kaufmann BN, Abernathy JB (1958) Effect of blood transfusion and hemorrhage on cardiac output and on the venous return curve. Am J Physiol 194:263–267
24. Marik PE, Monnet X, Teboul JL (2011) Hemodynamic parameters to guide fluid therapy. Ann Intensive Care 1:1