FLUID RESPONSIVENESS

FLUID RESPONSIVENESS is a strategy used to select patients that will respond with a positive reaction in a physiological parameter upon fluid administration. Curiously, there is no generally accepted definition of fluid responsiveness. A provisional definition of fluid responsiveness would be “the positive reaction of a physiological parameter of a certain size to a standardized volume of a certain type of fluid administered within a certain amount of time and measured within a certain interval”. It is clear that these issues need to be resolved before we can propose a more detailed and precise definition. The aim of predicting fluid responsiveness is to achieve this positive reaction while using the least amount of fluids.
Accurate prediction of fluid responsiveness to facilitate patient-tailored fluid titration is crucial, as has been shown that only half of critically ill patients will respond to fluid loading with an increase in cardiac output. Moreover, unnecessary fluid administration has shown to increase morbidity, mortality, hospital and intensive care stay. Over the last decade, the rise in the number of publications about fluid responsiveness in the intensive care and operating room has shown the increased interest in this topic. In this review, we describe the physiology, requirements and limitations of fluid responsiveness. Subsequently, using available literature, a practical definition on fluid responsiveness is proposed. The reliability of clinical, static and hemodynamic parameters is evaluated to predict the response to fluid loading in critically ill patients. Finally, the potential, shortcomings and use of passive leg raising is discussed in this review.

IMPORTANCE OF FLUID RESPONSIVENESS

Not until recently, a strategy of cardiac output (CO) maximization was employed to maximize oxygen delivery to vital organs of critically ill patients in order to prevent prolonged oxygen deficit leading to an inflammatory cascade resulting in multi-organ dysfunction. However, achieving a supra-physiological CO and systemic oxygen delivery through inotropics has shown to be detrimental, although some studies have shown improved outcomes upon oxygen delivery optimization. Moreover, overzealous fluid administration can lead to general and pulmonary edema, cardiac failure, anastomotic leakage, infections prolonging hospitalization and even cause death. As fluid administration is frequently employed as one of the first steps to improve hemodynamics, physicians caring for critically ill patients try to assess and optimize the volume status to preserve oxygen delivery to vital organs. Merely assessing volume status does not predict the response upon fluid loading. The prediction of fluid responsiveness is crucial as inotropic support may be indicated instead of fluid replacement in patients who are deemed fluid unresponsive. 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\%\textsuperscript{11}. Therefore, it is essential to select those patients that will respond with a positive reaction of a physiological parameter upon fluid loading, so called fluid responders. This selection can be made with the use of fluid responsiveness. Besides fluid responsiveness, other terms, like (biventricular) preload dependence and preload responsiveness have been used in the past\textsuperscript{12}. However, the administration of fluid does not necessarily lead to an increase in preload. Furthermore, preload is not easily obtained using the Law of Laplace and only indirectly estimated. Therefore, the term fluid responsiveness is preferred as it acknowledges the overall clinical hemodynamic effects of fluid administration on a patient.

**PHYSIOLOGY**

Otto Frank and Ernest Starling demonstrated increased ventricular contraction with stroke volume augmentation when the ventricle was stretched prior to contraction due to increased venous return\textsuperscript{13}. When stroke volume is set off against the sarcomere length of the cardiac muscle, the Frank-Starling curve is constructed. When CO, the product of stroke volume and heart rate, is plotted against right atrial pressure (RAP) as reflection of ventricular preload, the cardiac function curve is obtained. A patient’s response upon fluid loading can be clarified using the cardiac function curve (Fig 1).

Importantly, CO cannot increase without an increase in venous return as both have to be equal within a few heartbeats. Fluid loading does not guarantee an increase in preload as a considerable amount of volume residing in distensible capacitance veins does not create transmural pressure. This is the unstressed volume. Only the stressed volume that does create pressure determines mean systemic filling pressure (MSFP), which is the driving force behind venous return. MSFP is the pressure throughout the vascular system when CO would be zero. Therefore CO is indirectly driven by the pressure gradient (MSFP – RAP) limited by venous
flow resistance. MSFP can be increased by enlarging the stressed volume at the expense of unstressed volume by venoconstriction. However, venous return can be hampered by an increase in the resistance venous flow encounters. Increasing MSFP more than RAP through fluid loading can increase venous return and CO without this drawback.

CO RESPONSE

Different physiological parameters can be used to define fluid responders, such as urine output, blood pressure and CO. CO is often used as it constitutes an important part of tissue oxygen delivery together with the oxygen content of arterial blood. Furthermore, upon fluid loading CO is the resultant when described by the cardiac function curve. Consensus must be reached on what can be regarded as a clinically significant increase in CO after a standardized amount of fluid is administered. In current literature, the change in CO to discriminate between responders and non-responders after a fluid challenge varies between 6% and 25%.\textsuperscript{14-18} This inconsistency complicates direct comparison between studies and usage in clinical practice.

Previously, Critchley and Critchley defined a clinical significant change as a change of twice the standard deviation of the measurement method.\textsuperscript{19} The clinical significance of the change in CO thus predominantly depends on the accuracy of technique to measure CO. Only when a change in CO is larger than twice the measurement error of this technique, one can be confident that CO has truly increased or decreased. Therefore, it is reasonable to adapt the cut-off value to discriminate responders from non-responders depending on the used measurement technique. For instance, the error considered for thermodilution is reckoned to be close to 7% depending on measurement of three boluses averaged.\textsuperscript{20} A difference of $> 14\%$ ($7\% + 7\%$) before and after fluid loading is required to ensure that the validation of a responder is correct. Indeed, the cut-off point for increase in CO generally used for thermodilution measurements in the literature is 15% to define fluid responders.
Finally, many methods exist to measure CO including ultrasound, dilution techniques, Fick’s principle, arterial pulse contour analysis and bioreactance. Each method has distinct benefits and disadvantages. The value of different CO methods in predicting fluid responsiveness have not been extensively studied. More research is needed that directly compares different CO measurements as accuracies can vary between 5 and 25%. A fast responding, accurate and easy to use method is preferable, ideally applicable in a wide variety of clinical settings.

AMOUNT OF FLUID
The clinical significance of a change in CO does not only depend on the measurement technique but also on the amount of fluid used during the loading procedure. If 500 mL is administered, instead of for instance 250 mL, the change in CO from baseline can be expected to be larger. Although this may seem obvious, in the literature the total volume of administered fluid to determine fluid responsiveness varies widely between 4 mL·kg⁻¹ to 20 mL·kg⁻¹ or 100 mL to 1000 mL.

It is conceivable that a standard administered volume could potentially affect fluid responsiveness if not adjusted to weight, i.e. smaller patients becoming more likely to be assessed as fluid responders. However, no correlation between responders and weight has been reported in the literature using a standard volume regardless of individual weight.

To decide on the amount of fluid, clinical consequences need to be discussed. When the administered volume would be large, for instance 1000 mL, steps taken on the cardiac function curve are large and chances are greater that the patient will function on the flat part of the curve after fluid infusion. As overzealous fluid administration has shown to increase morbidity and mortality, patient tailored fluid titration is important advocating smaller fluid loading volumes. In order to approximate the position through changes in CO and RAP on the cardiac function curve upon fluid loading, large enough filling steps are needed taking into
account the measurement error described earlier.\textsuperscript{19} We advocate the use of a fluid bolus of 500 mL or 6 mL·kg\textsuperscript{-1}, which has most frequently been used in the literature. Using multiple fluid administrations will lead to CO optimization without over-increasing RAP and hydrostatic pressure causing pulmonary and general edema.

**TYPE OF FLUID**

Since different types of fluids with diverse characteristics are used in the literature and clinical practice, consensus must be reached on the type of fluid used in the evaluation of fluid responsiveness. The most obvious difference between the types of fluid administered is the time in which the administered fluid remains in the intra-vascular compartment. Colloids, for instance hydroxyethyl starch solutions, have the longest lasting effect of addition to the circulating volume of approximately 90 minutes and deliver a more linear increase in cardiac filling and stroke volume than crystalloids.\textsuperscript{29} Although the Surviving Sepsis Campaign guidelines\textsuperscript{30} do not discriminate between the use of crystalloids in fluid resuscitation, more and more proof is surfacing that colloids can result in adverse events. The Scandinavian Starch for Severe Sepsis/Septic Shock trial, also known as the 6S trial\textsuperscript{31}, even demonstrated an increase in mortality, confirming this alarming finding of previous studies.\textsuperscript{32} The use of colloids is associated with kidney dysfunction necessitating renal replacement therapy as well as coagulopathy requiring more red blood cell transfusions. It remains unclear if similar adverse events occur with the usage of gelatins, dextrans or albumin. In light of the absence of evidence supporting the use of colloids and others compared to crystalloids, we advocate the use of the latter to assess fluid responsiveness.\textsuperscript{33}

**TIMING**

Since a portion of administered fluids of any kind will eventually be lost to the extra-vascular compartment, the timing of the CO measurement is of importance.\textsuperscript{34} Therefore, certain time limits need to be determined. Two hours after fluid loading, regardless of type,
largely all of the administered volume has disappeared from the circulation.\textsuperscript{35} Thus if the time interval is chosen too late, the effect of increased preload on CO has potentially passed. Furthermore, rapid optimization of tissue oxygenation of septic patients has shown to improve outcome.\textsuperscript{36} On the other hand, too rapid infusion of fluids may accelerate a rise in cardiac filling pressures potentially inducing adverse affects as pulmonary edema. Dependent on cardiac function and pulmonary status, a duration of 15 minutes for fluid loading is proposed measuring its effect on CO within 15 minutes before crystalloids tend to migrate to the extra-vascular compartment.\textsuperscript{35}

**DEFINITION AND RESTRICTIONS**

When these considerations are taken into account, we ultimately come up with the following definition of fluid responsiveness “an improvement in a physiological parameter preferably cardiac output within 15 minutes superseding twice the error of the measuring technique following a 15-minute administration of 6 mL·kg\textsuperscript{-1} crystalloids”.

It is important to realize that the optimization of CO is only warranted in the treatment of tissue hypoperfusion. Patient’s inclusion in clinical trials for fluid loading were based on clinical evaluation, for instance decreased urine production, which have shown not to correlate with volemic state.\textsuperscript{37} Even during normovolemia fluid responsiveness can be present, frequently resulting in fluid over administration. Only if organ hypoperfusion is truly present, an increase in CO to facilitate tissue oxygen delivery is needed. Furthermore, an increase in CO does not guarantee that organ perfusion is improved as is frequently observed in sepsis.\textsuperscript{38} Fluid responsiveness is a commonly accepted approach to optimize volume status while minimizing deleterious fluid administration. Interestingly no study has yet been performed that proves an effect on intensive care stay, ventilator days, morbidity and mortality. It should be noted that fluid responsiveness could even have adverse effects on cardiac function as augmented CO increases myocardial workload and thus oxygen use and
demand potentially eliciting myocardial ischemia. Nevertheless, the restrictive use of fluids has regularly shown to be beneficial. When fluid responsiveness is tested in critically ill patients, approximately 50% will respond with an increase in CO > 15% coined fluid responders. Subsequently, half of patients will receive unnecessary fluid loading up to 500 mL knowing that a positive fluid status has been correlated with worse outcomes.

CLINICAL PARAMETERS

The initial assessment of volume status is most often based on clinical signs and symptoms in the prediction of fluid responsiveness, like skin turgor, urine color or production, fluid balance and the presence of peripheral edema. In a study by Stephan et al. hypovolemia was defined as a 10% lower circulating blood volume compared to a control population. Hypovolemia was present in 53% of critically ill patients. In a separate study they found that clinical signs do not prove to be useful to discriminate between hypovolemic and normovolemic individuals. In both conditions, fluid responsiveness can be present. The assessment of volume status using clinical parameters on their own appears unreliable to predict fluid responsiveness.

STATIC PARAMETERS

Mean arterial pressure (MAP) is a well-identified goal to maintain perfusion of vital organs, although it has not been studied extensively for its value to predict fluid responsiveness. There are only a couple of studies available that report on the reliability of MAP to predict fluid responsiveness. The low predictive value of MAP is likely related to the influence of changes in systemic vascular resistance by the disease state, for instance vasoplegia in sepsis, and pre-existing differences in normotensive values between individuals. The International Consensus Conference on Hemodynamic Monitoring in 2006 found moderate to low evidence to implement target blood pressures in the management of shock in the absence of relevant clinical studies.
Heart rate (HR) has been studied on a small scale. In theory, heart rate could be an accurate and non-invasive predictor of fluid responsiveness. However, the predictive value of baseline HR in patients undergoing cardiac or neurosurgery has been only fair.\textsuperscript{41,43} Mechanical ventilation and anesthesia are known to impede neural and humoral control. Furthermore, the large number of patients receiving negative chronotropic medication such as beta-blockade further complicates the possibility to use HR for the prediction of fluid responsiveness.

Central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are still the most often used hemodynamic parameter in the assessment of fluid responsiveness.\textsuperscript{44-46} However, multiple studies in patients with sepsis, trauma, acute respiratory failure, and in the perioperative phase of cardiovascular surgery have shown CVP and PAOP to be poor predictors of fluid responsiveness.\textsuperscript{47,48} CVP was found to have clinical significance only for very low and high values.\textsuperscript{47} PAOP showed a poor predictive values for fluid responsiveness in cardiac surgery patients.\textsuperscript{49,50} In Table 1 several studies performed in different clinical settings are displayed that reported on the prediction of fluid responsiveness by CVP and PAOP respectively.\textsuperscript{22,43,51-58}

Left ventricular end-diastolic area (LVEDA) has been viewed as a more direct estimation of preload than the above-mentioned parameters. Echocardiographic assessment of ventricular volumes has been in use in daily clinical care for decades and is now increasingly utilized in the critical care setting and becoming standard practice in particular high risk peri-operative patients.\textsuperscript{59-62} However, echocardiography is accompanied with great inter-operator variability. Sensitivity and specificity for LVEDA predicting fluid responsiveness vary between 60-90\.\textsuperscript{52,53,63-65} The predictive value of global end-diastolic volume index (GEDVI) obtained by transpulmonary thermodilution is also only modest with an area under the ROC curve between 0.23 and 0.70.\textsuperscript{25,66}
CO is frequently used as the physiological parameter in the determination of fluid responsiveness upon fluid loading. However, baseline CO measurements are not uniform in predicting fluid responsiveness. Baseline CO values to predict fluid responsiveness has been predominantly studied in cardiac surgery patients with only one study in septic patients. In both patient groups, baseline CO demonstrated only of moderate predictive value for fluid responsiveness.

In summary, measurement of static hemodynamic parameters such as CVP and LVEDA can not lead to a proper prediction of the response to the administration of fluid. Even baseline CO possesses only moderate predictive value as the cardiac function curve characteristics differ between patients as well as within patients with continuously changing pathophysiological constitutions. Moreover, a single value does not discriminate whether a patient is on the steep part or near the plateau on the curve. To attain whether a patient is a fluid responder or non-responder, at least two points on the curve are needed which necessitates the change in preload on one hand with the subsequent measurement of CO or another physiological parameter on the other hand.

DYNAMIC PARAMETERS

In recent years dynamic parameters have been the focus of interest in predicting fluid responsiveness. Variables based on heart-lung interaction have been an attractive way to predict fluid responsiveness. Already described a half century ago, mechanical ventilator-induced stroke volume variation (SVV) and pulse pressure variation (PPV) have shown to be reliable predictors of fluid responsiveness in different clinical settings (Table 2). These dynamic parameters have been increasingly employed in the operating room and intensive care, especially since more physicians use pulse contour methods that allow not only CO measurements but also obtain SVV and PPV. 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 and will need further (meta-
) analysis.

Furthermore, several restrictions apply to the use of ventilation-induced dynamic
parameters. First, cardiac arrhythmias significantly decrease the reliability of SVV and PPV.\(^2\)
Second, the use of these dynamic parameters has been validated in sedated and mechanically
ventilated patients without spontaneous breathing activity.\(^2^3\) Third, SVV and PPV require
mechanical ventilation with tidal volumes > 8 mL·kg\(^{-1}\), which has demonstrated to contribute
to mortality.\(^7^5\)-\(^7^8\) Tidal volumes < 8 mL·kg\(^{-1}\) in the context of lung protective ventilation has
shown to improve clinical outcome even in non-acute respiratory distress syndrome patients.\(^7^9\)
Finally, high frequency ventilation, increased abdominal pressure, open-chest conditions,
elevated pulmonary artery pressure and right ventricular dysfunction all lead to a loss of the
predictive value of ventilation-induced dynamic parameters.\(^8^0\)-\(^8^4\) This severely limits their use
in everyday clinical practice.\(^8^5\)

Other interesting dynamic parameters regard the echographic assessment of changes in
inferior and superior vena cava diameter. A superior vena cava collapsibility of 36% has
demonstrated a sensitivity of 90% and a specificity of 100% in predicting fluid responsiveness
in patients after CABG surgery.\(^8^6\) However, the superior vena cava diameter can only be
properly assessed with the use of transesophageal echocardiography. Similar assessment of
the inferior vena cava in twenty septic patients offered 90% sensitivity and specificity to
predict fluid responsiveness.\(^5^4\) The predictive value for fluid responsiveness of echographic
parameters in patients receiving mechanical ventilation seems to outscore the results for these
parameters in spontaneously-breathing patients.\(^8^7\) A couple of factors may frustrate the
application of echocardiography in the prediction of fluid responsiveness. Frequent
assessment is laboursome and non-continuous. Furthermore, echocardiographic measurements
are operator dependent influencing the use and reliability of echocardiographic assessment of fluid responsiveness.²

PASSIVE LEG RAISING

Passive leg raising (PLR), the passive 30°-45° elevation of straightened legs, was originally used by clinicians to assess hamstring muscle length and lumbar nerve root compression, as well as commonly used for the initial treatment of hypovolemic shock. PLR induces a reversible auto-transfusion resulting in an increase in right and left ventricular preload with a maximum within a minute.⁸⁸ Its effect vanishes completely when the legs are returned to the horizontal position and does not persist when the legs are held upright either.⁸⁹ PLR mimics temporary fluid loading and is the preferred challenge using postural changes. The head-down tilt test, commonly known as the Trendelenburg manoeuvre, has shown to have adverse effects on pulmonary blood flow and cerebral circulation.

EVIDENCE FOR PLR

In 2002, Boulain was the first to demonstrate a strong correlation between changes in stroke volume during PLR and by fluid loading.⁸⁸ Half a decade later, multiple studies confirmed the highly predictive power of PLR in forecasting fluid responsiveness with a sensitivity and specificity ranging between 85-95%.⁹⁰-⁹⁶ In contrast to the dynamic parameters SVV and PPV, similar predictive values were obtained with PLR in spontaneously breathing patients, regardless of cardiac rhythm.⁹⁷,⁹⁰,⁹³,⁹⁴ Changes in preload after PLR has now repeatedly shown to be highly predictive in a wide variety of clinical settings and using different hemodynamic parameters to assess its effect (Table 3).⁹⁰,⁹⁶-¹⁰¹ Novel challenges of the cardiac function curve without the necessity of fluid administration include the end-expiratory occlusion test, the upper arm occlusion pressure and the PEEP-induced increase in central venous pressure which are all potential alternatives requiring further development.⁹⁶,¹⁰²,¹⁰³ Especially the amount of preload change induced by these challenges
need to be verified in an large variety of patients. Based on its track record in different patient
groups, ease of use and robustness, PLR offers a promising non-invasive tool to test a
patient’s position on the cardiac function curve.

HEMODYNAMIC PARAMETERS DURING PLR

Multiple hemodynamic parameters have been used to assess the effects of PLR in
predicting fluid responsiveness including the change in pulse pressure, stroke volume, CO,
aortic blood flow and left ventricular stroke area. These parameters have been
acquired with different techniques such as pulse contour analysis, echo(cardio)graphy,
thermodilution and plethysmography. The latter is a non-invasive method and in theory
ideally suited for continuous monitoring of patients with no invasive arterial and/or central
venous catheter in place. However, plethysmographic waveform analysis had only weak
predictive value of fluid responsiveness in healthy volunteers upon PLR probably due to acute
changes in vasomotor tone. More recently, studies investigating bioreactance as monitoring
device upon PLR has proven to be an accurate non-invasive method warranting further
investigation.

The predictive value of changes in pulse pressure upon PLR can be improved when
used in combination with the concomitant change in CVP. However, the results of changes
in CO following PLR are significantly better than changes in blood pressure, i.e. pulse
pressure, as demonstrated in a meta-analysis of clinical trials. This can be explained by the
fact that PLR, through the increase in cardiac preload, stimulates cardiopulmonary receptors
resulting in an increase in CO output and dilatation of peripheral arteries respectively. These
two factors counterbalance any effect on blood pressure and heart rate during PLR with little
or no involvement of the arterial baroreceptors. However, when PLR does induce arterial
baroreceptor stimulation, for instance through pain, arterial compliance will alter causing
pulse pressure to inaccurately reflect stroke volume. Moreover, the response to PLR also
depends upon the ability to recruit stressed volume raising MSFP. During vasoconstriction, the cardiac preload and CO increase upon PLR is greater.\textsuperscript{110} By contrast, a vasodilatory state with a higher unstressed volume could potentially result in a lower increase in cardiac preload by PLR, falsely labelling a patient as a fluid non-responder. To assess the effect of PLR a fast response and direct measure of CO is recommended. Since PLR usually does not affect heart rate, the change in stroke volume can also be attained. Furthermore, it is promising that changes in end-tidal carbon dioxide have recently shown the ability to predict fluid responsiveness upon PLR as well.\textsuperscript{111,112}

POSITIONING FOR PLR

Currently two different procedures for PLR are described: classically the PLR maneuver was started with the patient in the supine position, although in recent trials using PLR to predict fluid responsiveness more often a semi-recumbent starting position is used (Fig 2).\textsuperscript{90,96-101} The classic PLR starting position is often present in the operating room, while most patients on the intensive care are positioned semi-recumbent. PLR from the semi-recumbent starting position not only transfers blood from the lower limbs, but mobilizes blood from the abdominal compartment as well, since the legs are lifted with the trunk placed from semi-recumbent to horizontal position. PLR is thought to be equivalent to 150-300 mL of fluid loading,\textsuperscript{88} and auto-transfusion of fluid volumes > 250 mL should be pursued considering the measurement error earlier described.\textsuperscript{19} The semi-recumbent starting position is therefore preferred, as it has shown to induce a larger increase in cardiac preload than the classic PLR started from the supine position.\textsuperscript{113} An increase between 9\% and 15\% in CO upon PLR has shown the ability to predict fluid responsiveness with an area under the Receiver Operating Characteristic Curve of $\geq 0.88$ (Table 3).
APPLICATION OF PLR

Using PLR to assess fluid responsiveness is attractive in that it produces a rapid and reversible fluid challenge feasible at the bedside even in spontaneously breathing patients with arrhythmia. There is growing evidence in a large variety of patients as a strong predictor of fluid responsiveness, especially when the effect of PLR is assessed by a direct measure of CO. Non-invasive methods are now available to assess the rapid hemodynamic changes as the auto-transfusion effect upon PLR is maximal within one minute. PLR thus provides a useful tool in a wide variety of clinical settings to predict fluid responsiveness, while using a desired reversible yet genuine fluid administration.

LIMITATIONS TO PLR

Special attention has to be paid for re-referencing of blood pressure transducers at the level of the tricuspid valve when performing PLR from the semi-recumbent starting position. Furthermore, the exact amount of auto-transfusion cannot be determined as this is in part dependent on volemic state, venous compliance and intra-abdominal pressure. As such, PLR has been implicated to be inaccurate in case of intra-abdominal hypertension impairing venous return.

Furthermore, PLR can interfere with echocardiographic assessment of CO. In addition, the effect of PLR has to be assessed by a real-time direct measure of CO capable of tracking changes within a short time frame as its effect is maximal within one minute. The risk of aspiration could increase performing the postural change, although this can be reduced by keeping the thorax in horizontal position during PLR. Moreover, intracranial pressure can increase limiting its use in patients with traumatic brain injury. Evidently, in patients after amputations or with fractures of lower extremities, PLR is either not possible or painful.

Several other limitations exist preventing its application in all patients, especially in the operating room. Thankfully, in those situations the requirements for reliable prediction
using ventilator-induced dynamic parameters SVV and PPV are frequently met peri-
operatively, such as absence of spontaneous breathing, regular heart rhythm and an arterial
and/or central venous catheter in place. Dynamic parameters, given their robust evidence in
various clinical settings and automatic calculation by most recent bedside hemodynamic
monitors, still have clinical use besides PLR as fluid responsiveness predictors.

CONCLUSIONS

The prediction of fluid responsiveness is vital to titrate fluids to critically ill patients
preventing organ hypoperfusion and potentially harmful over-resuscitation at the same time.
However, the definition of fluid responsiveness lacked consensus as the quantity and type of
administered fluids and the timing and cut-off values to define responders varied largely. We
propose to define fluid responsiveness as “an increase in a physiological parameter
preferably cardiac output within 15 minutes superseding twice the error of the measuring
technique following a 15-minute administration of 6 mL·kg⁻¹ crystalloids”. Clinical, static and
dynamic parameters all attempt to assess whether a patient will benefit from fluid
administration. There is clear indication that the use of clinical signs as well as pressure and
volumetric static parameters are unreliable to predict fluid responsiveness. Measurements of
dynamic parameters such as SVV and PPV have consistently shown to be more reliable than
static parameters in predicting fluid responsiveness. However, several requirements limit the
use of these dynamic parameters in critically ill patients. A brief, rapid but completely
reversible auto-transfusion by PLR provides accurate prediction of fluid responsiveness in a
wide variety of clinical settings in different patient populations, although some situations limit
its application. Studies on outcome using PLR to guide fluid titration are still lacking and
urgently needed.
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FIGURE LEGENDS

Fig 1. The effects of fluid loading on the relation between cardiac output (CO) and right atrial pressure (RAP) is shown in the cardiac function curve. A fluid responder operating on the steep part of the curve will show a larger increase in CO upon fluid loading when compared to a non-responder. The heart of a non-responder will operate near or at the plateau of the cardiac function curve resulting in a larger increase in RAP than a responder upon fluid loading.

Fig 2. The two starting positions for passive leg raising (PLR): the classic PLR maneuver started with the patient in the supine position mostly present in the operating room vs. the semi-recumbent starting position mainly employed in the intensive care. The semi-recumbent position mobilizes blood from the abdominal compartment as well, creating a larger venous return and elevation of biventricular preload compared to the classic PLR.
Table 1: Predictive value of CVP and PAOP on fluid responsiveness in different clinical settings

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>CVP Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
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<td>Neurorsurgery</td>
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<td>ARDS</td>
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<td>Decreased LVEF</td>
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<td>90%</td>
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<td>70%</td>
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Abbreviations: CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; ARDS, acute respiratory distress syndrome; LVEF, left ventricular ejection fraction; Cut-off, set value for prediction of fluid responsiveness (mmHg); AUROC, area under the Receiver Operating Characteristic curve (95% CI or ± SE)
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<td>Cardiac surgery</td>
<td>23</td>
<td>12.5</td>
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<td>71%</td>
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<tr>
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<td>43</td>
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<td>93%</td>
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<tr>
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<td>69</td>
<td>9</td>
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<td>91%</td>
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<tr>
<td>Liver transplantation</td>
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<td>94%</td>
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<tr>
<td>Pulmonary lobectomy</td>
<td>70</td>
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<td>82%</td>
<td>92%</td>
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<tr>
<td>Sepsis</td>
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<td>15.5</td>
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<td>80%</td>
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<td>PPV</td>
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<td></td>
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<td></td>
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<tr>
<td>Abdominal surgery</td>
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<td>13</td>
<td>88%</td>
<td>92%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>72</td>
<td>11.5</td>
<td>80%</td>
<td>74%</td>
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<tr>
<td>Hepatic surgery</td>
<td>53</td>
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<td>79%</td>
<td>93%</td>
</tr>
<tr>
<td>Scoliosis surgery</td>
<td>69</td>
<td>11</td>
<td>88%</td>
<td>82%</td>
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<tr>
<td>Liver transplantation</td>
<td>22</td>
<td>10</td>
<td>94%</td>
<td>94%</td>
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<tr>
<td>Circulatory shock</td>
<td>73</td>
<td>10</td>
<td>95%</td>
<td>95%</td>
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<tr>
<td>Sepsis</td>
<td>74</td>
<td>17</td>
<td>85%</td>
<td>100%</td>
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<tr>
<td>ARDS</td>
<td>25</td>
<td>11.8</td>
<td>68%</td>
<td>100%</td>
</tr>
<tr>
<td>Various</td>
<td>75</td>
<td>12</td>
<td>88%</td>
<td>89%</td>
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</tbody>
</table>

Abbreviations: SVV, stroke volume variation; PPV, pulse pressure variation; ARDS, acute respiratory distress syndrome; Cut-off, set value for prediction of fluid responsiveness (%); AUROC, area under the Receiver Operating Characteristic curve (95% CI or ± SE)
Table 3: Predictive value of PLR on fluid responsiveness in different clinical settings

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUROC</th>
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<tbody>
<tr>
<td>Cardiac surgery&lt;sup&gt;97&lt;/sup&gt;</td>
<td>3</td>
<td>93%</td>
<td>73%</td>
<td>0.81 (0.61-0.94)</td>
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<tr>
<td>Circulatory shock&lt;sup&gt;98&lt;/sup&gt;</td>
<td>9</td>
<td>94%</td>
<td>83%</td>
<td>0.94 (0.85-0.98)</td>
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<tr>
<td>Sepsis&lt;sup&gt;96&lt;/sup&gt;</td>
<td>10</td>
<td>91%</td>
<td>100%</td>
<td>0.94 (0.80-0.99)</td>
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<tr>
<td>ARDS with ECMO&lt;sup&gt;99&lt;/sup&gt;</td>
<td>10</td>
<td>62%</td>
<td>92%</td>
<td>0.88 (0.69-0.97)</td>
</tr>
<tr>
<td>General ICU&lt;sup&gt;100&lt;/sup&gt;</td>
<td>15</td>
<td>81%</td>
<td>93%</td>
<td>0.89 ± 0.04</td>
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<tr>
<td>Severe preeclampsia&lt;sup&gt;101&lt;/sup&gt;</td>
<td>12</td>
<td>75%</td>
<td>100%</td>
<td>0.93 (0.83-1.00)</td>
</tr>
<tr>
<td>Various&lt;sup&gt;96&lt;/sup&gt;</td>
<td>13</td>
<td>100%</td>
<td>80%</td>
<td>0.96 ± 0.03</td>
</tr>
</tbody>
</table>

Abbreviations: PLR, passive leg raising; ARDS, acute respiratory distress syndrome; ECMO, extra corporal membrane oxygenation; ICU, intensive care unit; Cut-off, set value for prediction of fluid responsiveness (%); AUROC, area under the Receiver Operating Characteristic curve (95% CI or ± SE)
Fig 1

Cardiac output

Right atrial pressure
Fig 2

classic

semi-recumbent

PLR