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## Fluid loading responsiveness

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## Chapter 9

### **Is arm occlusion pressure a predictor of fluid responsiveness?**

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Fluid therapy is an important tool in hemodynamic management of patients with suboptimal tissue perfusion. Excessive fluid resuscitation, however, can result in general and pulmonary oedema; increasing hospital stay and even mortality <sup>[1]</sup>. In ventilated patients with regular heart rhythm, stroke volume variation (SVV) and pulse pressure variation (PPV) perform well as predictors of a clinically significant increase in cardiac output (CO) after fluid administration (i.e. fluid loading responsiveness or FLR) <sup>[2,3]</sup>. In vasoplegic patients both indicators failed <sup>[4,5]</sup>. Furthermore, SVV and PPV have never been shown to perform as a measure of volume status. Therefore the search for a measure of volume status and a predictor of fluid loading responsiveness which can be used independent of respiratory settings and heart rhythm continues <sup>[6]</sup>.

A physiological measure of effective volume status is mean systemic filling pressure (MSFP); the equilibrium pressure anywhere in the circulation under circulatory arrest. The pressure gradient between static filling pressure and central venous pressure is the driving force for venous return and thus for cardiac output. Consequently, increasing MSFP and thereby the pressure gradient for venous return by fluid expansion should improve cardiac output, assuming a constant resistance to venous return and adequate myocardial function.

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In pharmacology research, upper arm occlusion pressure (Parm) has been used to determine (the effects of drugs on) venous capacitance and arterial resistance <sup>[7]</sup>. We hypothesize that Parm might function as an indicator of filling pressure and volume status. MSFP has never been studied as a predictor of fluid responsiveness. We determined Parm by measuring arterial pressure 30 seconds after stop-flow induced by inflating a cuff around the upper arm. The aim of this study was to explore the value of Parm as a predictor of fluid loading responsiveness. This approach is attractive, as it would provide the clinician with a simple, readily available and robust measure that can be obtained at the bedside. This method would be independent of sedation, arrhythmias and mechanical ventilation.

## Methods

Twenty-four patients undergoing elective-cardiac surgery were included after approval of the institutional ethics committee (P06.149, chairmen Prof. Dr. F.C. Breedveld, approval date 5 december 2006) and personal informed consent was obtained. All patients had symptomatic coronary artery or valvular disease with preserved ventricular function. Patients with aortic aneurysm, extensive peripheral arterial occlusive disease, postoperative severe arrhythmia, postoperative valvular insufficiency or the necessity for artificial pacing or use of a cardiac assist device were excluded.

Prior to surgery, each patient received a pulmonary artery catheter (Intellicath; Edwards Lifesciences; Irvine, CA, USA) to measure thermodilution COtd and CVP and a 20 G radial artery catheter (Prad). Patient's anaesthesia was continued with propofol ( $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) and sufentanil ( $0.06\text{-}0.20 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). The lungs were mechanically ventilated (Evita 4, Draeger, Lubeck, Germany) in a volume-control mode with standard settings ( $12 \text{ breaths} \cdot \text{min}^{-1}$ , tidal volume  $8\text{-}10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ,  $\text{FiO}_2$  0.4, PEEP  $5 \text{ cmH}_2\text{O}$ ). Airway pressure (Paw) was measured at the proximal end of the endotracheal tube. During the observation period the patients maintained the supine position. Use of sedative and vascular medication remained unchanged. No fluids were administered during the observation period outside the study protocol.

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An upper arm blood stop-flow was created with a rapid cuff inflator (Hokanson E20, Bellevue, Washington) and matching upper arm cuff. Duration of stop-flow was 35 seconds with a cuff pressure 50 mmHg above the patients' systolic blood pressure. Arm occlusion pressure (Parm) was calculated as the average arterial pressure during one second at 30 seconds after arm occlusion.

The arterial pressure Prad was analysed with the modelflow program (CO, FMS, Amsterdam, the Netherlands) to provide beat-to-beat values of CO. We calibrated the pulse contour cardiac output measurements with three thermodilution COtd measurements equally spread over the ventilatory cycle<sup>[8]</sup>. From these beat-to-beat cardiac output values, stroke volume variation (SVV) and pulse pressure variation (PPV) were determined. SVV and PPV were calculated for 5 ventilatory cycles and their values averaged.

Measurements of Parm, CVP, MAP, CO, SVV and PPV were done during baseline in supine position and 2-5 minutes after rapid fluid loading with 500 ml hydroxyethyl starch solution (Voluven®, Fresenius Kabi, Bad Homburg, Germany).

### Statistical methods

A formal power analysis was not performed since relevant data was not available from literature. However, study sample size is similar to other fluid loading responsiveness studies. We used a Kolmogorov-Smirnov test and a paired t-test. Fluid responsiveness was defined as a >10% increment of modelflow cardiac output after volume expansion. The 10% cut-off corresponds with more than twice the reported precision of the Modelflow method (i.e. twice the SD for repeated measurements) [14,15]. Hence, responders will experience clinically significant changes in CO. Prediction of fluid responsiveness for Parm, CVP, PVR, SVV and PPV was tested by calculating the area under the receiver operating characteristic (ROC) curve. All values are given as mean  $\pm$  SD. A p value < 0.05 was considered statistically significant.

### Results

152) Twenty-four patients (19 males) of  $64 \pm 10$  years with a BSA of  $2.0 \pm 0.2$  m<sup>2</sup> started and finished the study protocol. Seventeen received straightforward coronary artery by-pass grafting, seven (also) had single or two valve repair. Data was distributed normally. Pooled results of hemodynamic variables at baseline and after 500 ml fluid administration are shown in Table 1. After 500 ml fluid loading CO, Parm, MAP and CVP increased. HR did not change. PPV and SVV decreased.

**Table 1** Changes in hemodynamic parameters from baseline to after 500 ml fluid loading for all patients, responders and non-responders.

Parameters	All patients (n=24)			Responders (n=17)			Non-responders (n=7)		
	Baseline	500 ml	P value	Baseline	500 ml	P value	Baseline	500 ml	P value
CO (L·min <sup>-1</sup> )	5.2 $\pm$ 1.3	6.0 $\pm$ 1.4	< 0.001	5.1 $\pm$ 1.3	6.2 $\pm$ 1.4	< 0.001	5.5 $\pm$ 1.3	5.7 $\pm$ 1.3	0.148
Parm (mmHg)	18.6 $\pm$ 7.7	24.3 $\pm$ 8.7	< 0.001	16.2 $\pm$ 6.3	22.0 $\pm$ 7.6	< 0.001	24.3 $\pm$ 8.2	29.9 $\pm$ 9.1	< 0.001
MAP (mmHg)	82.3 $\pm$ 15.6	90.7 $\pm$ 16.1	< 0.001	78.9 $\pm$ 9.9	88.9 $\pm$ 11.2	< 0.001	90.4 $\pm$ 23.6	94.8 $\pm$ 25.2	0.056
CVP (mmHg)	9.0 $\pm$ 2.6	11.5 $\pm$ 2.9	< 0.001	8.6 $\pm$ 2.6	10.9 $\pm$ 2.5	< 0.001	9.9 $\pm$ 2.5	13.0 $\pm$ 3.4	0.004
PPV (%)	13.8 $\pm$ 9.0	8.0 $\pm$ 7.5	< 0.001	14.8 $\pm$ 7.8	8.1 $\pm$ 6.6	0.001	11.1 $\pm$ 11.5	7.7 $\pm$ 10.0	0.011
SVV (%)	15.5 $\pm$ 10.5	9.3 $\pm$ 9.3	0.001	16.5 $\pm$ 10.9	8.5 $\pm$ 6.5	< 0.001	13.0 $\pm$ 9.9	11.2 $\pm$ 14.6	0.627
HR (min <sup>-1</sup> )	83 $\pm$ 16	83 $\pm$ 14	0.908	83 $\pm$ 18	83 $\pm$ 16	1.000	81 $\pm$ 10	82 $\pm$ 11	0.860

CO is cardiac output, Parm is arm occlusion pressure, CVP is central venous pressure, MAP is mean arterial pressure and HR is heart rate

The population was divided into FLR responders (n=17) with an increase of at least 10% in COm after 500 ml fluid loading and non-responders (n=7). In the responder group CO, MAP, CVP increased and SVV and PPV decreased. Parm increased from 16 to 22 mmHg. In the non-responder group, Parm increased from 24 to 30 mmHg. CVP also increased. PPV decreased. CO, MAP, SVV and HR did not change significantly.

Receiver operating characteristic curves were used to qualify the prediction of fluid responsiveness for each parameter. The area under the curve (AUC) for prediction of fluid responsiveness for Parm was 0.786 (95% CI: 0.567 to 1.000). At a cut-off of 21.9 mmHg sensitivity is 71% and specificity 88% to predict FLR. The results for CO, Parm, MAP, CVP, PPV and SVV are in Table 2.

**Table 2** Area under the receiver operating characteristics curve to predict fluid loading responsiveness from baseline values.

	Area	95% confidence interval	
		Lower	Upper
Cardiac output (L·min <sup>-1</sup> )	0.588	0.355	0.821
Arm occlusion pressure (mmHg)	0.786	0.567	1.000
Mean arterial pressure (mmHg)	0.588	0.399	0.853
Central venous pressure (mmHg)	0.353	0.105	0.601
Pulse pressure variation (%)	0.853	0.693	1.000
Stroke volume variation (%)	0.761	0.531	0.990

## Discussion

Our study demonstrates that Parm was significantly lower in the responder group. Parm is a good predictor of fluid responsiveness in our studied group. We used Parm for the first time to study fluid loading responsiveness.

Both SVV and PPV have been reported to perform better as predictors of fluid responsiveness than static pressures (CVP and pulmonary artery occlusion pressure) [3,9-12]. However, SVV or PPV are influenced by ventilator settings as tidal volume [9,13], respiratory rate [14] and also to cardiac function. In patients with reduced cardiac function SVV is expected to be smaller, because stroke volume is obviously limited and consequently ventilator induced changes in stroke volume will be reduced [3,10]. Reuter and co-workers showed that SVV could still perform as a predictor of fluid loading responsiveness in patients with reduced cardiac function, although SVV was indeed smaller in patients with impaired cardiac function [13]. Furthermore, for the determination of SVV and PPV it is essential that patients are fully dependent on mechanical ventilation, and a regular heart rate is obligatory. In spontaneous breathing patients [4,5] and in mechanically ventilated patients with tidal volumes smaller than  $8 \text{ ml} \cdot \text{kg}^{-1}$  SVV and PPV failed to predict FLR accurately [9]. In our study patients, all after cardiac surgery, were mechanically ventilated with an averaged tidal volume of  $9.1 \text{ ml} \cdot \text{kg}^{-1}$  ( $7\text{-}12 \text{ ml} \cdot \text{kg}^{-1}$ ) predicted body weight. Thus, for some of our patients SVV and PPV may be less reliable. The Parm technique does not require specific tidal volume or respiratory rate. To measure Parm with the arm occlusion method only a peripheral arterial catheter is required. These requirements allow measurement in almost all operating rooms and intensive care patients. Its application is not limited to sedated and ventilated patients with a regular heart rhythm. In our study, Parm was a good predictor of fluid loading responsiveness, at least equal to SVV or PPV. However, our study patients were a relatively homogenous group.

### *Definition of fluid loading responsiveness*

There is no consensus on the amount of fluid or use of parameter to assess fluid loading responsiveness. Fluid amounts between 250-1000 ml are reported [3,5,15,16]. The outcome measures used were CO [4,5,16] and SV [15] or SV index [3]. A positive response was defined as a change in outcome parameter of more than 10%-25% [3,4,16]. We chose 10% change in pulse contour CO as cut-off level after fluid loading with 500 ml. The 10% increase in CO was chosen because this increase can be measured accurately with the modified Modelflow pulse contour method [17-20]. This value corresponds with the boundaries used in other studies where a 10% cut-off was used for 500 ml fluid loading responsiveness [4,21-23].

### *Considerations*

The number of patients (n=24) included in our study is relatively low and the distribution of (non)responders is unequal. Still with this low number of patients we were able to find highly significant results. Prediction of fluid loading responsiveness with baseline Parm was with a high sensitivity (71%) and specificity (88%). We theorize that these results can be explained by the similarity between Parm and mean systemic filling pressure. MSFP is the equilibrium pressure anywhere in the circulation under circulatory arrest, whereas Parm might be seen as the equilibrium pressure of the arm. We hypothesize that MSFP may be largely equal for different vascular compartments of the body because their venous outflow pressures and arterial input pressures are relatively similar. MSFP is a physiological measure of effective volume status <sup>[24,25]</sup>. The pressure gradient between MSFP and CVP is the driving force for venous return and thus for cardiac output. Increasing MSFP and thereby the pressure gradient for venous return by fluid expansion should improve cardiac output, assuming a constant resistance to venous return. If there is hypervolemia or a cardiac limitation, i.e. the heart operates on the flat part of the Frank-Starling curve, fluid loading will increase CVP along with MSFP, and venous return will not increase. It is important to stress that we excluded patients with previous myocardial infarction and patients with congestive heart failure (NYHA class 4). Therefore we must be careful to extrapolate to patients with heart failure. In our patients a low Parm (< 22 mmHg) could indicate fluid loading responsiveness. In the case of cardiac failure or tamponade, CVP will rise along with Parm during volume administration. This will result in an unchanged pressure gradient for venous return and thus will fail to induce an improvement in cardiac output. Therefore, we expect our results applicable to patients with uncompromised cardiac function. Rapid increments of CVP can than be seen as a warning of right ventricular limitation.

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### **Conclusions**

Arm occlusion pressure can be measured at the bedside. Unlike SVV, the measurement of Parm is relatively independent of heart rhythm, mechanical or spontaneous breathing or sedation. Parm seems to be a good predictor of fluid loading responsiveness, at least in cardiac surgery patients without severe heart failure.



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