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NON-INVASIVE HEMODYNAMIC MONITORING TECHNIQUES FOR DETECTING PRELOAD RESPONSIVENESS IN CRITICALLY ILL PATIENTS

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Summary

Volume expansion is the first-line treatment for acute circulatory failure in almost all cases. However, its inconsistent effectiveness and its side effects make it necessary to predict the effects before undertaking it. Several tests have been developed to detect this state of preload dependence, and we are interested in refining some of them and improve their use.

The end-expiratory occlusion (EEXPO) test consists in transiently stopping mechanical ventilation at end expiration to increase venous return and, thus, cardiac preload. In preload responder patients it is expected to increase cardiac output. We have gathered an amount of information from the existing literature, showing that its ability of detecting fluid responsiveness is very high, through a systematic review and meta-analysis.

The effects of this test must be assessed on cardiac output, and several methods have already been described for this. Bioreactance is a completely non-invasive technique to measure cardiac output, which has been demonstrated to be reliable in detecting preload responsiveness through a passive leg raising (PLR) maneuver. Nevertheless, its role in detecting a positive EEXPO test was never investigated. In the main study of this PhD project, we show that the current available commercial version of the bioreactance device is not suitable for this purpose, due to its very long averaging and refreshing times (24 and 4 seconds, respectively). However, when we used a research version of the device, which allowed us to reduce both intervals (8 and 1 second for averaging and refreshing times, respectively), bioreactance proved to be a reliable method to detect preload responsiveness through the EEXPO test.

We have also described an original and reliable method for measuring the effects of both PLR and EEXPO tests, which consists of measuring the perfusion index (PI), the ratio between the pulsatile and the non-pulsatile portion of the pulse oxygen saturation signal. Although the signal could not be collected stably in all patients, changes in this index during passive leg raising were able to measure the effects of the PLR test and predict the response to volume expansion. Similarly, PI measurements could identify a positive EEXPO test, even though their changes were of lower amplitude compared to those of a PLR test.

Our results open up the possibility of measuring the effects of these tests of preload responsiveness using non-invasive tools. This could prompt their use outside the intensive care unit, such as in the emergency department, where tracking changes of cardiac output during the first hours of the management of acute circulatory failure could lead to a more rational use of fluid administration.

Sommario

L'espansione volemica rappresenta il trattamento di prima linea in quasi tutti i pazienti con insufficienza circolatoria acuta. Tuttavia, tale azione non è sempre efficace e non è scevra di effetti collaterali. Per tale motivo gli effetti di una espansione volemica andrebbero previsti prima di metterla in atto. A tale proposito, numerosi test sono stati elaborati al fine di riconoscere la presenza di una precarico responsività, ed è stato nostro obiettivo poter aggiungere alcune evidenze a questi test ed ampliarne la loro applicazione.

Il test di occlusione tele-espiratoria (EEXPO test) consiste nell'interrompere la ventilazione meccanica al termine dell'espirazione in modo da far aumentare il ritorno venoso, e quindi il precarico del cuore destro. Nei pazienti precarico responsivi, questa manovra porta ad un aumento della gittata cardiaca. Partendo dalla letteratura esistente abbiamo aumentato la quantità di evidenza scientifica in favore di questo test, attraverso una revisione sistematica e una metanalisi, che hanno confermato l'elevata abilità nel riconoscere uno stato di fluido responsività.

Gli effetti di questo test devono essere monitorati attraverso la variazione della gittata cardiaca e, a tal proposito, molte metodiche sono state sviluppate. La bioreattanza è una tecnica completamente non invasiva per la misura della gittata cardiaca, che si è dimostrata affidabile nel riconoscere uno stato di precarico dipendenza attraverso una manovra di passive leg raising (PLR). Tuttavia, la sua abilità nel riconoscere un EEXPO test positivo non è mai stata investigata. Nello studio principale di questo progetto di Dottorato di Ricerca, abbiamo mostrato che la versione della bioreattanza attualmente disponibile in commercio non è in grado di riconoscere uno stato di precarico dipendenza all'EEXPO test, a causa degli intervalli troppo elevati sia di campionamento del segnale sia di refresh dei valori sullo schermo (24 e 4, rispettivamente). Tuttavia, quando abbiamo potuto utilizzare una versione di ricerca di tale dispositivo, che ci ha permesso di ridurre entrambi gli intervalli (a 8 e 1 secondo, rispettivamente), la bioreattanza si è dimostrata una metodica affidabile nel rilevare uno stato di precarico responsività attraverso l'EEXPO test.

Abbiamo poi descritto un metodo originale e credibile per misurare gli effetti sia di un PLR che di un EEXPO test, che consiste nel misurare l'indice di perfusione (PI), ossia il rapporto tra la porzione pulsatile e non pulsatile del segnale di saturazione d'ossigeno al pulsossimetro. Sebbene il segnale non sia stato raccolto in maniera stabile in tutti i pazienti, le variazioni di questo indice durante un passive leg raising sono risultate in grado di predire una risposta all'espansione volemica. Analogamente, la misura di PI è stata in grado di identificare la positività all'EEXPO test, sebbene con variazioni di amplitudine minore rispetto a quelle di un PLR test.

Questi risultati aprono la possibilità di valutare gli effetti di alcuni test di precarico responsività utilizzando metodiche non invasive per la misura della gittata cardiaca. Questo potrebbe promuovere il loro utilizzo anche fuori dalla terapia intensiva, per esempio in pronto soccorso, dove monitorare le variazioni della gittata cardiaca durante le prime ore di gestione di un paziente con insufficienza circolatoria acuta può portare ad un uso più razionale dell'espansione volemica.

First part: scientific context

I. Volume expansion – physiology

1. Current knowledge

1.1. The concept of volemia

Volemia corresponds to the total blood volume of the body and is normally situated in the range of 65 to 75 mL/kg. From a pathophysiological point of view, this volume is divided in "*stressed*" and "*unstressed*" volume. The stressed volume is not subjected to the pressure from the walls of the veins, which are extremely compliant, and does not participate to systemic venous return. Conversely, the pressure exerted by the venous walls on the stressed blood volume is responsible for the flow of venous blood to the right atrium.

From an anatomical point of view, the volume is distributed mainly in the systemic circulation and, for the rest, in the pulmonary circulation and the heart in diastole, whereas from a hemodynamic point of view, the distribution is made between the high pressure and low pressure area. Blood volume is estimated through either the volume of the heart chambers or the pressures in the right and left heart chambers.

1.2. Cardiac preload

The preload of the ventricles corresponds to the tension of their wall at the end of diastole. It depends on the end-diastolic filling volume, the transmural pressure of the ventricle and the end-diastolic wall thickness. Along with afterload and contractility, it is one of the determinants of ventricular stroke volume and, therefore, cardiac output [1–7]. In clinical practice, preload cannot be measured, but only estimated using either the dimensions of the ventricles or their filling pressure. However, none of these is a pure marker of ventricular preload and the relationship between them is not linear.

In fact, the greater is the volume, the higher is the diastolic elastance. Many factors increase diastolic elastance such as myocardial ischemia or hypertrophy, pericardial effusion, increased intrathoracic pressure or, for the diastolic elastance of the left ventricle, compression by a dilated right ventricle. Thus, in the presence of these factors, for the same ventricular transmural tele-diastolic pressure, the tele-diastolic volume is reduced.

1.3. Systolic function curve and preload reserve

Ventricular preload is a fundamental parameter that determines the contractile performance of the myocardial fiber. Indeed, the force that is generated depends on the length of the fiber just before the

contraction. This mechanism is applied up to a maximum fiber length, beyond which the force of contraction cannot longer increase, but even decreases. The healthy heart works at about 80% of this maximum length and, therefore, has a “preload reserve”.

The combination of a systolic performance index on the ordinate (systolic ejection volume or cardiac output) and a preload index on the abscissa (telediastolic volume of the left ventricle, transmural pressure of the right atrium or central venous pressure), allows the graphic representation of the ventricular function, conventionally called the Frank-Starling curve. This ventricular systolic function curve establishes the relationship between preload and stroke volume and reflects the fact that for a given level of afterload and ventricular contractility, an increase in ventricular preload will be responsible for an increase in the systolic ejection volume of the ventricle [8].

This increase in stroke volume, secondary to the increase in cardiac preload, is however not linear but rather curvilinear both for the left and the right ventricle. The curve schematically comprises two parts (**Figure 1**). The first part corresponds to the ascending portion and represents the "preload dependence". On this portion, an increase in preload, obtained for example by volume expansion, leads to a significant increase in stroke volume and a slight increase in transmural pressure. The second part of the curve corresponds to the plateau portion, where an increase in cardiac preload results in a significant increase in transmural pressure without a significant increase in stroke volume, representing the "preload independence". The increase in the transmural pressure is therefore not accompanied by a significant increase in tele-diastolic volume because the diastolic elastance of the ventricle is high.

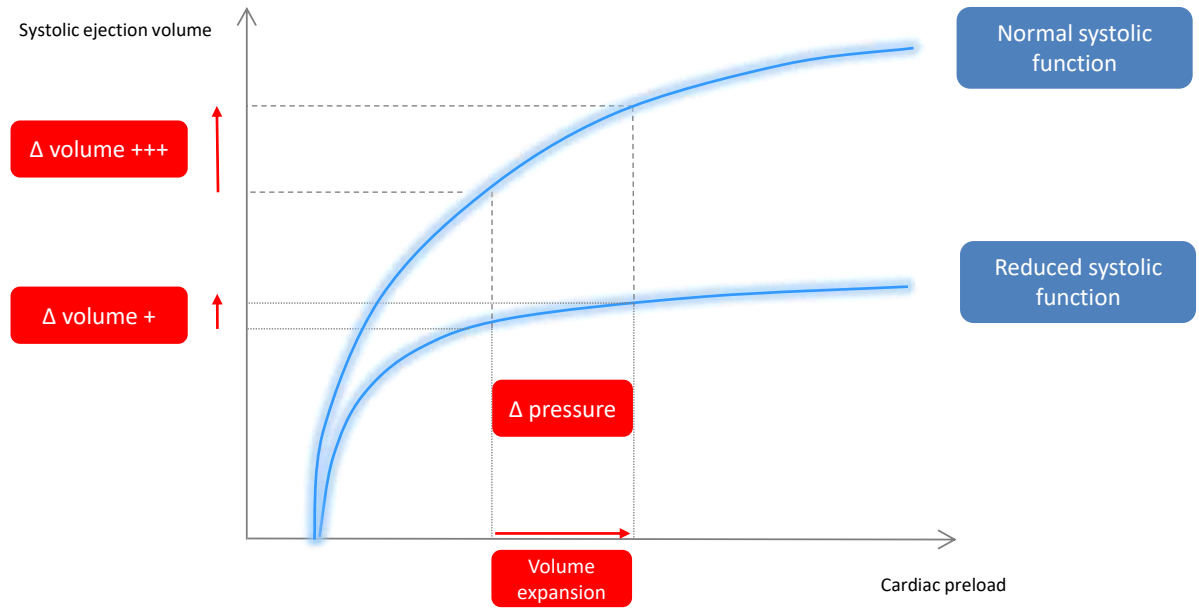

Figure 1 - Frank-Starling systolic function curve showing changes in stroke volume as a function of changes in cardiac preload, according to cardiac function.

In normal conditions both ventricles operate on the ascending portion of the curve, since the preload reserve is a physiological condition. It is more marked when the heart works on the initial part of the ascending portion of the systolic function curve, i.e. away from the plateau, and when the slope of the ascending portion is steep (inotropic function preserved or increased).

By analogy with an electrical circuit, the two ventricles are connected in series. For the stroke volume of the left ventricle to increase in response to an increase in right cardiac preload, both ventricles must be provided with a preload reserve.

1.4. Concept of systemic venous return

Systemic venous return is the flow of blood between the venous reservoir upstream and the right atrium downstream [1–5]. The venous system can be considered as a very compliant capacitance, schematically divided into unstressed blood volume, which does not generate pressure, and stressed volume, subjected to the pressure of the distended venous walls.

Systemic venous return is determined by the ratio between the pressure gradient of venous return and the resistance to venous return [9,10]. The venous return pressure gradient corresponds to the difference between the upstream pressure generated by the constrained blood volume, the mean systemic pressure, and the downstream pressure, which is the right atrial pressure [6,7,9,11].

Thus, the systemic venous return increases linearly with the decrease in right atrial pressure [1] (**Figure 2**). When the right atrial pressure drops below a critical value, usually below the atmospheric pressure, the transmural pressure of the vena cava becomes negative, the vein collapses, and the venous return can no longer increase (**Figure 2**). In hypovolemic states, both the mean systemic pressure and the pressure gradient of the venous return decrease, leading to a drop in peripheral venous return (**Figure 2**). When the venous resistance increases, venous return also augments but without an increase in the pressure gradient (**Figure 2**).

Although they may differ on a few heartbeats, venous return and cardiac output are the same at equilibrium. It is, thus, possible to graphically superimpose the systolic function curve and the venous return curve to determine the "equilibrium point", which defines the operating conditions of the heart (**Figure 3**). An increase in cardiac performance can improve venous return only through a decrease in right atrial pressure. Nevertheless, if this drops below the critical pressure, venous flow becomes independent of cardiac function [4,12]. It is then necessary to add circulating volume to re-establish the relation.

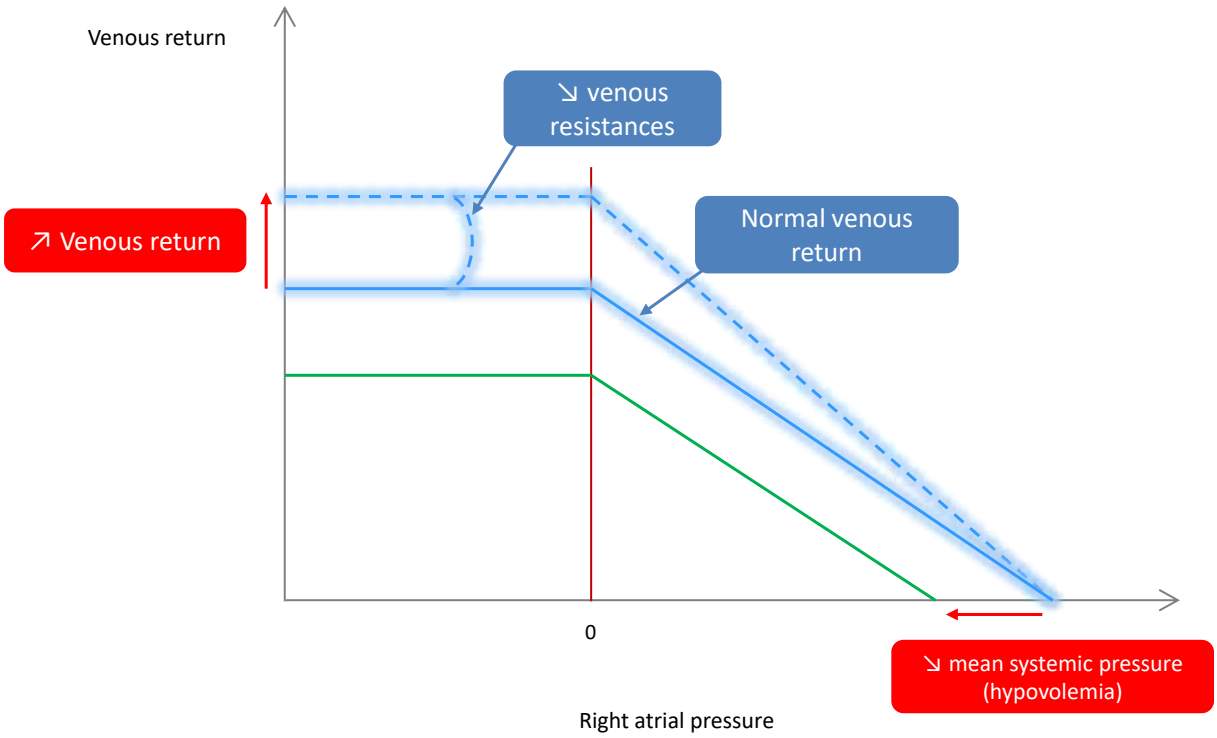

Figure 2 - Venous return curve showing variations in venous return as a function of pressure variations in the right atrium during hypovolemia and during vasodilation.

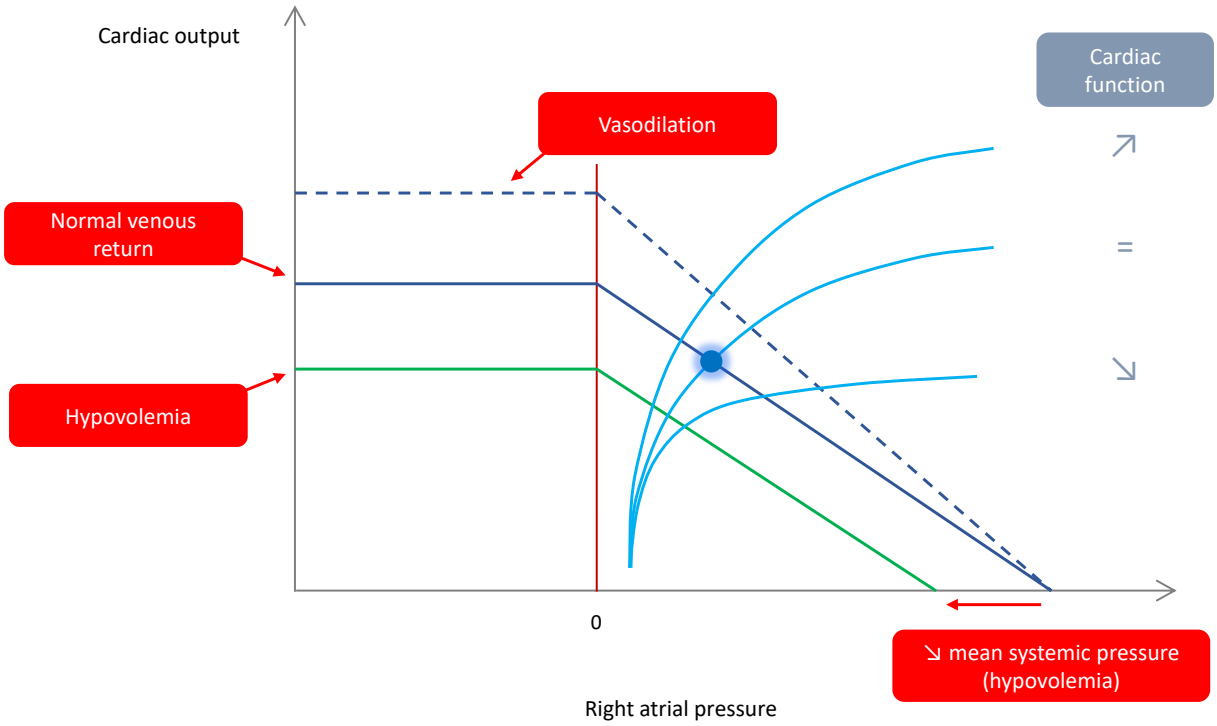

Figure 3 - Systolic function curve and venous return during hypovolemia, vasodilation, heart failure (decreased heart function ↘), normal heart function) or inotropic (increased heart function ↗).

1.5. Concept of hypovolemia

Absolute hypovolemia is defined as a decrease in the total circulating blood volume. It may be linked either to blood loss (hemorrhage) or to pure plasma losses (digestive, renal, skin losses). In the initial phase, an intravascular transfer of extravascular fluid, through the reduction of the intravascular hydrostatic pressure, allows the compensation for this volume loss.

After this phase, hypovolemia is responsible for a decrease of the stressed volume and therefore a decrease of the mean systemic pressure, systemic venous return, cardiac preload, and cardiac output. The reduction in the mean systemic pressure may also be secondary to an increase in venous capacitance during vasodilation, with the same hemodynamic consequences. Thus, volume expansion, by increasing the content, allows the restoration of venous return, thanks to the increase in the mean systemic pressure. Also, the administration of vasopressors determines a decrease in the container, increasing the mean systemic pressure and enhancing the effects of volume expansion.

2. Volume expansion

Volume expansion, which is the intravenous administration of fluid to increase circulating blood volume, is one of the most common procedures in critical care patients. It is the cornerstone of dealing with shock [13–15] .

2.1. Methods of carrying out volume expansion

The FENICE study, which analyzed the vascular filling practices in 2,213 intensive care patients around the world, showed great variability in its modalities, whether in terms of type of fluid used, quantity injected, pursued objectives and safety criteria used [16].

2.1.1 Type of fluid

In addition to products derived from blood (red blood cell concentrates, fresh frozen plasma) which have little discussed specific indications, the debate for many years concerned the choice between colloid solutes and crystalloids. On the one hand, the hemodynamic efficiency of colloid solutes, which exert greater volume expansion thanks to their oncotic effect, has been shown to be greater than that of crystalloid solutes [17]), allowing faster hemodynamic restoration and total delivery of less amount of fluid. In the specific case of albumin, beneficial effects specific to this natural molecule have also been described.

On the other hand, the cost of these solutions, the deleterious effects of many of them, have always hampered their prescription. The hemodynamic efficiency supposed to be superior to that of crystalloids was found to be more theoretical than real under conditions of shock states, where

damage to the capillary barrier would lead them to leak into the interstitial sector. Importantly, the nephrotoxic effects of hydroxyethyl starches, the most recent of synthetic colloid solutes, have been quickly established [18–22]. Osmotic nephrotic lesions appeared to be related to the amount of hydroxyethyl starch administered [23].

For a long time, the choice between colloid and crystalloid solutes depended on personal convictions and schools [22]. In 2010, an survey conducted among 391 intensive care units revealed that 48% of volume expansions were carried out with colloid solutions, 33% with crystalloid solutions and the rest with blood products; the choice was significantly influenced by the region in which the respondents to this survey exercised [24].

However, in the early 2010s, randomized controlled trials established quite convincingly the lack of benefit from the use of colloid solutions. Moreover, the 6S study, comparing tetraspan to Ringer's lactate in patients with sepsis, found a significant excess of mortality associated with the use of hydroxyethyl starch [22]. Subsequent meta-analyses confirmed this deleterious effect of hydroxyethyl starches on the prognosis of patients with septic shock [25,26]. Following them, the recommendations of the Surviving Sepsis Campaign in 2016 prescribed not to use these solutions in this context. In other clinical situations (postoperative effects, hemorrhagic and hypovolemic shock), the use of hydroxyethyl starches is still permitted, but very controversial. Supporting the use of starched hydroxyethyl solutes, the CRISTAL study conducted in patients with hypovolemic shock suggested a benefit of colloids over crystalloids in this condition [27].

More recently, the debate has revolved around the comparison of so-called "balanced" solutes and isotonic saline. Indeed, administration of large amounts of the latter could lead to hyperchloremic acidosis and significant hypernatremia. However, the randomized controlled trials SPLIT [28] and SALT [29] failed to show a prognostic benefit from the choice of a balanced solution rather than a saline solution. It must be recognized that the risk of hyperchloremia can only appear with large volumes of isotonic saline. In addition, the deleterious effects of hyperchloremia are debated, although it could induce kidney failure. The SMART study [30], however, demonstrated the reduction in the incidence of a composite endpoint (mortality, persistent renal failure, new extrarenal purification) if a balanced solution (Ringer's lactate or Plasma-Lyte A) was administered instead than isotonic saline.

2.1.2. Volume and duration of volume expansion

Recent expert recommendations suggested to administer 500 mL of solution over 10 to 15 minutes [31], according to suggestions that had come from fewer but prestigious experts [32].

In fact, the question of what the unit volume of a volume expansion should be and how long it should be administered has been the subject of much less investigation. Regarding the amount of volume, Aya et al. showed that a volume of 4 mL/kg of allowed one to induce a significant increase in mean

systemic pressure [33]. However, this "significance" was only defined by the smallest detectable change, which of course depends on the technique used to estimate it (brachial occlusion technique in the study in question [33]).

The duration has been even less studied. A study, published in abstract form at a congress, suggests that a shorter administration induces a maximal increase in the mean systemic pressure and a longer persistence of this increase [34].

3. Expected benefits of volume expansion

Basically, volume expansion is expected to increase cardiac output, leading to an improvement in tissue oxygenation by increasing oxygen transport. The cardiac output increase follows a rise in cardiac preload that should result from an increase in the mean systemic pressure **(Figure 4)**. However, none of these steps occurs systematically with the administration of a fluid bolus [35].

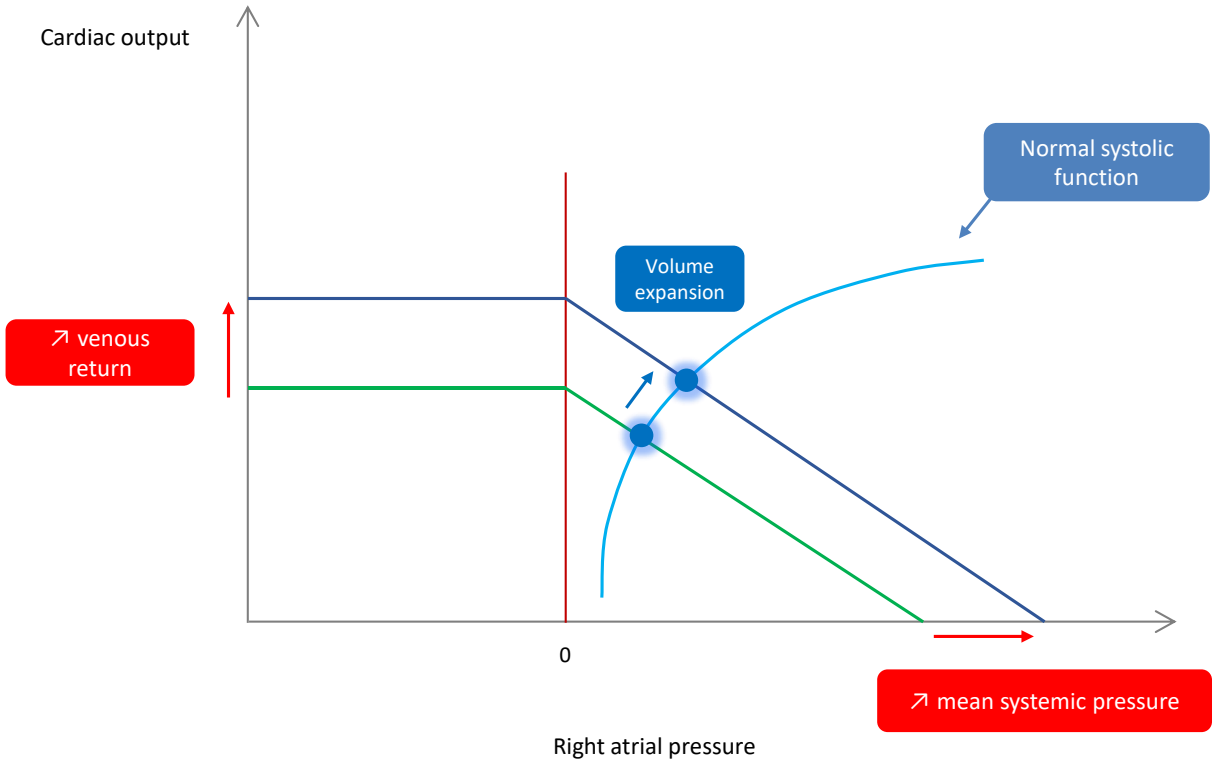

Figure 4 - Effects of volume expansion: increase in mean systemic pressure and venous return.

3.1. Volume expansion must increase the mean systemic pressure

This is the first step in the hemodynamic response to vascular filling, which should result from a significant increase in the stressed blood volume. Of course, this cannot happen if the volume of fluid

administered is too low [33] and when there is significant vasodilation, which increases the size of the venous system.

Even if it does occur, the increase in the mean systemic pressure is only transient. In this context, Aya et al. have shown that the hemodynamic effects of a 250 mL bolus of crystalloids disappear after only 10 minutes [36]. The phenomena of capillary leakage, shear stress or attenuation of the sympathetic stimulation [37] probably play a role in this dissolution. Pavot et al. found similar results during septic shock [34].

3.2. Volume expansion should increase cardiac output

Once the effects of volume expansion on cardiac output could be precisely measured, it appeared that the expected increase in cardiac output was not systematic. In 1981, Calvin et al. found an increase in stroke volume in only 20 of 28 ICU patients in whom 250 mL of albumin was administered [38]. Since then, this evaluation was made more and more frequently and it has been estimated that, on average, only half of patients respond to vascular filling with a significant increase in stroke volume and cardiac output [39].

The most likely explanation comes from the relationship between preload and cardiac output. The increased cardiac preload induced by vascular filling can only increase stroke volume if both ventricles are functioning in a dependent preload state. Otherwise, no increase in stroke volume and flow rate can be expected.

The hemodynamic behavior of responders and non-responders to volume expansion fundamentally differs in terms of changes in central venous pressure. Cecconi et al. [40] and Guérin et al. [41], using two different methods, demonstrated that the increase in the mean systemic pressure following vascular filling was similar both in responders and non-responders. However, in responders, the increase in central venous pressure was of lesser magnitude. Therefore, the pressure gradient of systemic venous return increased. Conversely, patients who did not respond to volume expansion were characterized by an increase in central venous pressure of an amplitude equal to that of the mean systemic pressure. In these patients, the venous return pressure gradient did not increase venous return and cardiac output remained unchanged [40,41].

3.3. Volume expansion should improve tissue oxygen consumption

This step is not systematic either. First, the increased arterial oxygen transport that must follow the rise in cardiac output is inevitably counterbalanced by the hemodilution induced by the infusion of fluids other than red blood cell concentrates. This hemodilution is probably not negligible. In a study in which Monnet et al. explored the effects of the administration of 500 mL of isotonic saline on tissue

oxygenation and vascular filling, the decrease in hemoglobin level was 8 ± 5%, attenuating by the same amount the increased arterial oxygen transport caused by the augmented cardiac output [42].

Moreover, even when volume expansion augments cardiac output and oxygen transport, the improvement in oxygen uptake is not systematic. It only occurs if the transport and the consumption of oxygen are dependent [43]. In the above-mentioned study, Monnet et al. showed that oxygen consumption increased by more than 15% in only 56% of patients receiving volume expansion [42].

The lack of improvement in oxygen uptake in some patients probably did not mean that volume expansion was unnecessary. Indeed, we can assume that it is beneficial to move the operating point of the oxygen transport/consumption relationship away (to the right) from the critical arterial oxygen transport point, to reduce possible risks coming from an even slight reduction in transport (**Figure 5**).

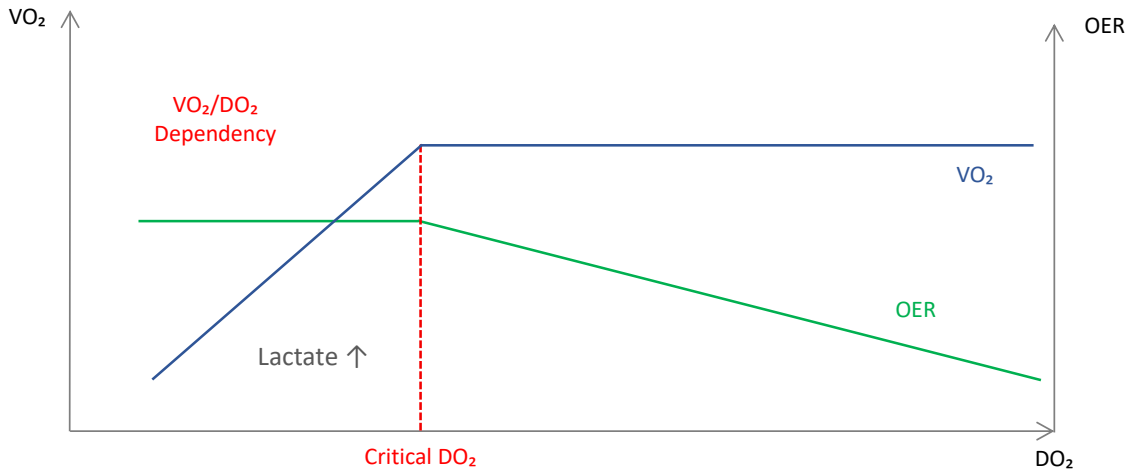

Figure 5 - DO_2/VO_2 relationship. DO_2: oxygen delivery, OER: oxygen extraction ratio, VO_2: oxygen consumption.

4. Deleterious effects of volume expansion

4.1. Fluid overload and organ dysfunction

As with any drug, vascular filling has harmful effects. It exposes people to risks either related to the products used or inherent to volume expansion [44]. The latter are mainly related to the increase in hydrostatic pressure in the capillaries, which according to Starling's law causes the filtration of liquid to the extravascular sector [37]. The amount of filtered volume is more important since the alveolar-capillary barrier is permeable, as during septic shock or in the inflammatory phase of all shock states. This risk is also increased when either the oncotic pressure is low (e.g. hypoalbuminemia) or the hydrostatic pressure level is already high. Due to these phenomena modulating the risk associated with fluid overload, it is better to define it by the presence of suggestive symptoms rather than by an increase in body weight of 10%, as sometimes done [45,46].

The tissue edema resulting from fluid overload alters to varying degrees the function of the organs it invades. If the brain is protected from this phenomenon by the regulation of intracerebral pressure, this is not the case for the myocardium, whose edema could lead to diastolic dysfunction or even a decrease in contractility, even though this has not been clearly demonstrated.

Renal and hepatic interstitial edema may also contribute to the dysfunction of these organs during shock. However, in the kidney and liver, more than the interstitial edema, it is rather the reduction in the perfusion pressure gradient that is probably responsible for the most significant deleterious effects. In fact, abundant vascular filling leads to an increase in central venous pressure, which is the downstream pressure of blood supply to these organs. In support of this hypothesis, a clear relationship between the level of central venous pressure and the risk of developing new or persistent renal failure has been demonstrated by Legrand et al. [47].

Fluid overload promotes the development of abdominal hypertension [48] which can worsen intra-abdominal organs function as part of abdominal compartment syndrome [49–51].

Of course, the major risk of fluid overload is for the lung. Due to altered alveolocapillary permeability, the impairment in gas exchange via a shunt effect is aggravated in acute respiratory distress syndrome (ARDS). The reduction in both pulmonary and chest wall compliance are also the consequences of significant fluid overload [44].

4.2. Fluid overload and worsening prognosis

Numerous studies report a significant association between fluid overload, reflected by positive fluid balance, and mortality in numerous clinical circumstances: septic shock state [46,52–56], ARDS [57,58] or acute renal failure [59].

4.3. Fluid administration strategy

Therefore, the management of a patient could be optimized in four stages: rescue, optimization, stabilization, and de-escalation [15,44,60]. During the first stage (rescue), the emphasis is on the appropriate use of volume expansion. During the optimization and stabilization steps, the emphasis is placed on maintaining proper infusion while avoiding additional volume overload. Finally, the last step (de-escalation) is centered on the elimination of the fluids used during the initial resuscitation.

5. Conclusion of the first chapter

Vascular filling should be considered as a drug: it has inconsistent effectiveness and potentially exerts serious effects. Therefore, several obvious facts stand out. First, it is necessary to systematically evaluate the response to volume expansion, by looking for the beneficial effects (increase in cardiac

output, improvement in tissue oxygenation, etc.) and deleterious effects (hemodilution, increase in central venous pressure, degradation of gas exchange etc.) [35].

Second, the association of an inconsistent response to vascular filling and a deleterious effect of fluid overload suggests the need to predict the response to vascular filling before undertaking it. In particular, this is the case for the response in terms of cardiac output. Searching for a state of preload independence, which suggests ineffectiveness of fluid administration, seems as logical as performing an antibiogram before starting antibiotic treatment. The detection of the preload dependence state is enabled by numerous tests and indices, which will be illustrated in the following chapter.

II. Prediction of fluid responsiveness

1. Introduction

Predicting the response of cardiac output to volume expansion consists on looking for a state of preload dependence. For many years, this prediction was made with "static" measurements of cardiac preload before dynamic tests and indices were developed to overcome the limits of such a strategy.

2. Static markers of preload responsiveness

The term "static markers" is used to designate all the indices which estimate a fixed value, isolated from the cardiac preload. The main indices used include central venous pressure, pulmonary artery occlusion pressure, end-diastolic volume or dimensions of the left ventricle and the diameter of the inferior vena cava.

2.1 Central venous pressure

The central venous pressure (CVP) is an index of right ventricular preload that has been used for many years to predict the response to volume expansion. The principle was that a low value of CVP was indicative of hypovolemia, thought to be associated with a significant response of cardiac output to vascular filling [61].

However, it is physiologically impossible that a given value of CVP can correspond to a state of preload dependence. The slope of the Frank-Starling curve varies in a given patient, but also from one patient to another depending on the systolic function of the ventricles [62] (**Figure 6**). For the same value of CVP, volume expansion can cause either a negligible or a significant increase in stroke volume and cardiac output.

Two other factors are likely to prevent the prediction of the response to volume expansion using a static measurement of CVP. First, the CVP is only an imperfect reflection of the right ventricular preload. In particular, the slope of the diastolic function curve plays a role that is not negligible. If this is altered, CVP can be associated with a high ventricular end-diastolic volume even for a relatively low value. The second factor are measurement errors. The values of this pressure are low, in comparison with arterial pressure for example, and an error in the position of the pressure sensor can have a very significant impact. Also, CVP is influenced by intrathoracic pressure and, in mechanically ventilated patients, by the level of positive end-expiratory pressure [63].

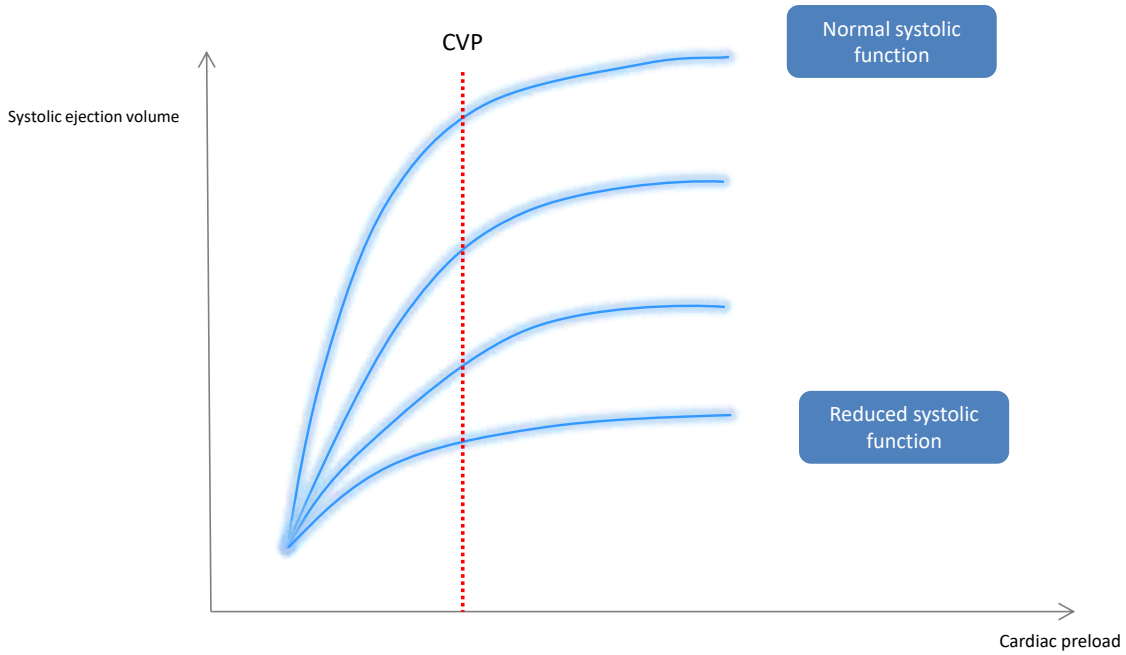

Figure 6 - Frank-Starling relationship, according to different performances of ventricular function. CVP: central venous pressure

It is now well demonstrated that CVP cannot reliably predict the response to volume expansion. This has been established by numerous studies and by several meta-analyses of these studies [40,64–67]. It is therefore surprising to note that despite this abundant and consistent literature, CVP continues to be used to decide on fluid administration [16,68].

It should be noted here that even though a static value of CVP does not predict the response to vascular filling, it remains an important physiological variable. Many arguments plead for its use in the therapeutic strategy of acute circulatory failure, for example as a marker of right ventricular insufficiency [62].

2.2 Inferior vena cava diameter

The tele-expiratory diameter of the inferior vena cava measured by transthoracic ultrasound is an estimate of the CVP [69–71]. As such, it does not make it possible to reliably detect a state of preload dependency, as was recalled in a recent study on a large population [72]. However, as with CVP, extreme values may have diagnostic value, although they are very rarely encountered [72]. This ultrasound index has the same limitations as the CVP it estimates, to which are added the limitations of the technique and in the patient himself. As an example, the study cited above clearly showed how the presence of abdominal hypertension further reduced its ability to detect a preload reserve [72].

3. Dynamic indices of preload responsiveness

These markers were developed to overcome the limitations of static indices. The principle is to detect preload dependence by observing the effects on cardiac output, ejection volume or their estimates of a change in preload, induced either by a test or by mechanical ventilation.

3.1 Fluid challenge

3.1.1. Principle

The simplest approach to assess the response to vascular filling is to administer one [32], which allows the patient's preload reserve to be directly tested [73]. The volume of fluid given for this test should be enough to increase the cardiac preload.

3.1.2. Practical arrangements

Vincent and Weil, revisiting the methodology of the fluid challenge, suggested that it should be carried out by injecting Ringer's lactate solution at a dose of 500 mL over 30 minutes [32]. However, the FENICE study showed great variability in the prescription of this fluid challenge [16], in terms of type of fluid injected, the amount, the therapeutic targets and the evaluation of its safety. More recently, a systematic review of the literature by Toscani et al. showed that these modalities varied considerably among clinical studies, also influencing the diagnosis of preload dependence [33]. As a matter of fact, a fluid challenge administered in less than 15 minutes was associated with a higher number of responders [33]. Finally, the time taken to evaluate the response to this fluid challenge did not affect the proportion of responders, whereas in the study by Aya et al. [36], the effect on cardiac output was maximal one minute after the end of the infusion. As mentioned above, the study of Pavot et al. showed that the faster was the administration of the fluid bolus, the greater was the effect on the mean systemic pressure [34].

3.1.3. Limits

The fluid challenge has two essential limits. The first is that to accurately assess its effects, a direct measurement of cardiac output is required [13,66,67]. Merely observing changes in blood pressure cannot predict response to volume expansion [74,75]. The second limitation of this test is that it is not a test, but the treatment itself. Once administered, it is not possible to reverse its effects, even when it has not led to a significant increase in cardiac output.

3.2 Mini Fluid Challenge

3.2.1. Principle

From then on, the idea to carry out a fluid challenge with a smaller volume appeared [76]. Several studies have now evaluated this mini fluid challenge in the operating room [77,78] as well as in the intensive care [79,80].

3.2.2. Validation and practical modalities

The method initially proposed by Muller et al. [79] involved the infusion of only 100 mL of colloid over one minute. An increase in stroke volume, estimated by velocity-time integral by transthoracic echocardiography of more than 6%, predicted a positive response to the remaining 400 mL of colloid. Due to the modest accuracy of echocardiography, the authors suggested to increase this diagnostic threshold to 10% [79].

Several studies confirmed the original study, and in a recent meta-analysis, the area under the Receiver Operating Characteristic (ROC) curve was 0.91 (95% confidence interval, 0.85-0.97), with a diagnostic threshold of 5% [81]. The effects of the mini fluid challenge were assessed via changes in the left-ventricular outflow tract velocity-time integral measured by transthoracic echocardiography [79], cardiac output derived from pulse contour analysis [77,80,82] or the carbon dioxide (CO_2) at the end of expiration [83]. Most studies used a 100-milliliter bolus infused over 60 seconds, but Wu et al. demonstrated that a 10% change in cardiac output after infusion of a 50 mL bolus over 10 seconds reliably predicted the response to volume expansion [84]. These results were not confirmed by Biais et al., who found low predictive value for this type of "micro-fluid challenge" [77].

3.2.3. Limits

Since a volume of fluid as low as 100 mL, or even 50 mL, can induce only small hemodynamic changes, a very precise technique is needed to detect them [66,76]. From this point of view, echocardiography is probably not the best method. The smallest significant change in the velocity-time integral is only 10%, and the smaller changes are less than the precision of the technique. The much more precise pulse wave contour analysis [85] is theoretically more appropriate for this purpose [77].

3.3. Arterial pulse pressure variation (PPV)

3.3.1. Principle

Mechanical ventilation with positive pressure causes, on inspiration, a decrease in preload and an increase in afterload of the right ventricle [86]. This decrease in preload is due to the decrease in the

pressure gradient of venous return secondary to the inspiratory increase in pleural pressure [86], while the increase in afterload is linked to the inspiratory increase in transpulmonary pressure [86]. Both load changes on the right ventricle cause a decrease in stroke volume. In the left heart, the preload of the left ventricle increases, and its afterload decreases. The left ventricular ejection volume increases, leading to an increase in systolic blood pressure on the blood pressure curve (Δup) and an increase in arterial pulse pressure (PPmax) (**Figure 7**).

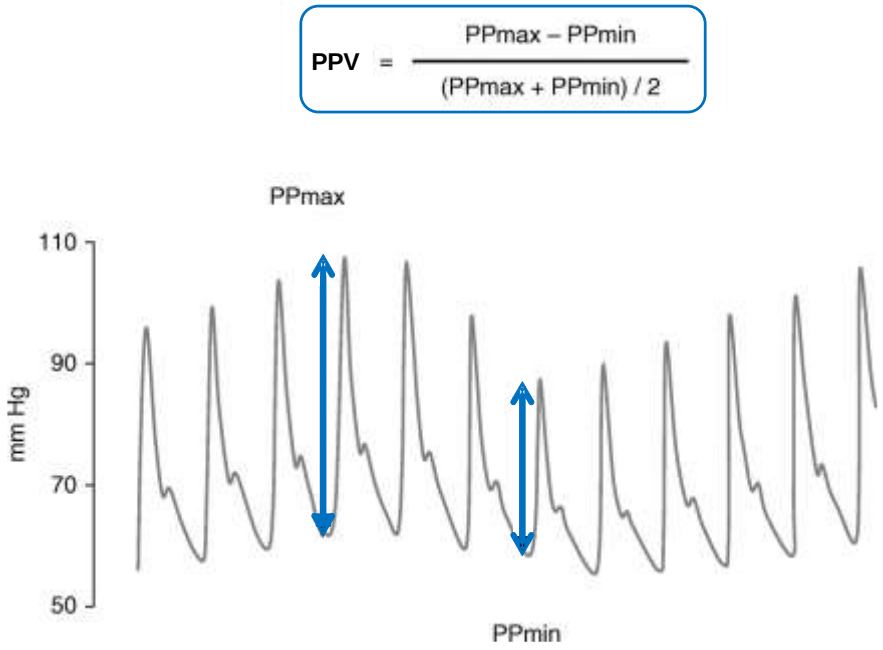

Figure 7 - Arterial pressure curve and calculation of the maximum and minimum pulse pressure (PP), and the respiratory variation of the PP (PPV).

During expiration, the decrease in the ejection volume of the right ventricle that has occurred on inspiration is transmitted, after the pulmonary transit time - which corresponds to a few heartbeats - to the left ventricle. The left ventricular ejection volume decreases. On the arterial pressure curve, systolic pressure decreases (Δdown), and arterial pulse pressure decreases (PPmin). Furthermore, on the right side, the rapid drop in intrathoracic pressure is associated with an increase in venous return, preload, and stroke volume of the right ventricle (**Figure 8**).

Thus, positive pressure ventilation generates a cyclical variation in cardiac preload [86,87]. The greater the magnitude of the cyclical changes in left ventricular stroke volume and arterial pulse pressure, the more likely the right and left ventricles are functioning on the ascending portion of the Frank-Starling curve [86]. F Michard and J-L Teboul proposed to quantify this cyclic variation of the arterial pulse pressure with the formula: PPV = (PPmax - PPmin) / [(PPmax + PPmin) / 2]. Today, PPV is calculated automatically by all monitors that collect a continuous blood pressure signal.

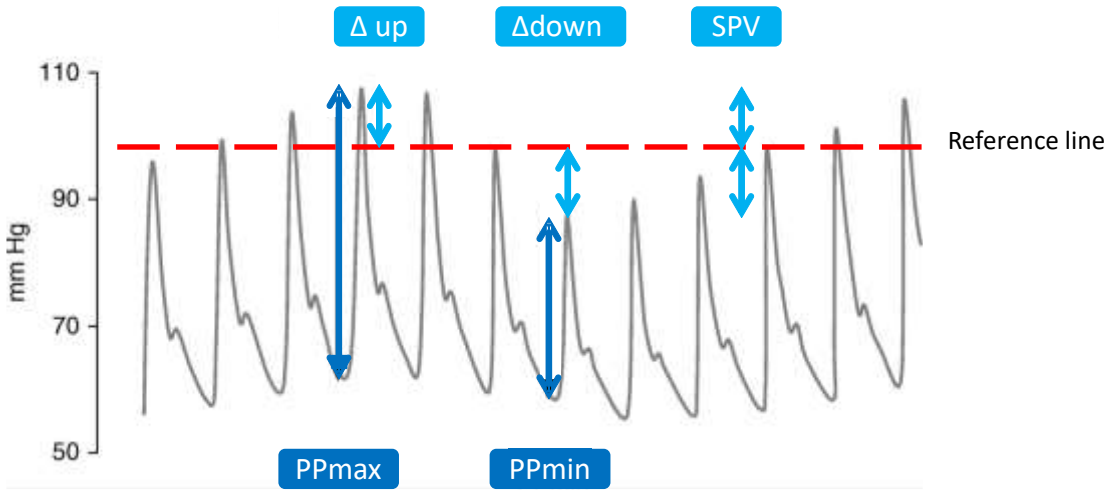

Figure 8 - Systolic pressure (SPV) calculated from Δup (difference between the maximum value of systolic pressure over a single respiratory cycle and the reference systolic pressure obtained after a tele-expiratory pause of a few seconds) and from Δdown (difference between the reference systolic pressure and the minimum value of the systolic pressure over a single respiratory cycle).

3.3.2 Validation

Following the first study which demonstrated that PPV can detect a state of preload dependence and predict the response to volume expansion [88], a large number of papers have been published, confirming these results. They have been regularly summarized in several meta-analyses [89,90], and it can be said that today, PPV is the index of preload dependency that has received the strongest validation. Therefore, it has been used as a reference method in the investigation of other indices of preload responsiveness. As an example, Cameli et al. demonstrated that the correlation between PPV and the left atrial longitudinal strain at speckle tracking echocardiography, allowed the latter to be considered as an interesting index of preload responsiveness.

3.3.4. Limits

PPV has many interpretive limitations and there are several clinical circumstances that impair its ability to detect preload reserve.

- Cardiac arrhythmias: the change in stroke volume during atrial fibrillation or atrial or ventricular extrasystoles is not due only to preload dependence in this case. Arrhythmias are responsible for false positives.
- Spontaneous breathing: the possible irregularity of the inspiratory efforts creates an inhomogeneity of the variations in stroke volume from one cycle to another and generates false-positives.

- Low tidal volume and low lung compliance: De Backer et al. showed for the first time that ventilation with low tidal volume resulted in false negatives for the detection of preload dependence [91]. In this circumstance, the tidal volume (Vt) challenge, which consists in transiently increasing the level of Vt, represents an interesting method to overcome this limitation of PPV.
- Tachypnea: De Backer et al. demonstrated that a very high respiratory rate could represent a limit to the use of PPV [92]. The principle is that, in this case, especially if the heart rate is relatively low, the changes in the amplitude of the blood pressure do not have time to develop during a respiratory cycle. In this study, this phenomenon occurred if the respiratory rate / heart rate ratio was > 3.6 [92].
- Intra-abdominal hypertension (IAH): the presence of IAH limits the predictive value of PPV [93] with a higher diagnostic threshold [94]. Due to the frequency of IAH, this is a significant limitation [95].

These limits of use and interpretation contribute to the extension of a zone of uncertainty known as the "*gray zone*" with values between 9% and 13% [96].

3.4. Variation in the diameter of the lower and upper vena cava

3.4.1. Principle

The changes in intrathoracic pressure induced by mechanical ventilation can induce variations in the diameter of the vessels close to the heart, especially when the central blood volume is low. This probably results from the conjunction of several phenomena. First, preload dependence is associated with respiratory variations in central venous pressure, the intramural pressure of the vena cava. Then, the compliance of the vena cava, which is higher when vessels are relatively empty, as in the case of hypovolemia, makes their diameter sensitive to this change in transmural pressure. In addition, for the inferior vena cava (IVC), the respiratory variations of the intra-abdominal pressure resulting from the thoraco-abdominal transmission of changes in intrathoracic pressure contribute to the change in its diameter. As a consequence, the variation in the diameter of the vena cava - in particular the inferior vena cava - is not directly related to the state of preload dependence, since other factors may determine them.

3.4.2. Validation

The diameter of the inferior vena cava is measured by transthoracic echocardiography in longitudinal section via subcostal approach in M mode, approximately 2 cm from the junction with the right atrium, and generally upstream of the entrance to the hepatic veins [97,98] (**Figure 9**).

Overall, the validation of vena cava variation to predict the response to vascular filling was quite disappointing. Several studies published after the ones describing the indices [99,100] found less good results than these. The results of the studies diverge [72,98,101–103], with thresholds varying from study to study, from 12 to 18% for the inferior vena cava and from 21 to 36% for the superior vena cava [101,104–106] (**Table 1**).

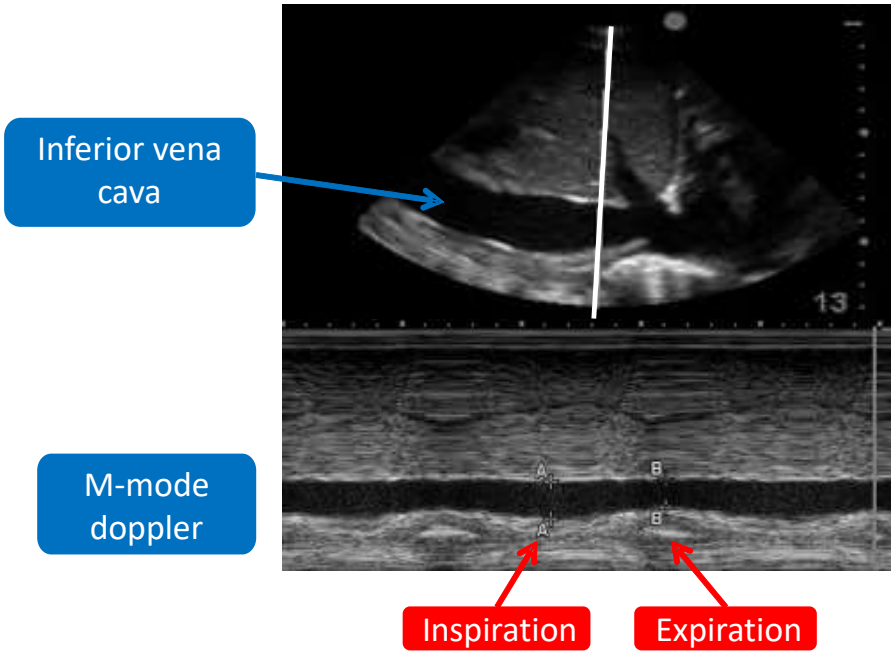

Figure 9 - Subcostal echocardiography, in M mode, centered on the inferior vena cava, allowing measurement of variations in diameter in inspiration (A) and expiration (B).

These studies were included in meta-analyses which have confirmed the disappointing predictive value of these indices. In particular, the three most recent ones have shown a low ability to predict preload responsiveness [102,103,107].

3.4.3. Limits

With the development of ultrasound in intensive care and perioperative medicine, these indices quickly became very popular. However, in addition to their relatively poor reliability, these cava vein variability indices have many limitations. As expected, respiratory variations in IVC diameter suffer from most of the limitations of PPV [102,107,108]. In particular, patients must be optimally adapted to the ventilator, as the precision of changes in the diameter of the IVC is lower in spontaneously breathing patients [65,107]. Nevertheless, a recent study found that variations in the diameter of the IVC induced by deep inspiration in non-intubated patients provided a good prediction of the response to volume expansion [109]. The presence of abdominal hypertension can also induce false positives or negatives for the variation of the inferior vena cava [101,108]. Unlike PPV, respiratory variations in the diameter of the IVC can be used in patients with cardiac arrhythmias [108].

3.5 Passive leg raising (PLR)

3.5.1. Principle

The passive leg raising test consists in transferring a patient from a semi-recumbent supine position to a position in which the trunk is horizontal and the lower limbs elevated 30-40°. This maneuver mobilizes part of the blood volume of the lower limbs and the splanchnic territory by gravity towards the right cardiac chambers, mimicking a fluid challenge without administration of fluid [66,110]. The advantage over the fluid challenge is that the maneuver is completely reversible and has no deleterious effect in non-preload dependent patients. The PLR test can thus be considered as an "internal preload challenge" [66].

Boulain et al. have shown that this postural maneuver leads to an increase in the preload of the right and left ventricles [111]. The changes in stroke volume induced by PLR and volume expansion are strongly correlated [111]. The PLR test mobilizes around 300 mL of blood [111], even if this volume greatly varies from one patient to another, and allows a significant increase in the mean systemic pressure while the resistance to venous return remains unchanged [41]. In a patient called "*PLR responder*", venous return and cardiac output increase by increasing the pressure gradient of venous return, by increasing the mean systemic pressure more than PVC. In so-called "*PLR non-responder*" patients, the pressure gradient is unchanged and does not increase venous return [41].

3.5.2. Validation

It is now clearly established through two meta-analyses that the PLR test can reliably detect the response to volume expansion [112,113] with an area under the ROC curve at 0.95 and with a diagnostic threshold of 10% increase in cardiac output [112] (**Table 1**). The test has the advantage of being reliable even in case of spontaneous ventilation [112–115], in patients with cardiac arrhythmia [116,117], regardless of tidal volume and lung compliance.

The reliability of this test has probably contributed to its popularity and widespread use. It is recommended in the consensus on the hemodynamic management of patients with acute circulatory failure [14], as well as in the guidelines of the Surviving Sepsis Campaign [118].

3.5.3. Practical aspects

The technique of performing the PLR test is now well described and must respect certain rules [110,119]. The patient should be placed in a semi-seated position with the head of the bed raised to 45° [119] (**Figure 10**). The bed is tilted in the supine position, mobilizing blood from the splanchnic territory and the lower limbs. It is best to use the automated bed to change position because manual stimulation could increase sympathetic tone [110] decreasing accuracy [119]. The effects of PLR should

be assessed by direct, continuous, real-time measurement of cardiac output with a technique sensitive enough to detect its maximum effects at approximately one minute [110,115].

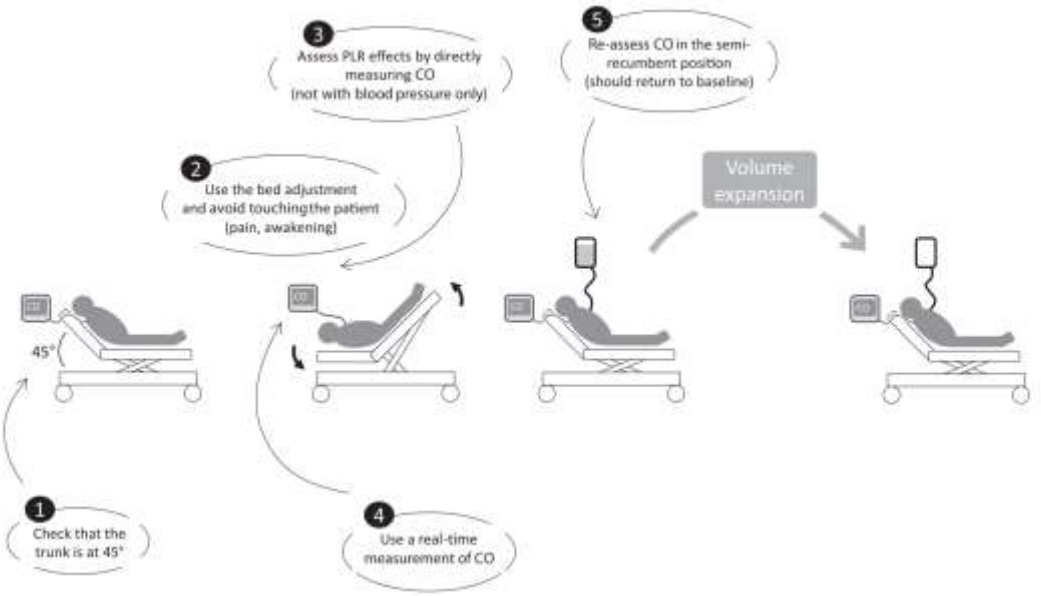

Figure 10 – The passive leg raising maneuver (from Monnet and Teboul: *Passive leg raising: five rules, not a drop of fluid!* Critical Care 2015).

3.5.4. Limits

First, it should be emphasized again that the PLR test requires a direct, real-time measurement of cardiac output [110]. Second, some confounding factors such as pain, cough, discomfort, and patient awakening may lead to a potential misinterpretation with false positives changes in cardiac output by adrenergic stimulation [110]. The presence of venous compression stockings for the lower limbs [120], by reducing the volume of blood mobilized, creates false-negatives. The same is probably the case with amputation of the lower limbs. Also, intra-abdominal hypertension may reduce the reliability of the test [121]. Intracranial hypertension, which the test may worsen [66,67,122], is a contraindication.

3.6 The end-expiratory occlusion test

3.6.1. Principle

The end-expiratory occlusion test (EEXPO) consists in stopping the ventilator at the end of expiration for 15 to 30 seconds and evaluating the resulting changes in cardiac output. During positive pressure ventilation insufflation increases intrathoracic pressure, which is transmitted to the right atrial pressure, so that right cardiac preload decreases. When ventilation is stopped at expiration, at positive expiratory pressure, the cyclic obstruction of venous return is interrupted, and the right cardiac preload reaches its maximum. If the EEXPO is long enough, the increase in right cardiac preload is

transmitted to the left side of the heart. A consequent increase in stroke volume and cardiac output theoretically indicates a state of preload dependence of the two ventricles (**Figure 11**).

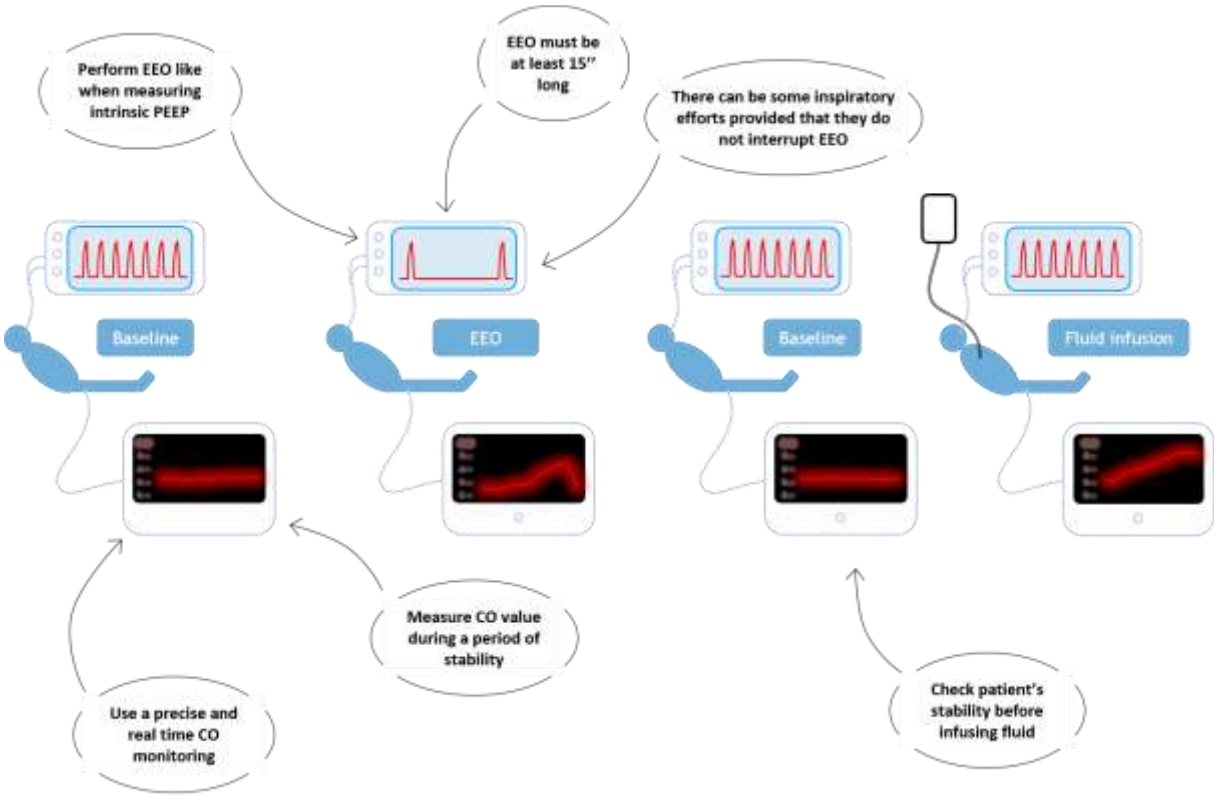

Figure 11 - The end-expiratory occlusion test (from Gavelli, Teboul and Monnet: *The end-expiratory occlusion test: please, let me hold your breath!* Critical Care 2019)

3.6.2. Validation

Several studies have shown that an increase in cardiac output during an EEXPO of 15 to 30 seconds reliably detects preload dependence, including in cases of cardiac arrhythmia or moderate spontaneous breathing [114,123–125] (**Table 1**). A further validation of the EEXPO test through a systematic review and meta-analysis is one of the elements of this thesis that will be found in the next section.

3.6.3 Practical aspects

The effects of the EEXPO test should be observed on cardiac output or its substitutes. Arterial pulse pressure, which corresponds to stroke volume, has been used in the seminal study [114] with good results which must however be confirmed. The scale at which blood pressure is displayed on monitors makes it difficult to quantify its changes over a short period of time. A direct measurement of cardiac

output is more suitable, but it must be precise and provide real-time values. The very precise pulse contour analysis method has been used in most studies validating the EEXPO test [126].

Ultrasounds techniques, such esophageal Doppler and echocardiography, measure cardiac output beat-by-beat, but are not very precise. As a matter of fact, the smallest significant change in velocity-time integral (VTI) obtained by echocardiography is only 10% [127], which is too large compared to the diagnostic threshold of 5% of the EEXPO test [126]. To overcome this problem, a study proposed to combine the results of two tests carried out sequentially: an EEXPO of 15 seconds and an occlusion of 15 seconds and at the end of inspiration (EIXPO, for end-inspiratory occlusion) [128]. The hypothesis was that EEXPO should increase VTI in preload dependent patients, while EIXPO should decrease it in these patients. When the percentages of variation of the VTI induced by the EEXPO and EIXPO were added, the "EEXPO + EIXPO" test was as reliable as the EEXPO test alone, but with a threshold of 13%, which is more compatible with the precision of echocardiography. Similar results have been reported using esophageal Doppler [129].

3.6.4. Limits

- Intense spontaneous breathing activity: a 15 second breathing pause cannot be sustained by some conscious patients. However, the test can be performed even in some patients who are lightly sedated. Of course, the test is not suitable for patients without mechanical ventilation.
- Positive end-expiratory pressure (PEEP) level: during EEXPO, airway pressure is reduced to PEEP level, the latter of which may affect the reliability of the EEXPO test. Nevertheless, one study showed that the reliability was similar for positive expiratory pressure of 5 cmH_2O and 14 cmH_2O [125]. Thus, in the range used today, the reliability of the EEXPO test may not depend on the level of PEEP.
- Low tidal volume: two studies have shown that the EEXPO test is reliable with a tidal volume of 8 but not 6 mL/kg [125,130]. Nevertheless, since many studies confirming the reliability of the EEXPO test have included patients with tidal volumes less than 8 mL/kg and even less than 7 mL/kg, this point certainly deserves further study.
- Prone position: the only study that looked at the EEXPO test while the patient was on prone position found poor reliability [131]. Sensitivity and specificity were only acceptable in patients in whom central venous pressure increased during EEXPO. Since there is no obvious reason why the test should be less reliable in the prone position than in supine position, this result should be confirmed.

Test	*Threshold*	*Limitations*
Fluid challenge (500 mL)	15%	Requires a direct measurement of cardiac output; not reversible; risk of fluid overload
Mini fluid challenge (100 mL)	6%	Requires a very precise method for cardiac output measurement
Pulse pressure variation	12%	Not suitable for spontaneously breathing patients, in case of cardiac arrhythmias, low tidal volume, low respiratory compliance, high respiratory rate
Inferior vena cava diameter variation	12%	Not suitable for spontaneously breathing patients, in case of low tidal volume, low respiratory compliance, abdominal hypertension
Superior vena cava diameter variation	36%	Not suitable for spontaneously breathing patients, in case of cardiac arrhythmias, low tidal volume, low respiratory compliance. Requires trans-esophageal echocardiography
Passive leg raising	10%	Requires a direct measurement of cardiac output; not suitable in case of intracranial hypertension, abdominal hypertension, venous compression stockings
End-expiratory occlusion	5%	Requires a very precise direct method for cardiac output measurement; requires a 15-second stop in mechanical ventilation
End-expiratory occlusion + End-inspiratory occlusion	13%	Requires two consecutive 15-second stops in mechanical ventilation

Table 1 - Summary of the various dynamic tests to detect the preload responsiveness, with relative thresholds and main limits.

4. Practical use of the tests of preload responsiveness

4.1 To decide on the administration of fluids

Predicting the response to volume expansion helps one to answer the questions: when to start, when to continue, and when to stop volume expansion. Before starting fluid administration, it should be remembered that the response to volume expansion is a physiological phenomenon. A positive preload dependence test does not necessarily indicate the need of fluid administration. Indeed, the main objective of this treatment is to increase cardiac output, oxygen supply and ultimately oxygen consumption [31]. Thus, the issue of fluid administration only makes sense in patients with a state of preload dependence and signs of tissue hypoxia [31].

In addition, although it is recommended to predict the response to volume expansion in patients with acute circulatory failure [14], this recommendation does not apply to the initial phase of hypovolemic or septic shock, where hypovolemia is constant [132]. Within the first hour of resuscitation (this time frame is not precisely known), volume expansion should be administered urgently at a rate of approximately 10 mL/kg [133]. This rate must of course be adapted to the clinical situation, such as during bleeding where the rate must be increased or *vice versa* if signs of pulmonary edema appear during the infusion or in the event of serious lung injury [133].

4.2. To decide not to give fluid

This is, in fact, the most important practical utility of tests of preload responsiveness. Since positive fluid balance is associated with increased mortality in many clinical situations [52–54,57], it is justified to administer fluid only with the virtual certainty that the expected effect on cardiac output will occur. From this point of view, tests of preload responsiveness allow an individual assessment of the benefit /risk balance of fluid administration.

4.3. To manage water depletion

In the late phase of the management of a state of shock, called the “de-resuscitation” or “de-escalation” phase [134], it is common to decide for water depletion by diuretics or ultrafiltration to improve the patient's clinical condition [15,49,60]. However, sometimes the risk of this intensive depletion is to exceed its goal, leading to dehydration [135], reduced cardiac output and low blood pressure.

Based on the principle that a drop in cardiac output results from salt and water depletion in preload dependent patients, a study showed that a positive PLR test before starting ultrafiltration reliably

predicted an episode of hypotension during the treatment [136]. The practical use that can be made of these results is first not to undertake depletion when the patient is in a state of preload dependence.

4.4. To guide weaning from mechanical ventilation

Another clinical application of the tests of preload responsiveness is to predict failure of weaning from mechanical ventilation. Weaning-induced pulmonary edema is one of the most common causes of weaning failure [137,138] with a high incidence of 58% in difficult-to-wean patients [139].

Assuming that pulmonary edema associated with withdrawal from mechanical ventilation occurs when the heart cannot cope with the load changes caused by spontaneous ventilation, Dres et al. showed that a negative PLR test predicted weaning failure due to pulmonary edema with an area under the ROC curve of 0.88 [140]. Conversely, the presence of non-preload dependence, assessed by a negative PLR test, predicts weaning failure due to pulmonary edema [139].

5. Conclusion of the second chapter

While it is clearly established that static markers of cardiac preload should not be used to predict the response to volume expansion, there are numerous tests and clues that allow this to be reliably done. PPV is a very reliable indices, but it can only be used in a minority of cases today. The PLR test is well established, and is particularly appreciated for its ease of performance, its validity, and the fact that it can be used in spontaneous breathing patients, regardless of the tidal volume of mechanical ventilation, pulmonary compliance, or heart rate. The EEXPO test can be used only in mechanically ventilated patients. However, as we will see further in this manuscript, its validity is strong enough to prompt its use in intensive care patients.

One should, however, bear in mind the reasons to perform these tests as well as the following actions that should and should not be taken.

Second part: clinical studies

The core of this research project is divided in three parts:

1) In the preliminary part we aimed at validating the EEXPO test, by analyzing the existing literature and providing a pooled evidence through a systematic review and meta-analysis, to highlight strengths and limitations of the test.

2) The main part of the thesis investigates the role of bioreactance, a completely non-invasive method for cardiac output monitoring, in detecting preload responsiveness through the EEXPO test. By increasing the amount of evidence in favor of this technology, which has been investigated during fluid administration and PLR in critically ill and operating room patients, we hope to contribute to its future use outside the intensive care unit, especially in the Emergency Department.

3) The ancillary part investigates a new technology for non-invasive cardiac output monitoring, the Perfusion Index. By analyzing the variation of the pulsatile over the non-pulsatile part of the plethysmographic signal, this method is expected to track rapid changes in cardiac output. We investigated its ability to detect preload responsiveness both during PLR and EEXPO.

Finally, I will provide an overview of other clinical studies I was involved in, as part of my PhD program, in the field of hemodynamics.

Preliminary part: The end-expiratory occlusion test for detecting preload responsiveness: a systematic review and meta-analysis

Gavelli F, Shi R, Teboul J-L, Azzolina D, Monnet X. Ann Intensive Care. 2020;10:65. *doi: 10.1186/s13613-020-00682-8.*

Introduction

Over the last 20 years, many dynamic tests were developed and validated for predicting before administering a fluid bolus whether it will increase cardiac output (CO) significantly [141]. They all consist in observing the effects on CO of variations in cardiac preload occurring under different circumstances. The variations of arterial pulse pressure and stroke volume induced by mechanical ventilation are very reliable indices of preload responsiveness [142,143], but they are strongly limited by the restricted conditions in which they can be used. Administering small amounts of fluid may predict the response to larger ones [79], but such "mini fluid challenges" require a very precise measurement of CO and, if repeated, may contribute to fluid overload. Passive leg raising, which has been widely validated, reversibly mimics fluid infusion and detects preload responsiveness very reliably [112], but intra-abdominal hypertension is responsible for some false negatives [121] and it is not very convenient to perform [110].

In this context, the transient interruption of mechanical ventilation at end-expiration has been proposed ten years ago for testing preload responsiveness through heart-lung interactions [114]. By interrupting the impediment to venous return induced by each mechanical insufflation, the expiratory hold allows the cardiac preload to augment, which, in case of preload responsiveness, leads to a significant increase of CO [126].

Some studies testing the diagnostic accuracy of the end-expiratory occlusion (EEXPO) test have been published after that first one, with different methods of CO measurement, durations of expiratory hold and clinical settings. Thus, we conducted a new systematic review of all the studies testing the diagnostic accuracy of the EEXPO test. In particular, taking the advantage of the large number of patients pooled, we aimed at looking for factors influencing the reliability of the EEXPO test.

Methods

Clinical research question

The clinical research question was: *What is the sensitivity and specificity of the EEXPO test to detect preload responsiveness when its effects are assessed on cardiac output?*

PICO statement

The PICO statement was the following:

- P – patient, problem or population: surgical or critically ill patients under mechanical ventilation in whom the effect of volume expansion on CO needs to be predicted.
- I – intervention: EEXPO test performed by holding the patient's breath at the end of expiration during invasive mechanical ventilation and by measuring the induced changes in CO, measured by any available monitoring device.
- C – comparison, control or comparator: preload responsiveness defined as either a 10 to 15% increase in CO during volume expansion (250-500 mL of fluid in ≤30 minutes) or 10% during passive leg raising (PLR), measured by any available monitoring devices.
- O – outcomes: ability of the EEXPO test to detect preload responsiveness, defined in each study according to the pre-specified threshold of CO increase after either volume expansion or PLR.

Identification of records

Our aim was to identify all studies evaluating the ability of the EEXPO test to predict a significant increase in CO or surrogate (velocity time integral of the left ventricular outflow tract with echocardiography, blood velocity of the descending aorta with esophageal Doppler) compared to the one induced by a subsequent volume expansion or by a PLR test. We included into our analysis only studies that provided sensitivity, specificity and the area under the receiver operating characteristic curve (AUROC) of the EEXPO test with the corresponding diagnostic threshold. Moreover, only studies on adults, that were published in full text or accepted for publication in indexed journals were included into analysis. No language restriction was applied.

We searched the US National Library of Medicine's MEDLINE database, the EMBASE database and the Cochrane Database of Systematic Reviews for relevant studies published from 1960 to 1st October 2019. We used the following medical subject headings and key-words: "end expiratory occlusion", "end expiratory", "volume expansion", "fluid challenge", "fluid administration", "fluid responsiveness", "preload responsiveness". The complete searching strategy is reported in the (**Additional file 1: Supplemental S1)**. We also looked for relevant articles cited in reviews, articles and editorials. The search was performed by two independent investigators (FG and RS) until no new record could be found. Conflicts regarding inclusion or exclusion of studies were resolved by consensus with a third investigator (XM). The meta-analysis was performed according to the PRISMA statement

(http://www.prisma-statement.org). The study protocol was prospectively registered in PROSPERO (CRD42019138265 – Submission 7th June 2019, approval 29th August 2019).

Data extraction

Using a standardized form, two investigators (FG and SR) independently extracted several data from the selected studies, including demographic characteristics of the investigated population, ventilatory variables, the duration of the EEXPO test, the method used to assess its hemodynamic effects on CO or its surrogate, the amount and type of fluid infused and the duration of the infusion of volume expansion, when performed, as well as the criteria used to define preload responsiveness. Moreover, the number of true positives, true negatives, false positives, and false negatives as well as sensitivity and specificity, the AUROC and the best EEXPO-induced increase in CO or surrogates able to detect preload responsiveness were collected.

Assessment of risk of bias in included studies

Two authors (FG and RS) independently assessed the overall quality of evidence at the outcome level according to the GRADE system [144]. Moreover they assessed the risk of bias of the included studies by following the criteria specified in the QUADAS-2 scale [145]. For each criterion, the risk of bias was judged as high, low or unclear. Disagreements between the reviewers were resolved by consensus with a third investigator (XM). Then, as described elsewhere [112], points were given to each issue of the QUADAS-2 evaluation (three points for “high”, two points for “unclear” and one point for “low) and summed. “Overall higher” and “overall lower” risk of bias was defined with reference to the median of the risk bias of all studies [112].

Statistical analysis

Study description

Study-specific sensitivities and specificities values have been computed considering a 0.5 continuity correction as indicated in the literature (**Additional file 1: Supplemental S2**). The 95% confidence intervals have also been calculated using the Wilson [146] method. A graphical representation of the data has been provided. Paired forest plots on sensitivity and specificity and confidence ellipses (95%) plots have also been reported. The correlation of sensitivities and false-positive rates has been reported to investigate a possible threshold effect.

For the principal analysis, if more than one technique was used to assess the hemodynamic effects of the EEXPO test, we chose the one considered to be the most reliable: when both esophageal Doppler and end-tidal carbon dioxide were used, we only considered esophageal Doppler and when both echocardiography or esophageal Doppler and calibrated pulse contour analysis were used, we

considered only pulse contour analysis. Finally, for that analysis, in studies in which the EEXPO test was performed at different positive end-expiratory pressure (PEEP) or tidal volume levels, we selected the ones that provided the highest AUROC.

Bivariate random effect model

The bivariate random-effects model by Reitsma [147] has been computed to estimate the area under the summary receiver operating characteristic (AUSROC) curve accounting for correlation between sensitivity and specificity. The model has been estimated via a restricted maximum likelihood (REML) approach. In the bivariate model, the logit sensitivity, and the logit specificity are assumed to be bivariate normal random variables across the studies considering also a variance and covariance matrix for the random effect component. A bivariate version of I^2 statistics has been computed to investigate the presence of heterogeneity on sensitivity and specificity outcome, as indicated in the literature [148]. A value of $I^2 \geq 75\%$ was considered as indicating a high heterogeneity [149].

Investigation of heterogeneity sources

The potential sources of heterogeneity have been investigated considering a Reitsma bivariate random effect metaregression model. Separate metaregression models have been calculated considering, as covariate:

- Tidal volume: ≤7 *vs*. >7 mL/kg
- Pulse contour analysis *vs.* other hemodynamic monitoring methods
- EEXPO duration: ≤15 *vs.* >15 seconds
- PEEP level: ≤7 *vs.* >7 cmH_2O
- Setting of the study: intensive care unit (ICU) *vs.* operating room (OR)
- Risk of bias: “overall lower” *vs*. “overall higher”, as described above.

The covariate effects on the sensitivity and false positive rate (FPR) have been reported together with p-values and 95% confidence intervals. The likelihood ratio test (LRT) has been carried out comparing a null model with a model with a covariate. A significant LRT indicates that the covariate is a potential source of heterogeneity across studies. Publication bias was investigated using the Deek’s test [150]. The statistical significance was set at a p value <0.05. The analyses were performed using R 3.3.5 [151] with mada [152] package.

Results

Characteristics of the included studies

We identified 13 studies (530 patients) [128,129,153,130,131,114,154,123,155,156,124,125,157] that reported the ability of the EEXPO test to assess preload responsiveness. Flowchart in **Figure 12** illustrates the study selection, and the main characteristics of the included studies are reported in **Table 2**. Nine studies [114,123–125,128–131,156] were performed in the ICU and four in the OR [153–155,157]. In one study in the ICU [131], the EEXPO test was performed during prone positioning. All patients were mechanically ventilated with a tidal volume ranging between 5.8 mL/kg [129] and 8.2 mL/kg [155], with a median value of 6.95 mL/kg. In two studies [130,153], the diagnostic ability of the EEXPO test was assessed under a tidal volume at 6 mL/kg and repeated at a tidal volume at 8 mL/kg. The PEEP level was set between 4 cmH_2O [155] and 14 cmH_2O [125], with a median value of 7 cmH_2O. The results of the QUADAS-2 evaluation are reported on **Additional file 1: Supplemental S3**. Following the GRADE system, the overall quality of evidence for the included studies was assessed as very low (**Additional file 1: Supplemental S4**).

Hemodynamic monitoring

Four studies provided more than one method for CO measurement [114,128,129,155]. In eight of the included studies [114,123–125,128–131] CO was evaluated through the calibrated pulse contour analysis and in two through the uncalibrated one [153,154]. Three studies [128,156,157] evaluated the effects of EEXPO test on CO with echocardiography: two with transthoracic [128,156] and one with transoesophageal echocardiography [157]. Oesophageal Doppler was used in two studies [129,155], end-tidal carbon dioxide monitoring [155] and pulse pressure [114] in one study each.

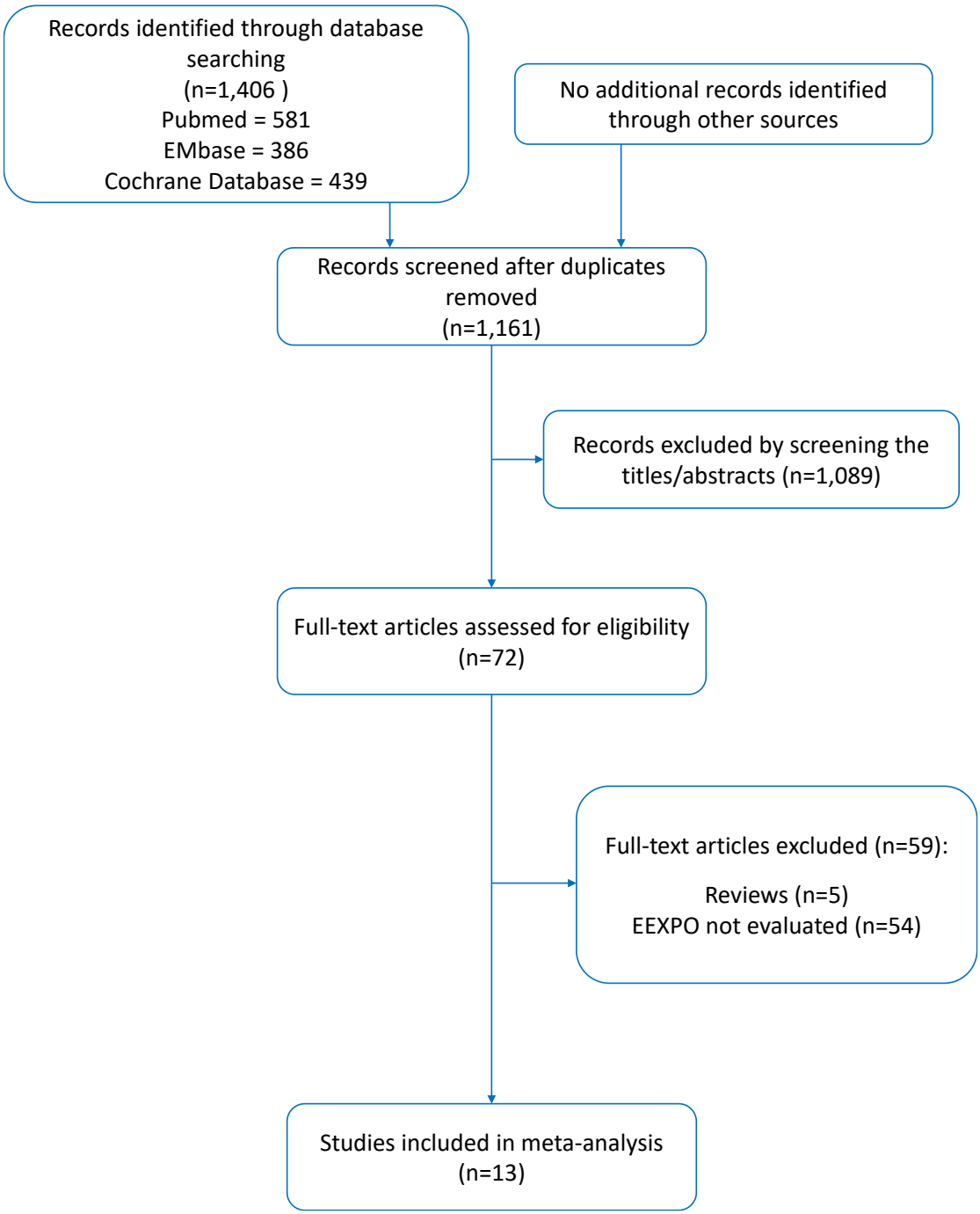

Figure 12 - Flowchart of study selection.

Fluid responsiveness

Preload responsiveness was defined according to CO changes induced by fluid administration in 12 studies [114,123,155,154,130,131,128,156,124,129,153,157]. In these studies, preload responsiveness was defined by a fluid-induced increase in CO ≥15% [114,123,155,130,131,128,156,124,129,157] or 10% [153,154]. Preload responsiveness was defined according to CO changes induced by PLR in one study, with a threshold of CO increase of 10% [125].

	Year	No. of patients	Setting	PEEP (cmH_2O)	Tidal volume (mL/kg)	Respiratory system compliance (mL/cmH_2O)	HD monitoring #1	HD monitoring #2
Monnet et al.[114]	2009	34	ICU	8±3	6.8±1.1	*NA*	Calibrated PC	PP
Monnet et al. [124]	2012	39	ICU	7±3	7.9±2.5	36±16	Calibrated PC	*NA*
Monnet et al.[123]	2012	54	ICU	7±3	7.9±1.1	33±6	Calibrated PC	*NA*
Silva et al.[125]	2013	34	ICU	5±0 *vs.* 14±0	6.8±0.2	27±3 *vs.* 31±1	Calibrated PC	*NA*
Guinot et al.[155]	2014	42	OR	4±2	8.2±0.8	*NA*	ODM	$EtCO_2$
Biais et al.[154]	2017	41	OR	5±0	6.9±0.6	40±10	Uncalibrated PC	*NA*
Myatra et al.[130]	2017	30	ICU	9±3	6.0±0.1 *vs.* 8.0±0.0	25±4 *vs.* 32±4	Calibrated PC	*NA*
Yonis et al.[131]	2017	33	ICU	8±1	6.0±0.1	30±5	Calibrated PC	*NA*
Jozwiak et al.[128]	2017	30	ICU	10±4	6.2±0.2	35±3	TTE	Calibrated PC
Georges et al.[156]	2018	50	ICU	6±2	6.9±0.7	50±17	TTE	*NA*
Dépret et al.[129]	2019	28	ICU	12±3	5.8±0.6	39±10	ODM	Calibrated PC
Messina et al.[153]	2019	40	OR	5±0	6.0±0.0 *vs.* 8.0±0.0	65±4 *vs.* 83±4	Uncalibrated PC	*NA*
Xu et al.[157]	2019	75	OR	5±0	8±0.1	*NA*	TOE	*NA*

Table 2 – Studies characteristics.

$EtCO_2$: end-tidal carbon dioxide; HD: hemodynamic; ICU: intensive care unit; NA: not available; ODM: oesophageal doppler monitoring; OR: operating room; PC: pulse contour; PEEP: positive end-expiratory pressure; TOE: trans-oesophageal echocardiography; TTE: trans-thoracic echocardiography.

Fluid infusion was performed with normal saline in 11 studies [114,123,154,130,131,128,156,124,125,129,157], with Ringer solution in the other two studies [153,155], with infused volumes of 500 mL in most of the cases [114,123,155,131,128,156,124,125,129]. However in two studies [153,154], the volume of the fluid bolus was of 250 mL and in two others it was tailored according to patient's body weight [130,157] (**Table 3**).

Prediction of fluid responsiveness by the EEXPO test-induced changes in CO

The duration of the expiratory hold was reported in all the included studies and it ranged between 12 seconds [156] and 30 seconds [153,154]. All the studies reported the AUROC curve for the EEXPO test to detect preload responsiveness [114,123,155,154,130,131,128,156,124,125,129,153,157], as well as sensitivity, specificity and the best diagnostic threshold (**Table 4**).

For the EEXPO test-induced changes in CO, the pooled sensitivity and specificity were 0.85 [0.77-0.91] (I^2=62.6%) and 0.88 [0.83-0.91] (I^2=6.0%), respectively, while the AUSROC curve was 0.91 [0.86-0.94] (**Figure 13** and **Figure 14**). The corresponding best diagnostic threshold was 5.1±0.2%. The Spearman correlation of sensitivities and false positive rates was 0.27 [0.32-0.72].

High vs. low tidal volume

For the nine studies with a tidal volume ≤ 7 mL/kg [114,125,128–131,153,154,156], the AUSROC curve was 0.96 [0.92-0.97] (sensitivity and specificity 0.89 [0.70-0.96] and 0.92 [0.83-0.96], respectively), while in the six studies with a tidal volume > 7 mL/kg [123,124,130,153,155,157], it was 0.89 [0.82-0.95] (sensitivity and specificity 0.85 [0.78-0.90] and 0.87 [0.78-0.92], respectively). No significant difference was observed between pooled AUSROCs (p=0.44) (**Additional file 1: Supplemental S5.1**).

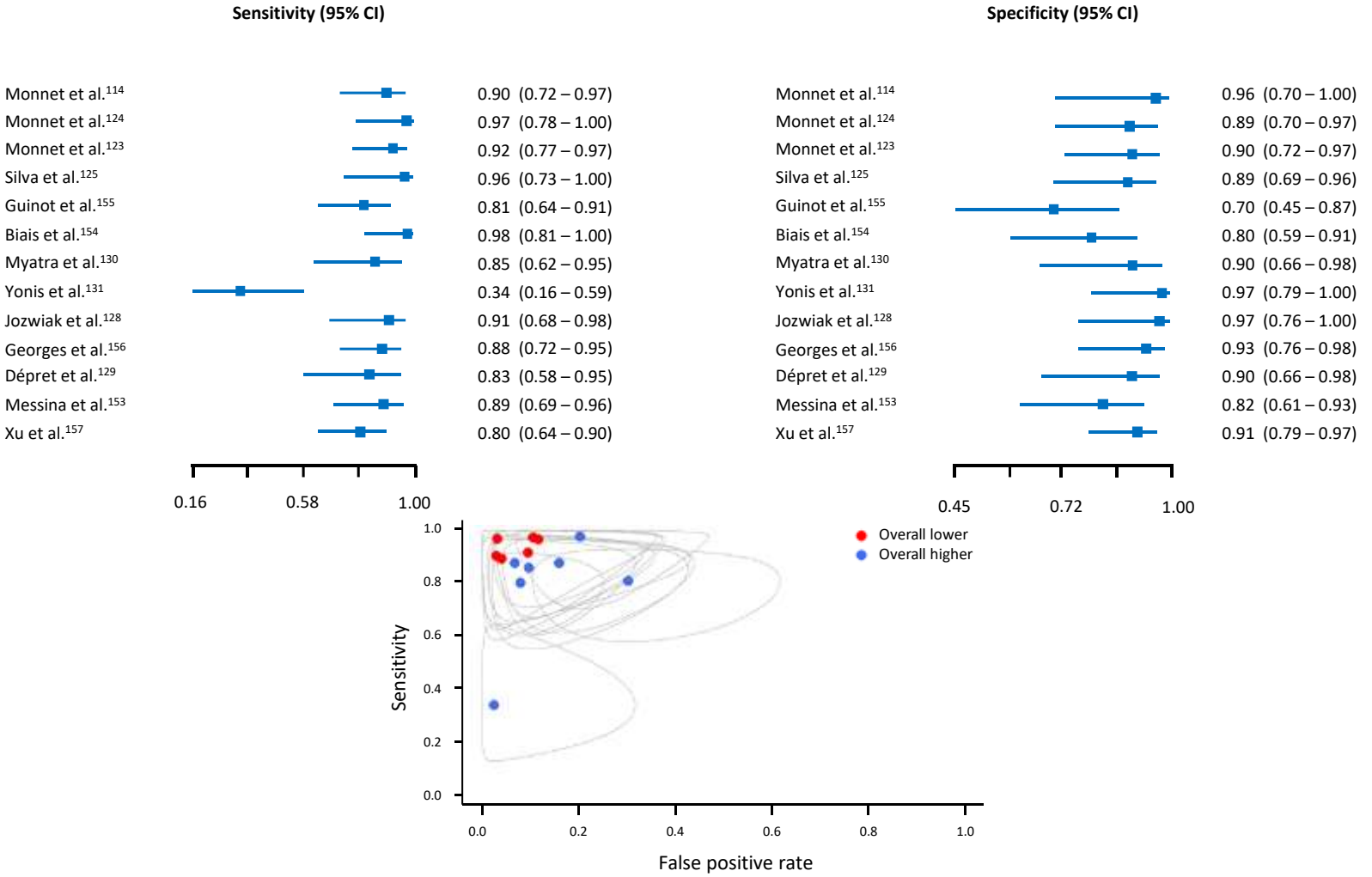

Figure 13 - Paired sensitivity and specificity forest plots (top) and confidence ellipses plot (bottom) according to "Overall lower" and "Overall higher" QUADAS-2 risk of bias. The Spearman correlation of sensitivities and false positive rates is 0.27 [-0.32 - 0.72].

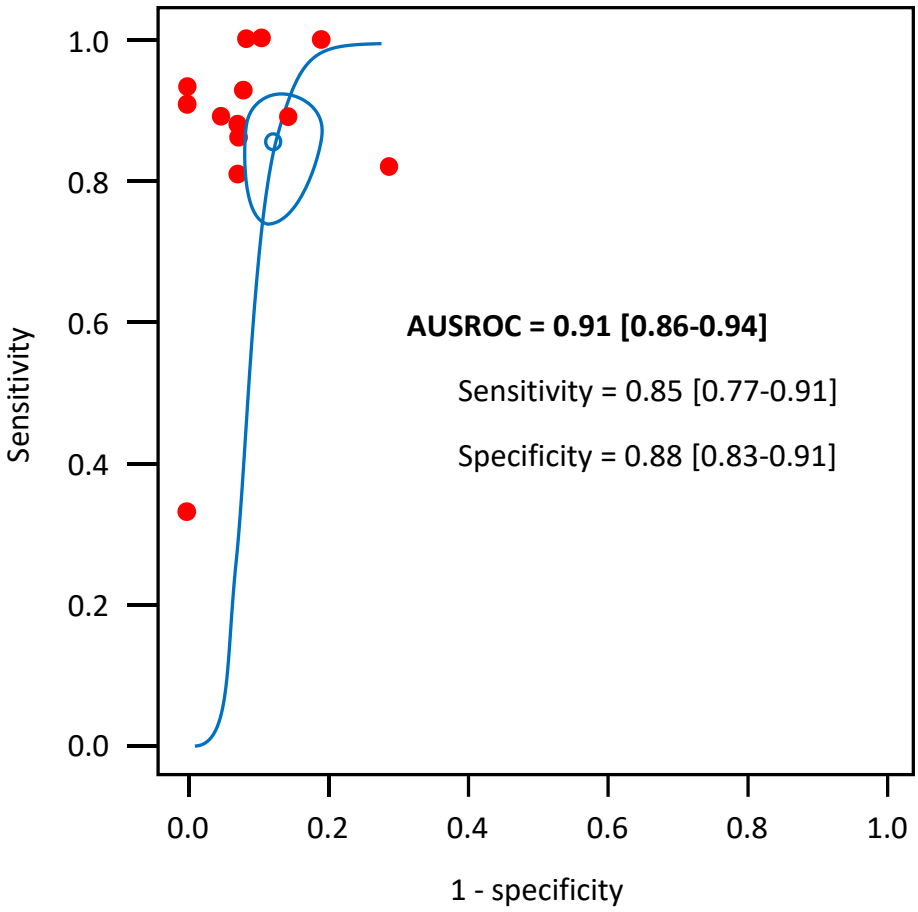

Figure 14 - AUSROC curve for the Reitsma et al. [147] bivariate model. Pair of pooled accuracies together with a 95%-confidence region are represented. AUSROC: area under the summary receiver operating characteristic.

Pulse contour analysis vs. other hemodynamic monitoring techniques

Among the ten studies in which CO was measured through pulse contour analysis [114,123–125,128–131,153,154], the AUSROC curve was 0.93 [0.91-0.95] (sensitivity and specificity 0.87 [0.75-0.94] and 0.89 [0.83-0.93], respectively), while among those that measured it through other methods [114,128,129,155–157], it was 0.87 [0.82-0.96] (sensitivity and specificity 0.84 [0.78-0.89] and 0.88 [0.72-0.95], respectively). The comparison between the two AUSROCs did not show a significant difference (p=0.62) (**Additional file 1: Supplemental S5.2**).

EEXPO test duration

Among the ten studies in which the duration of the EEXPO test was ≤15 seconds [114,123,155,130,131,128,156,124,125,129], the AUSROC curve was 0.93 [0.90-0.96] (sensitivity and specificity 0.86 [0.75-0.93] and 0.89 [0.83-0.94], respectively), while among those in which the EEXPO test duration was >15 seconds [153,154,157], it was 0.93 [0.88-0.95] (sensitivity and specificity 0.87

[0.72-0.95] and 0.86 [0.74-0.93], respectively). There was no statistically significant difference between the two AUSROCs (p=0.20) (**Additional file 1: Supplemental S5.3**).

PEEP level

Among the eight studies [123–125,153–157] in which the level of PEEP was ≤7 cmH_2O, the AUSROC curve was 0.89 [0.83-0.95] (sensitivity and specificity 0.86 [0.80-0.91] and 0.86 [0.79-0.91], respectively), while among those in which the PEEP level was >7 cmH_2O [114,125,128–131], it was 0.95 [0.92-0.97] (sensitivity and specificity 0.85 [0.62-0.95] and 0.93 [0.85-0.97], respectively). There was no statistically significant difference between the two AUSROCs (p=0.386) (**Additional file 1: Supplemental S5.4**).

Setting

Among the nine studies performed in the ICU [114,123–125,128–131,156], the AUSROC curve was 0.95 [0.93-0.96] (sensitivity and specificity 0.88 [0.74-0.95] and 0.92 [0.87-0.96], respectively), while among those performed in the OR [153–155,157], it was 0.86 [0.82-0.93] (sensitivity and specificity 0.83 [0.74-0.90], and 0.83 [0.71-0.90], respectively). There was no statistically significant difference between the two AUSROCs (p = 0.66) (**Additional file 1: Supplemental S5.5**).

Risk of bias

When we divided the studies according to the global risk of bias, no significant difference was observed in AUSROCs between studies with overall lower [114,123–125,128,129] (0.96 [0.92-0.97]; sensitivity and specificity 0.92 [0.85-0.96] and 0.91 [0.84-0.95], respectively) and overall higher [130,131,153–157] risk of bias (0.91 [0.83-0.95]; sensitivity and specificity 0.81 [0.65-0.91] and 0.87 [0.78-0.93], respectively) (p=0.45) (**Additional file 1: Supplemental S5.6**).

Sources of heterogeneity and publication bias

At the Reitsma bivariate random effect metaregression models, only the overall risk of bias emerged as a potential source of heterogeneity (p=0.049) (**Additional file 1: Supplemental S5.6**). On the contrary, none of the other covariates was identified as a source of heterogeneity. According to the results of the Deek's test, we did not detect publication bias in the studies that evaluated the diagnostic performance of the EEXPO test (p=0.864) (**Additional file 1: Supplemental S6**).

	Year	No. of patients	Responders	Non-responders	FC duration (min)	FC volume (mL)	Reference defining preload responsiveness	CO increase defining responsiveness (%)	EEXPO duration (sec)
Monnet et al.[114]	2009	34	23	11	10	500	Saline infusion	15	15
Monnet et al. [124]	2012	39	17	22	30	500	Saline infusion	15	15
Monnet et al.[123]	2012	54	30	24	20	500	Saline infusion	15	15
Silva et al.[125]	2013	34	13	21	-*	-*	PLR	10	15
Guinot et al.[155]	2014	42	28	14	10	500	Ringer/Ringer lactate infusion	15	15
Biais et al.[154]	2017	41	20	21	10	250	Saline infusion	10	30
Myatra et al.[130]	2017	30	16	14	10	7 mL/kg	Saline infusion	15	15
Yonis et al.[131]	2017	33	15	18	15	500	Saline infusion	15	15
Jozwiak et al.[128]	2017	30	15	15	10	500	Saline infusion	15	15
Georges et al.[156]	2018	50	28	22	15	500	Saline infusion	15	12
Dépret et al.[129]	2019	28	14	14	10	500	Saline infusion	15	15
Messina et al.[153]	2019	40	21	19	10	250	Ringer lactate infusion	10	30
Xu et al.[157]	2019	75	36	39	10	6 mL/kg	Saline infusion	15	20

Table 3 – Modalities of the end-expiratory occlusion test and of fluid. CO: cardiac output; EEXPO: end-expiratory occlusion; FC: fluid challenge; PLR: passive leg raising. * In this study, a fluid challenge was performed in some patients, but preload responsiveness was defined according to the result of the PLR test (performed in all patients).

	No. of patients	AUROC	95% CI	Threshold*	Sensitivity	Specificity	PPV	NPV
Monnet et al.[114]	34	0.97	0.85 - 1.00	5%	91%	100%	100%	84%
Monnet et al. [124]	39	0.97	0.91 - 1.00	5%	100%	91%	90%	100%
Monnet et al.[123]	54	0.95	NA	5%	93%	92%	94%	91%
Silva et al.[125]	34	0.96	0.82 - 0.99	6%	100%	90%	86%	100%
Guinot et al.[155]	42	0.78	0.63 - 0.89	2.3%	82%	71%	85%	66%
Biais et al.[154]	41	0.91	0.81 - 1.00	5%	100%	81%	83%	100%
Myatra et al.[130]	30	0.95	0.88 - 1.00	4.1%	88%	93%	93%	87%
Yonis et al.[131]	33	0.65	0.46 - 0.84	10%	33%	100%	100%	64%
Jozwiak et al.[128]	30	0.98	0.85 - 1.00	4%	93%	100%	100%	93%
Georges et al.[156]	50	0.96	NA	9%	89%	95%	96%	87%
Dépret et al.[129]	28	0.95	0.79- 0.99	3%	86%	93%	92%	87%
Messina et al.[153]	40	0.93	0.84 - 1.00	3.6%	89%	86%	87%	88%
Xu et al.[157]	75	0.9	0.83 - 0.97	5%	81%	93%	91%	84%

Table 4 – Diagnostic accuracy of the end-expiratory occlusion test in the including studies. AUROC: area under the receiver operating characteristic; CI: confidence interval; NA: not available; NPV: negative predictive value; PPV: positive predictive value. * Threshold of increase in cardiac output induced by the test reported as providing the best compromise between sensitivity and specificity.

Discussion

This meta-analysis of 13 studies performed in 530 patients shows that the changes in CO induced by the EEXPO test reliably detect preload responsiveness with excellent sensitivity and specificity (0.85 [0.77-0.91] and 0.88 [0.83-0.91], respectively). The AUSROC curve was 0.91 [0.86-0.94] and the best diagnostic threshold for the EEXPO-induced increase in CO was 5.1±0.2%. No difference was observed for the diagnostic ability of the EEXPO test when different conditions, settings and methods for CO monitoring were compared.

Heart-lung interactions are the basis on which stands the EEXPO test. During positive pressure ventilation, insufflation increases the intrathoracic pressure and the right atrial pressure, impeding venous return [142]. It interrupts the increase in cardiac preload that occurred during exsufflation. Then, EEXPO stops this cyclic impediment of venous return and allows cardiac preload to increase. Right cardiac preload increases first and, provided that the EEXPO is long enough for allowing the transit of this increase through the pulmonary vasculature, it is followed by the increase of left cardiac preload. The interruption of ventilation also stops the cyclic compression of the pulmonary vasculature, which facilitates the transference of preload increase from the right to the left side. The transient increase in cardiac preload induced by the EEXPO test can be seen as a small “self-preload challenge” which might be used to assess preload responsiveness [126].

A number of studies have now tested the reliability of the EEXPO test. Many were positive but some of them showed some contradicting results, which led us to perform a meta-analysis. Despite these studies, we report that the AUSROC of the EEXPO test to detect preload responsiveness is high, comparable to the one reported in meta-analyses for pulse pressure variation [89] and the passive leg raising test [112], and higher than the one found for the respiratory variations in the inferior or superior vena cava [158]. The present meta-analysis confirms another one recently published by Messina et al. [81], which included five less studies [124,125,129,153,157].

Importantly, the novelty of our meta-analysis is that it allowed us to investigate some of the factors which may, in theory, alter the test reliability and which have not been investigated in the former meta-analysis. First, no significant difference was observed between studies in which the duration of the respiratory hold was ≤15 seconds and studies in which it was longer, which indicates that a duration of 15 seconds appears enough. In practice, this is an important point since all ventilators do not allow respiratory holds ≥15 sec.

Second, the level of PEEP might be theoretically important, since it is the level to which the airway pressure is reduced during EEXPO. However, in a previous study in which two levels of PEEP were

compared in the same patients, the diagnostic accuracy of the EEXPO test was unchanged [125]. The present meta-analysis tends to confirm this, since the AUROC was similar among studies with high or low PEEP levels. Nevertheless, both levels were defined according to the median value of PEEP levels, which was only 7 cmH_2O. One should keep in mind that in theory, the hemodynamic effects of the EEXPO test should more depend on the respiratory driving pressure than on the PEEP alone, a hypothesis that remains to be tested. Of note, the worst reliability of the EEXPO test was reported by a study performed in prone positioning [131], in which the PEEP level was 8 cmH_2O on average. Since there is no clear reason why prone positioning should change the reliability of the EEXPO test, and since this was reported in that single study, no clear conclusion about this point could be drawn without further investigations.

A third factor that might theoretically affect the EEXPO test reliability is the tidal volume. Two studies which have compared these two levels of tidal volume reported that diagnostic accuracy was correct at 8 mL/kg but poorer at 6 mL/kg [130,153]. However, even if they did not directly compare different tidal volume levels, some of the other studies which reported excellent diagnostic accuracy had included some patients with low tidal volume values, as indicated by the mean and standard deviation reported in their whole population. If the test reliability had been poor in these patients, the averaged reliability could not have been so good. In line with these studies, the present meta-analysis did not show any difference in AUSROC when studies were compared with respect to the median of reported tidal volumes. These conflicting results suggest that the question to know whether the tidal volume actually influences the EEXPO test reliability is still unanswered.

A fourth and important issue is the method which is used for measuring the EEXPO-induced changes in CO. One advantage of the present meta-analysis was that it included studies using the devices that are the most used in the ICU nowadays [159]. As a matter of fact, the small threshold defining the test positivity may require precise CO monitoring devices. The least significant change of echocardiography [127] and esophageal Doppler [129] is close to the diagnostic threshold of the EEXPO test. This is the reason why two studies performed with esophageal Doppler [129] and echocardiography [128] have overcome this issue by combining the changes in CO induced by both end-expiratory and end-inspiratory holds. The present meta-analysis could not test the advantage of this strategy which was evaluated in these two studies only. However, even though the precision of pulse contour analysis [85] is higher than for the other tested methods, no significant difference has emerged when it was used to track CO changes compared to other methods. One study assessed the EEXPO effects through the changes in end-tidal carbon dioxide [155]. Of note, this way of tracking the EEXPO-induced changes in CO has been questioned [160]. However, the fact that the diagnostic accuracy of the EEXPO test is not influenced by the used CO monitoring methods, is a strong argument in favor of the reliability of the

test at the bedside. Finally, the reliability of the EEXPO test was excellent in both the ICU and OR settings, but there is no obvious reason why it should not be the case.

The heterogeneity of the included studies is one of the limitations of our meta-analysis. However, the metaregression analysis has investigated several possible sources of heterogeneity, identifying one of them (**Additional file 1: Supplemental S5).** Another limitation is that the studies included were all one-center and enrolled relatively small number of patients. Nevertheless, this is the interest of a meta-analysis to merge these small-size studies in order to draw more solid conclusions. Some of the studies suffered from biases as assessed with the QUADAS-2 (**Additional file 1: Supplemental S3**). Nevertheless, to better investigate their role as possible causes of heterogeneity, we performed a prespecified subgroup analysis by dividing the studies according to the global risk of bias: no difference was observed in the accuracy of the EEXPO test between studies with overall lower and higher risk of bias. We also evaluated the overall quality of evidence of the studies included in the meta-analysis according to the GRADE system, with a whole judgement of "very low" (**Additional file 1: Supplemental S3**). Nonetheless, we believe that these findings should be extensible to each sample of EEXPO test studies, considering their recurrent weakness, related to small sample sizes, no power analysis and clinical heterogeneity. Finally, a large number of the included studies were performed by the same team, which has described the EEXPO test for the first time [114].

Conclusion

This meta-analysis demonstrates that the EEXPO test is accurate in predicting fluid responsiveness both in the ICU and in the OR, regardless of the ventilatory settings and the duration of the expiratory hold. The accuracy is not different when the EEXPO test-induced changes on CO are detected by the pulse contour analysis or by other CO monitoring techniques.

Main part: Bioreactance reliably detects preload responsiveness by the end-expiratory occlusion test when averaging and refresh times are shortened

Gavelli F, Beurton A, Teboul J-L, De Vita N, Azzolina D, Shi R, Pavot A, Monnet X. Ann Intensive Care. 2021;11:133. *doi: 10.1186/s13613-021-00920-7*

Background

Over the last decade, much effort has been put into the development of methods monitoring cardiac index (CI) non-invasively [159,161–165]. Among them, bioreactance estimates cardiac output by analyzing the phase shift between an inward current that is sent through the thorax and the resulting outward current [161]. The principle of the technique is that this phase shift is determined by the variation of the volume of the thorax. From beat to beat, this variation is related to the variation of the volume of blood in the descending aorta and, thus, to stroke volume [166]. Bioreactance is considered as an improvement of bioimpedance which might be less sensitive to artifacts and the patient's movements. The technique is totally non-invasive, as it only requires electrodes pasted on the thorax.

It has been shown to detect real-time changes of CI (ΔCI) induced by a passive leg raising (PLR) test and volume expansion [167]. Besides the PLR test, the end-expiratory occlusion (EEXPO) test is another test assessing preload responsiveness which can be used in mechanically ventilated patients. It consists in interrupting mechanical ventilation at end-expiration for a few seconds, which increases cardiac preload, and in observing the ΔCI which occurs in cases of preload responsiveness. Its accuracy has been established [114,126,168] and it is easy to perform.

Nevertheless, the duration of EEXPO is only 15 seconds, and the induced ΔCI are relatively small [126]. It is then uncertain whether the available commercial version of the bioreactance device, which averages the CI signal over 24 seconds and refreshes the displayed value every 4 seconds, is adequate for monitoring the effects of EEXPO. Thus, the primary goal of this study was to test whether the commercial version of the bioreactance device accurately detects preload responsiveness through the EEXPO-induced ΔCI. The secondary goal was to assess whether shortening the averaging and refresh times of the device improves this detection. We hypothesized that bioreactance can monitor the EEXPO effects on CI, provided that the time over which it averages CI and after which it refreshes its displayed value is short.

Patients and Methods

Patients

This prospective study was conducted in a 25-bed intensive care unit (ICU) and approved by an Institutional Review Board (No. IDRCB:2018-A02825-50). At the time of inclusion, patients' next of kin were informed of the study protocol and of the option to refuse participation. As soon as clinical conditions improved and patients were able to give consent, the same opportunity was given to them. All patients and/or relatives agreed to participate.

Patients were included if they met the following inclusion criteria: age ≥18 years, admission to the ICU for less than 24 hours, invasive mechanical ventilation, PiCCO2 device already in place (Pulsion Medical Systems, Feldkirchen, Germany) and decision by the attending clinicians to perform a PLR test. Exclusion criteria were intra-abdominal hypertension and venous compression stockings (which may decrease the PLR test reliability) [121], intracranial hypertension (which is a contra-indication for PLR) and inability of the patients to sustain a 15-second EEXPO. Patients were included depending on the availability of the investigators. The study report complies with the Standards for Reporting Diagnostic Accuracy (STARD) statement [169].

Bioreactance measurements

The Starling v5.5 device (Baxter, Deerfield, IL, USA) requires 4 double-electrode sensors pasted on the thorax skin, creating a "virtual box" around the heart. The upper sensors are placed on the mid-right and mid-left clavicles and the lower sensors on the mid-right and mid-left last ribs. In each electrode pair, the outer one delivers a current with known alternating high frequency, detected by the inner electrode pair. The phase modulation between currents recorded at the inner and outer electrodes is altered by the changes in thoracic pulsatile blood volume, which allows a proprietary algorithm to derive stroke volume and CI (**Figure 15**) [161,170,171].

Figure 15 – Starling v5.5 device, Baxter

The Starling v5.5 device displays a CI value which corresponds to the moving average of the raw values that have been measured over the last 24 seconds (**Figure 16**). The displayed average is refreshed on the screen every 4 seconds. The CI value measured in this way will hereafter be called "$CI_{Starling\text{-}24.4}$".

We also extracted raw data from our recordings by the Starling device. In a post-hoc analysis, we changed the averaging time to 8 seconds, instead of 24. This duration was the shortest possible time that could be achieved, according to the technological limitations of the currently available device. We judged this interval as appropriate for estimating the effects of the 15-second EEXPO.

The refreshing delay was reduced to one second, instead of 4. The CI value obtained in this way will be called "$CI_{Starling\text{-}8.1}$" (**Figure 16**).

Transpulmonary thermodilution and pulse contour analysis measurements

The PiCCO2 device measures CI through transpulmonary thermodilution, which is performed by injecting three 15-mL boluses of cold saline in the superior vena cava [172,173], and through pulse contour analysis (CI_{pulse}), which is calibrated by transpulmonary thermodilution [174]. The value of CI_{pulse} provided by pulse contour analysis is averaged over 12 seconds, with values that are refreshed every second. CI_{pulse} was continuously recorded by the PiCCOWin software (Pulsion Medical Systems).

Other measurements

In addition to arterial pressure, heart rate and CI, we measured central venous pressure at end-expiration. Respiratory variables such as positive end-expiratory pressure, plateau pressure, respiratory rate and tidal volume (Vt) were also collected. Intra-abdominal pressure was measured through the bladder pressure as previously described [51].

Arterial, central venous and airway pressures were continuously recorded by data acquisition software (HEM-3.5, Notocord, Croissy-sur-Seine, France).

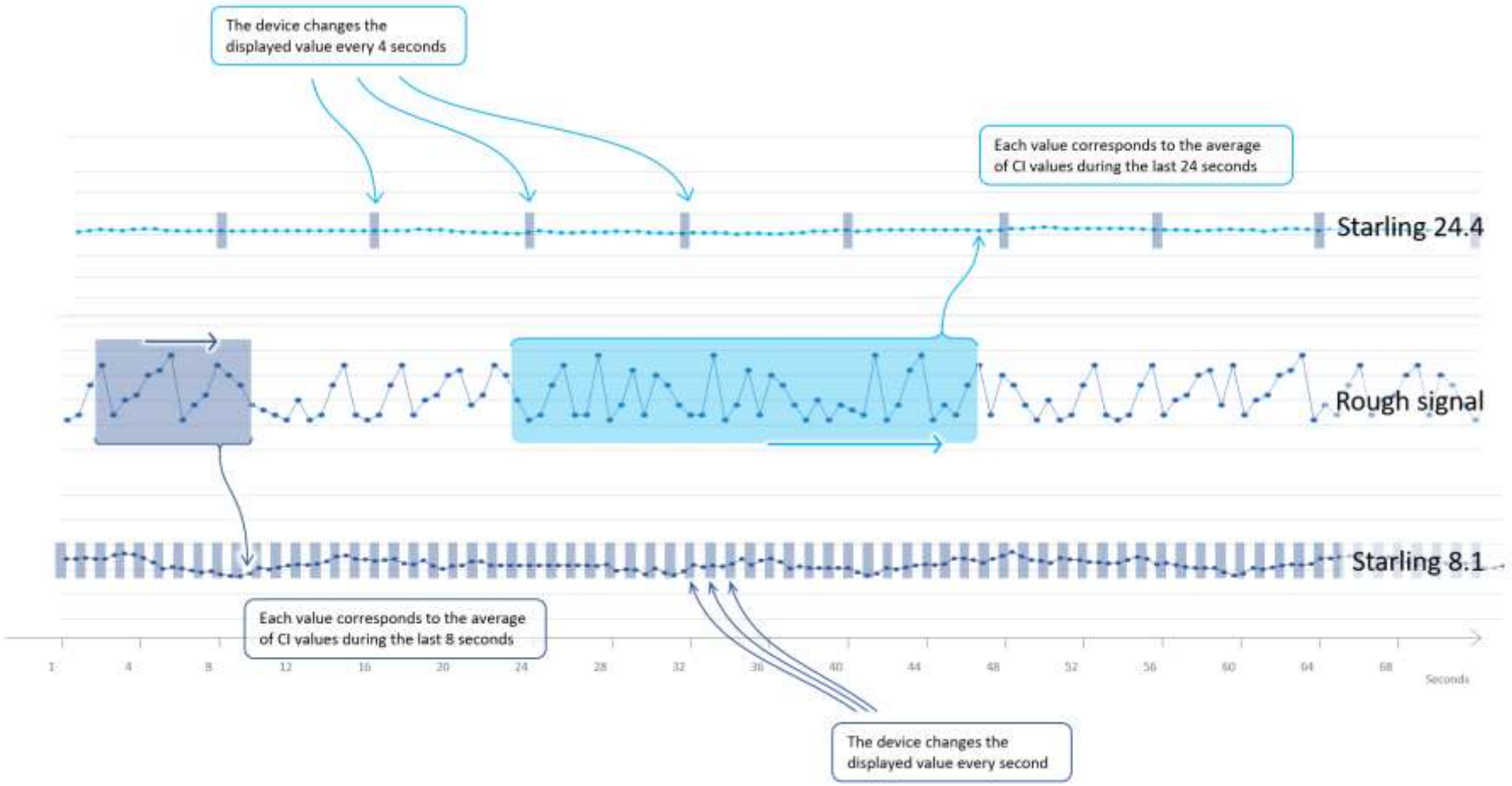

Figure 16 – Averaging and refresh times of both the commercial (Starling-24.4 – upper panel) and research (Starling-8.1 – lower panel) bioreactance devices.

CI: cardiac index; Starling-24.4: commercial version of the Starling device (averaging time 24 seconds, refresh time 4 seconds); Starling-8.1: research Starling device (averaging time 8 seconds, refresh time 1 second).

Study protocol

At baseline, a set of thermodilution measurements was performed and CI_{pulse} was calibrated. Once hemodynamic stability was observed (change in mean arterial pressure <5% over 4 minutes) ($EEXPO_{start}$), CI_{pulse}, $CI_{Starling\text{-}24.4}$, $CI_{Starling\text{-}8.1}$ and other hemodynamic measurements were collected. A 15-second EEXPO was then initiated as previously described [126]. At the end of the EEXPO test ($EEXPO_{end}$), the same variables were recorded. Subsequently, once the values of the hemodynamic variables had returned to baseline, another set of measurements were performed (PLR_{start}). A PLR maneuver was performed as previously described [110], and, after one minute of PLR, measurements were collected again (PLR_{end}) (**Figure 17**). If the ΔCI_{pulse} between PLR_{start} and PLR_{end} was ≥10%, the patient was defined as a "preload responder". This threshold corresponds to the increase in CI that has been demonstrated to indicate preload responsiveness with the best combination of sensitivity and specificity [112]. Sedative drugs, catecholamines and ventilatory settings were kept unchanged during the study period.

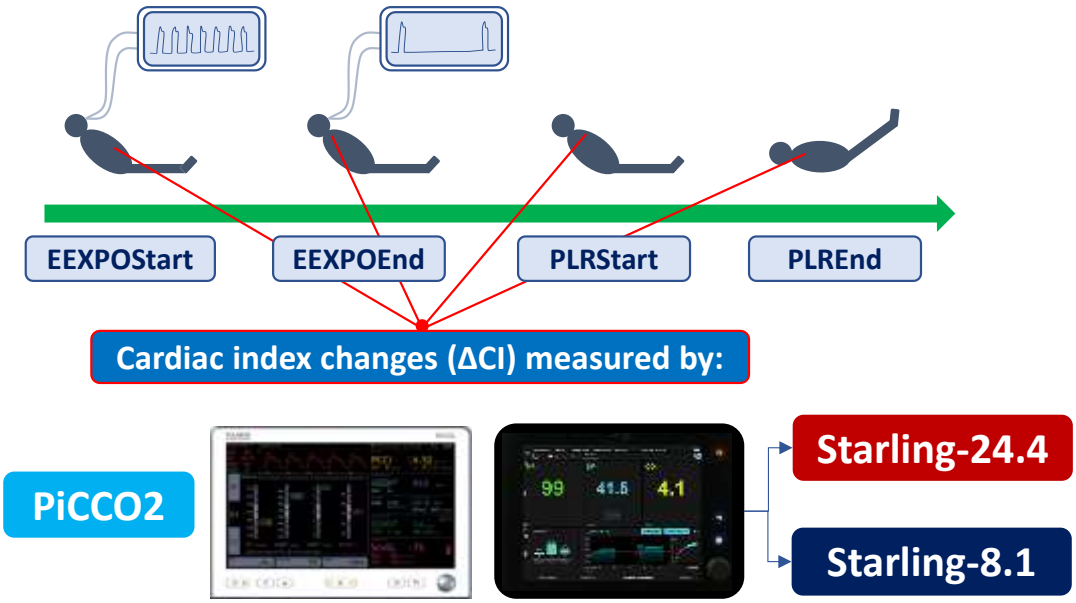

Figure 17 – Design of the study.

Statistical analysis

Based on a previous study by our group [167], to detect an increase in CI of at least 5% measured by the Starling device, expecting a baseline value of 3.1 L/min/m^2, we estimated that 42 pairs of measurements were required. This assessment was performed taking into account an α risk of 5% and a β risk of 20%, estimating that half of the patients would be preload responders. The minimal change of 5% was chosen because it corresponds to the best threshold of EEXPO-induced CI changes that detects preload responsiveness [168]. It is compatible with the least significant change of CI_{pulse} [85].

Data are summarized as mean ± SD or median [interquartile range, IQR] as appropriate. The normality of distribution was evaluated visually. Pairwise comparisons of data were done with the paired Student's t-test or Wilcoxon test. The two-tailed Student's t-test or Mann-Whitney U-test compared preload responders and non-responders.

To assess the significance of changes of variables over time during different interventions, we used a linear mixed-effect model to evaluate the group (preload responders and non-responders) and time ($EEXPO_{start}$, $EEXPO_{end}$, PLR_{start}, PLR_{end}) effects on hemodynamic variables. Time and groups were assumed as fixed effects, also considering the interaction component. A random intercept term was considered in patients to account for correlation among repeated measurements. The post-hoc pairwise comparison was reported by adjusting p-values for multiple testing, using the Holm method [175]. Regarding our primary goal, receiver operating characteristic curves for EEXPO-induced relative $\Delta CI_{Starling\text{-}24.4}$ to predict preload responsiveness were built, providing sensitivity, specificity and the best threshold, and their area under the receiver operating characteristic curve (AUROC) was measured. The same analysis was performed for $\Delta CI_{Starling\text{-}8.1}$ to assess our secondary goal, and the AUROC were compared with the Hanley-McNeil test [176]. The ability of both $\Delta CI_{Starling\text{-}24.4}$ and $\Delta CI_{Starling\text{-}8.1}$ to detect preload responsiveness was subsequently tested in the subgroup of patients with and without norepinephrine infusion and in patients with a high and a low body mass index (BMI). "High" and "low" BMI values were defined according to the median of the variable measured in the whole population. To evaluate the overall concordance between absolute values of CI_{pulse} and both $CI_{Starling\text{-}24.4}$ and $CI_{Starling\text{-}8.1}$ for EEXPO, we reported the intraclass correlation coefficient (ICC). Pearson's correlation coefficient tested the correlations between the EEXPO-induced ΔCI_{pulse} and both $\Delta CI_{Starling\text{-}24.4}$ and $\Delta CI_{Starling\text{-}8.1}$, and these coefficients were compared for relative changes.

We compared the absolute values of CI_{pulse} and $CI_{Starling\text{-}24.4}$ and the absolute values of CI_{pulse} and $CI_{Starling\text{-}8.1}$ recorded during $EEXPO_{end}$, $EEXPO_{end}$, PLR_{start} and PLR_{end} by using the Bland-Altman analysis. Limits of agreement plots were defined as accounting for repeated measurements with possibly heteroscedastic measurement errors [177]. A Critchley polar plot analysis was performed [178] for assessment of the trending ability of $CI_{Starling\text{-}24.4}$ and $CI_{Starling\text{-}8.1}$, to compare the concordance in terms of relative ΔCI_{pulse} vs. $\Delta CI_{Starling\text{-}24.4}$ and $\Delta CI_{Starling\text{-}8.1}$, both for EEXPO and PLR. Radial limits of agreement <30° are considered to indicate good trending ability.

Statistical significance was set at a p-value <0.05 and statistical analysis was performed with MedCalc software 19.1 (Mariakerke, Belgium) and R 3.5.2 statistical software with lme4, MethodCompare and irr packages [151].

Results

Patients

Forty-two patients were included between April and September 2019. No patient was excluded due to inability to sustain a 15-second respiratory hold (**Figure 18**). All patients were sedated with propofol and remifentanil (**Table 5**). Eight (19%) patients were paralyzed at the time of inclusion and no patient exhibited spontaneous breathing activity. No patient was in the prone position or had renal replacement therapy in place. Two patients had atrial fibrillation, whereas the others were in sinus rhythm (**Table 5**).

Hemodynamic changes during interventions

Twenty-six (62%) patients were defined as preload responders, according to the results of the PLR test. The changes in hemodynamic variables in both groups are shown in **Table 6**.

PLR induced a ΔCI_{pulse} of 16.8 [12.0 - 24.4.3]% in responders and 2.2 [1.3 - 4.5]% in non-responders ($p<0.0001$). It induced a $\Delta CI_{Starling\text{-}24.4}$ of 21.7 [14.3 - 43.8]% in responders and 0.0 [0.0 - 4.1]% in non-responders ($p<0.0001$). PLR induced a $\Delta CI_{Starling\text{-}8.1}$ of 49.7 [29.3 - 74.4]% in responders and 5.1 [-0.4 - 11.1]% in non-responders ($p<0.0001$) (**Table 6**).

The EEXPO test induced a ΔCI_{pulse} of 5.3 [4.1 - 7.5]% in responders and 1.2 [0.5 - 2.4]% in non-responders ($p<0.0001$). It induced a $\Delta CI_{Starling\text{-}24.4}$ of 5.5 [-0.2 - 7.1]% in responders and 0.1 [-0.1 - 0.1]% in non-responders ($p=0.049$). The EEXPO test induced a $\Delta CI_{Starling\text{-}8.1}$ of 12.8 [7.8 - 22.2]% in responders and 0.9 [-1.1 - 4.8]% in non-responders ($p=0.0001$) (**Table 6**).

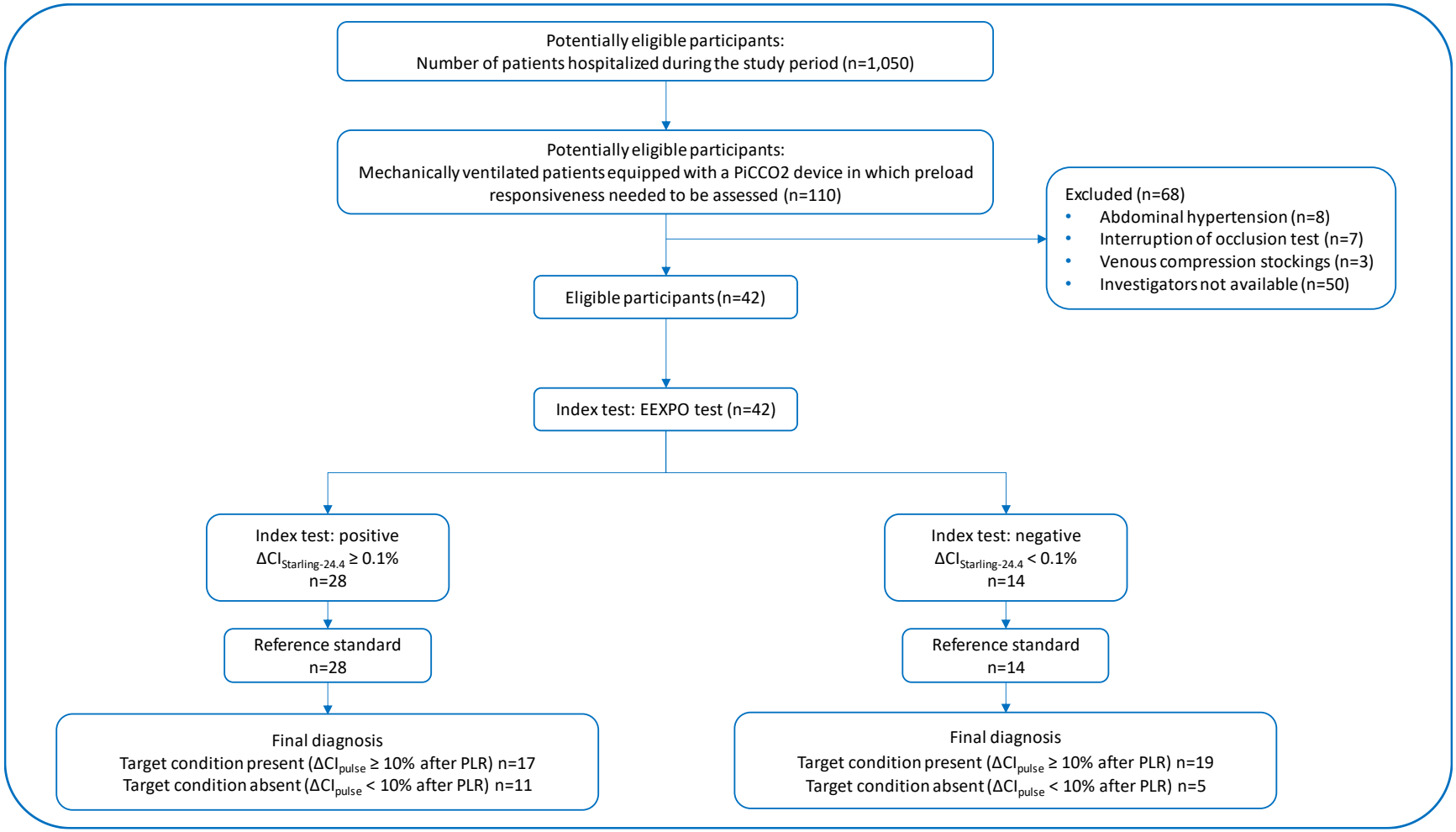

Figure 18 - STARD flow-chart. EEXPO: end-expiratory occlusion; PLR: passive leg raising; ΔCI_{pulse}: changes in cardiac index detected by the pulse contour analysis method; $\Delta CI_{Starling\text{-}24.4}$: changes in cardiac index detected by the commercial version of the Starling device (averaging time 24 seconds, refresh time 4 seconds).

Patient characteristics (n = 42)	
Age (years)	60 ± 9
Male gender (n, %)	21 (50%)
Body mass index (kg/m^2)	24 [21 – 27]
Simplified Acute Physiologic Score II on inclusion	49 [31 – 55]
Richmond Agitation Sedation Scale score	-5 [-5 to -4]
Left ventricular ejection fraction (%)	45 ± 6
Intra-abdominal pressure (mmHg)	13 ± 4
Type of shock (n, %)	
Septic	36 (85.7%)
Cardiogenic	4 (9.5%)
Hypovolemic	1 (2.4%)
Distributive non-septic	1 (2.4%)
Atrial fibrillation (n, %)	2 (4.8%)
Cumulative fluid balance (mL)	1035 [734 – 1655]
ICU length of stay (days)	17 [7 – 44]
Mortality at day-28 (n, %)	13 (31%)
Norepinephrine	
Number of patients (%)	27 (64%)
Dose of norepinephrine (µg/kg/min)	0.28 [0.13 – 0.43]
Ventilator settings	
Tidal volume (mL/kg of PBW)	6.0 [5.1 - 6.0]
Respiratory rate (breaths/min)	28 ± 5
Fraction of inspired oxygen	0.51 ± 0.16
Positive end-expiratory pressure (cmH_2O)	12 ± 3
Plateau pressure (cmH_2O)	25 ± 5

Table 5 - Patient characteristics. ICU: intensive care unit, PBW: predicted body weight.

Variables	$EEXPO_{start}$	$EEXPO_{end}$	PLR_{start}	PLR_{end}
Heart rate (min^{-1})				
Preload responders (n = 26)	95 ± 16	96 ± 17	96 ± 17	93 ± 18**
Preload non-responders (n = 16)	93 ± 23	93 ± 23	93 ± 22	93 ± 22
Systolic arterial pressure (mmHg)				
Preload responders (n = 26)	120 ± 17	121 ± 17	122 ± 20	136 ± 16**
Preload non-responders (n = 16)	134 ± 24[a]	134 ± 24[a]	132 ± 18	139 ± 18
Diastolic arterial pressure (mmHg)				
Preload responders (n = 26)	60 ± 11	60 ± 10	62 ± 11	67 ± 11**
Preload non-responders (n = 16)	68 ± 11[a]	68 ± 11[a]	67 ± 11	71 ± 9
Mean arterial pressure (mmHg)				
Preload responders (n = 26)	82 ± 12	82 ± 11	83 ± 13	93 ± 12**
Preload non-responders (n = 16)	92 ± 12[a]	92 ± 13[a]	91 ± 11[a]	96 ± 9
Central venous pressure (mmHg)				
Preload responders (n = 26)	11 ± 5	11 ± 4	12 ± 4	14 ± 5**
Preload non-responders (n = 16)	14 ± 4[a]	13 ± 4	14 ± 4	15 ± 3
PiCCO2 Cardiac Index ($L/min/m^2$)				
Preload responders (n = 26)	2.95 ± 1.05	3.12 ± 1.06*	2.89 ± 0.94	3.40 ± 1.03**
Preload non-responders (n = 16)	3.03 ± 0.87	3.08 ± 0.89	2.97 ± 0.78	3.08 ± 0.89
Starling-24.4 Cardiac Index ($L/min/m^2$)				
Preload responders (n = 26)	2.8 ± 0.5	3.0 ± 0.6*	2.8 ± 0.5	3.5 ± 0.7**
Preload non-responders (n = 16)	2.4 ± 0.4[a]	2.3 ± 0.4[a]	2.6 ± 0.5	2.6 ± 0.5[a]
Starling-8.1 Cardiac Index ($L/min/m^2$)				
Preload responders (n = 26)	2.83 ± 0.58	3.25 ± 0.71*	2.69 ± 0.55	3.98 ± 0.86**
Preload non-responders (n = 16)	2.45 ± 0.41	2.48 ± 0.39[a]	2.63 ± 0.50	2.79 ± 0.51[a]

Pulse pressure variation (%)				
Preload responders (n = 26)	10 ± 6	-	11 ± 7	10 ± 6
Preload non-responders (n = 16)	10 ± 9	-	11 ± 8	10 ± 9
Stroke volume variation (%)				
Preload responders (n = 26)	12 ± 6	-	12 ± 6	11 ± 6
Preload non-responders (n = 16)	11 ± 8	-	11 ± 8	11 ± 8

Table 6 - Hemodynamic measurements. a: $p < 0.05$ vs. Preload responders. *: $p < 0.05$ vs. $EEXPO_{start}$; **: $p < 0.05$ vs. PLR_{start}.

Ability of the EEXPO-induced ΔCIStarling-24.4 to detect preload responsiveness

The relative EEXPO-induced ΔCI_{pulse} detected preload responsiveness, as defined by a positive PLR test, with an AUROC of 0.983 ± 0.018. The cut-off corresponding to the best Youden index was 3.3% (**Table 7**).

The relative EEXPO-induced $\Delta CI_{Starling-24.4}$ detected preload responsiveness with an AUROC of 0.680 ± 0.086 and a best Youden index cut-off of 0.1% (**Figure 19**, **Table 7**).

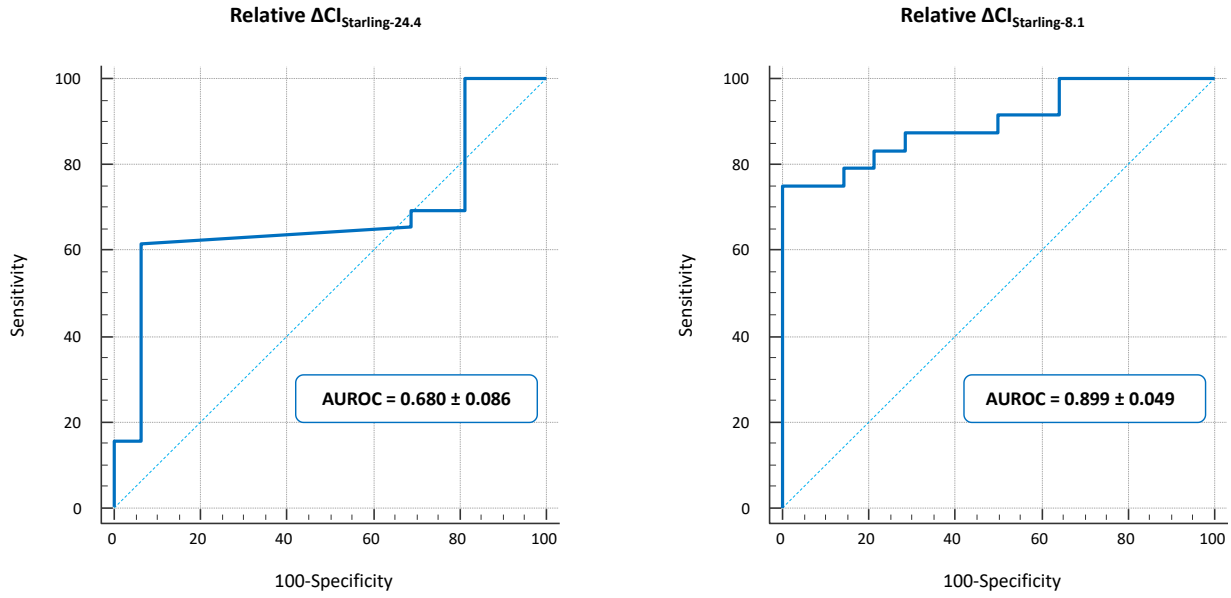

Figure 19 - Ability of relative $\Delta CI_{Starling-24.4}$ (left) and $\Delta CI_{Starling-8.1}$ (right) to detect preload responsiveness at the EEXPO test.

Ability of the EEXPO-induced ΔCIStarling-8.1 to detect preload responsiveness

Relative EEXPO-induced $\Delta CI_{Starling\text{-}8.1}$ detected preload responsiveness with an AUROC of 0.899 ± 0.049 and a cut-off of 5.1% (**Figure 19**, **Table 7**). The comparison with the AUROC of the EEXPO-induced $\Delta CI_{Starling\text{-}24.4}$ was significant (p=0.027). At the EEXPO test, Starling-24.4 classified 10 patients as false negative and one as false positive, while Starling-8.1 classified 3 patients as false negative and 2 as false positive. When the same analysis was performed both in patients with and without norepinephrine infusion and in patients with high and low BMI, we observed similar results (**Table 8**, **Table 9**).

Ability of the PLR-induced ΔCIStarling-24.4 and ΔCIStarling-8.1 to detect preload responsiveness

Relative PLR-induced $\Delta CI_{Starling\text{-}24.4}$ detected preload responsiveness, as defined by the increase in ΔCI_{pulse} ≥10% during PLR, with an AUROC of 0.929 ± 0.039. The cut-off corresponding to the best Youden index was 10%. Similarly, PLR-induced relative $\Delta CI_{Starling\text{-}8.1}$ detected preload responsiveness with an AUROC of 0.970 ± 0.024 and a best Youden index cut-off of 15% (**Table 10**).

Concordance analysis

When considering all the changes observed during the study (n = 84) at Bland-Altman analysis, absolute values of both $CI_{Starling\text{-}24.4}$ and $CI_{Starling\text{-}8.1}$ showed a regressive pattern vs. CI_{pulse}, with the bias line moving for higher values (**Figure 20**). The percentage error was 67% for $CI_{Starling\text{-}24.4}$ and 65% for $CI_{Starling\text{-}8.1}$.

The ICC for absolute value comparison vs. CI_{pulse} at the EEXPO test (n=42) was higher for $CI_{Starling\text{-}8.1}$ than for $CI_{Starling\text{-}24.4}$ (0.60 vs. 0.48, respectively; p=0.04). Again, when considering only the changes observed during EEXPO, a significant correlation was observed between relative ΔCI_{pulse} and $\Delta CI_{Starling\text{-}8.1}$ (r = 0.42; p=0.009), but not between ΔCI_{pulse} and $\Delta CI_{Starling\text{-}24.4}$ (p=0.40). When considering only the changes observed during PLR, a significant correlation was observed both between ΔCI_{pulse} and $\Delta CI_{Starling\text{-}8.1}$ and between ΔCI_{pulse} and $\Delta CI_{Starling\text{-}24.4}$ (r = 0.70 and r = 0.60, respectively; p<0.0001 for both).

When considering only the changes observed during EEXPO (n = 42) at polar plot analysis, after removing from the central exclusion data points for which ΔCI were less than 1.5% [85], the ability to track ΔCI was higher for $CI_{Starling\text{-}8.1}$ (polar concordance: 83%) than for $CI_{Starling\text{-}24.4}$ (polar concordance: 71%) (**Figure 21**). When considering only the changes observed during PLR (n = 42), the ability to track ΔCI was similar for $CI_{Starling\text{-}8.1}$ (polar concordance: 81%) and for $CI_{Starling\text{-}24.4}$ (polar concordance: 86%) (**Figure 22**).

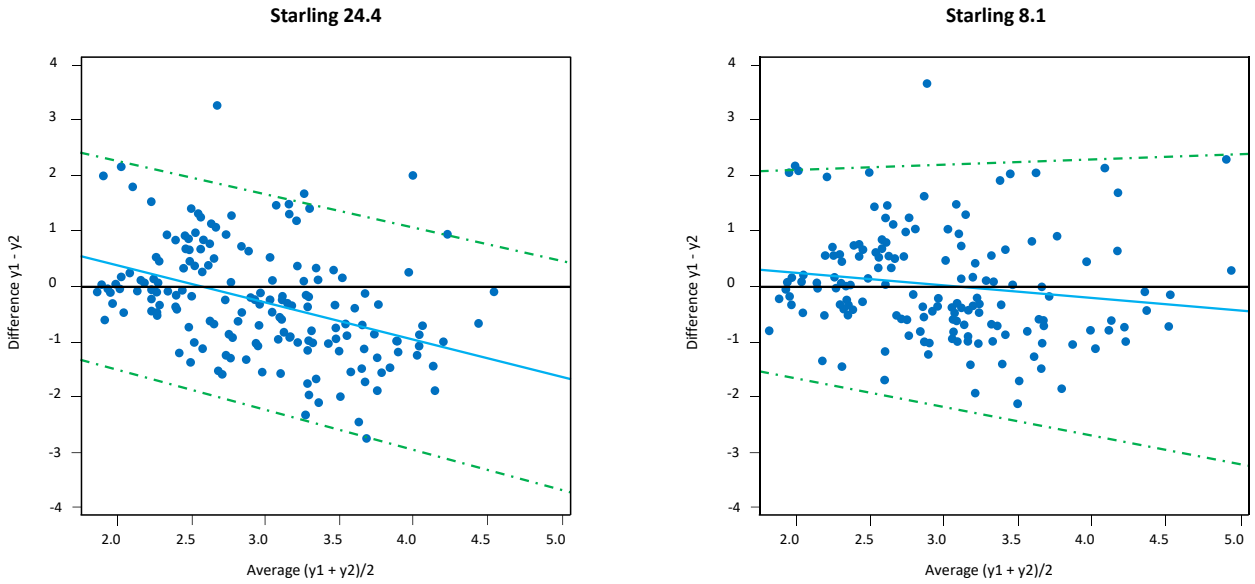

Figure 20 - Bland-Altman plots for measurements performed at all time points. Concordance analysis for absolute values at $EEXPO_{start}$, $EEXPO_{end}$, PLR_{start} and PLR_{end} for $CI_{Starling-24.4}$ vs. CI_{pulse} (left) and $CI_{Starling-8.1}$ vs. CI_{pulse} (right). Green dashed lines represent Bland-Altman 95% limit of agreement for repeated measurements. Light blue continuous line represents regression line.

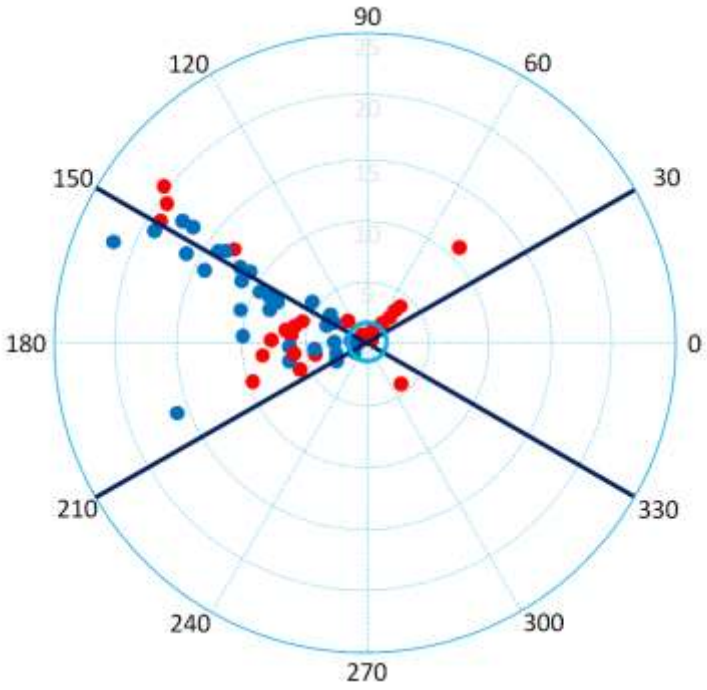

Figure 21 - Polar plot analysis during the EEXPO test. Polar plot analysis for relative changes in $CI_{Starling-24.4}$ (red dots) and $CI_{Starling-8.1}$ (blue dots) compared to the changes in CI_{pulse} during the EEXPO test. The radial limits of the agreement have been reported. The central exclusion zone (continuous light blue circle) removes data points where the changes in cardiac index are small (less than 1.5%). The polar concordance at 30 degrees is 83% for Starling-8.1.1 and 71% for Starling-24.4.

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
EEXPO - Relative ΔCI_{pulse}	0.983 ± 0.018	1.00 (0.87-1.00)	0.94 (0.70-1.00)	16.0 (2.4-106.7)	-	3.3%	< 0.0001
EEXPO - Relative $\Delta CI_{Starling-24.4}$	0.680 ± 0.086	0.62 (0.41-0.80)	0.94 (0.70-1.00)	9.9 (1.4-67.3)	0.4 (0.2-0.7)	0.1%	0.036
EEXPO - Relative $\Delta CI_{Starling-8.1}$	0.899 ± 0.049	0.79 (0.59-0.93)	0.86 (0.57-0.98)	5.54 (1.5-20.3)	0.24 (0.1-0.5)	5.1%	< 0.0001

Table 7 - Ability of the end-expiratory occlusion test to detect preload responsiveness using three different methods for measuring cardiac index. AUROC: area under the receiver operating characteristic curve; EEXPO: end-expiratory occlusion; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PLR: passive leg raising; SE: standard error; 95% CI: 95% confidence interval; ΔCI_{pulse}: changes in cardiac index measured through the pulse contour analysis method; $\Delta CI_{Starling-24.4}$: changes in cardiac index detected by the commercial version of the Starling device (averaging time 24 seconds, refresh time 4 seconds); $\Delta CI_{Starling-8.1}$: changes in cardiac index derived through raw data analysis of the Starling device (averaging time 8 seconds, refresh time 1 second).

BMI ≥ 24 kg/m²

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
EEXPO - Relative ΔCI_{pulse}	1.000 ± 0.000	1.00 (0.69-1.00)	1.00 (0.72-1.00)	-	-	3.0%	<0.0001
EEXPO - Relative $\Delta CI_{Starling-24.4}$	0.591 ± 0.143	0.50 (0.19-0.89)	1.00 (0.72-1.00)	-	0.50 (0.30-0.90)	0.1%	NS
EEXPO - Relative $\Delta CI_{Starling-8.1}$	0.918 ± 0.063	0.80 (0.44-0.98)	1.00 (0.72-1.00)	-	0.20 (0.06-0.70)	9.5%	<0.0001

BMI < 24 kg/m²

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
EEXPO - Relative ΔCI_{pulse}	0.957 ± 0.032	0.88 (0.62-0.98)	1.00 (0.48-1.00)	-	0.13 (0.0-0.5)	4.1%	< 0.0001
EEXPO - Relative $\Delta CI_{Starling-24.4}$	0.681 ± 0.136	0.69 (0.41-0.89)	0.80 (0.28-1.00)	3.44 (0.60-20.5)	0.39 (0.20-0.90)	0.1%	NS
EEXPO - Relative $\Delta CI_{Starling-8.1}$	0.905 ± 0.078	0.86 (0.57-0.98)	1.00 (0.29-1.00)	-	0.14 (0.00-0.05)	1.5%	< 0.0001

Table 8 - Ability of the end-expiratory occlusion test to detect preload responsiveness using three different methods for measuring cardiac index in patients with Body mass index ≥ 24 kg/m² and < 24 kg/m².

Without norepinephrine infusion

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
EEXPO - Relative ΔCI_{pulse}	1.000 ± 0.000	1.00 (0.69-1.00)	1.00 (0.48-1.00)	-	-	3.0%	< 0.0001
EEXPO - Relative $\Delta CI_{Starling-24.4}$	0.700 ± 0.138	0.50 (0.19-0.81)	1.00 (0.48-1.00)	-	0.50 (0.30-0.90)	0.1%	NS
EEXPO - Relative $\Delta CI_{Starling-8.1}$	0.840 ± 0.110	0.80 (0.44-0.98)	1.00 (0.48-1.00)	-	0.20 (0.06-0.70)	4.8%	0.0019

With norepinephrine infusion

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
EEXPO - Relative ΔCI_{pulse}	0.977 ± 0.026	1.00 (0.79-1.00)	0.91 (0.59-1.00)	11.00 (1.70-71.30)	-	3.3%	< 0.0001
EEXPO - Relative $\Delta CI_{Starling-24.4}$	0.699 ± 0.108	0.69 (0.41-0.89)	0.91 (0.59-1.00)	7.56 (1.10-50.40)	0.34 (0.20-0.70)	0.1%	NS
EEXPO - Relative $\Delta CI_{Starling-8.1}$	0.921 ± 0.055	0.79 (0.49-0.95)	1.00 (0.66-1.00)	-	0.21 (0.10-0.60)	9.5%	< 0.0001

Table 9 - Ability of the end-expiratory occlusion test to detect preload responsiveness using three different methods for measuring cardiac index in patients without and with norepinephrine infusion.

Variable	AUROC ± SE	Sensitivity (95% CI)	Specificity (95% CI)	LR + (95% CI)	LR - (95% CI)	Cut-off	p
PLR - Relative $\Delta CI_{Starling-24.4}$	0.929 ± 0.039	0.85 (0.65-0.96)	1.00 (0.79-1.00)	-	0.15 (0.1-0.4)	10%	< 0.0001
PLR - Relative $\Delta CI_{Starling-8.1}$	0.970 ± 0.024	0.92 (0.73-0.99)	0.93 (0.66-1.00)	12.8 (1.9-8.15.2)	0.01 (0.0-0.3)	15%	< 0.0001

Table 10 – Ability of the PLR-induced changes in cardiac index obtained by the two bioreactance methods to predict preload responsiveness.

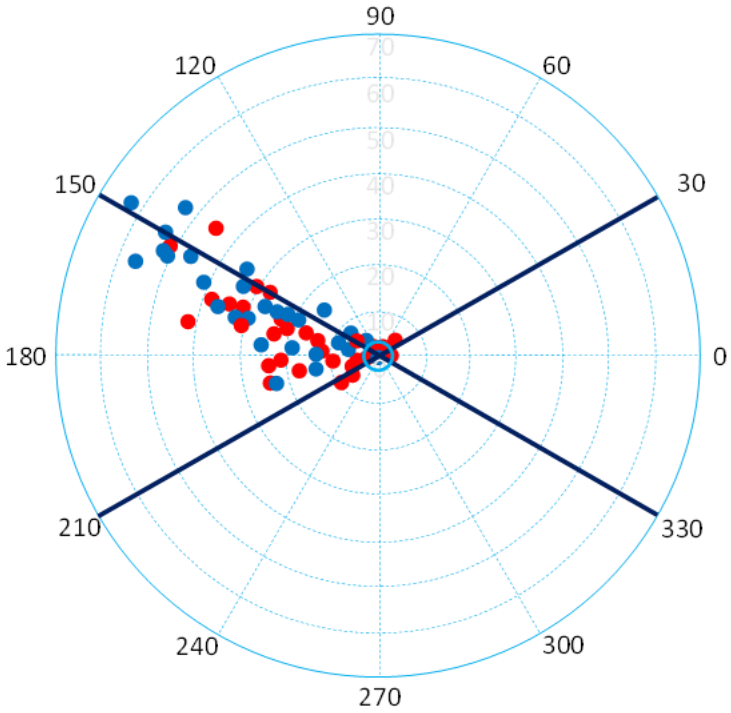

Figure 22 - Polar Plot Analysis for relative changes in $CI_{Starling\text{-}24.4}$ (red dots) and $CI_{Starling\text{-}8.1}$ (blue dots) compared to the changes in CI_{pulse} during PLR. The radial limits of the agreement have been reported. The central exclusion zone (continuous light blue circle) removes data points where the changes in cardiac index are small (less than 1.5%). The polar concordance at 30 degrees is 81% for $CI_{Starling\text{-}8.1}$ and 86% for $CI_{Starling\text{-}24.4}$.

Discussion

This study shows that the commercial version of the Starling device poorly detects preload responsiveness through the EEXPO test. However, when the hemodynamic effects of the EEXPO test are tracked with a modified version of the Starling device, where the averaging time is reduced to 8 seconds and the refresh time to one second, the ability to detect preload responsiveness is good. Also, this study confirms that bioreactance reliably follows the PLR-induced ΔCI, whichever setting is used.

Over the years, different tests have been developed to detect preload responsiveness before deciding to infuse fluids or not [179]. However, these tests differ not only in the amplitude of ΔCI they induce, but also in the time over which these changes occur [114,180]. In particular, the EEXPO test was performed over 12 to 30 seconds in the studies that tested its reliability [154,156].

Regarding the different techniques estimating CI, the issue of averaging and refresh times is often neglected. Averaging the beat-to-beat values of CI allows the smoothing of CI changes, due either to its physiological instability or to the lack of precision of the technique that estimates it. Without any average, it would be difficult to distinguish small changes from the noise of the signal. Conversely, if

the averaging period is very long, the signal could be so smoothed that small changes would be undetectable. Besides the averaging time, the frequency at which every new CI value is displayed is also crucial. If the value is refreshed at each cardiac beat, the displayed value may be very unstable, again impairing the assessment of significant changes. Conversely, in the event of infrequent refreshments, acute changes may be masked.

Our team has demonstrated that bioreactance did not reliably detect ΔCI induced by a 1-min PLR if the averaging time was 30 seconds [181]. A version of the NICOM device using a moving averaging period of 8 seconds was much better for this purpose [167]. In the present study, we investigated the ability of bioreactance to assess the EEXPO test, the duration of which is much shorter than that of the PLR test. For this purpose, we changed the averaging time and the refresh time from the raw values of CI estimated by bioreactance.

Regarding our primary goal, the EEXPO test was unable to detect preload responsiveness if assessed with the commercial version of the Starling device, which should not be used for this purpose. As a matter of fact, 11 (26%) patients were wrongly classified by Starling-24.4 at the EEXPO test. Regarding our secondary goal, we confirmed that the EEXPO test was correctly assessed if the averaging and refresh times were reduced to 8 and one seconds, respectively. In the overall population, all but 5 patients were correctly defined as “preload responders” and “preload non-responders” by the Starling-8.1 device. However, among 2 of the 3 false negatives, the $\Delta CI_{Starling\text{-}8.1}$ was close to the 5% cut-off value (respectively 4.7% and 4.8%). This was also the case in one of the 2 false positives (5.7%). Our results suggest that bioreactance can be used to perform the EEXPO test only if the averaging and refresh times of the device are shortened, at least transiently.

Our Bland-Altman and concordance analyses showed that the estimation of the absolute value of CI by bioreactance was far from perfect. The percentage error was high, confirming previous studies [167,182]. The Bland-Altman analysis did not provide different results for $CI_{Starling\text{-}8.1}$ and $CI_{Starling\text{-}24.4}$. On the contrary, the trending ability of the device was much better. In particular, the polar plot analysis of changes provided acceptable results. Interestingly, when changes were assessed during EEXPO, the trending ability of $CI_{Starling\text{-}8.1}$ was better than that of $CI_{Starling\text{-}24.4}$, confirming that these short-term changes were better tracked by the former version than by the latter.

Of note, the present study also contributes to the validation of the EEXPO test. The EEXPO-induced ΔCI measured by pulse contour analysis well detected preload responsiveness, which was estimated through the PLR-induced ΔCI. The AUROC was above 0.900, a level achieved only by very reliable tests and indices of preload responsiveness [89,112]. The fact that these results were obtained in patients ventilated with a Vt ≤6 mL/kg confirms that low Vt ventilation does not make the EEXPO test unreliable,

despite studies affirming the contrary [128,129]. Also, it confirms that in the presence of low Vt, the reliability of both PPV and SVV is limited: as shown in **Table 6**, no significant differences were observed between preload responders and non-responders. Of note, a limitation of the EEXPO test is that the patients must be able to sustain a rather long ventilator occlusion. In the present study, the Richmond Agitation Sedation Scale score was quite high.

Limitations

First, we defined preload responsiveness by a positive PLR test and a fluid bolus was not infused in all the patients. However, the demonstration of PLR test reliability is likely strong enough today to allow one to consider it as a reliable surrogate of a fluid bolus [112]. Second, we investigated only a 15-second EEXPO test; a duration of 30 seconds has also been described [154]. With a longer EEXPO, the performances of $CI_{Starling\text{-}8.1}$ and $CI_{Starling\text{-}24.4}$ in tracking ΔCI might have differed less. Third, we included only hemodynamically stable patients who did not require changes in vasopressor dosage: we cannot, therefore, address the issue of whether the reliability of bioreactance could be influenced by short-term changes in afterload. Also, sepsis was the cause of circulatory failure in most of the patients (86%). Thus, in theory, our results should apply only to this specific population. Finally, we investigated only ICU patients, though the best reliability of bioreactance has been demonstrated in normal subjects [183,184] or in the peri-operative setting [185,186].

Conclusion

The Starling bioreactance device reliably detects preload responsiveness through the EEXPO test, provided that its averaging time is reduced to 8 seconds and its refresh time to one second.

Ancillary part (I): The effects of passive leg raising can be detected by the plethysmographic oxygen saturation signal

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Introduction

Volume expansion is often the first line treatment used to increase cardiac index (CI) in patients with acute circulatory failure [66]. However, increasing cardiac preload with fluid administration does not always induce the increase in CI that was expected from it. Moreover, excessive fluid loading with positive cumulative fluid balance may have deleterious effects and impair prognosis of critically ill patients, especially in cases of septic shock [52,54] and acute respiratory distress syndrome [57,58].

If preload responsiveness is not obvious, as in cases of fluid loss or at the initial phase of septic shock, it is crucial to predict the response of cardiac output to fluid administration before performing it. The passive leg raising (PLR) test is one of the methods currently available for this purpose [66]. It consists in moving the patient from the semi-recumbent position to a position in which the trunk is horizontal and the inferior limbs are passively elevated at 45° [110]. The PLR induces the transfer of some venous blood from the lower part of the body toward the cardiac cavities. It increases the mean systemic pressure [41], resulting in an increase in the pressure gradient of venous return and in CI in preload responsive patients [66,115]. The test has been demonstrated to be reliable by many studies and two meta-analyses [112,113]. Nevertheless, to detect the changes in CI induced by the PLR test, a direct and real-time measurement of CI is needed [110], which is often invasive.

The peripheral perfusion index (PI) is derived from the plethysmographic signal of pulse oximetry, which is obtained from the amount of infrared (940 nm) light transmitted through the vascular bed of a finger. The plethysmography signal has two components. The pulsatile component reflects changes in the finger blood volume during one cardiac cycle, which may depend on the changes in stroke volume [187], while the non-pulsatile component is related to the light absorbed by the other tissues, such as connective tissue, bone, and venous and capillary blood [188,189]. Some plethysmography devices like the Radical 7 (Masimo Corp., Irvine, CA, USA) automatically calculate the ratio of the pulsatile over the non-pulsatile component of the plethysmographic signal, which is called PI, and reflects the quality of skin perfusion [188–191]. Then, the changes in the ratio of pulsatile over not pulsatile component of the plethysmographic signal may depend on the changes in CI.

In this context, monitoring PI might be an attractive method for assessing the effects of the PLR test when no direct measurement of CI is available. The goal of our study, conducted in critically ill patients with acute circulatory failure, was to test if PI changes could accurately detect a positive response of CI to a PLR test.

Patients and Methods

Patients

This prospective study was conducted in the 25-bed medical intensive care unit of a university hospital. It was approved by the Institutional Review Board of our institution (Comité pour la Protection des Personnes, Ile-de-France VII, ID RCB: 2016-A00959-42). All patients or their relatives accepted to participate in the study. They were included if they were more than 18 years old, if they were routinely equipped with a PiCCO2 device (Pulsion Medical Systems, Feldkirchen, Germany) and if clinicians in charge decided to perform a PLR test. Fifty (69%) patients were included during the resuscitation or stabilisation phase of shock, defined by an increase in the dose of norepinephrine during the last 24 hours, and 22 (31%) patients were included at the de-resuscitation phase, defined by a decrease in the dose of norepinephrine over the last 24 hours. Patients were excluded a priori if the PLR test was contra-indicated (head trauma, deep vein thrombosis in the inferior limbs, venous compression stocking) or supposed to be unreliable (intra-abdominal hypertension, defined as an intra-abdominal pressure (IAP) > 12mmHg [51]) and a posteriori if the plethysmographic signal was absent and unstable. Plethysmographic signal instability was defined by a precision of PI ≥10%.

PiCCO2 device and hemodynamic variables

The PiCCO2 system is composed of a central jugular venous catheter and a thermistor-tipped arterial femoral catheter (PC8500, Pulsion Medical Systems, Feldkirchen, Germany) that are connected to a specific device. CI was measured by calibrated pulse contour analysis [174] and by transpulmonary thermodilution [173]. Transpulmonary thermodilution measurements were performed by the injection of cold boluses of 15 mL of 0.9% saline into the central venous tract. The average of three consecutive measurements was recorded and averaged [172]. The systemic arterial and central venous pressure curves were recorded continuously by using a data acquisition software (HEM 4.2, Notocord, Croissy-sur-Seine, France). Cardiac index was continuously recorded by the PiCCO Win 4.0 software (Pulsion Medical Systems). We measured IAP from the bladder pressure by injecting 25 mL of saline in the bladder after clamping the urinary drainage bag (AA6118 FOLYSIL, Humlebaek, Denmark). The abdominal pressure transducer was fixed to the patient on the lateral side of the pelvis, 2 cm below the anterior superior iliac spine. IAP was measured at end-expiration, in the absence of abdominal muscle contractions, which was checked by clinical examination. During PLR, it was carefully checked

that the height of this transducer remained unchanged. We defined intra-abdominal hypertension as IAP ≥12mmHg [51].

Perfusion index

The PI was automatically calculated from the plethysmogram by the Radical-7 device (**Figure 23**) as the ratio between the amplitude of the pulsatile and of the non-pulsatile components of the light received by the detector of the pulse oximeter, expressed as a percentage (**Figure 24**). It was measured by a sensor placed on the 3rd or 4th finger, by choosing the one with the highest PI value, as recommended by the constructor. If no signal was obtained on these fingers, we did not attempt to obtain signal at another site of measurement. The device offers two methods for displaying PI values. With the "short time" method, PI is displayed in real time with no averaging. With the "long time" method, the displayed PI values result from a 30-second moving average. We chose the "short time method", and averaged the PI values over 12 seconds, because it is the same time that is used by the PiCCO2 device for averaging pulse contour analysis-derived CI values.

Figure 23 – Radical 7 device, Masimo SET®

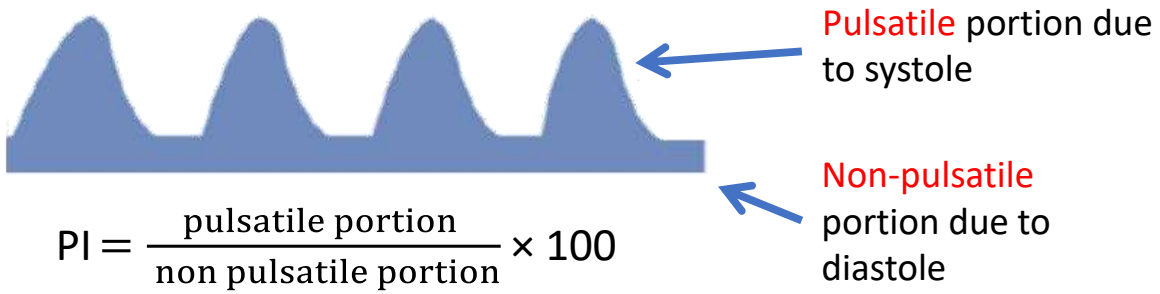


Figure 24 – Calculation of the Perfusion Index

Study design and measurements

Immediately after inclusion of the patients, when patients were in the semi-recumbent position, we collected demographic characteristics, PI and hemodynamic variables, including heart rate, arterial and central venous pressure. Stroke volume index (SVI) and CI were measured by transpulmonary thermodilution. The pressure sensors connected to the arterial and central venous catheters were fixed on the upper arm of the patient at the estimated level of the right atrium. A PLR was then performed by transferring the patient to the PLR position, in which the lower limbs are passively elevated at 45° and the trunk is horizontal [110]. When the PLR test had induced its maximal effect on CI, which occurs within one minute, we performed another set of measurements including CI. At this time, CI was measured by pulse contour analysis, because the effects of PLR may decrease after reaching their maximum in some patients, so that transpulmonary thermodilution may miss the maximal effects because of the time required for performing three boluses injections [110]. Then, we moved the patient back to the semi-recumbent position. We performed a third set of measurements, including heart rate, arterial and central venous pressure, PI and CI measured by transpulmonary thermodilution.

The PLR test could be planned in view of infusing fluid. In such cases, in case of a positive PLR test, clinicians could decide to perform a volume expansion with 500-mL of saline, weighting its risks and benefits. The PLR test could also be performed for guiding the decision of fluid removal [136] In such cases, a negative PLR test could lead to fluid removal, again depending on the decision of the clinicians in charge. Immediately after the end of fluid infusion, we performed the last set of measurements of mean arterial pressure, heart rate, central venous pressure, PI and CI (transpulmonary thermodilution). Catecholamines and sedative drugs doses as well as ventilation settings were kept constant during the study.

Measurement of the precision of PI

In each patient, during a period of time when the hemodynamic status was stable (change in pulse contour analysis-derived cardiac output <10%), we recorded five successive values of PI each averaged over 12 seconds. During this time, the sensor of plethysmography was kept unchanged. We calculated the coefficient of variation of PI as being the standard deviation divided by the mean of the five measurements [172–174]. The coefficient of variation is a relative measure of the dispersion of the data around the mean. It allows the comparison of the degree of variation from one sample to another, even if the averages are different. The precision was calculated as being two times the coefficient of variation, and the least significant change as coefficient of variation x 1.96 x √2 [172,192,193]. The least significant change is the most interesting variable to observe, since it indicates the minimum change

measured by the device that can be trusted as a real change of measurement [193]. It must be compared to the changes that have been actually observed during the study.

Statistical analysis

The PLR test was defined as positive if it increased CI ≥10%. The response to volume expansion was defined as positive if CI increased ≥15% just after fluid administration. Data were expressed as mean ± standard deviation, median [interquartile range, IQR] and number (percentage). Normality was assessed by the Kolmogorov–Smirnov test. Pairwise comparisons of values between different study times were performed by paired Student *t* tests. Comparisons between patients with positive PLR vs. patients with negative PLR were performed by two-tailed Student *t* tests or the Wilcoxon tests.

We compared the relative changes of CI to those of PI by linear regression analysis (for percent changes). To assess the trending ability of PI, we constructed a regression curve. This allowed the calculation of the percentage of total data points for which the directional changes of PI were concordant with those of CI. Correlations were assessed by the Spearman coefficient. Receiver operating characteristic (ROC) curves (with 95% confidence interval, [CI]) were generated for describing the ability of the PLR-induced percent changes in PI to detect the PLR-induced percent changes in CI. The areas under ROC curves were compared by the Hanley-McNeil test [194]. The Youden index was calculated as sensitivity + specificity – 1 and was used to determine the diagnostic threshold.

The calculation of the sample size was based on areas under the ROC curves. Considering a null hypothesis at 0.90, expecting an area under the curve for the PLR-induced changes in PI of 0.75, taking into account an α risk at 5% and a β risk at 10%, we planned to include 34 patients per group. Statistical analysis was performed using MedCalc 11.6.0 software (Mariakerke, Belgium).

Results

Patient characteristics

We initially screened 85 patients which characteristics are detailed in **Table 11**. Among the 85 screened patients, seven were excluded because of intra-abdominal hypertension (IAP: 18 ± 3mmHg). Three other ones were excluded because the plethysmography signal was not obtained. Their characteristics were not different from the other ones in terms of arterial pressure, dose of norepinephrine or shock origin (septic for eight patients and hypovolemic for two). Three patients presented an unstable plethysmography signal. Two of these three patients were the only screened ones who presented atrial fibrillation. No patient presented frequent atrial or ventricular extrasystoles. Eventually, 72 patients were included. A flow chart is displayed on **Figure 25**.

Patients (n=72)	
Age (mean±SD, years)	64 ± 13
Gender (male, n,%)	56 (77%)
Weight (mean±SD, kg)	72 ± 16
Height (mean±SD, cm)	168 ± 10
SAPS II (mean±SD)	60 ± 20
Type of shock (n,%):	
Septic	51 (70%)
Cardiogenic	12 (17%)
Hypovolemic	9 (13%)
Catecholamines	
Norepinephrine (n,%)	52 (72%)
Dose of norepinephrine (median [interquartile range], µg/kg/min)	0.5 [0.1 - 0.6]
Dobutamine (n,%)	8 (11%)
Dose of dobutamine (median [interquartile range], µg/kg/min)	16 [14 - 20]
Respiratory settings	
Mechanical ventilation (n,%)	56 (78%)
Tidal volume (mean±SD, mL/kg of PBW)	5.8 ± 1.4
Plateau pressure (mean±SD, cmH_2O)	23.5 ± 3.8
Positive end-expiratory pressure (mean±SD, cmH_2O)	9.8 ± 3.5

Table 11 – Patient characteristics (n=72)

No patient had an acute cor pulmonale or severe valvular disease. The IAP was 4 ± 3mmHg. Among the 20 (28%) patients who had no norepinephrine at the time of inclusion, it had been stopped in 13 (18%) patients, who were in the stabilisation phase of their disease, and it had not been administered before

in seven (10%) patients. The lactate at the time of inclusion was 1.8 ± 1.1mmol/L. Most of the patients (56 (78%)) were mechanically ventilated.

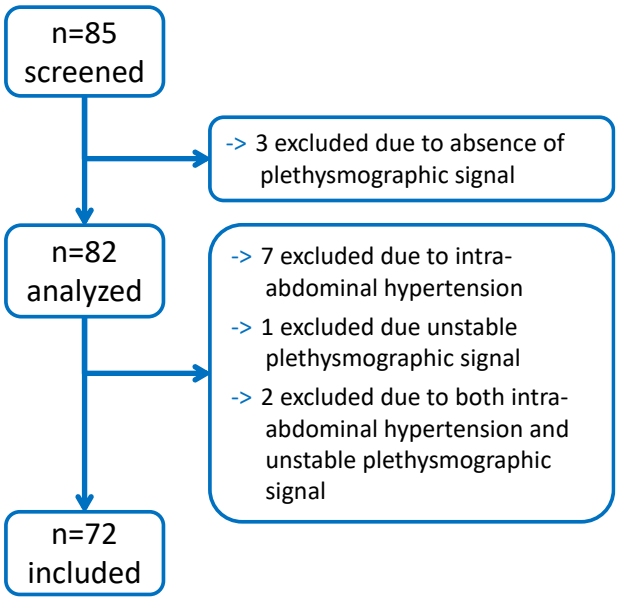


Figure 25 - Flow chart of patients' selection.

Effects of PLR and volume expansion on PI

The hemodynamic variables and their time course are reported in **Table 12**. The changes in CI and PI during a PLR test in a typical fluid responder and a typical non-responder are displayed on **Figure 26**. The PLR test was positive (PLR-induced increase in CI ≥10%) in 34 patients. In these patients during PLR, CI, SVI and PI significantly increased by 21 ± 10%, 18 ± 19% and 54 ± 53%, respectively ($p<0.001$ for both) (**Figure 27**). The PLR test was negative (CI increased by <10%) in 38 patients. In these patients, CI and SVI significantly increased during PLR by 2 ± 4% and 2 ± 7%, respectively. PI did not significantly change during PLR.

	Baseline 1	PLR test	Baseline 2	After volume expansion
Heart rate (beats/min)				
• **Positive PLR test** (n=34)	94 ± 16	95 ± 20	97 ± 17	93 ± 15ǂ
• **Negative PLR test** (n=38)	90 ± 20	89 ± 20	88 ± 20	
Systolic arterial pressure (mmHg)				
• **Positive PLR test** (n=34)	115 ± 23	128 ± 29*	112 ± 28	122 ± 34ǂ
• **Negative PLR test** (n=38)	125 ± 20	130 ± 21*	123 ± 20	
Diastolic arterial pressure (mmHg)				
• **Positive PLR test** (n=34)	58 ± 11	63 ± 10*	57 ± 13	61 ± 15ǂ
• **Negative PLR test** (n=38)	60 ± 9	63 ± 9*	59 ± 9	
Mean arterial pressure (mmHg)				
• **Positive PLR test** (n=34)	77 ± 13	87 ± 21*	75 ± 17	80 ± 19ǂ
• **Negative PLR test** (n=38)	81 ± 12	85 ± 13*	80 ± 12	
Central venous pressure (mmHg)				
• **Positive PLR test** (n=34)	10 ± 5	13 ± 5*	10 ± 4	11 ± 5ǂ
• **Negative PLR test** (n=38)	10 ± 5	14 ± 5*	9 ± 5	
Cardiac index (L/min/m²)				
• **Positive PLR test** (n=34)	3.38 ± 1.21	4.03 ± 1.31*	3.20 ± 1.20	4.02 ± 1.35ǂ
• **Negative PLR test** (n=38)	3.19 ± 1.26	3.26 ± 1.32*¨	3.15 ± 1.31	
GEDV (mL)				
• **Positive PLR test** (n=34)	766 ± 165		768 ± 205	789±127ǂ
• **Negative PLR test** (n=38)	800 ± 242		792 ± 219	
SVI (mL/m²)				
• **Positive PLR test** (n=34)	37 ± 13	44 ± 15*	36 ± 12	43 ± 15ǂ
• **Negative PLR test** (n=38)	37 ± 15	38 ± 16	37 ± 17	

PPV (%)‡				
• **Positive PLR test (n=28)**	10 ± 4		9.8 ± 5.9	11.9 ± 16.2
• **Negative PLR test (n=28)**	8.0 ± 5.1		8.5 ± 4.7	
PI (%)				
• **Positive PLR test (n=34)**	2.9 ± 2.0	4.1 ± 2.3*	2.1 ± 1.4	3.0 ± 1.9ᵗ
• **Negative PLR test (n=38)**	2.0 ± 1.8	2.0 ± 2.0¨	2.1 ± 1.9	

Table 12 – Hemodynamic variables. PLR: passive leg raising test; GEDV: global end-diastolic volume; SVI: stroke volume index; PPV: pulse pressure variation; PI: perfusion index. *p<0.05 vs baseline 1, ᵗp<0.05 vs baseline 2, ¨p<0.05 between positive and negative PLR test, ‡ in mechanically ventilated patients.

Volume expansion was decided after 26 positive PLR tests. Twenty-five of these patients were eventually fluid responders (fluid-induced increase in CI ≥15%). In these patients after volume expansion, CI and PI significantly increased by 28 ± 14% and 53 ± 63%, respectively (p<0.001 for both). Only one patient with a positive PLR test was fluid non-responder. In this patient, the fluid-induced increase in CI was 9%, whereas the PLR-induced increase in CI was 15%.

Ability of PI changes to detect a positive PLR test

During PLR, if PI increased by >9%, a positive response of CI (increase by >10%) to PLR could be diagnosed with a sensitivity of 91% (76-98%) and a specificity of 79% (63-90%), a positive predictive value of 80% (64-91%) and a negative predictive value of 91% (76-98%). The area under the ROC curve was 0.89 (95% confidence interval: 0.80-0.95, p<0.0001) (**Figure 28**). PI increased by >9% in 31 patients under 34 with a positive PLR.

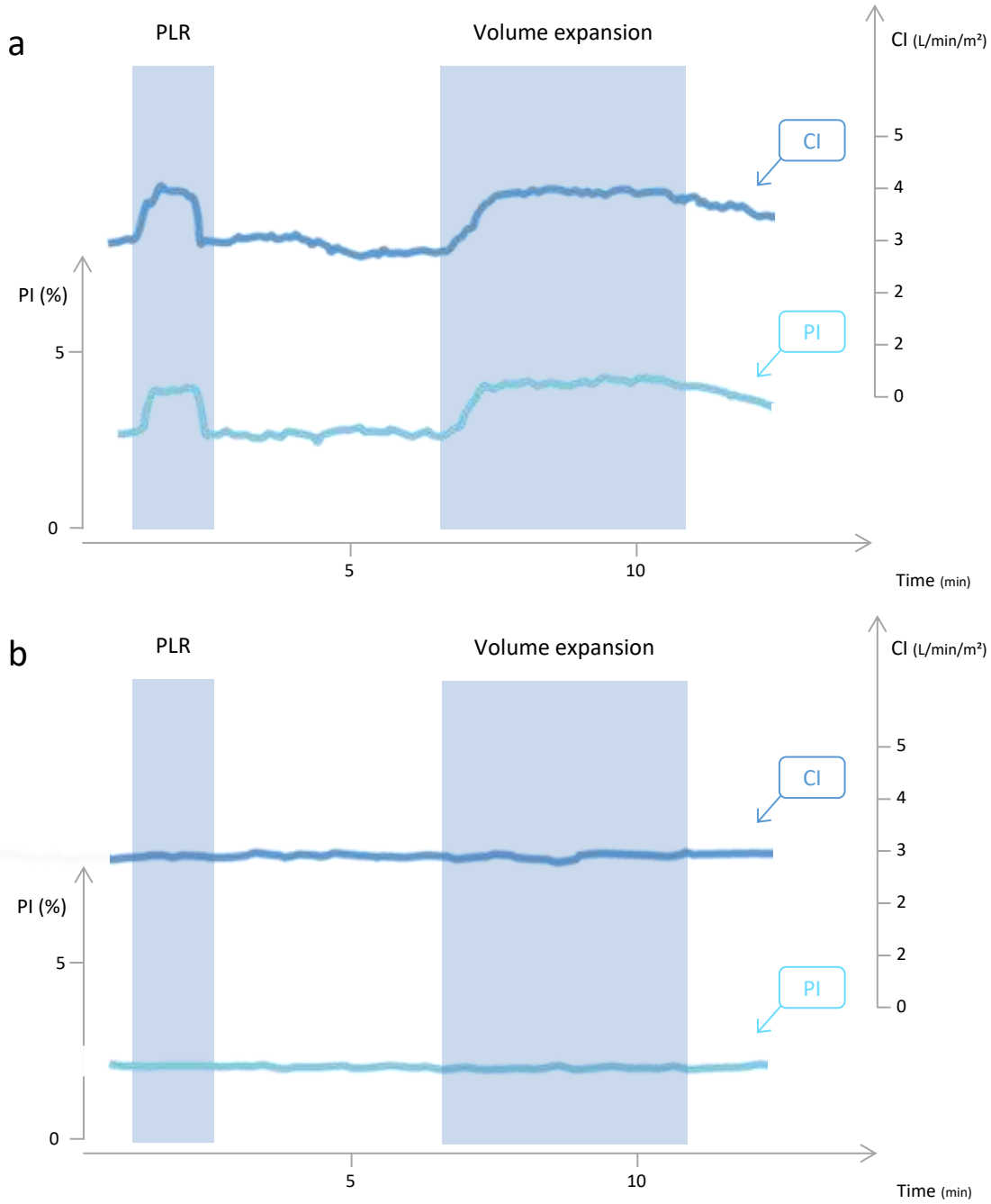


Figure 26 – Typical waveform of perfusion index (PI), cardiac index (CI) signals during a passive leg raising (PLR) test and a volume expansion (VE) in preload responders (**Figure a**) and preload non-responders (**Figure b**).

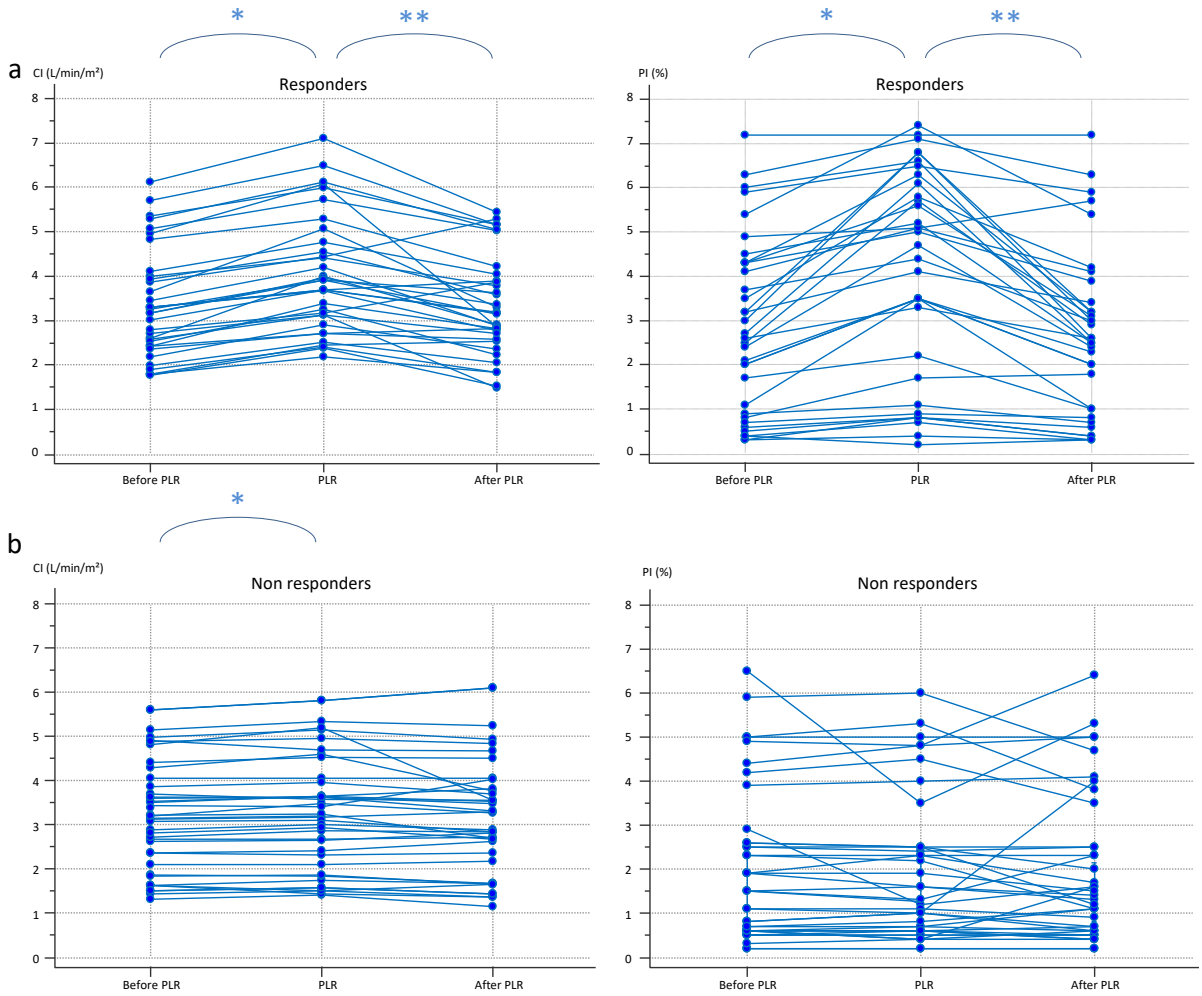


Figure 27 – Changes in perfusion index (PI) and cardiac index (CI) during a passive leg raising (PLR) test in responders (n=34) (**Figure a**) and in non-responders (n=38) (**Figure b**).

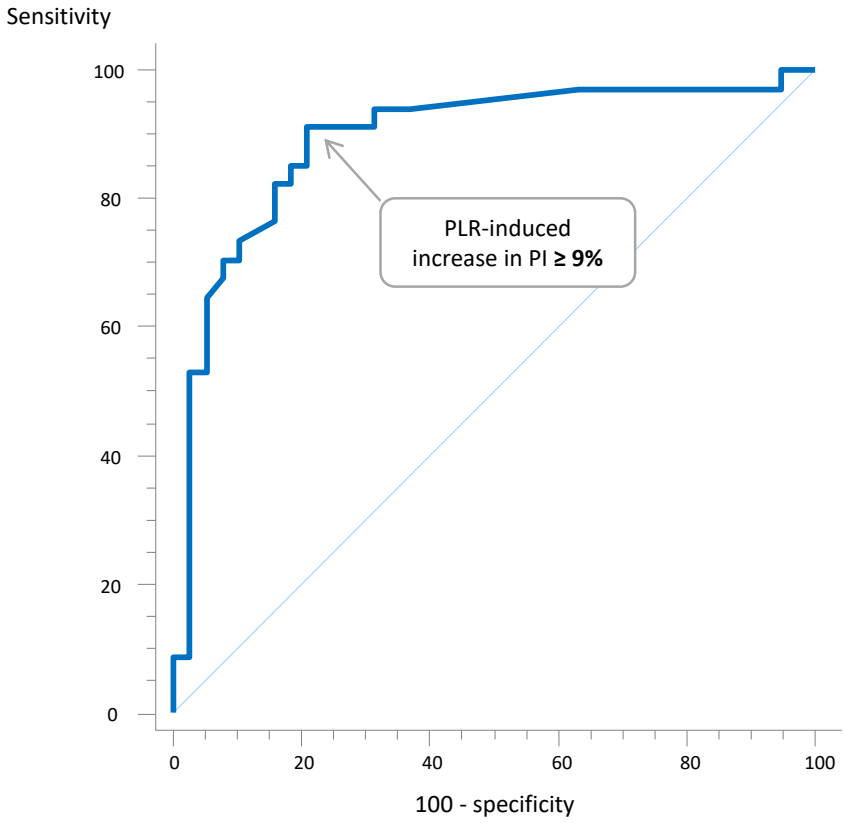


Figure 28 – Area under the receiver operating characteristics curve generated for the detection of a positive passive leg raising (PLR) test by the changes in perfusion index (PI) The Youden index was calculated as sensitivity + specificity – 1.

Ability of PI changes to track changes in CI and SVI

The changes in PI and the changes in CI were correlated when considering all interventions (PLR in 72 patients and volume expansion in 27 patients) ($r = 0.63$, $p<0.0001$, concordance rate = 73%, **Figure 29**) or PLR only ($r = 0.64$, $p<0.0001$). This was also the case for the changes in PI and the changes in SVI when considering all interventions ($r = 0.26$, $p=0.02$, concordance rate = 59%) or PLR only ($r = 0.33$, $p<0.005$, concordance rate = 63%).

The absolute value of PI at baseline was correlated with the dose of norepinephrine ($r = -0.29$, $p=0.04$). The absolute value of PI was similar in patients with and without norepinephrine infusion (2.5 ± 1.9% vs. 2.2 ± 1.8%, respectively, $p=0.39$), as well as in patients with and without mechanical ventilation (2.5 ± 1.9% vs. 1.6 ± 1.7%, respectively, $p=0.56$). It was also similar between patients receiving the lowest and the highest dose of norepinephrine, as defined according to its median value (2.6 ± 2.0% vs. 2.6±2.0%, respectively, $p=0.56$) (**Table 11**). The absolute value of PI at different study times was correlated with mean arterial pressure ($r = 0.20$, $p = 0.003$) and with the diastolic arterial pressure ($r = 0.16$, $p = 0.01$).

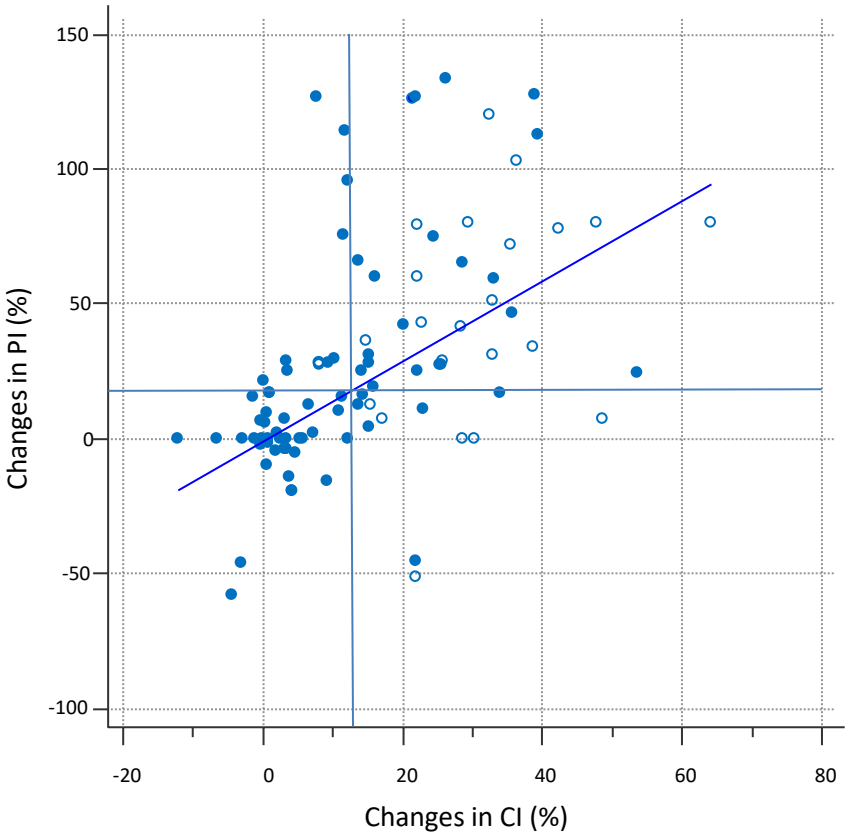


Figure 29 – Correlation between perfusion index (PI) changes and cardiac index (CI) changes during passive leg raising and volume expansion.

Precision of PI measurements

In included patients, the mean of PI values in measurements performed for assessing the precision was 1.37 ± 0.03% (in absolute value). In these patients, the coefficient of variation was 3.2%, the precision of PI was 1.2% and the LSC was 1.6%.

In patients excluded due to instability of the PI signal, the mean of PI values in measurements performed for assessing the precision was 1.3 ± 0.2%. In these patients, the precision of PI was 14%, and the LSC was 19%.

Discussion

This study suggests that, in patients in whom PI could be measured reliably, the PLR-induced increase in PI detected a positive response of CI to PLR with good accuracy.

The PLR test is an easy and reliable method to predict fluid responsiveness [112,195] which is now accepted in clinical practice [14,66,113]. Nevertheless, its main drawback is that, like the fluid challenge, its effects must be assessed by a direct measurement of CI, which must be precise and able to detect short-term changes with precision [110]. Our study suggests that the change in PI might be used as a surrogate of the change in CI during PLR and then could be used to assess preload responsiveness with an acceptable accuracy.

The PI has been proposed to reflect the quality of skin perfusion in particularly in anesthesia [189–191,196]. Stroke volume should influence PI by increasing the arterial blood volume in the finger. Nevertheless, the relationship between PI and CI should not be straightforward. First, the arterial blood flow at the periphery also depends on local factors that can change with local vasomotor tone. In addition, PI is also partly explained by the venous blood flow. A decrease in venous blood flow might cause a stagnation of venous blood in the fingers, an increase in the non-pulsatile component and eventually a decrease in PI independently from changes in arterial blood flow.

In spite of these potential limitations, some studies have suggested that changes in PI reflect changes in CI [187,197] or in the amplitude of arterial pressure [198] in various settings. Desgranges et al. have shown that the changes in PI measured at the forehead was able to detect the fluid-induced changes in CI with reliable accuracy [199] after induction of anesthesia. On the other hand, discrepant results were reported [196,199,200]. In particular, Broch et al. did not find any significant changes in PI during a PLR maneuver [196]. Nevertheless, in this study, PLR was performed by starting from the horizontal, not the semi-recumbent position, what might significantly reduce the hemodynamic response to the test. In all these negative studies, the quality of the PI was not mentioned.

Clearly, our results do not support that PI is a perfect surrogate of CI. First of all, the plethysmographic signal was absent in three patients and was unstable in three. Except in two patients with atrial fibrillation, we could not easily find an explanation to this instability. In turn, the PI analysis was impossible in 6 out of 85 patients (7%). Also, the correlation between changes in PI and CI was not perfect. In spite of this limitation, we really think that our data provide new information. Moreover, the rate of excluded patients might be less in other clinical settings, like the peri-operative period. Some technological improvements might also occur and reduce the proportion of patients in whom the perfusion index cannot be used to estimate cardiac output changes. Second, the correlation

between changes in PI and CI was not perfect. Nevertheless, in patients with stable signal, PI was very precise. The precision was much lower than the threshold found to detect a positive PLR test, what means that the PI is a suitable CI surrogate for this purpose. We think that this fact deserves our attention and should stimulate further investigation. Also, studies should investigate cases where both CI and skin perfusion might be affected concomitantly, like during vasopressors or dobutamine administration for instance. In our study, the absolute value of PI at baseline was poorly correlated with the dose of norepinephrine or with the mean arterial pressure. It was also similar between patients receiving the lowest and the highest dose of norepinephrine.

Limitations

There are several limitations to our study. First, patients with a negative PLR test did not receive fluids, so that we could not conclude regarding the ability of PLR-induced changes in PI to predict fluid responsiveness. Nevertheless, the reliability of the PLR test can be considered as well established [112]. In the present study, only one patient in whom the PLR test was positive did not respond to fluid administration. In this patient, the PLR-induced increase in CI was close to 10%, and the fluid-induced increase in CI was also close form 15%. Second, we included only critically ill patients while results regarding PI might differ in other contexts, especially because PI is influenced by skin perfusion, which might for instance be different in the perioperative period. Third, we investigated only the PI at the finger level, while its relationship to stroke volume might differ among the site where it is measured [197,199]. Forth, we averaged the real-time value of PI over 12 seconds, which is not performed by the commercial version of the device. Nevertheless, we think this was the only way allowing a comparison with pulse contour analysis-derived CI, which is averaged over 12 seconds. Moreover, we did not test the “long average” version of the device, which averages PI over 30 seconds.

Conclusion

In critically ill patients in whom it could be measured, the changes in PI during PLR test appears a reliable way to assess the hemodynamic effects of the PLR test, and thus to assess preload responsiveness, in a totally non-invasive way. This proof of concept opens the door for further investigations.

Ancillary part (II): Changes in the plethysmographic Perfusion Index during an end-expiratory occlusion detect a positive passive leg raising test.

Beurton A, **Gavelli F**, Teboul J-L, De Vita N, Monnet X. Crit Care Med. 2021;49:e151–60. *doi: 10.1186/s13054-019-2306-z11*

Background

In critically ill patients, detecting preload responsiveness allows one to avoid any fluid infusion which would not increase cardiac output [44]. The end-expiratory occlusion (EEXPO) test consists in interrupting ventilation at the end of expiration for 15 to 30 seconds and assessing the induced changes in cardiac index (CI) or its substitutes [126]. Our group showed that an increase in CI ≥ 5% reliably predicts the response of cardiac output to volume expansion [114]. These results have been confirmed in a number of other studies [114,123–125,128–131,153–157,168].

The peripheral perfusion index (PI) is the ratio of the pulsatile and non-pulsatile components of the plethysmographic waveform. Plethysmography, which basically measures the volume of blood beneath the sensor, creates a signal that is made of two components. The pulsatile component, which is often called the “AC” component, represents the increased light attenuation associated with the increase in microvascular blood volume with each heartbeat. It is superimposed on a larger “DC” component that relates to the average blood volume within the sample [201]. Then, PI is mainly determined by the degree of vasoconstriction and by stroke volume [187,190,199,202–204]. Provided that the vasomotor tone remains stable, its changes should reflect changes in stroke volume and cardiac output.

Recently, our group has reported that PI allows the detection of the CI changes induced by a passive leg raising (PLR) test [162]. De Courson et al. recently reported that the changes in PI should also reflect the changes in stroke volume during lung recruitment maneuvers, which also allows the detection of preload responsiveness [205].

The accuracy of PI for detecting CI changes during EEXPO has not been investigated until now. If this was the case, this would allow the assessment of the EEXPO test in an easy and totally non-invasive way. The primary goal of our study was to test if PI changes could accurately detect a positive response of CI to an EEXPO test and if they could detect a positive PLR test in critically ill patients. The secondary goal was to confirm the ability of PLR-induced changes in PI to detect the PLR-induced changes in CI.

Patients and methods

Patients

This study was conducted in the 25-bed medical intensive care unit of a university hospital. Patients or their relatives all accepted to participate in this study, which was approved by an Institutional Review Board (Comité pour la Protection des Personnes, Ile-de-France VII, ID RCB: 2016-A00959-42).

We prospectively included patients if they presented the following criteria: age ≥18 years old, mechanical ventilation in the volume assist-controlled mode (Evita 4, Dräger Medical, Lübeck, Germany), PiCCO2 device already in place (Pulsion Medical Systems, Feldkirchen, Germany) and decision taken by the clinicians in charge of performing the PLR and EEXPO tests. Patients were excluded in case of atrial fibrillation, spontaneous breathing activity impeding the maintenance of a 15-sec EEXPO and situations in which the PLR test is contra-indicated (deep vein thrombosis of the inferior limbs, head trauma) or possibly unreliable (venous compression stocking, intra-abdominal hypertension, defined as intra-abdominal pressure > 12mmHg [121]).

PiCCO2 device and hemodynamic variables

The PiCCO2 system is composed of a central jugular venous catheter and a thermistor-tipped arterial femoral catheter (PC8500, Pulsion Medical Systems, Feldkirchen, Germany) which are connected to a specific device. CI was measured by calibrated pulse contour analysis [174] and by transpulmonary thermodilution [173]. Transpulmonary thermodilution measurements were performed by the injection of cold boluses of 15 mL of 0.9% saline into the central venous tract. The average of three consecutive measurements was recorded [172].

The pressure sensors connected to the arterial and central venous catheters were fixed on the upper arm of the patient at the phlebostatic level. The CI measured by transpulmonary thermodilution and pulse contour analysis was continuously recorded by the PiCCO Win 4.0 software (Pulsion Medical Systems). The systemic arterial and central venous pressure curves and airway pressure signals were continuously recorded by using data acquisition software (HEM 4.2, Notocord, Croissy-sur-Seine, France).

Perfusion index

The PI, expressed as a percentage, was automatically calculated by the pulse oximeter Radical-7 device (Masimo Corp., Irvine, CA, USA). As recommended by the constructor, PI was measured by a sensor placed on the 3rd or 4th finger, choosing the one providing the highest value. The device offers two methods for displaying PI values. With the “short time” method, PI is displayed in real time with no averaging. With the “long time” method, the displayed PI values result from a 30-second moving

average. We chose the “short time method”, and averaged the PI values over 12 seconds, because it is the same time that is used by the PiCCO2 device for averaging pulse contour analysis-derived CI values. The PI values were extracted from the Radical-7 device and a curve of PI values changing over time was constructed on an Excel sheet (Microsoft Inc, Redmond, WA, USA).

Study design and measurements

After inclusion of the patients, in the semi-recumbent position, a transpulmonary thermodilution was performed, and we collected demographic characteristics and hemodynamic variables, including heart rate, arterial and central venous pressure, PI and CI measured by transpulmonary thermodilution. We performed an EEXPO test for 15 seconds [126]. At the end of the respiratory hold, we performed another set of measurements as previously described, including CI measured by pulse contour analysis.

When CI was return to its baseline value, a PLR test was performed by putting the patient in the PLR position, in which the lower limbs are passively elevated at 45° and the trunk is horizontal [110]. When the PLR test had induced its maximal effect on CI, which occurs within one minute, we performed another set of measurements.

Then, we moved the patient back to the semi-recumbent position. After hemodynamic stabilization, we performed another set of measurements as previously described, including CI measured by transpulmonary thermodilution. Finally, depending on the decision of attending physicians, who particularly took in account the balance between the response to the PLR test and the risk of fluid administration, volume expansion was performed in some patients with 500 mL of normal saline infused over 10 minutes. In this subgroup, measurements were recorded immediately after fluid infusion, including CI measured by thermodilution. Ventilatory settings and other treatments were unchanged during the study period.

Measurement of the precision of PI

We recorded five successive values of PI, each averaged over 12 seconds, for all the patients, during a period in which the hemodynamic status was stable (change in pulse contour analysis-derived CI <10%). During this time, the position of the plethysmographic sensor was kept unchanged. We calculated the coefficient of variation of PI as being the standard deviation divided by the mean of the five measurements [136,172,192]. The coefficient of error was calculated by divided the coefficient of variation and √n where n is the number of replicates that the PI examination per-former would choose to average in theory within one PI examination. The precision was calculated as being two times the coefficient of error and the least significant change as the coefficient of error × 1.96 × √2 [193].

Statistical analysis

The PLR and EEXPO tests were defined as positive if they increased pulse contour analysis-derived CI ≥ 10% [112] ≥ 5% [126] respectively. A positive response to volume expansion was defined as an increase in CI ≥ 15% after fluid infusion [172]. The changes in PI were defined as absolute changes (PI value after the test – PI value before the test) and as relative changes ((PI value after the test – PI value before the test) / PI value before the test)) x 100). CI changes were all expressed in percent relative changes ((CI value after the test – CI value before the test) / CI value before the test)) x 100).

Data were expressed as mean ± standard deviation, median [interquartile range, IQR] and number (percentage). Normality was assessed by the Kolmogorov-Smirnov test. Pairwise comparisons of values between different study times were performed by paired Student t tests. Comparisons between patients with positive and negative PLR tests were performed by two-tailed Student t or Wilcoxon tests. We compared the percent relative changes of CI to those of PI by linear regression analysis. Correlations were assessed by the Spearman coefficient.

Receiver operating characteristic (ROC) curves (with 95% confidence interval) were generated for describing the ability of the PLR and the EEXPO-induced changes in PI (in absolute changes or in relative changes) to detect the PLR and the EEXPO-induced changes in CI. The areas under ROC curves (AUROC) were compared by the Hanley-McNeil test [194]. The best threshold discriminating a positive PLR or EEXPO test and a negative one was chosen as the one providing the best Youden index. As the Radical-7 device displays PI values with one decimal, we also investigated the diagnostic ability of an EEXPO-induced and a PLR-induced absolute increase in PI (PI value after the test – PI value before the test) by 0.1% or more.

Considering an α risk at 5% and a β risk at 20%, making the hypothesis that the EEXPO-induced relative increase in PI was going to be 12% on average [114], with a standard deviation of 15% [162], from a baseline value of 3% [162] in responders to PLR, we estimated that 15 responders were required to detect such an increase and, thus, that 30 patients should be included in total. Statistical analysis was performed using MedCalc 11.6.0 software (Mariakerke, Belgium).

Results

Patient characteristics

We included 31 mechanically ventilated patients. Their characteristics are detailed in **Table 13**. No patient was excluded due to an absent or unstable plethysmographic signal. Nineteen (61%) patients presented acute respiratory distress syndrome. No patient exhibited *acute cor pulmonale* or severe valvular disease. The lactate level at the time of inclusion was 1.9 ± 0.9 mmol/L.

Patients (n = 31)	
Age (mean±SD, years)	61±10
Gender (male, n,%)	17 (55%)
Weight (mean±SD, kg)	67±14
Height (mean±SD, cm)	167±7
SAPS II (mean±SD)	60±20
Type of shock (n,%)	
Septic	23 (74%)
Cardiogenic	2 (7%)
Hypovolemic	0 (0%)
Vasoplegic non-septic	6 (19%)
Catecholamines	
Norepinephrine (n,%)	28 (90%)
Dose of norepinephrine (median [interquartile range], µg/kg/min)	0.9 [0.8-1.5]
Dobutamine (n,%)	2 (6%)
Dose of dobutamine (median [interquartile range], µg/kg/min)	20 [20-20]
Respiratory settings	
Mechanical ventilation (n (%))	31 (100%)
Tidal volume (mean±SD, mL/kg of PBW)	6±0
Plateau pressure (mean±SD, cmH2O)	24±6
Positive end-expiratory pressure (mean±SD, cmH2O)	11±3

Table 13 - Patient characteristics (n=31)

PI absolute values

At baseline, the value of PI was 2.3 ± 1.6%, ranging from 0.1 to 5.5%. It was lower than 1% in eight patients. These patients with PI ≤ 1% did not differ from the other ones in terms of lactate level at baseline (2.2 ± 0.8 vs. 1.5 ± 1.6 mmol/L, respectively, p = 0.19), time elapsed between the onset of shock and the inclusion (48 ± 96 vs. 36 ± 66 h, respectively, p = 0.35) or Simplified Acute Physiology Score II (61 ± 19 vs. 58 ± 15, respectively, p = 0.37). The dose of norepinephrine was higher in this subgroup than in the other one (1.9 [0.0-3.6] vs. 0.9 [0.8-0.8] µg/kg/min, respectively, p = 0.02). The value of PI at baseline was not correlated with the dose of norepinephrine (r = 0.02, p = 0.91). Baseline PI was similar between patients receiving the lowest and the highest doses of norepinephrine, as defined according to its median value (2.5 ± 1.0 vs. 2.6 ± 2.5%, respectively, p = 0.85). Taking into account all the absolute values of PI measured at different study times, PI was correlated with mean (r = 0.28, p = 0.0001) and diastolic (r = 0.31, p = 0.0001) arterial pressure.

Effects of PLR test, EEXPO test and volume expansion on PI

The hemodynamic variables and their time course are reported in **Table 14**. The PLR test was positive in 19 (61%) patients. The PI and CI values at baseline were lower in these patients than in the group with a negative PLR test (**Table 14**). In the group with a positive PLR test, compared to the value before PLR and expressed in relative percent change ((value during PLR–value before PLR) / value before PLR x 100), CI and PI significantly increased during PLR by 17 ± 7% and 49 ± 23%, respectively (p < 0.001 for both). In the same group, compared to the value before EEXPO and expressed in relative percent change ((value at the end of EEXPO–value before EEXPO) / value before EEXPO x 100), CI and PI significantly increased at the end of EEXPO by 6 ± 2% and 11 ± 8%, respectively (p < 0.01 for all) (**Table 14, Figure 28**).

Haemodynamic variables	Baseline	Start EEXPO	End EEXPO	Start PLR	End PLR
Heart rate (beats/min)					
Positive PLR test (n=19)	96±17	93±16	95±17	93±16	92±18
Negative PLR test (n=12)	84±22	83±23	83±23	85±22	83±22
Systolic arterial pressure (mmHg)					
Positive PLR test (n=19)	121±16	116±16	117±16†	122±21	136±15¨
Negative PLR test (n=12)	125±23	129±27	129±27	125±18	135±19¨
Diastolic arterial pressure (mmHg)					
Positive PLR test (n=19)	58±9	57±9	57±9	59±9	66±11¨
Negative PLR test (n=12)	62±9	63±8	63±8	62±9	68±7¨
Central venous pressure (mmHg)					
Positive PLR test (n=19)	9±4	9±3	9±3	9±4	12±3¨
Negative PLR test (n=12)	12±5	14±3$	13±3†$	14±2$	16±1¨$
Cardiac index (L/min/m²)					
Positive PLR test (n=19)	2.7±0.7	2.5±0.8	2.6±0.9†	2.5±0.8	2.9±0.9¨
Negative PLR (n=12)	3.4±1.0$	3.2±1.1$	3.3±1.1†	3.1±0.9	3.2±1.1¨
PPV (%)					
Positive PLR test (n=19)	10±5	9±5	8±5†	10±5	9±7¨
Negative PLR test (n=12)	5±2$	5±2$	4±2$	5±2$	5±3$
PI (%)					
Positive PLR test (n=19)	1.8±1.3	1.7±1.3	1.9±1.4†	1.7±1.2	2.5±1.6¨
Negative PLR test (n=12)	3.1±1.7$	3.1±1.7$	3.1±1.7	3.2±1.5$	3.2±1.7

Table 14 - Hemodynamic variables (n=31)- EEXPO: end-expiratory occlusion; PI: perfusion index; PLR: passive leg raising; PPV: pulse pressure variation; SVI: stroke volume index. A positive PLR test was defined by a PLR-induced increase in CI ≥10%. *p<0.05 vs. baseline, †p<0.05 end EEXPO vs. start EEXPO and ¨p<0.05 end PLR test vs. start PLR test, $p<0.05 between positive and negative PLR group.

The PLR test was negative (increase in CI by <10%) in 12 patients. In these patients, CI significantly increased during PLR by 4 ± 4% and during EEXPO by 1 ± 2%. PI did not significantly change (**Table 14**, **Figure 30**).

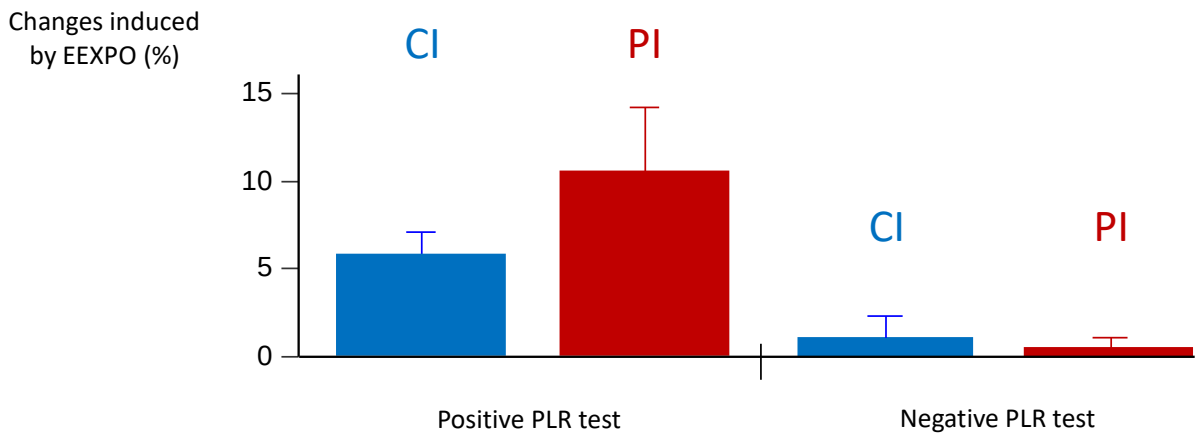


Figure 30 - Changes in perfusion index (PI) and cardiac index (CI) during an end-expiratory occlusion (EEO) test in patients with a positive (n=19) and negative (n=12) passive leg raising (PLR) test. Values are expressed in percent changes ((value during EEO –value before) / value before x 100).

Volume expansion was decided after a positive PLR test in four patients. All were fluid responders. In these patients, after fluid infusion, compared to the value before fluid infusion and expressed in percent change, CI and PI had significantly increased by 14 ± 2% and 38 ± 16%, respectively ($p < 0.05$ for both).

Ability of PLR- and EEXPO-induced changes in PI to detect a positive PLR test and a positive EEXPO test

The ability of changes in PI, expressed as relative changes, and in CI to detect a positive PLR test in terms of sensitivity, specificity, positive, and negative predictive values is summarized in **Table 15** and illustrated in **Figure 31**. An absolute increase in PI (value during EEXPO – value before EEXPO) ≥0.05%, i.e. the increase which systematically increases the PI value by at least one decimal, detected a positive PLR test with a sensitivity of 63 (38-84)% and a specificity of 100 (74-100)%, a positive predictive value of 100% and a negative predictive value of 56 (40-72)%.

In the subgroup of patients with PI ≤1% at baseline, the AUROC of the PLR-induced relative changes in PI to detect a positive response to PLR was similar to the AUROC of these changes in patients with PI >1% at baseline (1.00 (0.63-1.00) *vs*. 0.89 (0.70-0.98), respectively, p = 0.81). This was also the case for the AUROC of the EEXPO-induced relative changes in PI to detect a positive response to PLR (1.00 (1.00-1.00) in patients with baseline PI ≤1% *vs*. 0.93 (0.81-1.00) in patients with baseline PI >1%).

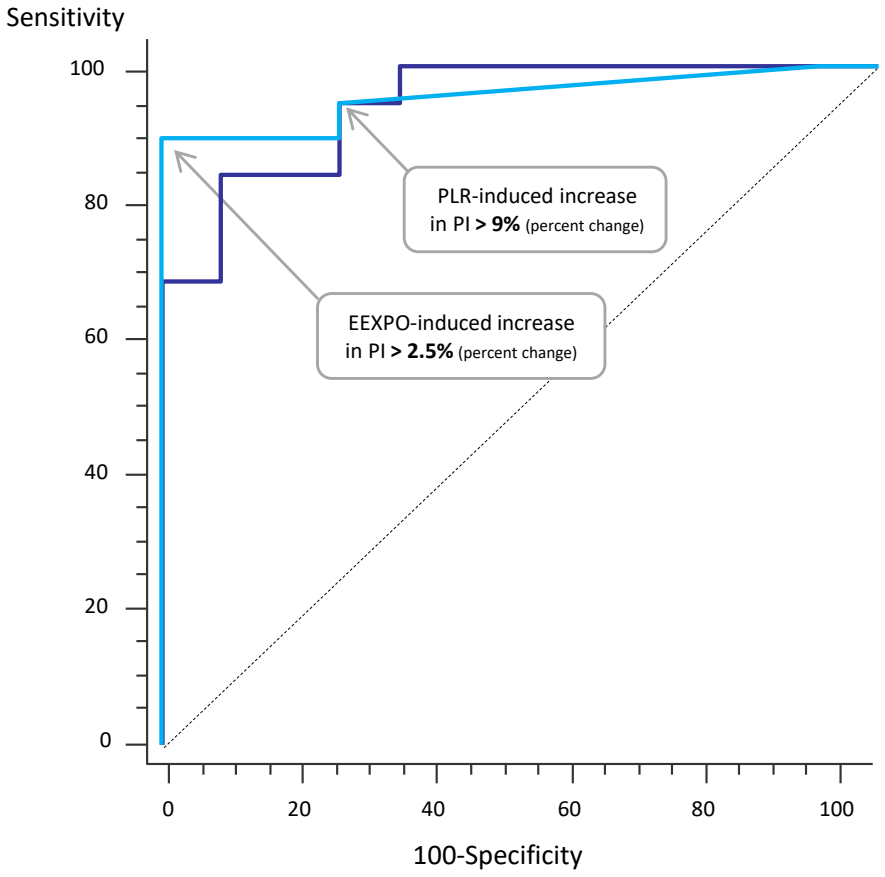


Figure 31 - Area under the receiver operating characteristics curve generated for the detection of preload dependence by the changes in perfusion index during a passive PLR test and an EEXPO test. Values are expressed in percent changes ((value during EEXPO or PLR–value before) / value before x 100).

Ability of PI changes to track changes in CI

When considering all the changes observed during PLR, EEXPO and volume expansion, the correlation between the relative percent changes of PI and CI was significant (r = 0.83, p<0.0001 (**Figure 32**).

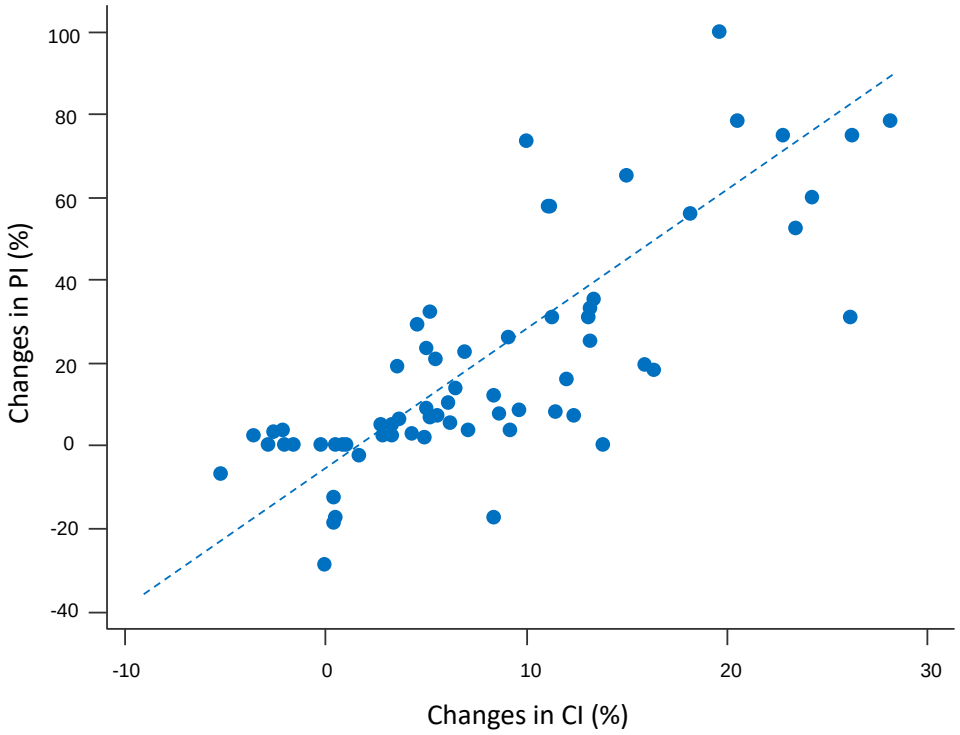


Figure 32 - Correlation between perfusion index (PI) changes and cardiac index (CI) changes during an end-expiratory occlusion test, passive leg raising test and volume expansion.

Precision of PI measurements

The mean of PI values in measurements performed for assessing the precision in patients with a stable plethysmographic signal was 2.05 ± 0.03%. In these patients, the precision of PI was 1.24 ± 0.68 % and the least significant change was 1.62 ± 0.90%.

Tests to predict a positive PLR test	**AUROC**	**P value *vs.* 0.5**	**Threshold***	**Sensitivity**	**Specificity**
ΔPI during PLR	0.94±0.04	<0.001	>9%	95 [74-100]	75 [43-95]
ΔPI during EEXPO	0.96±0.03	<0.001	>2.5%	89 [67-99]	100 [74-100]
ΔCI during EEXPO	0.95±0.03	<0.001	>3.3%	84 [60-97]	92 [62-100]

Table 15 - Diagnostic ability of the changes in perfusion index and cardiac index induced by different tests to predict a positive passive leg raising test. AUROC: area under the receiver operating characteristic curves; ΔCI: relative changes in cardiac index; EEXPO: end-expiratory occlusion; ΔPI: relative changes in perfusion index; PLR: passive leg raising test.

Discussion

This study suggests that the changes in PI can be considered as reliable estimates of changes in CI for assessing preload responsiveness. To accurately detect a positive PLR test, the best PI threshold during a 15-sec EEXPO test was 2.5% (relative increase in percent change of the baseline value). An absolute increase in PI during a 15-sec EEXPO test ≥0.05%, i.e. the increase which systematically increases the PI value by at least one decimal, detected a positive PLR test with a sensitivity of 63% and a specificity of 100%. In addition, the percent changes in PI during a PLR test were reliable surrogates of the PLR-induced changes in CI, confirming our previous results [162].

The good diagnostic ability of the EEXPO test has been confirmed by several studies [114,123–125,128–131,153–157,168,205]. Because the effects of the EEXPO test are short-term and of relatively small amplitude, in our study, as in several ones [168], we assessed these effects with pulse contour analysis, which provides a real-time and very precise [85] estimation of CI. Nevertheless, the technique requires an arterial catheter.

PI quantifies the relative amplitude of the plethysmographic signal. Basically, PI is determined by the degree of vasoconstriction, which tends to reduce the volume of oxygenated hemoglobin behind the sensor, and by stroke volume, which generates a pulsatile increase of this volume. Provided that the degree of vasoconstriction is constant, PI may estimate stroke volume and cardiac output [201,204]. Actually, some studies have shown that changes in PI reflected changes in cardiac output [162,204–207], even if discordant results have been reported [196,200]. In a previous study , our group reported that PI was able to detect the changes in CI during a PLR test [162]. Højlund *et al.* also showed an increase of PI, stroke volume and cardiac output during head-down tilt during general anesthesia, even in cases of vasoconstriction due to phenylephrine administration [204]. De Courson *et al*. later showed that changes in PI were also able to reflect CI changes during lung recruitment maneuvers in ventilated patients [205]. In line with these previous studies, our present results showed that the EEO changes in PI allowed the detection of a positive PLR test. The diagnostic value was intact in cases in which the PI value at baseline was below 1%. We also confirm that PI reliably tracks the changes in CI during a PLR maneuver, as we showed previously [162].

This was not obvious before performing the study, especially because the changes in CI induced by the EEXPO are smaller than observed for instance during a PLR maneuver. The diagnostic threshold for EEXPO-induced relative changes in PI providing the best Youden index, i.e. the best compromise between sensitivity and specificity, was small, but it was larger than the least significant change of PI. Besides the issue of precision of the PI signal, small changes may be too small for being displayed by the device that measures them. Nevertheless, our analysis of the absolute changes in PI showed that

an increase in the PI value ≥0.05%, i.e. the increase which systematically increases the PI value by at least one decimal, detected a PLR test with a specificity of 100%, though the sensitivity was 63%.

Regarding the clinical application of our results, EEXPO is suitable only for patients under mechanical ventilation, and who can sustain an interruption of ventilation during 15 sec. Though it is possible during light sedation, some patients interrupt EEXPO before its end. Monitoring EEXPO with PI might be interesting when no cardiac output monitoring is in place, even in patients with an arterial line. Indeed, monitoring the effects of EEXPO with arterial pressure is possible but not easy, since the value of pulse pressure is not displayed on bedside monitors. Whether our results could apply for patients in the operating room remains to be demonstrated. Of note, this study further contributes to the validation of the EEXPO test.

Limitations

The first limitation of our study is that only four positive PLR tests lead to a volume expansion, so we could not conclude that PLR or EEXPO-induced changes in PI predict fluid responsiveness. However, the reliability of the PLR test to detect preload responsiveness is now well established [67]. The decision to give fluid in case of a positive PLR test was left at the decision of attending clinicians. They likely estimated for the majority of the patients, that the risk of fluid infusion was high compared to the expected benefit. Second, we included only critically ill patients in whom skin hypoperfusion may have impaired the PI signal. This could worsen the value of PI as a reflection of CI changes. Moreover, the ability of PI to reflect CI changes during recruitment maneuvers was good also in the study by De Courson *et al.,* who included patients undergoing neurosurgery [205]. Third, we did not test other sites of measurement of PI even if different values depending on the site were previously reported [197,199]. Fourth, we tested only the Radical 7 device for measuring PI, although other devices also provide this measurement. Fifth, we excluded patients with atrial fibrillation from the study, so that such patients should be investigated in further studies. Sixth, we could not access the two elements of the PI fraction (pulsatile part (AC) divided by constant baseline part (DC)). We could not investigate why the response of PI to PLR were so larger than its change during EEXPO, which was not the case of CI. It might be possible that PLR and EEXPO change the DC part in a different way, for instance because the increase in the upper part of the blood volume, which determines DC, is increased by gravitation during PLR. Finally, we used pulse contour analysis during PLR and EEXPO, though it is assumed to be less reliable than thermodilution-based methods [174]. Nevertheless, pulse contour analysis detects changes of CI in real time, which is mandatory for assessing the short-term effects of PLR and EEXPO [126]. It is also precise enough for assessing the small effects of EEXPO on CI [85].

Conclusion

This study shows that a relative increase in PI ≥2.5% during an EEXPO test accurately detects a positive PLR test. An increase in PI by one decimal or more is very specific of a positive PLR test. We also confirm that the PLR-induced changes in PI are reliable surrogates of the PLR-induced changes in CI.

Other hemodynamic projects

Do changes in pulse pressure variation and inferior vena cava distensibility during passive leg raising and tidal volume challenge detect preload responsiveness in case of low tidal volume ventilation?

Taccheri T, **Gavelli F**, Teboul J-L, Shi R, Monnet X. Crit Care. 2021;25:110. *doi: 10.1186/s13054-021-03515-7.*

Introduction

In patients ventilated with tidal volume (Vt) <8 mL/kg, pulse pressure variation (PPV) and, likely, the variation of distensibility of the inferior vena cava diameter (IVCDV) are unable to detect preload responsiveness. In this condition, passive leg raising (PLR) could be used but it requires a measurement of cardiac output. The tidal volume (Vt) challenge (PPV changes induced by a 1-min increase in Vt from 6 to 8 mL/kg) is another alternative, but it requires an arterial line. We tested whether, in case of Vt=6mL/kg, the effects of PLR could be assessed through changes in PPV or in IVCDV rather than changes in cardiac output, and whether the effects of the Vt challenge could be assessed by changes in IVCDV rather than changes in PPV.

Methods

In 30 critically ill patients without spontaneous breathing and cardiac arrhythmias, ventilated with Vt=6 mL/kg, we measured cardiac index (CI) (PiCCO2), IVCDV and PPV before/during a PLR test and before/during a Vt challenge. A PLR-induced increase in CI ≥10% defined preload responsiveness.

Results

At baseline, IVCDV was not different between preload responders (n=15) and non-responders. Compared to non-responders, PPV and IVCDV decreased more during PLR (by -38±16% and -26±28%, respectively) and increased more during the Vt challenge (by 64±42% and 91±72%, respectively) in responders. ΔPPVPLR, expressed either as absolute or percent relative changes, detected preload responsiveness (area under the receiver operating curve, AUROC: 0.98±0.02 for both). ΔIVCDVPLR detected preload responsiveness only when expressed in absolute changes (AUROC: 0.76±0.10), not in relative changes. ΔPPVVt, expressed as absolute or percent relative changes, detected preload responsiveness (AUROC: 0.98±0.02 and 0.94±0.04, respectively). This was also the case for ΔIVCDVVt but, the diagnostic threshold (1 point or 4%) was below the least significant change of IVCDV (9[3-18]%).

Conclusions

During mechanical ventilation with Vt=6 mL/kg, the effects of PLR can be assessed by changes in PPV. If IVCDV is used, it should be expressed in percent and not absolute changes. The effects of the Vt challenge can be assessed on PPV, but not on IVCDV, since the diagnostic threshold is too small compared to the reproducibility of this variable.

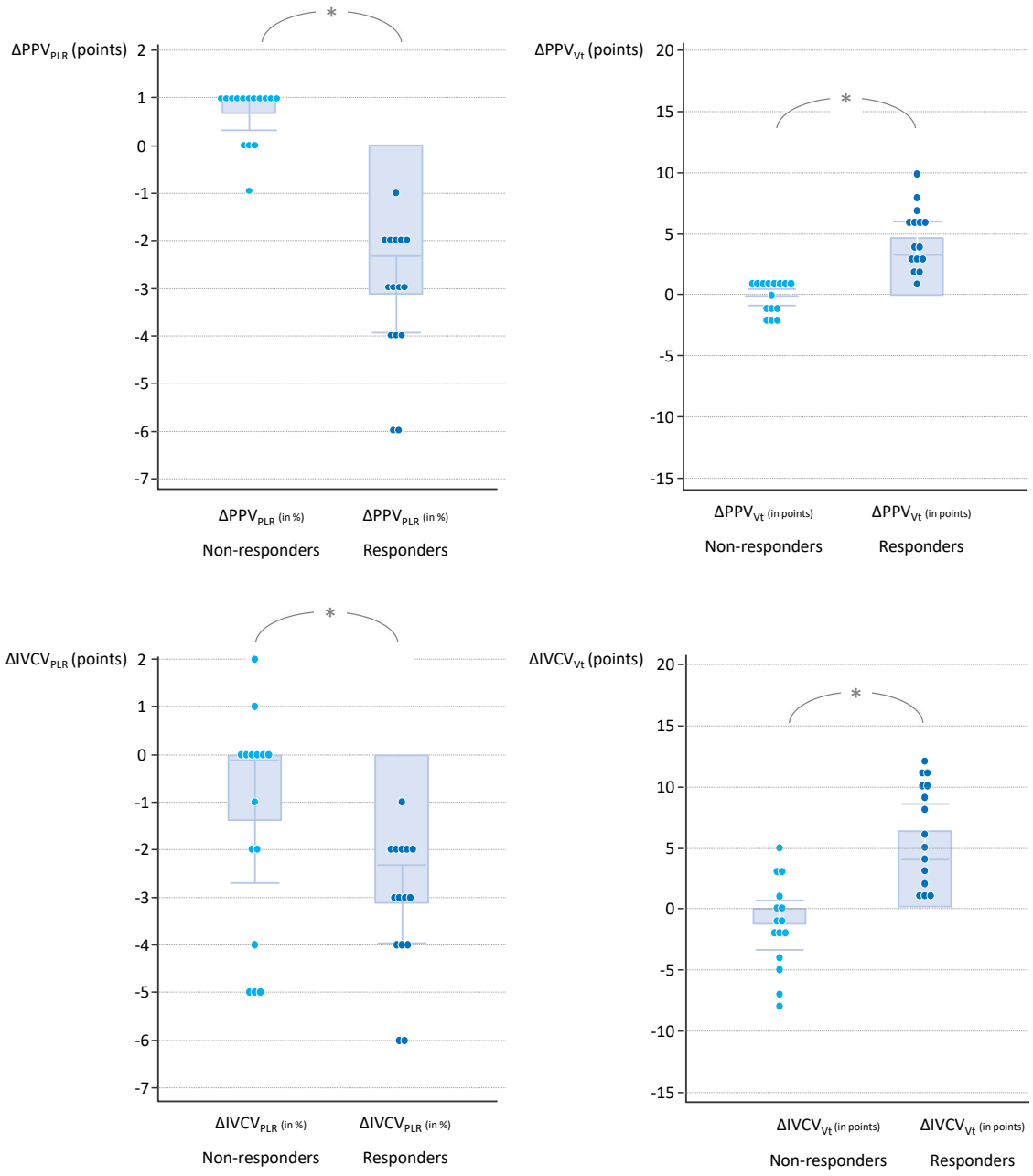


Figure a

Upper panel: PLR-induced percent changes in pulse pressure variation during a passive leg raising test (ΔPPV_{PLR}) (expressed in percent changes relative to baseline) and a tidal volume challenge (ΔPPV_{Vt}) (expressed in absolute changes) in preload responders and non-responders.

Bottom panel: PLR-induced percent changes in inferior vena cava variation during a passive leg raising test ($\Delta IVCDV_{PLR}$) (expressed in percent changes relative to baseline) and a tidal volume challenge ($\Delta IVCDV_{Vt}$) (expressed in absolute changes) in preload responders and non-responders.

* p<0.05 preload responders vs. preload non-responders.

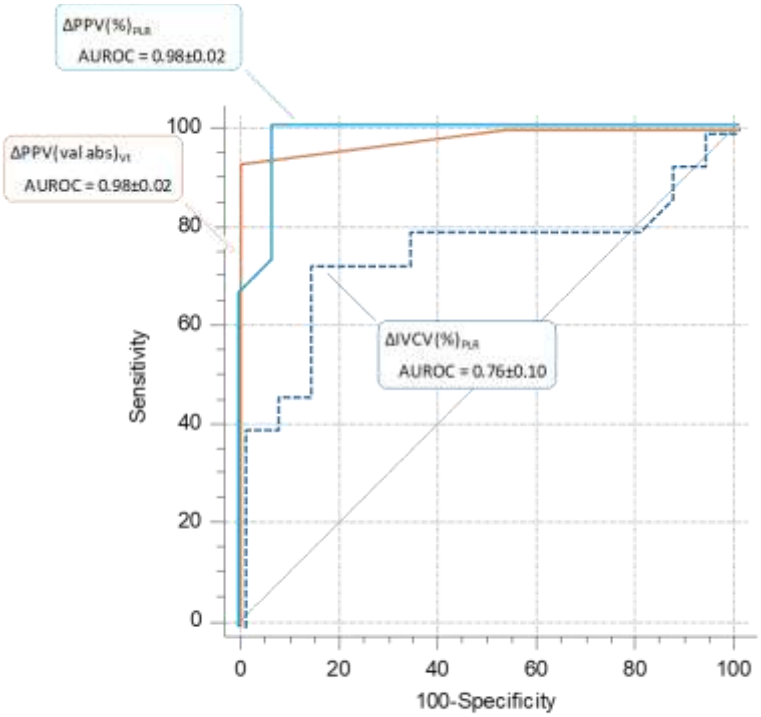


Figure b

Receiver operating characteristic curves describing the ability to diagnose preload responsiveness of the changes in passive leg raising-induced changes of pulse pressure variation in percent ($\Delta PPV(\%)_{PLR}$), passive leg raising-induced changes and of inferior vena cava variation in percent ($\Delta IVCDV(\%)_{PLR}$), and of the tidal volume challenge-induced changes of pulse pressure variation in absolute value ($\Delta PPV(valabs)_{Vt}$).

AUROC: area under the receiver operating characteristic curve (expressed as mean ± standard deviation).

Transpulmonary thermodilution detects rapid and reversible increases in lung water induced by positive end-expiratory pressure in acute respiratory distress syndrome

Gavelli F, Teboul J-L, Azzolina D, Beurton A, Taccheri T, Adda I, Lai C, Avanzi GC, Monnet X. Annals of Intensive Care. Annals of Intensive Care. 2020;10:28. *doi: 10.1186/s13613-020-0644-2.*

Introduction

It has been suggested that, by recruiting lung regions and enlarging the distribution volume of the cold indicator, increasing the positive end-expiratory pressure (PEEP) may lead to an artefactual overestimation of extravascular lung water (EVLW) by transpulmonary thermodilution (TPTD).

Methods

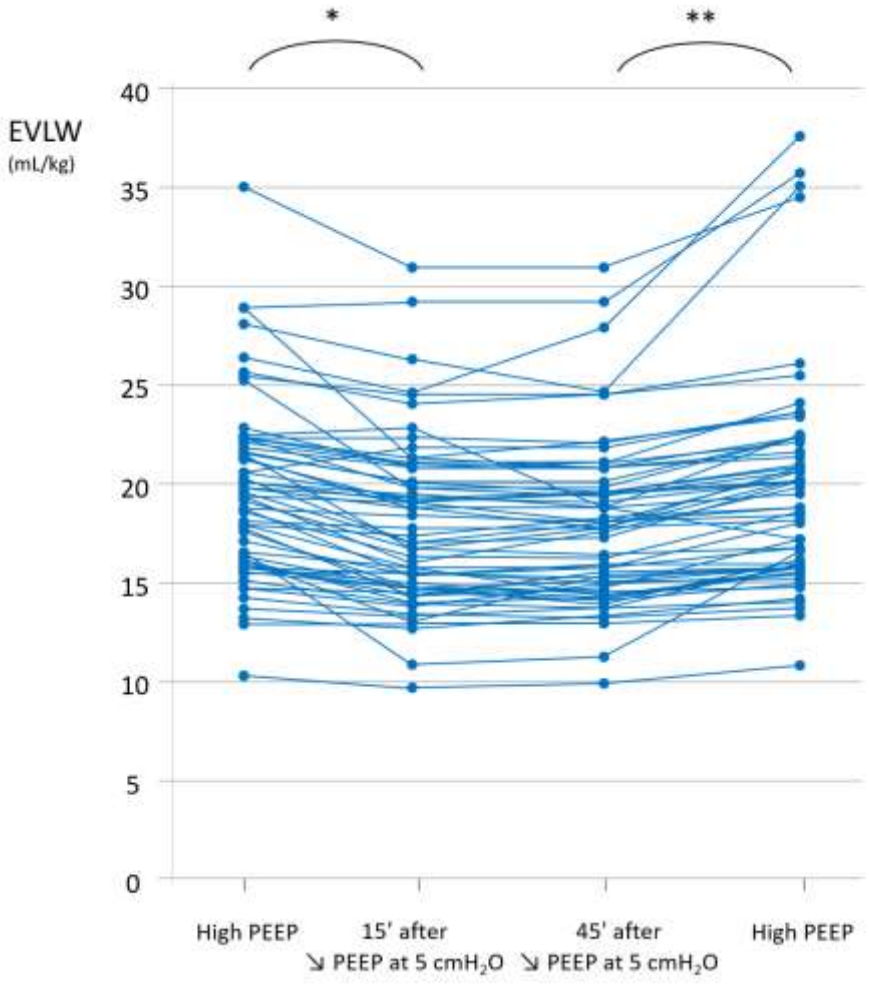
In 60 ARDS patients, we measured EVLW (PiCCO2 device) at a PEEP level set to reach a plateau pressure of 30cmH_2O ($HighPEEP_{start}$) and 15 and 45 minutes after decreasing PEEP to 5cmH_2O ($LowPEEP_{15'}$ and $LowPEEP_{45'}$, respectively). Then, we increased PEEP back to the baseline level ($HighPEEP_{end}$). Between $HighPEEP_{start}$ and $LowPEEP_{15'}$, we estimated the degree of lung derecruitment either by measuring changes in the compliance of the respiratory system (Crs) in the whole population, or by measuring the lung derecruited volume in 30 patients. We defined patients with a large derecruitment from the other ones as patients in whom the Crs changes and the measured derecruited volume were larger than the median of these variables observed in the whole population.

Results

Reducing PEEP from $HighPEEP_{start}$ (14±2cmH_2O) to $LowPEEP_{15'}$ significantly decreased EVLW from 20±4 to 18±4mL/kg, central venous pressure (CVP) from 15±4 to 12±4mmHg, the arterial oxygen tension over inspired oxygen fraction (PaO_2/FiO_2) ratio from 184±76 to 150±69mmHg and lung volume by 144[68–420]mL. The EVLW decrease was similar in “large derecruiters” and the other patients. When PEEP was re-increased to $HighPEEP_{end}$, CVP, PaO_2/FiO_2 and EVLW significantly re-increased. At linear mixed effect model, EVLW changes were significantly determined only by changes in PEEP and CVP ($p<0.001$ and $p=0.03$, respectively, n=60). When the same analysis was performed by estimating recruitment according to lung volume changes (n=30), CVP remained significantly associated to the changes in EVLW ($p<0.001$).

Conclusions

In ARDS patients, changing the PEEP level induced parallel, small and reversible changes in EVLW. These changes were not due to an artefact of the TPTD technique and were likely due to the PEEP-induced changes in CVP, which is the backward pressure of the lung lymphatic drainage.



Individual values of extravascular lung water (EVLW) at different study times. PEEP: positive end-expiratory pressure. *p < 0.05 vs. High PEEP, **p < 0.05 vs. 45’ after decreasing PEEP at 5 cmH2O.

Extravascular lung water levels are associated with mortality – A systematic review and meta-analysis

Gavelli F, Shi R, Teboul J-L, Azzolina D, Mercado P, Jozwiak M, Chew M, Huber W, Kirov MY, Kuzkov VV, Lahmer T, Malbrain MLNG, Mallat J, Sakka SG, Tagami T, Pham T, Monnet X. *Submitted for publication*.

Abstract presented at ESICM Lives 2019 32nd annual congress of the European Society of Intensive Care Medicine; 28 September – 2 October 2019, Berlin, Germany.

Introduction

The role of extravascular lung water (EVLW) measured by transpulmonary thermodilution (TPTD) in the management of critically ill patients remains a matter of debate. We performed a systematic review and meta-analysis of studies assessing the effects of elevated TPTD-estimated EVLW on mortality in critically ill patients.

Methods

MEDLINE, EMBASE and Cochrane Database were screened for original articles. Bivariate random-effects meta-analysis determined the Area Under the Summary Receiver Operating Characteristic (AUSROC) curve of elevated EVLW as a predictor of mortality. Missing data were provided by the authors of the original studies. The study was enregistered on PROSPERO (CRD42019126985).

Results

Eighteen studies (1296 patients) were included. Both the baseline and the maximal EVLW values were significantly different among survivors and non-survivors, as well as EVLW variation over time. The AUSROC for elevated EVLW levels, estimated from 16 studies, was 0.76 [0.70 – 0.83]. The pooled sensitivity and specificity were 0.73 [0.63 – 0.81] and 0.72 [0.68 – 0.77], respectively. The association of EVLW with mortality was similar when AUROCs for baseline, 3-Day and maximal EVLW levels were compared. Subgroup analyses comparing indexation of EVLW to actual *vs.* predicted body weight and specific populations of ARDS patients *vs.* other ones were consistent with primary analysis. According to the multivariable analysis performed in seven studies, the odds ratio of elevated EVLW for mortality ranged from 1.01 to 6.21.

Conclusions

The level of EVLW measured by TPTD and its changes over time are associated with mortality in critically ill patients, which may emphasize its clinical value.

Study	Survivors			Non-survivors			Weight (fixed)	Weight (random)	Mean difference (95%IC)
	Mean	SD	Total	Mean	SD	Total			
Martin et al.	8.0	3.7	7	14.0	3.1	12	1.4%	5.6%	-6.0 [-9.3; -2.8]
Kuzkov et al.	8.3	2.7	6	9.6	5.0	22	2.4%	6.2%	-1.3 [-3.8; -1.2]
Chung et al.	8.5	1.7	16	21.0	3.8	17	3.7%	6.6%	-12.5 [-14.5; -10.5]
Phillips et al.	11.6	1.9	12	20.6	4.6	7	1.1%	5.3%	-9.0 [-12.6; -5.4]
Chung et al.	12.2	5.8	34	24.4	10.6	33	0.9%	4.9%	-12.2 [-16.3; -8.1]
Craig et al.	10.6	2.4	32	17.5	2.0	12	7.4%	7.0%	-6.9 [-8.3; -5.5]
Chew et al.	9.1	1.3	36	10.6	1.2	15	26.5%	7.3%	-1.5 [-2.2; 0.9]
Cordemans et al.	9.8	3.9	58	10.5	5.2	65	5.6%	6.8%	-0.7 [-2.3; 0.9]
Mallat et al.	14.5	1.6	32	15.8	3.3	23	6.8%	6.9%	-1.3 [-2.8; 0.2]
Brown et al.	12.0	5.0	41	17.0	9.0	18	0.7%	4.6%	-5.0 [-9.4; -0.6]
Jozwiak et al.	16.0	7.0	92	17.0	9.0	108	3.0%	6.4%	-1.0 [-3.2; 1.2]
Tagami et al.	18.4	6.7	133	18.3	6.5	59	3.6%	6.6%	0.1 [-1.9; 2.1]
Zhao et al.	13.0	3.6	13	11.0	3.0	8	1.8%	5.9%	-6.0 [-8.9; -3.1]
Wang et al.	11.0	3.6	45	11.9	4.1	60	6.7%	6.9%	-0.9 [-2.4; 0.6]
Ma et al.	11.2	3.4	23	13.8	6.1	18	1.5%	5.7%	-2.6 [-5.7; 0.5]
Shi et al.	14.0	2.0	47	17.0	2.0	73	27.1%	7.3%	-3.0 [-3.73: -2.27]
Total			**637**			**550**		**100.0%**	**-4.1 [-5.7; -2.6]**

Heterogeneity Tau² = 8.6733, Chi²= 205.98, df=15 (P<0.01); I²=93%

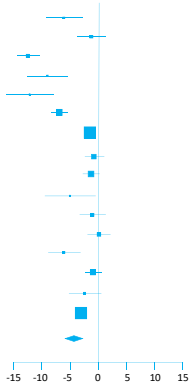


Figure a

Mean difference in extravascular lung water levels between survivors and non-survivors according to baseline levels of EVLW. EVLW: extravascular lung water; SD: standard deviation.

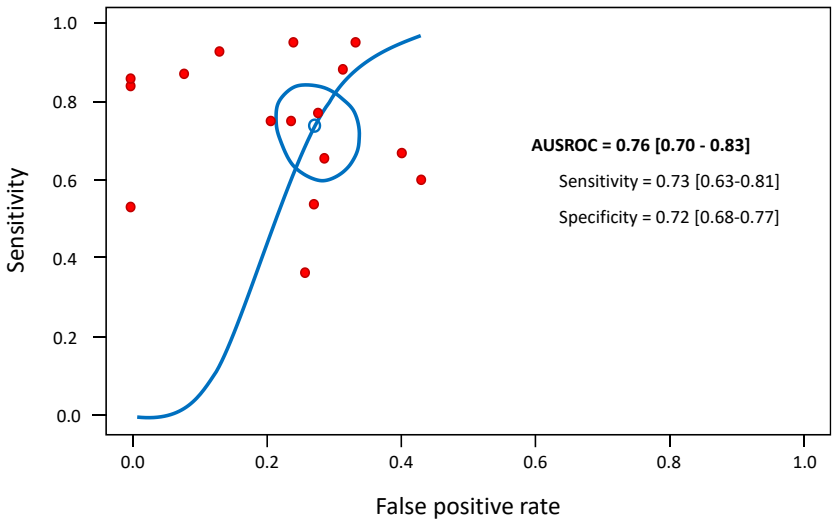


Figure b

AUSROC curve for the Reitsma et al. bivariate model. Pair of pooled accuracies together with a 95%-confidence region are represented. AUSROC: area under the summary receiver operating characteristic.

General conclusion

The detection of preload responsiveness has been gradually established as one of the necessary practices during the hemodynamic management of acute circulatory failure. This is motivated both by the inconstant response of cardiac output to volume expansion and by the risk of inducing fluid overload. Thus, fluids should be seen as a real treatment, a drug, with possible dangerous side effects, which should be predicted before administration.

By the time we started our work, the concept of preload dependency was well established, and many tests had already been developed. Our research focused on two main objectives, in order to extend knowledge in the field. On the one hand, we were able to provide a more solid and comprehensive validation of a relatively new test of preload responsiveness, the EEXPO test. In particular, we have shown that its reliability is very high and that the situations in which this test is applicable are very wide, provided that the patient is under invasive mechanical ventilation.

The second objective concerned the investigation of non-invasive hemodynamic monitoring techniques which can be used to measure the effects of preload dependency tests on cardiac output. We showed that bioreactance, which is reliable for detecting PLR-induced changes on cardiac output, cannot be used to evaluate the effects of the EEXPO test. However, when we could use a research version of the device and we were able to shorten both the time over which the bioreactance signal is averaged and the interval over which the value of cardiac output is refreshed on the screen, we observed encouraging results. We hope that the possibility to make such changes will be available in all the new versions of the Starling device. Also, we demonstrated that the amplitude of the plethysmography signal quantified by PI made it possible to follow changes in cardiac output, both during the PLR and the EEXPO and tests in two other studies.

Even though we believe these results are solid, they require confirmation from further studies. Nevertheless, they are quite encouraging and could prompt the use of such non-invasive devices for hemodynamic monitoring outside the intensive care unit.

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Additional files

Additional file 1 - The end-expiratory occlusion test for detecting preload responsiveness: a systematic review and meta-analysis

Supplemental S1 - Searching strategy

#1 End expiratory occlusion

#2 End expiratory

#3 #1 OR #2

#4 fluid challenge

#5 volume expansion

#6 fluid administration

#7 volume challenge

#8 fluid responsiveness

#9 preload responsiveness

#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 #4 AND #10

Example, PubMed:

((End[All Fields] AND ("exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "expiratory"[All Fields]) AND ("dental occlusion"[MeSH Terms] OR ("dental"[All Fields] AND "occlusion"[All Fields]) OR "dental occlusion"[All Fields] OR "occlusion"[All Fields])) OR (End[All Fields] AND ("exhalation"[MeSH Terms] OR "exhalation"[All Fields] OR "expiratory"[All Fields]))) AND ((((((preload[All Fields] AND responsiveness[All Fields]) OR (fluid[All Fields] AND responsiveness[All Fields])) OR (volume[All Fields] AND ("Challenge (Atlanta Ga)"[Journal] OR "challenge"[All Fields]))) OR (fluid[All Fields] AND ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "administration"[All Fields]))) OR (volume[All Fields] AND expansion[All Fields])) OR (fluid[All Fields] AND ("Challenge (Atlanta Ga)"[Journal] OR "challenge"[All Fields])))

Supplemental S2 – Continuity correction for diagnostic accuracy of the end-expiratory occlusion test in the including studies.

	Sensitivity	Sensitivity 95% CI	Specificity	Specificity 95% CI	False positive	True negative	False negative	True Positives
Monnet et al.[114]	0.9	0.72 - 0.97	0.96	0.7 - 1	0	11	2	20.93
Monnet et al. [124]	0.97	0.78 - 1	0.89	0.7 - 0.97	2	20	0	17
Monnet et al.[123]	0.92	0.77 - 0.97	0.9	0.72 - 0.97	2	22	2	27.9
Silva et al.[125]	0.96	0.73 - 1	0.89	0.69 - 0.96	2	19	0	13
Guinot et al.[155]	0.81	0.64 - 0.91	0.7	0.45 - 0.87	4	10	5	22.96
Biais et al.[154]	0.98	0.81 - 1	0.8	0.59 - 0.91	4	17	0	20
Myatra et al.[130]	0.85	0.62 - 0.95	0.9	0.66 - 0.98	1	13	2	14.08
Yonis et al.[131]	0.34	0.16 - 0.59	0.97	0.79 - 1	0	18	10	4.95
Jozwiak et al.[128]	0.91	0.68 - 0.98	0.97	0.76 - 1	0	15	1	13.95
Georges et al.[156]	0.88	0.72 - 0.95	0.93	0.76 - 0.98	1	21	3	24.92
Dépret et al.[129]	0.83	0.58 - 0.95	0.9	0.66 - 0.98	1	13	2	12.04
Messina et al.[153]	0.89	0.69 - 0.96	0.82	0.61 - 0.93	3	16	2	18.774
Xu et al.[157]	0.8	0.64 - 0.9	0.91	0.79 - 0.97	3	36	7	29.16

Sensitivities and specificities have been reported. A continuity correction of 0.5 has been considered for computation. 95% Wilson confidence interval (CI) are also reported.

Supplemental S3. Results of QUADAS-2 analysis.

	Patient selection		Index test		Reference standard		Flow and timing
	Risk of bias	Applicability	Risk of bias	Applicability	Risk of bias	Applicability	Risk of bias
Monnet et al.[114]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Monnet et al. [124]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Monnet et al.[123]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Silva et al.[125]	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Guinot et al.[155]	🔴	🟢	🟢	🔴	🟢	🟢	🟢
Biais et al.[154]	🔴	🟢	🟢	🟢	🟡	🟢	🟢
Myatra et al.[130]	🟡	🟢	🟢	🟢	🟡	🟢	🟢
Yonis et al.[131]	🟢	🟢	🟡	🟡	🟢	🟢	🟢
Jozwiak et al.[128]	🟡	🟢	🟢	🟢	🟢	🟢	🟢
Georges et al.[156]	🟡	🟢	🟢	🟡	🟢	🟢	🟢
Dépret et al.[129]	🟡	🟢	🟢	🟢	🟢	🟢	🟢
Messina et al.[153]	🟡	🟢	🟢	🟢	🟡	🟢	🟢
Xu et al.[157]	🟡	🟢	🟢	🟢	🟡	🟢	🟢

🔴 : high; 🟢 : low; 🟡 : unclear.

Patient Selection
Risk of Bias (RB): Could the selection of patients have introduced bias? [Signaling question (SQ)1: Was a consecutive or random sample of patients enrolled? SQ2: Was a case-control design avoided? SQ3: Did the study avoid inappropriate exclusions?].

Index Test
RB: Could the conduct or interpretation of the index test have introduced bias? (SQ1: Were the index test results interpreted without knowledge of the results of the reference standard? SQ2: If a threshold was used, was it prespecified?).

Reference Standard
RB: Could the reference standard, its conduct, or its interpretation have introduced bias? (SQ1: Is the reference standard likely to correctly classify the target condition? SQ2: Were the reference standard results interpreted without knowledge of the results of the index test?).

Flow and Timing
RB: Could the patient flow have introduced bias? (SQ1: Was there an appropriate interval between the index test and reference standard? SQ2: Did all patients receive the same reference standard? SQ3: Were all patients included in the analysis?).

Supplemental S4 - Overall quality assessment of the diagnostic accuracy of studies enrolled following the GRADE system

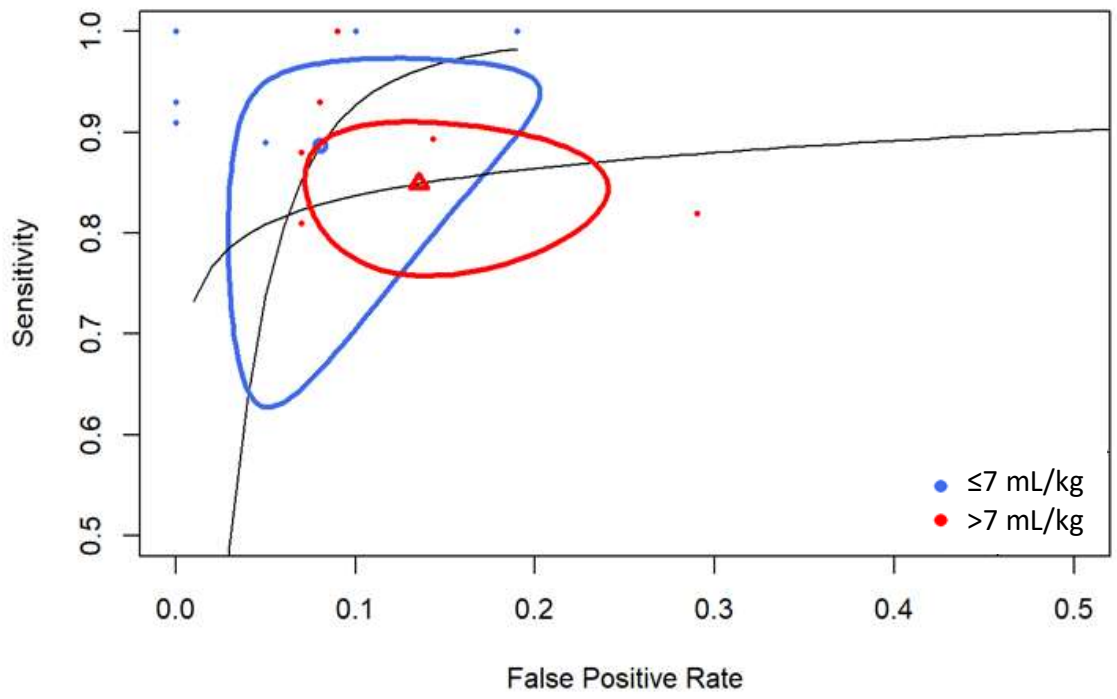
Quality assessment							Summary of findings				
							No. of patients		Effect		Quality
No. of studies	Design	Limitations	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Preload responders[1]	Non preload responders[2]	Relative (95% CI)	Absolute (95% CI)[3]	
13 studies (530 adult patients)	13 prospective observational studies	Some limitations exist[4]	Serious[5]	Serious[6]	Serious[7]	The QUADAS-2 outcome suggested a high risk of bias for 2 studies[8]	276	254	-	From 35.42 to 123.97	⊕OOO VERY LOW

[1] Patients preload responders [True Positives (patients preload responders) and False Negatives (patients incorrectly classified has not being preload responders)].
[2] Patients non preload responders [True Negatives (patients non preload responders) and False Positives (patients incorrectly classified has being non preload responders)].
[3] 95% Confidence interval (CI) of the conventional pooled diagnostic odds ratio (DOR) calculated with MetaDisc
[4] Short duration of the EEXPO test (1 study), low accuracy of the method used for hemodynamic monitoring (1 study).
[5] Different cut-off values for preload responsiveness definition (≥10% in 3 studies, ≥15% in 10 studies).
[6] Wide variation in the DOR estimates 95% Cis, I^2 for sensitivity 70.8% with $p<0.001$.
[7] Small samples size; one-centre studies.
[8] For more details, see Supplemental material S2.

Each domain was evaluated according to Ryan R, Hill S (2016) How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group. Version 3.0 December 2016. Available on: http://cccrg.cochrane.org/author-resources (last access: June 15, 2018). The table structure and quality of evidence were showed according to Schünemann H, Brożek J, Guyatt G, Oxman A (2013) GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available on: https://gdt.gradepro.org/app/handbook/handbook.html (last access: May 19, 2018), and Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ (2013) GRADE guidelines: 12. Preparing Summary of Findings tables - binary outcomes. J Clin Epidemiol 66:158-172 (doi: 10.1016/j.jclinepi.2012.01.012).

Supplemental S5– Metaregression analysis

Supplemental S5.1 – Metaregression analysis on Tidal Volume (≤7 *vs.* >7 mL/kg)

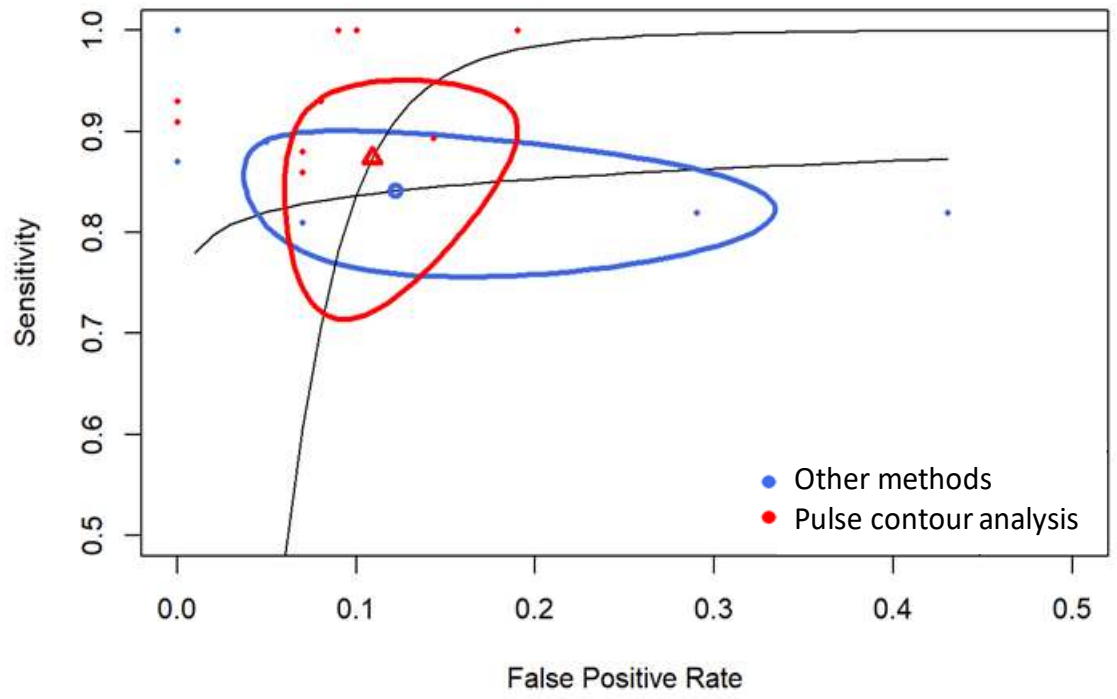


Panel A – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for Tidal volume ≤7 mL/kg is 0.96 [0.92 - 0.97] and for Tidal volume >7 mL/kg is 0.89 [0.82-0.95].
Bootstrap p-value for difference in separate AUC estimates is 0.44.

	Log OR	p value	95% LB	95% UB
Sens	-0.015	0.982	-1.321	1.29
FPR	0.463	0.339	-0.486	1.412

Panel B – Metaregression. Tidal volume adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.
The p-value for the Likelihood ratio test considering the Metaregression model in comparison with a model without covariate is 0.68.

Supplemental S5.2 – Metaregression analysis on hemodynamic monitoring (pulse contour analysis vs other methods)



Panel C – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for pulse contour analysis is 0.93 [0.91-0.95] and for other monitoring methods is 0.87 [0.82-0.96].

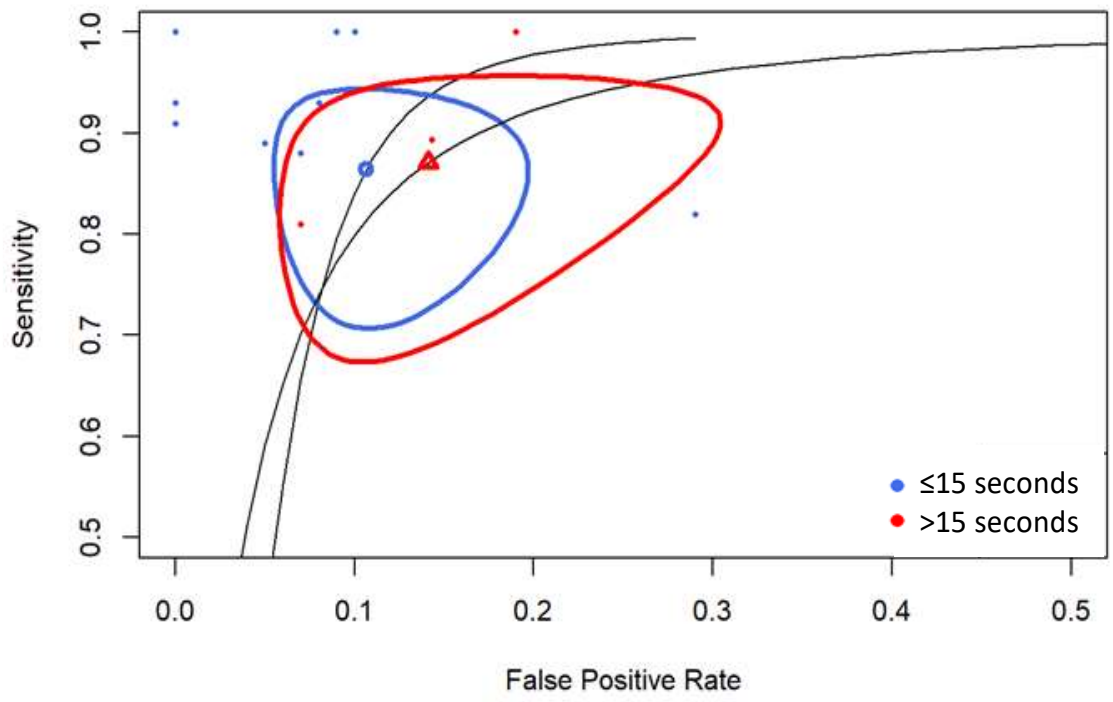
Bootstrap p-value for difference in separate AUC estimates is 0.62.

	Log OR	p value	95% LB	95% UB
Sens	0.08	0.852	-0.851	1.03
FPR	-0.401	0.41	-1.355	0.552

Panel D – Metaregression. Hemodynamic monitoring adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.

The p-value for the Likelihood ratio test considering the Metaregression model in comparison with model without covariate is 0.683.

Supplemental S5.3 – Metaregression analysis on EEXPO duration (≤15 seconds *vs.* >15 seconds)



Panel E – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for EEXPO ≤15 seconds is 0.93 [0.90-0.96] and for EEXPO > 15 seconds is 0.93 [0.88-0.95].

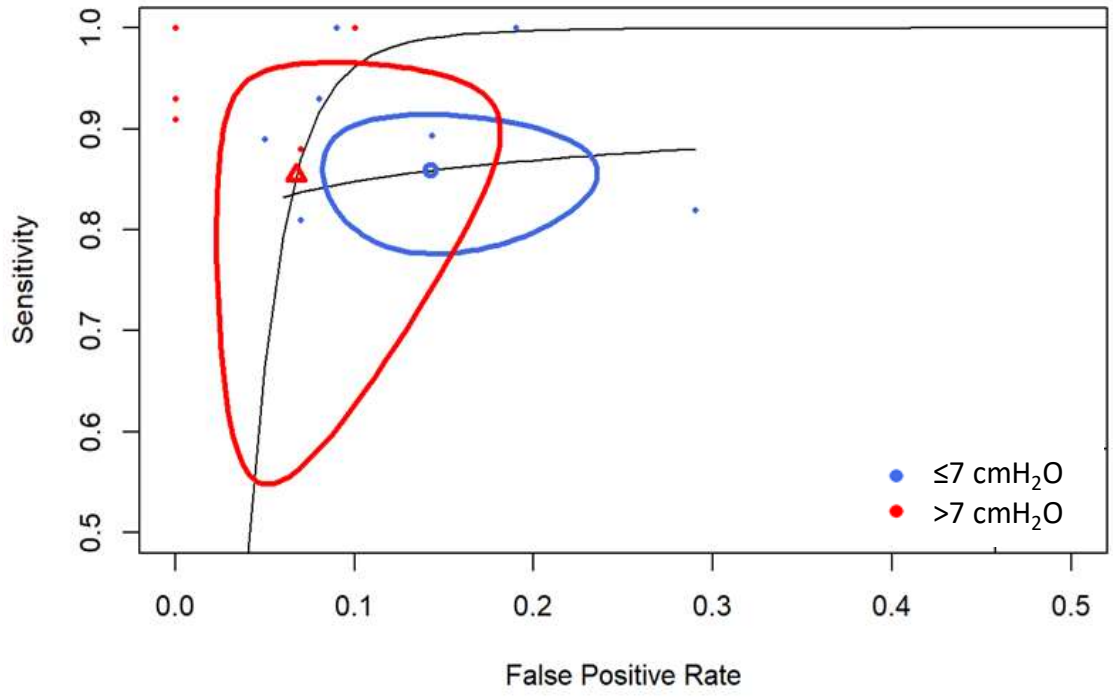
Bootstrap p-value for difference in separate AUC estimates is 0.2.

	Log OR	p value	95% LB	95% UB
Sens	0.203	0.792	-1.305	1.712
FPR	0.328	0.493	-0.611	1.268

Panel F – Metaregression. EEXPO duration adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.

The p-value for the Likelihood ratio test considering the Metaregression model in comparison with model without covariate is 0.786.

Supplemental S5.4 – Metaregression analysis on PEEP level (≤7 *vs.* >7 cmH_2O)



Panel G – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for PEEP values ≤7 cmH_2O is 0.89 [0.83-0.95] and 0.95 [0.92-0.97] for PEEP values >7 cmH_2O.

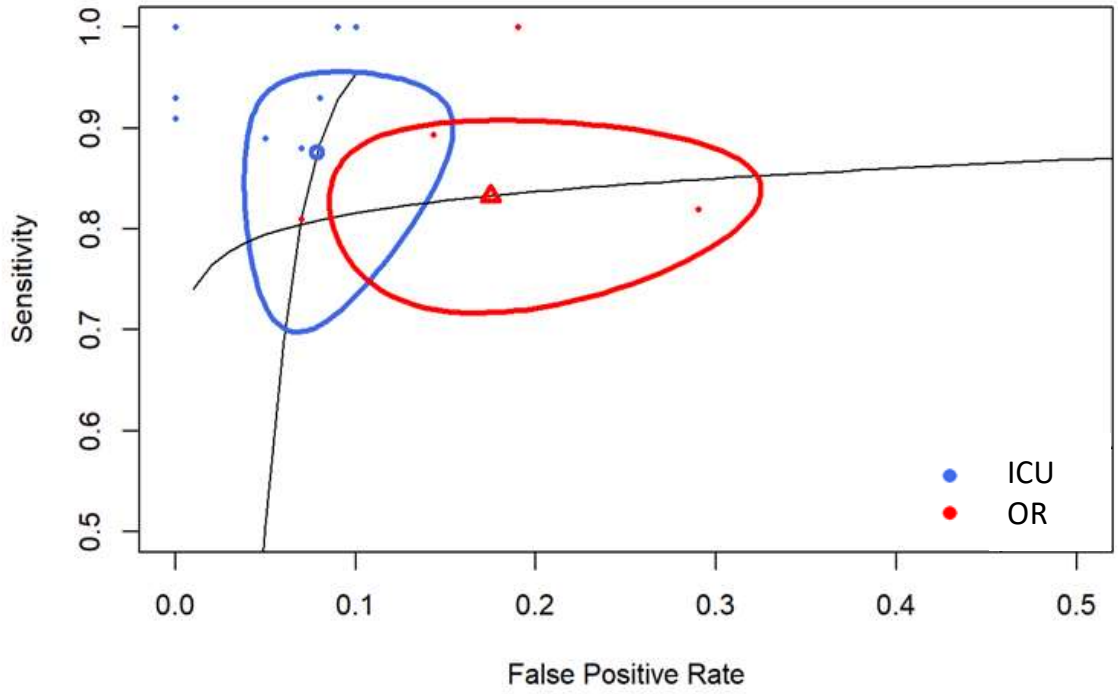
Bootstrap p-value for difference in separate AUC estimates is 0.386.

	Log OR	p value	95% LB	95% UB
Sens	-0.418	0.52	-1.691	0.855
FPR	-0.783	0.11	-1.743	0.177

Panel H – Metaregression. PEEP level adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.

The p-value for the Likelihood ratio test considering the Metaregression model in comparison with model without covariate is 0.683.

Supplemental S5.5 – Metaregression analysis on EEXPO setting (OR *vs*. ICU)

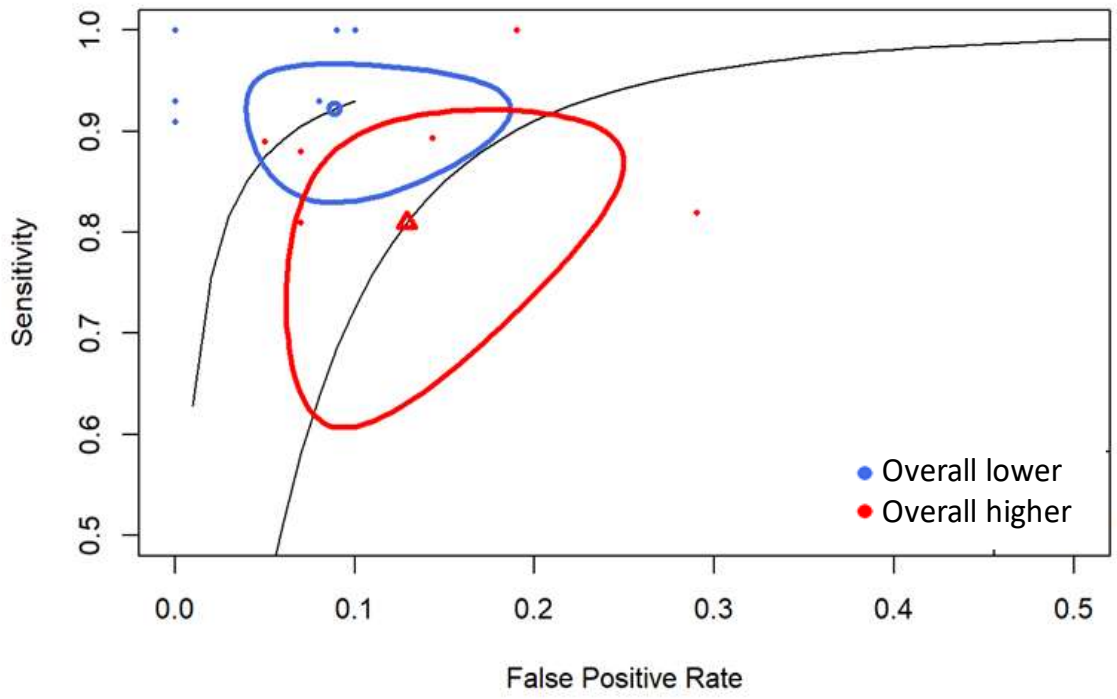


Panel I – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for ICU setting is 0.95 [0.93-0.96] and 0.86 [0.82-0.93] for OR setting.
Bootstrap p-value for difference in separate AUC estimates is 0.66.

	Log OR	P value	95% LB	95% UB
Sens	-0.085	0.903	-1.446	1.276
FPR	0.908	0.036	0.058	1.757

Panel B – Metaregression. Setting adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.
The p-value for the Likelihood ratio test, considering the Metaregression model in comparison with a model without covariate, is 0.09.

Supplemental S5.6 – Metaregression analysis on Risk of Bias (Overall lower *vs.* Overall higher)



Panel J – Bivariate Model AUC estimate and SROC curve for the Reitsma et al. (2005) model. Separate model Estimated AUC for overall lower risk of bias is 0.96 [0.92-0.97] and is 0.91 [0.83-0.95] for overall higher risk of bias.

Bootstrap P-Value for difference in separate AUC estimates is 0.45.

	Log OR	p value	95% LB	95% UB
Sens	-1.167	0.051	-2.339	0.005
FPR	0.514	0.281	-0.419	1.446

Panel K – Metaregression. Risk of bias adjusted bivariate model. Log OR covariate effects on sensitivity and FPR (1-specificity) have been reported with 95% CI.

The p-value for the Likelihood ratio test considering the Metaregression model in comparison with model without covariate is 0.049.

Supplemental S6 – Publication bias

	Coefficient	Standard error	t	p > t	95% Lower CI	95% Upper CI
Biais	2.45027	13.93579	0.18	0.864	-28.22195	33.123
Intercept	3.774129	2.137803	1.77	0.105	-.0931142	8.479401

CI : confidence interval.