Fluid loading responsiveness

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Chapter 5

Fluid loading responsiveness: what parameter can we use?

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On a daily basis physicians asses the volume status of individual patients. Volume status optimization is required to maximize oxygen delivery to vital organs, like brain, kidneys and heart. Prolonged oxygen deficit can lead to an inflammatory cascade resulting in multi-system organ dysfunction [1]. Conversely, unnecessary fluid administration can lead to anasarca, pulmonary oedema, cardiac failure, anastomotic leakage, infections prolonging hospitalization or even causing death [2]. In these cases, pharmacological support may be indicated instead of fluid replacement. Several studies have shown the beneficial effects of restrictive use of fluids during and after operations resulting in a reduction of hospital stay up to 10% [3]. Therefore, the selection of critically-ill patients that will benefit from fluid loading is essential. This selection can be made with the use of fluid loading responsiveness (FLR). In this review, we ask ourselves: "Which measurable determinant(s) can be used to predict a clinically significant effect of fluid administration on cardiac output (CO)?"

Methods

MEDLINE, EMBASE and CENTRAL databases were searched for all publications on prospective observational studies in adult patients in the intensive care unit (ICU) or operating room (OR) that assessed FLR up to 2010. To maximise the practical guidance for
90) the ICU clinician with this review, studies were included only when a specific cut-off value to predict FLR and its respective sensitivity and specificity derived from receiver operating curves (ROC) was reported. ROC curves describe sensitivity and specificity characteristics over a spectrum of cut-off points. An area under the ROC curve of 1.00 is optimal; both sensitivity and specificity are 100% [4].

Fluid loading responsiveness

The selection of patients that are likely to respond to fluid loading is traditionally based on clinical signs. Subsequently, other parameters are taken into consideration like central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) [5]. In recent years, new variables based on heart-lung interaction, i.e. respiratory-induced stroke volume variation (SVV) and pulse pressure variation (PPV) have been introduced in the ICU. Reversible autotransfusion by passive leg raising (PLR) has also become the subject of intense interest. In this review, a wide range of parameters is assessed for its value for the prediction of FLR.

Clinical signs and symptoms

The initial assessment of volume status is most often based on clinical signs and symptoms, like skin turgor, urine colour or production, fluid balance and the presence of peripheral oedema. Stephan *et al.* [6] measured circulating blood volume (CBV) with human-serum albumin in 36 patients. Hypovolaemia, defined as a 10% lower CBV compared to a control

population, was present in 53% of the patients. However, clinical signs did not prove to be useful to discriminate between hypovolaemic and normovolaemic individuals. For instance, the presence of skin mottling had a sensitivity of 28% and specificity of 78%, while absence of peripheral oedema had a sensitivity of 64% and specificity of 56% to predict hypovolaemia. The definition of hypovolaemia could be subject of critique in this study and fluid loading responsiveness was not measured. However, there is a clear indication that the use of isolated or combinations of clinical signs are unreliable to predict FLR.

Static/ filling pressures

Besides clinical signs, traditional hemodynamic parameters, like central venous pressure and pulmonary artery occlusion pressure (PAOP) are often used in the assessment of FLR [5,7]. Although multiple studies have reported positive results, the use of these parameters in patients with sepsis, trauma, acute respiratory failure, and in the per-operative phase of cardiovascular surgery is found controversial. Moreover, these studies could not show that changes in CVP and PAOP after volume loading are correlated with changes in stroke volume or cardiac output [8-13]. CVP was found to have clinical significance (i.e. it correlates to CBV) only for extreme values (<2 mmHg or >18 mmHg) [14]. PAOP studied by Lattik and Wyffels showed a poor predictive values for FLR in cardiac surgery patients with area under the ROC curves of 0.63 (95% CI between 0.44 and 0.82, n=15) and 0.58 (95% CI between 0.39 and 0.75, n= 32) respectively [15,16]. In Table 1 and 2 an overview is given of literature that reported on FLR and CVP and PAOP.

Table 1 Reliability of baseline central venous pressure to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Barbier, *et al.* [8]	20	Sepsis	12 mmHg	90%	30%	0.57 ± 0.13
Cannesson, *et al.* [9]	25	Cardiac surgery *	3.5 mmHg	77%	63%	0.75 ± 0.11
Osman, *et al.* [10]	96	Sepsis *	8 mmHg	62%	54%	0.58 (0.49-0.67)
Reuter, *et al.* [11]	12	Cardiac surgery *	6 mmHg	50%	90%	0.71 (0.50-0.92)
Reuter, *et al.*[11]	14	Cardiac surgery *	10 mmHg	71%	62%	0.71 (0.54-0.88)
Biais, *et al.* [12]	35	Circulatory failure	9 mmHg	61%	82%	0.68 (0.50-0.83)
Vistisen, *et al.* [13]	23	Cardiac surgery	8 mmHg	35%	100%	-
Muller, *et al.* [48]	33	Circulatory failure	7 mmHg	54%	100%	0.77 ± 0.10

* Multiple measurements in same patients

Table 2 Reliability of baseline pulmonary artery occlusion pressure to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Osman, *et al.* [10]	96	Sepsis	11 mmHg	77%	51%	0.63 (0.55-0.70)
Reuter, *et al.* [11]	12	Cardiac surgery *	7 mmHg	79%	70%	0.77 (0.58-0.96)
Reuter, *et al.* [11]	14	Cardiac surgery *	8 mmHg	59%	75%	0.70 (0.52-0.88)

* Multiple measurements in same patients

It seems that CVP and PAOP are not suitable for standard evaluation of FLR. This is most like due to the large differences in myocardial function. Especially in critically ill, myocardial function is oftentimes depressed. Since CVP and PAOP are directly related to the function of the heart as well as mechanical ventilation, the absolute magnitude of these parameters in itself are not reliable in predicting FLR.

Although mean arterial pressure (MAP) is a well-identified goal to maintain perfusion of vital organs, it has not been studied extensively for its value to predict FLR. There are only two studies available that report on the reliability of MAP to predict FLR; Preisman and Kramer studied the reliability of baseline mean arterial pressure to predict fluid responsiveness and found areas under the ROC curves of 0.73 (95% CI between 0.60 and 0.87, n=18) and 0.81 (95% CI between 0.62 and 1.00, n=21) respectively [17,18]. Preisman found MAP at a cut-off of 76.5 mmHg to have a sensitivity of 64% and a specificity of 77% to predict FLR in 18 post-elective CABG surgery.

The low predictive value of MAP is likely related to the influence of disease state, for instance vasoplegia in sepsis, and pre-existing differences in normotensive values in-between individuals. These differences also complicate consensus on target blood pressures to guarantee perfusion of the brain and other vital organs. The International Consensus Conference on Hemodynamic Monitoring in 2006 found moderate to low evidence to implement target blood pressures in the management of shock [19]. This because relevant clinical studies were absent.

Heart rate

Heart rate (HR) has been studied on a small scale. Kramer *et al.* [18] reported baseline HR to predict FLR with an area under the ROC curve of 0.81 (95% CI between 0.61 and 1.00) in coronary by-pass grafting surgery patients. Berkenstadt [20] reported an AUC of 0.59 (95% CI between 0.44 and 0.64) under the ROC curve to predict FLR in patients undergoing neurosurgery.

In theory, heart rate is considered to be a good predictor of FLR. For instance, in young spontaneous-breathing trauma patients, tachycardia is indicative of severe haemorrhage.

However, in patients fully under mechanical ventilation and anaesthesia, neuronal and humoral control seems completely blocked. Consequently a relation is lacking between baseline or change in HR and changes in CO due to fluid loading. Moreover, a large number of patients are receiving beta-blockade further complicating the possibility to use heart rate to predict FLR.

Cardiac output

CO has been used to predict FLR. However, results concerning the reliability of baseline cardiac output measurements to predict FLR are non-uniform. Baseline cardiac output to predict FLR has been predominantly studied in coronary by-pass surgery patients; AUC under the ROC curve vary from 0.52 ± 0.12 to 0.74 ± 0.07 [21,22]. In 30 septic patients, the AUC of the ROC of baseline triplicate trans-pulmonary thermodilution CO was 0.77 (95% CI between 0.60 and 0.94) to predict FLR [23]. Monnet *et al.* [24] reported a sensitivity of 78%, a specificity of 54% and a cut-off of 2.8 $L \cdot min^{-1} \cdot m^{-2}$. Although the predictive value of different cardiac output methods have not been directly studied, Biais *et al.* [12] found responder classification with CO Vigileo (Edwards Lifesciences, Irvine CA, USA) to correspond in 97% of the cases with pulmonary-artery-catheter thermodilution or trans-thoracic echography CO in liver-transplant patients. Research is needed that directly compares different cardiac output methods to determine their predictive value for FLR as accuracy of a CO method can vary between 3,5 and 25% [25,26].

Moreover, if we take in mind the Starling curve; a patient can be either on the upslope of the Starling curve, on the plateau or in-between. There is a large variability between patients for the maximum cardiac output that can be reached. This implies that a low baseline value for cardiac output does not necessarily mean that fluid loading will lead to an increase in cardiac output. Pharmacological or even mechanical intervention will probably have a similar chance to lead an improvement in CO.

Volumetric or echographic parameters

The above parameters represent an indirect estimate of preload, more direct estimation could be provided by ventricular volumes determined with echographic measurement for instance. Hemodynamic parameters determined with trans-thoracic or trans-oesophageal echography have been used in daily clinical care for decades. We highlight the results of the most studied parameters here; results for left ventricular end-diastolic area (LVEDA) [11,27-30] vary with sensitivity reported to be between 60 to 89%, specificity between 58 and 91% and the AUC of the ROC curve between 0.24 ± 0.11 and 0.78 (95% CI between 0.59 and 0.97) [11,28]. For global end-diastolic volume index (GEDVI) [26,31-33] the AUC of the ROC curves is between 0.23 and 0.70 (0.46-0.94) [32,33].

Other interesting parameters linked to echography are measurement of the inferior or superior vena cava. Vieillard-Baron and colleagues [34] reported that a superior vena cava collapsibility of 36% has a sensitivity of 90% and a specificity of 100% and an AUC of the ROC curve of 0.99 ± 0.01 in 66 patients after CABG surgery. Similar assessment of the inferior vena cava in 20 septic patients offered 90% sensitivity and specificity to predict FLR [8]. The vena cava diameter can only be properly assessed with the use transesophageal echography.

In theory, these echographically determined volume parameters of the heart are supposed to be highly reliable. The volume changes within the heart or vena cava are directly linked to cardiac function; when wall movement is limited inotropic assistance is warranted. And when filling of the ventricles is not optimal, fluid administration is indicated. Study results are very promising [35]. Several factors may frustrate these results. Operator-related factors, like level of experience, changes in probe position and intermittent application, greatly influence the reliability and robustness of echographic monitoring [36]. The predictive value for FLR of echographic parameters in patients receiving mechanical ventilation seems to outscore the results for these parameters in spontaneously-breathing patients [37].

Dynamic parameters: cyclic changes due to mechanical ventilation

In recent years dynamic parameters have been the focus of interest. Especially since more physicians use pulse contour methods that allow not only directly-available estimation of beat-to-beat cardiac output but also delivers stroke volume variation (SVV), pulse pressure variation (PPV) and systolic pressure variation (SPV) [38]. The results of literature review for the reliability of SVV to predict FLR is shown in Table 3.

Table 3 Reliability of stroke volume variation to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Hofer, *et al.* [26]	40	Cardiac surgery	12.5%	74%	71%	0.82 (0.68-0.97)
Reuter, *et al.* [11]	12	Cardiac surgery *,†	9.5%	71%	80%	0.76 (0.59-0.96)
Reuter, *et al.*[11]	14	Cardiac surgery *,†	9.5%	78%	85%	0.88 (0.77-0.99)
Preisman, *et al.* [17]	18	Cardiac surgery	11.5%	81%	82%	0.87 (0.79-0.96)
Hofer, *et al.* [31]	40	Cardiac surgery	9.6%	91%	83%	0.82 (0.68-0.97)
Hofer, *et al.* [31]	40	Cardiac surgery	12.1%	87%	76%	0.86 (0.75-0.97)
Berkenstadt, *et al.* [20]	15	Brain surgery	9.5%	79%	93%	0.87 (0.81-0.90)
Biais, *et al.* [12]	35	Liver transplant OR	10%	94%	94%	0.95 (0.81-0.99)
De Waal, *et al.* [33]	22	Cardiac surgery	8%	100%	78%	0.91 (0.78-1.00)
Cannesson, *et al.* [49]	25	Cardiac surgery	10%	82%	88%	0.87 ± 0.09
Biais, *et al.* [50]	30	ICU general	13%	100%	80%	-
Biais, *et al.* [50]	30	ICU general	16%	85%	90%	-
Derichard, *et al.* [51]	11	Major abd surgery	12%	86%	91%	0.95 (0.65–1.00)
Lahner, *et al.* [52]	20	Major abd surgery	8.5%	77%	43%	0.51 (0.32-0.70)
Monge Garcia, *et al.* [53]	38	Circulatory shock	13%	100%	80%	-

* Multiple measurements in same patients
† spontaneous breathing

(95

Pulse pressure (PP) is defined as the beat-to-beat difference between the systolic and the diastolic pressure. PPV is the amplitude of cyclic changes induced by mechanical ventilation. The variations in pulse pressure and stroke volume induced by mechanical ventilation have been linked to volume status [39]. PPV is thought to be directly proportional to stroke volume variation [40]. The reliability for SVV and PPV varies from lower sensitivity and specificity of 70% to over 90% to predict FLR (Tables 3, 4 and 5). Although SVV is a direct measure of variation in cardiac output, results for SVV are scattered. Even though PPV is used as an indirect measure for SVV, results for PPV seem superior which may be especially true in septic patients [23], where vasoplegia is less likely to cause a reliable SVV measurement result. We need to consider that the calculation of SVV requires beat-to-beat SV measurements using a pulse contour analysis algorithm whereas PPV is measured directly from the arterial waveform. SVV will require an ongoing validation in clinic conditions as algorithms are developing with time [41]. In that context it is noteworthy that more recent publications report lower area under the ROC curves than older publications. Whether this depends on publication bias, a decrease in the accuracy of newer pulse-contour methods to determine SVV or more frequent improper use remains uncertain.

Table 4 Reliability of pulse pressure variation to predict fluid loading responsiveness.

	N	Patients	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Cannesson, *et al.* [28]	18	Cardiac surgery	12%	92%	83%	0.91 ± 0.07
Feissel, *et al.* [54]	20	Sepsis ‡	17%	85%	100%	0.96 ± 0.03
Kramer, *et al.* [18]	21	Cardiac surgery	11%	100%	93%	0.99 (0.96-1.00)
Feissel, *et al.* [55]	23	Sepsis ‡	12%	100%	70%	0.94 ± 0.05
Cannesson, *et al.* [21]	25	Cardiac surgery	11%	80%	90%	0.85 ± 0.08
Soubrier, *et al.* [56]	32	Circulatory failure †	12%	92%	63%	0.81 ± 0.08
Hofer, *et al.* [26]	40	Cardiac surgery	13.5%	72%	72%	0.81 (0.67-0.95)
Auler, *et al.* [22]	59	Cardiac surgery	12%	97%	95%	0.98 ± 0.01
De Backer, *et al.* [57]	60	Critically ill, Vt ≤ 8 $ml \cdot kg^{-1}$	12%	60%	74%	0.89 ± 0.07
De Backer, *et al.* [57]	60	Critically ill	12%	88%	89%	0.76 ± 0.06
Preisman, *et al.* [17]	18	Cardiac surgery	9.4%	86%	89%	0.95 (0.89-1.00)
Wyffels, *et al.* [16]	32	Cardiac surgery	11.8%	95%	92%	0.94 (0.79-0.99)
Michard, *et al.* [58]	40	Sepsis	13%	94%	96%	0.98 ± 0.03
Cannesson, *et al.* [9]	25	Cardiac surgery	12%	88%	100%	0.92 ± 0.06
Vieillard-Baron, *et al.* [34]	66	Sepsis	12%	90%	87%	0.94 ± 0.04
Feissel, *et al.* [55]	23	Sepsis	12%	100%	70%	0.99 (0.98-1.00)
Lafanachere, *et al.* [59]	22	Circulatory failure †	12%	70%	92%	0.78 ± 0.12
Huang, *et al.* [32]	22	ARDS	11.8%	68%	100%	0.77
Vistisen, *et al.* [13]	23	Cardiac surgery	7.5%	94%	83%	-
Derichard, *et al.* [51]	11	Major abd surgery	13%	88%	92%	0.96 (0.70–1.00)
Monge Garcia, *et al.* [53]	38	Circulatory shock	10%	95%	95%	0.97 ± 0.03
De Waal, *et al.* [33]	22	Cardiac surgery	10%	64%	100%	0.88 (0.74-1.00)
Hofer, *et al.* [26]	40	CABG	12.5%	74%	71%	0.82 (0.68-0.97)
Reuter, *et al.* [11]	12	Cardiac surgery *,†	9.5%	71%	80%	0.76 (0.59-0.96)
Reuter, *et al.* [11]	14	Cardiac surgery *,†	9.5%	78%	85%	0.88 (0.77-0.99)
Preisman, *et al.* [17]	18	CABG	11.5%	81%	82%	0.87 (0.79-0.96)
Hofer, *et al.* [31]	40	CABG, SVV flotrac	9.6%	91%	83%	0.82 (0.68-0.97)
Hofer, *et al.* [31]	40	CABG, SVV picco	12.1%	87%	76%	0.86 (0.75-0.97)
Berkenstadt, *et al.* [20]	15	Brain surgery	9.5%	79%	93%	0.87 (0.81-0.90)
Biais, *et al.* [12]	35	Liver transplant OR	10%	94%	94%	0.95 (0.81-0.99)
de Waal, *et al.* [33]	22	CABG	8%	100%	78%	0.91 (0.78-1.00)
Cannesson, *et al.* [49]	25	CABG OR	10%	82%	88%	0.87 ± 0.09
Biais, *et al.* [50]	30	ICU general	13%	100%	80%	-
Biais, *et al.* [50]	30	ICU general	16%	85%	90%	-
Lahner, *et al.* [52]	20	Major abd surgery	8.5%	77%	43%	0.51 (0.32-0.70)
Monge Garcia, *et al.* [53]	38	Circulatory shock	11%	79%	89%	0.89 + 006
Cannesson, *et al.* [21]	25	Cardiac surgery	10%	88%	87%	0.86 ± 0.08

† spontaneous breathing
‡ Semi-recumbent position

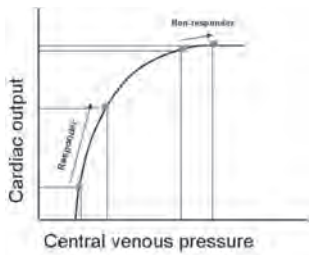
Several restrictions apply to the use of dynamic parameters. First, cardiac arrhythmias significantly decrease the reliability of SVV and PPV [36]. Second, the use of these dynamic parameters has been validated in sedated and mechanically ventilated patients without spontaneous breathing activity. Third, SVV, and probably PPV, is not only influenced by intravascular volume but also by the depth of the tidal volume used in mechanical ventilation of the lungs [11].

Table 5 Reliability of changes in parameters after a hemodynamic challenge to predict fluid loading responsiveness.

	N	Patients	Challenge	Parameter	Cut-off	Sensitivity	Specificity	Area under ROC curve ± SD (95% CI)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dPP	5%	87%	100%	0.96 (0.83-0.99)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dSP	4%	67%	82%	0.71 (0.53-0.86)
Perel, *et al.* [60]	14	Abd aorta surgery	RSVT	RSVT	0.24	88%	83%	0.90 (0.73-1.00)
Preisman, *et al.* [17]	18	CABG	RSVT	RSVT	0.51	93%	89%	0.96 (0.92-1.00)
Monge Garcia, *et al.* [53]	30	General ICU	10 s Valsalva	dPPV	52%	91%	95%	0.98 (0.84-0.99)
Monge Garcia, *et al.* [53]	30	General ICU	10 s Valsalva	dSPV	10%	73%	90%	0.90 (0.73-0.98)
Maizel, *et al.* [61]	34	Circulatory shock	Passive leg raising	dCO	5%	94%	83%	0.89 (0.73-0.97)
Monnet, *et al.* [24]	34	Circulatory shock	Passive leg raising	dCI	10%	91%	100%	0.94 (0.80-0.99)
Monnet, *et al.* [24]	34	Circulatory shock	15-s end-exp occlusion	dCI	5%	91%	100%	0.97 (0.85-1.00)
Maizel, *et al.* [61]	34	Circulatory shock	Passive leg raising	dSV	8%	88%	83%	0.90 (0.74-0.97)
Lamia, *et al.* [37]	24	Circulatory failure	Passive leg raising	dSV	12.5%	77%	100%	0.96 ± 0.04
Biais, *et al.* [50]	34	Circulatory shock	Passive leg raising	dSV TTE	13%	100%	80%	0.96 ± 0.03
Biais, *et al.* [50]	34	Circulatory shock	Passive leg raising	dSV	16%	85%	90%	0.92 ± 0.05
Thiel, *et al.* [62]	89	General ICU	Passive leg raising	dSV	15%	81%	93%	0.89 ± 0.04
Lafanechere, *et al.* [59]	22	Circulatory failure	Passive leg raising	dABF	8%	90%	83%	0.95 ± 0.04
Monnet, *et al.* [42]	71	General ICU	Passive leg raising	dABF	10%	97%	94%	0.96 ± 0.02
Monnet, *et al.* [42]	71	General ICU	Passive leg raising	dPP	12%	60%	84%	0.75 ± 0.06
Monnet, *et al.* [24]	34	Circulatory shock	Passive leg raising	dPP	11%	48%	91%	0.68 (0.50-0.83)
Monnet, *et al.* [42]	19	General ICU	Passive leg raising	dPP	8%	88%	46%	0.56 ± 0.14
Monnet, *et al.* [42]	30	General ICU	Passive leg raising	dPP	12%	88%	93%	0.91 ± 0.05
Cannesson, *et al.* [28]	18	Cardiac surgery	Passive leg raising	dSA	16%	92%	83%	0.91 ± 0.07

** Mixed spontaneous breathing and mechanical ventilation population
† Spontaneous breathing
‡ During surgery additional fluids were administered and measurements were repeated within individuals
dPP is change in pulse pressure, dSP is change in systolic pressure, RSVT is respiratory systolic variation test, dPPV is change in pulse pressure variation, dSPV is change in change in systolic pressure variation, dCO is change in cardiac output, dCI is change in cardiac index, dSV is change in stroke volume, dABF is change in aortic blood flow, dSA is variations in left ventricular stroke area

Figure 1 Cardiac function curve: a small fluid challenge or autotransfusion provocation with passive leg raising (PLR) is used to predict the effects of fluid loading. On the Y-axis cardiac output is shown and central venous pressure on the X-axis. The effects of fluid loading on central venous pressure (CVP) and cardiac output (CO) are shown. The heart of the non-responder will operate near or at the plateau of the Starling curve. A responder will show a larger change in CO when either PLR or a small fluid challenge are performed compared to a non-responder. The changes in CVP and CO caused by PLR or small fluid provocation will mimic changes of significant fluid loading.



Dynamic parameters: other challenges to the circulation

Another approach to determine FLR is a provocation method; the application of increased PEEP or an auto-transfusion with 30° to 45° passive leg raising (PLR). Particularly, the groups of Boulain, Monnet and Teboul studied the reliability of parameters during PLR to predict FLR [42,43]. The robustness and reliability of the "static parameters" during the challenge can be explained by the direct use of the Starling curve. These challenges change the working point on the Starling curve of the patient (Figure 1). The amplitude of the change in CO can be used to predict FLR. These challenges are reversible, standardized and easily performed. Results for these challenges are shown in Table 5.

Since the Starling-curve characteristics are different for each individual, with its own pathophysiological constitution, we can make use of challenge-induced changes to pinpoint the working point on the curve and answering the question: Will this patient be a responder?

Conclusions

Two adequate candidate parameters for FLR in everyday medical practise seem present. First, PPV and SVV in patients fully dependant on mechanical ventilation and secondly an auto-transfusion challenge with PLR using changes in CO, MAP or CVP. However, trials have to be performed to determine the effect of the fluid loading responsiveness strategy on hospital stay and mortality.

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