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Ciclo XXVII

Hemodynamic evaluation of ICU patients undergoing partial ventilatory assistance: role of asynchrony.

Settore Scientifico Disciplinare: Anestesiologia (MED41)

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PHYSIOLOGICAL BACKGROUND

Introduction

Volume expansion is a frequently used therapy in critically ill patients with acute circulatory failure. The expected haemodynamic benefit of volume expansion is an increase in left ventricle (LV) LV stroke volume, and hence in cardiac output. The relationship described by Frank and Starling between preload and stroke volume is not linear, but rather is curvilinear (Fig. 1)[1, 2]. Thus, an increase in preload will induce a significant increase in stroke volume only if the ventricle operates on the ascending portion of the relationship (condition of ventricular preload dependence). In contrast, if the ventricle operates on the flat portion of the curve, a similar increase in preload will not induce any significant change in stroke volume (condition of preload independence). Therefore, a patient is a 'responder' to volume expansion only if both ventricles operate on the ascending portion of the Frank–Starling curve (biventricular preload dependence). In contrast, if one of the ventricle or both ventricles operate on the flat portion of the curves, then the patient is a 'non-responder' (ie his/her cardiac output will not increase significantly in response to volume expansion)[3].

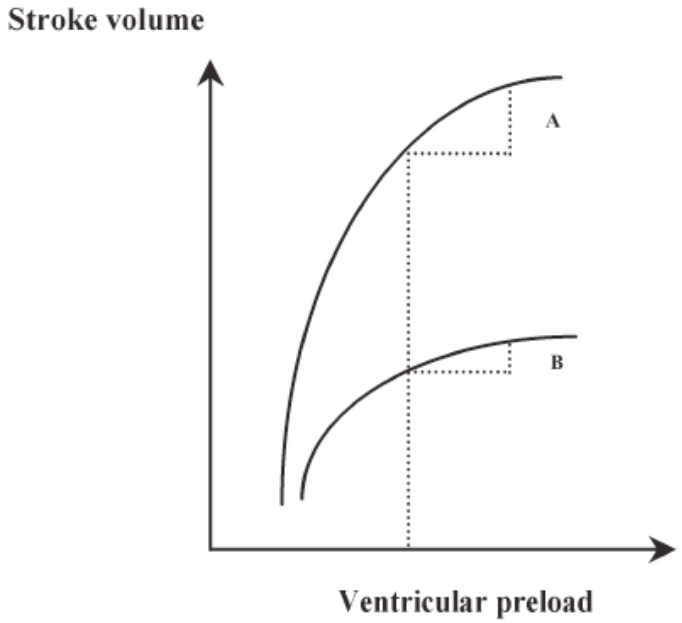

Figura 1. Schematic representation of Frank–Starling relationships between ventricular preload and stroke volume in a normal heart (A) and in a failing heart (B). A given value of preload can be associated with preload dependence in a normal heart or with preload independence in a failing heart.

In normal physiological conditions, both ventricles operate on the ascending portion of the Frank–Starling curve. This mechanism provides a functional reserve (preload reserve) to the heart in situations of acute stress. In normal individuals, increase in preload was reported to result in a significant change in stroke volume. In contrast, analysis of the literature indicates that, in patients with acute circulatory failure, the mean rate of responders to volume expansion is only around 50% [3]. This finding emphasizes the need for predictive factors of volume expansion efficacy in order to select patients who could benefit from volume expansion and to avoid ineffective or even deleterious fluid therapy (worsening of pulmonary oedema, haemodilution, etc) in 'nonresponder' patients, in whom inotropic and/or vasopressor support should preferentially be used[3].

How to predict fluid responsiveness in critically ill patients?

In many patients with acute circulatory failure, a positive response to fluid therapy can be observed despite the lack of clinical and biological indicators of hypovolaemia. Therefore, bedside indicators of right ventricle (RV) or LV preload are usually used when deciding whether to give fluid.

A recent postal survey performed in Germany showed that central venous pressure and pulmonary artery occlusion pressure are used, respectively, by 93 and 58% of intensive care unit physicians in the decision-making process regarding volume expansion[4]. However, many clinical studies have emphasized the poor value of right atrial pressure and pulmonary artery occlusion pressure in predicting volume expansion efficacy. Indeed, in most studies, the mean baseline value of right atrial pressure and of pulmonary artery occlusion pressure was not significantly different between responders and non- responders to volume expansion[4].

Even when a significant difference was reported, a marked overlap of individual baseline values was observed, so that no threshold value could help to discriminate responder and non-responder patients. Other bedside indicators of preload, such as the RV end-diastolic volume (evaluated by thermodilution) and the LV end-diastolic area (measured by echocardiography) have also been tested as predictors of fluid responsiveness. Unfortunately, these parameters were not found to be able to differentiate accurately between responder and non-responder patients before fluid infusion was given.

All of these findings may be explained as follows. The right atrial and pulmonary artery occlusion pressures do not always reflect transmural pressures in patients with external or intrinsic positive end-expiratory pressure (PEEP). Pulmonary artery occlusion pressure is not always a good indicator of LV preload, in particular in patients with a decreased LV compliance. Measurement of RV end-diastolic volume by thermodilution is influenced by tricuspid regurgitation, which is frequently encountered in critically ill patients with pulmonary hypertension. LV end-diastolic area is not always a good indicator of the LV end-diastolic volume, and hence of the LV preload. RV dilatation may offset any beneficial haemodynamic effect of volume expansion, even in case of a low LV preload. Finally, the preload-induced changes in stroke volume depend also on contractility and afterload. For example, a given

value of preload can be associated with preload dependence in normal hearts or with preload independence in failing hearts (Fig. 1). Therefore, assessment of preload is of poor value in predicting fluid responsiveness in critically ill patients[4].

Respiratory changes in LV stroke volume in mechanically ventilated patients

In mechanically ventilated patients, the magnitude of the respiratory changes in LV stroke volume can be used to assess fluid responsiveness. Intermittent positive-pressure ventilation induces cyclic changes in the loading conditions of right and left ventricles (Fig. 2). Mechanical insufflation decreases preload and increases afterload of the right ventricle[4]. The RV preload reduction is due to the decrease in the venous return pressure gradient that is related to the inspiratory increase in pleural pressure. The increase in RV afterload is related to the inspiratory increase in transpulmonary pressure (alveolar minus pleural pressure)[4]. The reduction in RV preload and the increase in RV afterload both lead to a decrease in RV stroke volume, which is therefore at its minimum at the end of the inspiratory period. The inspiratory impairment in venous return is assumed to be the main mechanism of the inspiratory reduction in RV ejection[1, 2].

The inspiratory reduction in RV ejection leads to a decrease in LV filling after a phase lag of two to three heart beats because of the long blood pulmonary transit time. Thus, the LV preload reduction may induce a decrease in LV stroke volume, which is at its minimum during the expiratory period. Two other mechanisms may also occur: mechanical insufflation may induce a squeezing of blood out of alveolar vessels, and thus transiently increase LV preload; and the inspiratory increase in pleural pressure may decrease LV afterload and thus facilitate LV ejection (Fig. 2)[4]. The first mechanism in hypervolaemic conditions and the second mechanism in case of LV systolic dysfunction may induce a slight increase in LV stroke volume during the inspiratory period. However, experimental data suggest that these two mechanisms are only minor determinants of the respiratory changes in LV stroke volume, even in the cases of hypervolaemia and LV dysfunction[4].

In summary, intermittent positive-pressure ventilation induces cyclic changes in LV stroke volume (maximum during the inspiratory period and minimum during the expiratory

period), which are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in RV filling and ejection (Fig. 2)[1, 2].

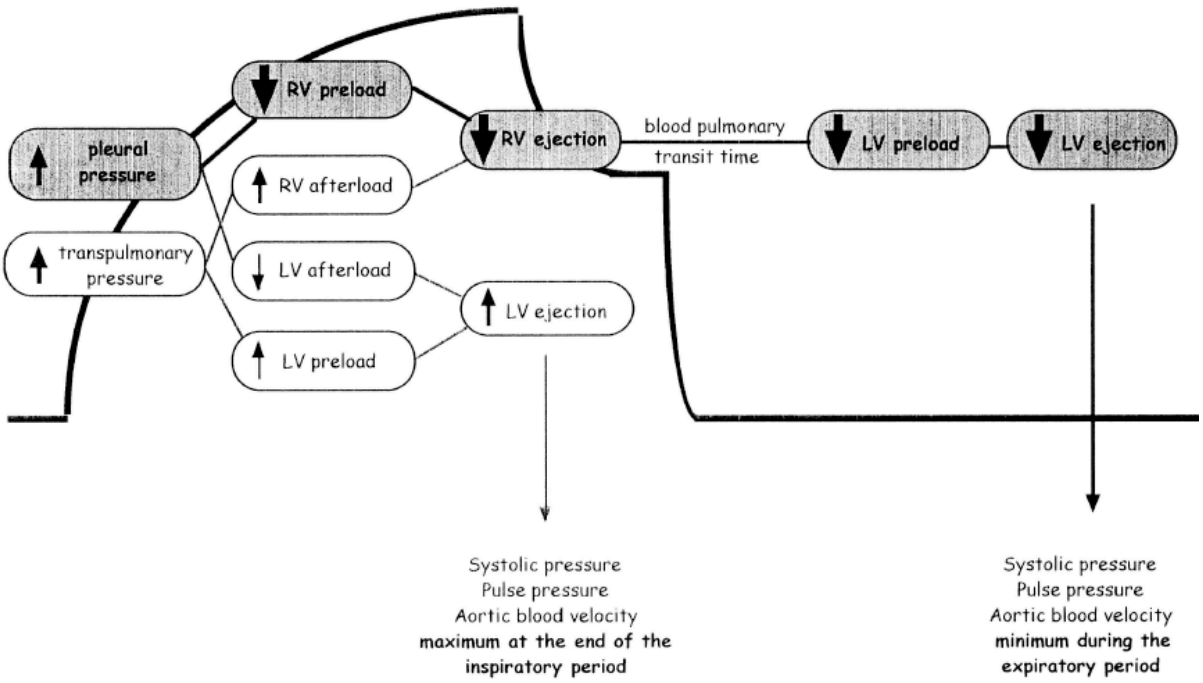

Figura 2. Haemodynamic effects of mechanical insufflation. The LV stroke volume is maximum at the end of the inspiratory period and minimum two to three heart beats later (ie during the expiratory period). The cyclic changes in LV stroke volume are mainly related to the expiratory decrease in LV preload due to the inspiratory decrease in RV filling and output.

Interestingly, the cyclic changes in RV preload induced by mechanical ventilation should result in greater cyclic changes in RV stroke volume when the right ventricle operates on the steep rather than on the flat portion of the Frank–Starling curve. The cyclic changes in RV stroke volume, and hence in LV preload, should also result in greater cyclic changes in LV stroke volume when the left ventricle operates on the ascending portion of the Frank–Starling curve. Thus, the magnitude of the respiratory changes in LV stroke volume should be an indicator of biventricular preload dependence.

Respiratory changes in systolic pressure

Because LV stroke volume is a major determinant of systolic arterial pressure, analysis of respiratory changes in systolic pressure has been proposed to assess the respiratory changes in LV stroke volume during mechanical ventilation. The respiratory changes in systolic pressure can be analyzed by calculating the difference between the maximal and the minimal value of systolic pressure over a single respiratory cycle (Fig. 3). This difference was called 'systolic pressure variation' (SPV) and was divided into two components (Δup and Δdown). These two components are calculated using a reference systolic pressure, which is the systolic pressure measured during an end-expiratory pause[3].

Δup is the difference between the maximal value of systolic pressure over a single respiratory cycle and the reference systolic pressure. It reflects the inspiratory increase in systolic pressure, which results either from increase in LV stroke volume related to the increase in LV preload (squeezing of blood out of alveolar vessels) or a decrease in LV afterload, or both; or an increase in extramural aortic pressure related to the rise in pleural pressure[3].

Δdown is the difference between the reference systolic pressure and the minimal value of systolic pressure over a single respiratory cycle. It reflects the expiratory decrease in LV preload and stroke volume related to the inspiratory decrease in RV stroke volume (see above)[3]. In normo or hypovolaemic conditions, Δdown is the main component of SPV and haemorrhage increases SPV and Δdown. The amount of blood loss is closely correlated with SPV and Δdown and volume expansion decreases SPV and Δdown. Finally, LV dysfunction and hypervolaemia increase Δup, but decrease Δdown and SPV such that, in this setting, SPV is minimal and Δup is the main component of SPV[3].

In mechanically ventilated patients, haemorrhage has also been shown to increase SPV and Δdown, whereas volume expansion has been shown to decrease SPV and Δdown.

Δdown can be considered as an indicator of fluid responsiveness, because the higher Δdown before volume expansion, the greater the increase in cardiac index in response to fluid infusion. However, the respiratory changes in systolic pressure result from changes in transmural pressure (mainly related to changes in LV stroke volume) and also from changes in

extramural pressure (ie from changes in pleural pressure).

Therefore, respiratory changes in systolic pressure may be observed despite no variation in LV stroke volume. In this regard, has been demonstrated that changes in systolic pressure may reflect changes in airway pressure and pleural pressure better than they reflect concomitant changes in LV haemodynamics [3].

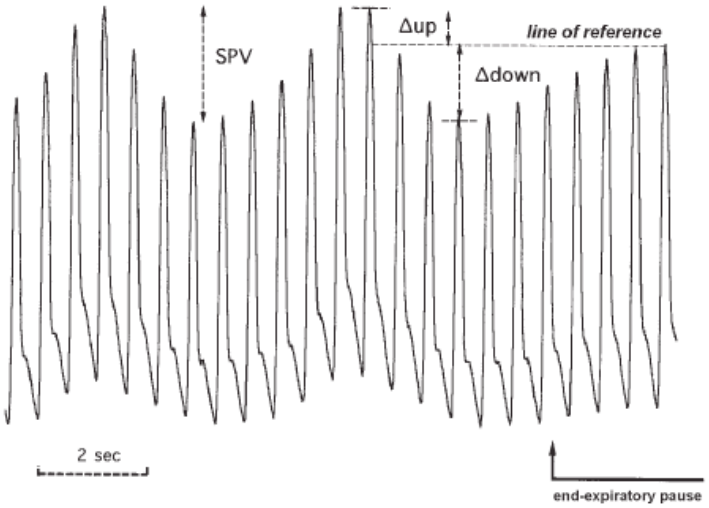

Figura 3. Respiratory changes in systolic pressure in a mechanically ventilated patient. The difference between the maximal and minimal value of systolic pressure over a single respiratory cycle is called SPV (for Systolic Pressure Variation). The reference systolic pressure is measured during an end-expiratory pause (line of reference) and SPV is divided in two components: Δup and Δdown. Dup is the difference between the maximal and the reference systolic pressure. Δdown is the difference between the reference and the minimal systolic pressure.

Respiratory changes in pulse pressure

The pulse pressure (defined as the difference between the systolic and the diastolic pressure) is directly proportional to LV stroke volume and inversely related to arterial compliance[1, 2]. The pulse pressure is not directly influenced by the cyclic changes in pleural pressure, because the increase in pleural pressure induced by mechanical insufflation affect

both diastolic and systolic pressures. In this regard, the respiratory changes in LV stroke volume have been shown to be reflected by changes in peripheral pulse pressure during the respiratory cycle. There- fore, it was recently proposed that fluid responsiveness may be assessed by calculating the respiratory changes in pulse pressure (ΔPP) as follows:

$$\Delta PP\ (\%) = 100 \times \frac{(PPmax - PPmin)}{(PPmax + PPmin)/2}$$

where PPmax and PPmin are the maximal and minimal values of pulse pressure over a single respiratory cycle, respectively (Fig. 5).

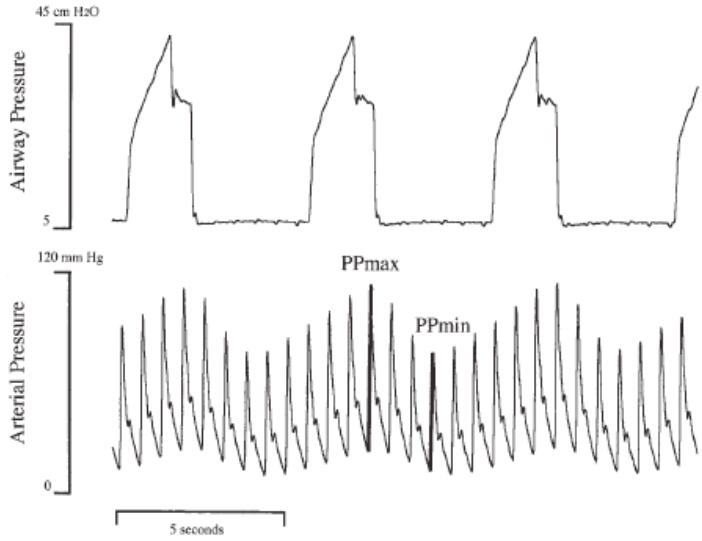

Figura 4. Respiratory changes in airway and arterial pressures in a mechanically ventilated patient. The pulse pressure (systolic minus diastolic pressure) is maximal (PPmax) at the end of the inspiratory period and minimal (PPmin) three heart beats later (ie during the expiratory period). The respiratory changes in pulse pressure (DPP) are calculated as the difference between PPmax and PPmin, divided by the mean of the two values, and expressed as a percentage.

In 40 patients with acute circulatory failure related to sepsis, Michard et al demontrated

the following. First, ΔPP accurately predicted the haemodynamic effects of volume expansion; a threshold value of 13% allowed dis- crimination between responder (defined as patients who experienced an increase in cardiac index ≥15% in response to volume expansion) and nonresponder patients with a sensitivity and a specificity of 94 and 96%, respectively. Second, the baseline value of ΔPP was closely correlated with the percentage increase in cardiac index in response to volume expansion; the higher ΔPP was before volume expansion, the greater the increase in cardiac index (Fig. 6). Third, ΔPP was a more reliable indicator of fluid responsiveness than were the respiratory changes in systolic pressure. Finally, the decrease in ΔPP induced by volume expansion was correlated with the increase in cardiac index, such that changes in ΔPP could be used to assess the haemodynamic effects of volume expansion[3].

In summary, calculation of ΔPP may be of particular help in the decision-making process regarding whether to institute volume expansion. Indeed, if ΔPP is low (<13%), then a beneficial haemodynamic effect of volume expansion is very unlikely, and inotropes or vasoactives drugs should be pro- posed in order to improve haemodynamics. In contrast, if ΔPP is high (>13%), then a significant increase in cardiac index in response to fluid infusion is very likely. However, the decision regarding whether to institute volume expansion must take into account the risk of fluid therapy (worsening in gas exchange), and a decrease in the mean airway pressure (ie a decrease in tidal volume or in PEEP) is an alternative therapeutic approach in this instance[3].

Interestingly, the assessment of cardiac preload dependence is not only useful in predicting volume expansion efficacy, but also in predicting the haemodynamic effects of any therapy that induces changes in cardiac preload conditions. In this regard, ΔPP has been shown to be useful in monitoring the haemodynamic effects of PEEP in mechanically ventilated patients with acute lung injury. Indeed, the decrease in mean cardiac output induced by PEEP and the decrease in RV stroke volume induced by mechanical insufflation share the same mechanisms (ie the negative effects of increased pleural pressure on RV filling and of increased transpulmonary pressure on RV afterload). Thus, the magnitude of the expiratory decrease in LV stroke volume would correlate with the PEEP- induced decrease in mean cardiac output.

In 14 mechanically ventilated patients with acute lung injury the following was

demonstrated. First, ΔPP on zero end-expiratory pressure (ZEEP) was closely correlated with the PEEP-induced decrease in cardiac index; the higher ΔPP was on ZEEP, the greater the decrease in cardiac index when PEEP was applied (Fig. 7). Also, the increase in ΔPP induced by PEEP was correlated with the decrease in cardiac index, such that changes in ΔPP from ZEEP to PEEP could be used to assess the haemodynamic effects of PEEP without the need for a pulmonary artery catheter. Finally, when cardiac index decreased with PEEP, volume expansion induced an increase in cardiac index that was proportional to ΔPP before fluid infusion[5].

It is likely that analysis of the respiratory changes in LV stroke volume could also be useful to monitor the haemodynamic effects of ultrafiltration during dialysis or of any change in ventilatory parameters.

Limitations of PPV

Analysis of the respiratory changes in arterial pressure is not possible in patients with cardiac arrythmias. Moreover, these parameters have been validated in sedated and mechanically ventilated patients. Therefore, whether the respiratory changes in LV stroke volume predict fluid responsiveness in non sedated and in spontaneously breathing patients remains to be evaluated[6].

The respiratory changes in LV stroke volume might also result from a decrease in LV afterload caused by the inspiratory increase in pleural pressure.

Thus, the respiratory changes in LV stroke volume could theoretically be an indicator of afterload dependence, rather than of preload dependence, for example in patients with congestive heart failure. In fact, it is unlikely that the inspiratory increase in LV stroke volume can be responsible for large variations in LV stroke volume and hence in arterial pressure, even in the case of LV dysfunction. In animals, induction of an experimental cardiac dysfunction was showed to result in a decrease rather than an increase in systolic pressure variation[6].

Because the pulse pressure depends not only on stroke volume, but also on arterial compliance, large changes in pulse pressure could theoretically be observed despite small changes in LV stroke volume if arterial compliance is low (elderly patients with peripheral

vascular disease). Similarly, small changes in pulse pressure could be observed despite large changes in LV stroke volume if arterial compliance is high (young patients without any vascular disease). In fact, a close relationship between baseline ΔPP and the changes in cardiac index induced by volume expansion was observed in a series of patients with a large range of ages and comorbidities, suggesting that the arterial compliance poorly affected the relationship between respiratory changes in LV stroke volume and ΔPP[6].

Spontaneous respiratory movements can affect ΔPP through different pathways. First, respiratory changes in alveolar and pleural pressure are lower during spontaneous breaths than during mechanically assisted breaths. However, this factor may only account for patients breathing spontaneously through a face mask. Patients ventilated with pressure support ventilation experienced a range of driving pressures similar to those observed in other studies. Second, active expiratory movements, which can occur both during spontaneous breathing and during mechanical ventilation, can alter the cyclic changes in alveolar pressure[6].

The active expiratory contraction of abdominal muscles flushes blood from the abdominal compartment into the thorax, increasing the right ventricular preload and later the LV preload. Active expiration also induces a decrease in left ventricular afterload. This may counterbalance the cyclic modifications induced by the passive changes in intrathoracic pressure occurring in mechanically ventilated patients without spontaneous breathing movements. These changes may result in both false negative and false positive tests. Third, the respiratory rate may be higher in patients with spontaneous respiratory movements, so that the number of cardiac beats per respiratory cycle may be reduced, and hence the chance to detect respiratory variations in stroke volume. Finally, patients under less sedation may also experience variations in cardiac output independently of their preload status[6].

They may be more sensitive to various stimuli (such as pain, noise, anxiety, or dyspnea), resulting in transient increases in oxygen consumption and consequently in cardiac output. This could have happened at any time during the evaluation of the response to VE, affecting its interpretation.

Role of asynchrony

As previous explained, mechanical ventilation induces cyclic changes in intrathoracic and transpulmonary pressures [7-9] that transiently affect venous return and consequently right and left ventricular stroke volume (SV) in those patients who are preload-dependent [1, 2]. PPV was shown to predict fluid responsiveness in patients receiving controlled mechanical ventilation (CMV), the diagnostic threshold being between 11 and 13% [4, 10], in particular for tidal volume (V_T) ≥ 8 ml/kg [11]. In patients receiving partial ventilatory assistance [6, 12], however, PPV was shown to be an unreliable predictor of volume responsiveness [13]. This poor prediction of volume responsiveness has been attributed to multiple causes such as the preload increase induced by the negative intrathoracic pressure swing during the patient's inspiratory effort [14], the occurrence of expiratory muscle activity flushing blood from the abdominal compartment into the thorax [6], and the characteristics of the breathing pattern, sometimes characterized by high respiratory rate (RR) and low and/or variable V_T [6, 14].

A poor patient-ventilator interaction determines asynchronies, which have been recently reported to be more frequent than previously considered [15-19], reaching up to 25% of the total number of breaths in patients ventilated for more than 24 hours [15], and are predominantly due to the occurrence of ineffective efforts (IEs) [15-17]. IEs determine negative intrathoracic pressure swings with no change in lung volume that may potentially weaken the correlation between PPV and volume responsiveness.

Early discontinuation of CMV in favour of forms of partial support is nowadays a cornerstone of the management of ICU patients [20]. In particular, pressure support ventilation (PSV) is increasingly used, particularly during the weaning process [21]. Only few studies investigated the efficacy of PPV during partial support in general and PSV in particular. In a heterogeneous subgroup of 19 patients receiving partial ventilatory assistance (5 in PSV and 14 in assist/control), Monnet et al found that sensitivity and specificity of PPV ≥ 12% were 75% and 46%, respectively [12]. Heenen et al. [6] found a poor correlation between PPV and fluid responsiveness (AUC = 0.64 ± 0.26) in a subgroup of 9 patients undergoing PSV. Therefore, while PPV is the best available dynamic index in CMV [4], its performance in actively breathing patients becomes quite poor [14], which increases the risk of inappropriate fluid therapy and

potentially affects the outcome of the weaning process.

We therefore designed a clinical study is to investigate the influence of patient-ventilator asynchrony on PPV ability to predict fluid responsiveness in ICU patients undergoing PSV.

Role of echocardiography in the evaluation of hemodynamically unstable ICU patients.

Critical care ultrasonography, including general ultrasonography and echocardiography, is routinely used in intensive care units of many hospitals worldwide, where it is often regarded as a first-line diagnostic tool. Although the usefulness of ultrasound in the ICU environment is widely acknowledged, physicians who want to become proficient in ultrasound techniques often struggle to obtain adequate training. One of the difficulties is that teaching of these techniques has not yet been incorporated into the formal training curriculum of intensive care medicine, and to date only a few countries have developed specific programs for this purpose. Recently, a comprehensive list of competencies required by intensive care physicians using ultrasonography has been formulated and published in a competence statement emanating from two critical care societies [22]. These competences cover the fields of abdominal, pleural, lung, and vascular ultrasound (general critical care ultrasonography, GCCUS) as well as cardiac examination (critical care echocardiography, CCE). CCE was divided into ‘‘basic’’ and ‘‘advanced’’ levels of knowledge[22].

Determining Cardiac Output (CO) is helpful to manage critically ill patients with severely impaired hemodynamics and discriminate between low (cardiogenic or non-cardiogenic) and high CO shock, in order to adopt the proper treatment. Many different techniques are currently available in Intensive Care Unit (ICU) to determine CO [23, 24]. Accuracy and reproducibility, invasiveness and related risks, ease of use, time expenditure, and costs of the different techniques and influence their choice, which is generally consequent to considering and balancing different aspects such as clinical severity and underlying disorders.

Right heart catheterization through the pulmonary artery catheter [25] is considered a cornerstone of CO estimation [26] and a guiding treatment in severely unstable patients requiring cardiovascular support [27, 28]. Its extensive application, however, did not prove to

effectively reduce mortality in a general population of ICU patients [23, 29-33]. Furthermore, although the rate of PAC side effects and complications is relatively low [34], the invasiveness of this technique limit its use. As a matter of fact, the use of PAC is nowadays overall declining and advised only for the most complex and severe [23, 35, 36]. Several alternative techniques have been proposed in recent years to determine CO in critically ill patients [37-39], but in some instances they are not free of invasiveness and are frequently more expensive [39, 40]. In addition, the clinical utility of these devices in either ascertaining the determinants of hemodynamic instability and establishing a prompt and effective treatment has never been demonstrated [34]. A spot evaluation of CO in patients with acute cardiovascular failure in ICU or in the Emergency setting may be sufficient in several instances to differentiate between low and high CO states and facilitate proper inotropic or vasopressive treatment.

More than 25 years ago, a fast and accurate method based on transthoracic echocardiography (TTE) was validated, when performed by experienced cardiologists, which allows non-invasively estimation of CO (CO_{TTE}) in clinically stable patients with chronic heart failure [41-45]. Surprisingly, however, to our knowledge no previous study evaluated the possibility to use this technique in the acute setting. We therefore designed a clinical study, involving a part of our ICU equip, to compare CO_{TTE} performed by non-cardiologist ICU physicians with a relatively brief training in TTE, with CO measured using the PAC (CO_{PAC}), in ICU patients with shock requiring inotropic or vasopressive drugs and receiving mechanical ventilation.

PATIENT-VENTILATOR ASYNCHRONY AFFECTS PULSE PRESSURE VARIATION PREDICTION OF FLUID RESPONSIVENESS DURING PRESSURE SUPPORT.

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Name of Department and Institution: The present study was performed in the ICU of the A.O.U. Maggiore della Carità, Corso Giuseppe Mazzini, 18, 28100 Novara (NO) – ITALY.

SUBMITTED to ANESTHESIA AND ANALGESIA. UNDER REVISION.

Introduction

Preload assessment fails to estimate fluid responsiveness in about one-half of Intensive Care Unit (ICU) patients [13, 14]. Predicting fluid responsiveness avoids unnecessary or even harmful volume expansion in patients for whom inotropic agents and/or vasopressors are indicated. Static indexes, such as central venous pressure and pulmonary artery occluded pressure, are poor predictors of fluid responsiveness [13, 46, 47]. Dynamic indexes have been shown to better predict the response to fluid loading in patients under controlled mechanical ventilation (CMV)[48], which induces cyclic changes in intrathoracic and alveolar pressure [7-9]. This affects, in patients who are preload-dependent, venous return and right ventricular afterload, influencing both pre-load and stroke volume of the left ventricle [1, 2]. Pulse pressure variation (PPV) is a dynamic index shown to predict fluid responsiveness in patients under CMV with tidal volume (V_T) ≥ 8 ml/kg [4, 11].

In patients with spontaneous breathing activity, PPV is unreliable in predicting volume responsiveness [6, 13, 14], because the inspiratory decrease in intrathoracic pressure increases to a variable extent venous return and right ventricular stroke volume, making the variations in pulse pressure no longer univocally related to the volemic status. During partial ventilatory assistance, the intrathoracic pressure is decreased by the spontaneous inspiratory effort and increased by the ventilator insufflation.

When the respiratory drive is low, consequent to a combination of factors including high support and sedation, the patient exerts a minimal effort just sufficient to trigger the ventilator and then relax. In this condition, the effect of the spontaneous effort on venous return should be minimal and, if the respiratory drive is constant, stable in rhythm and magnitude. An altered respiratory drive, however, worsens patient-ventilator interaction and causes asynchronies, recently recognized to be more frequent than previously considered [15-18, 49] _ENREF_14

The most common form of asynchrony are first the ineffective triggering (IT), a negative intrathoracic pressure swings with no change in lung volume, and then double-triggering, two consecutive ventilator insufflations separated by a very short expiratory time, and auto-

triggering, mechanical assistance unrelated to patient's effort [15-17]. We hypothesize that, although through different mechanisms, these asynchronies affect the cyclical changes in intrathoracic pressure, resulting in unpredictable and persistent variations of right ventricular preload and left ventricular stroke volume, altering the reliability of PPV in assessing fluid responsiveness. We therefore designed this study 1) to evaluate in patients receiving partial ventilatory support the effect of asynchronies on PPV ability to predict fluid responsiveness, and 2) to assess their influence on PPV reliability, compared to other respiratory variables, such as V_T and respiratory rate, insofar considered the most influential.

Methods

Patients

The study was performed in the ICU of the University Hospital "Maggiore della Carità" in Novara, in accordance with the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study. Patient informed consent was written and obtained according to the Italian regulations. Patients were enrolled from September 2012 to June 2013.

All patients were ventilated in Pressure Support Ventilation (PSV) mode using last generation ICU ventilators displaying online flow, volume and airway pressure waveforms. Inclusion criteria were: 1) clinical indication to fluid challenge, as defined by the presence of at least one of the following: a) heart rate ≥ 100/min), b) systolic blood pressure ≤ 90 mmHg (or a decrease ≤ 50 mmHg in hypertensive patients), c) need for vasoactive drugs (dobutamine or dopamine ≥ 5 mcg/kg/min; epinephrine or norepinephrine irrespective of the dose), d) urine output ≤ 0.5 mL/kg/hr for 2 consecutive hours; 2) Positive End Expiratory Pressure (PEEP) ≥ 5 cmH_20 and ≤ 10 cmH_20 and inspiratory support level ≥ 10 and ≤ 15 cmH_20, 3) stable ventilatory pattern. Exclusion criteria were: 1) age < 18 years, 2) New York Heart Association (NYHA) class III or IV, 3) severe valvular diseases, 4) any cardiac arrhythmias, 5) moderate to severe ARDS [50], 6) need for haemodialysis or continuous hemofiltration, 6) inclusion in other research protocols, 7) consent denied.

Two experienced ICU physicians of our group (DC and GC), previously involved in several studies evaluating patient-ventilatory asynchrony, independently and blindly assessed the occurrence of IT, double-triggering and auto-triggering, by visually inspecting ventilator waveforms during 3 consecutive minutes just before the fluid challenge. When the two examiners agreed that no asynchrony occurred, the patient was considered synchronous (Synch); when they both counted a number of asynchronies of at least 10% of the overall breaths the patient was considered asynchronous (Asynch) [15-17, 51]. When the asynchronous events were less than 10% of the overall breaths or there was no agreement between the two blinded examiners on the presence and extent of asynchronies, the patient was excluded.

We included an equal number of consecutive patients in two groups, Synch and

Asynch, whose demographic and clinical characteristics at enrolment are shown in Table 1.

Protocol

Sedation and analgesia were administered according to standard ICU protocols and included remifentanil, propofol and/or midazolam. The fluid challenge consisted in the infusion of 500 mL of saline over a 10-minute period [12]. Patients who showed an increase in cardiac index (CI) ≥ 15% after fluid infusion were considered responders [10]. Ventilator settings, vasoactive and sedative infusions were kept constant throughout the study period. The physician who infused the fluids and performed the hemodynamic measurements was blinded to ~~AI~~ the assessment of asynchronous events. Hemodynamic measurements were obtained with the patient lying supine through arterial waveform analysis by PRAM® (pressure recording analytical method; MOSTCARE system; Vygon Health, Padua, Italy) through a catheter introduced within either the femoral or the radial artery. PRAM® provided beat-by-beat systolic, diastolic and mean arterial pressure, heart rate, and calculates CI and PPV [52-54]. All these values are automatically averaged over a 30-second period, as recommended by the manufacturer. The hemodynamic data recorded by PRAM® were transferred on a data card and then exported into a spreadsheet through dedicated software (MOSTCARE Data Card Reader® 4.0.11). Hemodynamic measurements were determined and averaged over one minute before (baseline) and immediately after fluid challenge.

Statistical analysis

Based on a previously reported value of the area under the curve (AUC) of 0.64 in patients undergoing PSV [6], we calculated that enrolling 27 patients for each of the two groups would allow detecting an increase in AUC up to 0.85, *a priori* considered clinically relevant, with type 1 and 2 errors of 0.05 and 0.20, respectively. Data are expressed as mean ± standard deviation or median (25–75% interquartile range) according to distribution. To ascertain differences between baseline Synch and Asynch data, independent sample t-test or Mann-Whitney U test were used, as indicated. To detect differences between hemodynamic variables before and after fluid challenge we used the paired t-test or Wilcoxon test, as indicated. We determined the overall Receiver Operator Characteristic (ROC) and compared

AUC (5-95% confidence interval) for Synch and Asynch groups. Post-hoc ROC analysis with backward logistic regression was performed to assess whether PPV prediction of fluid responsiveness was affected by occurrence of asynchronies, V_T (cut-off 8 ml/kg)[11], RR (cut-off 14 breaths/min)[55].

A 2x2 contingency table was used to ascertain the percentage of correct classification ([true positive + true negative] / total number of patients) for a V_T cut-off of 8 ml/kg, both in Synch and Asynch groups of patients. The patients with PPV ≥ 13% [5] and CI increase ≥ 15% [10] were considered true positive, while those with PPV < 13% and CI increase < 15% true negative.

For all comparisons, p values < 0.05 were considered significant.

Results

Demographic and other baseline characteristics were similar in the two groups of patients (Table 1). In the Asynch group, IT was the most common form of asynchrony (81.5%), while the rates of double-triggering and auto-triggering were 11% and 7.5%, respectively. The hemodynamic response to the fluid challenge is presented in Table 2 for responders and non-responders. Overall, 23 patients (42.5%) resulted to be fluid responders, 9 in the Synch group and 14 in the Asynch group ($p = 0.27$).

Figure 1 displays ROCs for PPV in the overall population (solid line), Synch (dotted line), and Asynch (dashed line). The AUCs were 0.71 (IC 0.57 – 0.83) for the overall population, 0.86 (IC 0.68 – 0.96) and 0.53 (IC 0.33 – 0.73) for Synch and Asynch, respectively ($p = 0.018$). The best cut-off based on ROC curve analysis was 10% for Synch (sensitivity 89% and specificity 72%) and 11% for Asynch (sensitivity 36% and specificity 38%). When considering PPV ≥ 13%, which is the PPV threshold utilized during CMV [10], sensitivity was 78% in the Synch group and 36% in the Asynch group, and specificity 89% and 46% respectively.

Worth remarking, regardless of the occurrence of asynchrony, the AUCs for $V_T \geq 8$ ml/Kg (0.78 [IC 0.53 – 0.94]) and < 8 ml/Kg (0.65 [IC 0.47 – 0.80]), and for RR ≤ 14 breaths/min (0.82 [IC 0.67 – 0.94]) and > 14 breaths/min (0.62 [IC 0.42 – 0.79]) were not significantly different ($p = 0.40$ and $p = 0.16$ for V_T and RR, respectively). In addition, backward logistic regression showed that the variable presence/absence of asynchrony was the only parameter affecting PPV efficacy in predicting fluid responsiveness [$p < 0.005$; OR 7.3 (1.8 – 29.0)].

In the Synch group, the rate of correct classification was 100% for the 12 patients (9 non-responders and 3 responders) with $V_T \geq 8$ ml/Kg and 73% for the 15 patients with $V_T < 8$ ml/Kg. Ten patients in the Asynch group also had a $V_T \geq 8$ ml/Kg, but the rate of correct classification was lower than 50% regardless of V_T.

Discussion

Our study shows that patient-ventilator asynchrony is one of the factors affecting PPV ability to predict fluid responsiveness during partial ventilatory support.

In the Synch group the best sensitivity (89%) was reached when the PPV was ≥10%, while the highest specificity (89%) was achieved when PPV was ≥ 13%. The cut-off values for partitioning between responders and non-responders may vary and a higher sensitivity or specificity may be preferred depending on the clinical scenario [11]. The rate of fluid responders in our population was 42.5%, a value similar to the one reported in previous studies [10, 56], but lower than the average 50% [3, 14], which can be explained by the fact that some of our patients had previously received fluid resuscitation for hemodynamic instability.

PPV is a valuable dynamic index during CMV under certain conditions [4, 11, 55, 57], but it performs poorly in actively breathing patients [14]. This greatly limits its clinical use because early discontinuation of CMV in favour of forms of partial support is nowadays a cornerstone of the management of ICU patients [20] and PSV is increasingly used, particularly during the weaning process [21]. It has been recently shown by a multicenter point-prevalence study that PPV can be properly used to evaluate fluid responsiveness only in a small fraction of ICU patients who satisfy all the validity criteria for this index [58]. In this study, of 121 rhythmic patients undergoing invasive mechanical ventilation 77 were excluded *a priori* because of partial ventilatory support with spontaneous breathing activity [58]. Only two small studies, however, provide some information on PPV performance during partial ventilatory assistance in general and PSV in particular. In a subgroup of 19 patients receiving partial ventilatory assistance, 5 in PSV and 14 in assist/control (A/C), Monnet et al found that sensitivity and specificity of PPV ≥ 12% were 75% and 46%, respectively [22]. Heenen et al. observed a poor correlation between PPV and fluid responsiveness in a subgroup of 9 patients undergoing PSV [6].

Consistent with these previous studies [6, 12], the AUC of our overall population was much lower than that reported in patients undergoing CMV [4]. This discrepant PPV behaviour between forms of partial support, i.e., PSV and A/C, and CMV has been attributed to either the characteristics of the breathing pattern and the respiratory muscles activity [11, 14]. No study has

so far assessed the effects of patient-ventilator asynchrony on PPV ability to predict fluid responsiveness. IT is the most common asynchrony during both A/C [15, 18] and PSV [15-17, 49], as also observed in the present study. IT occurs when patient's inspiration is not followed by ventilator assistance, and may be then considered as an inspiratory effort against a quasi-occluded airway. By determining a negative swing in intrathoracic pressure associated with little or no V_T, ITs would determine an irregular and variable increase in venous return and right ventricular filling that may hamper left ventricular filling, which in the end reduces pulse pressure and affects PPV [1, 59].

Our study has potential clinical implications. When patient's breathing frequency and ventilator rate of cycling are matched, PPV performance results to be highly improved. As shown in figure 2, consistent with the findings of previous studies evaluating PPV during CMV [4], the rate of correct classification reached 100% for the 12 patients (9 non-responders and 3 responders) with $V_T \geq 8$ ml/Kg, while it resulted to be only 73% for the 15 patients with $V_T < 8$ ml/Kg, making prudent and advisable to assess fluid responsiveness with the use of other manoeuvres, such as passive leg raising, shown to be effective in predicting fluid responsiveness in ICU patients with spontaneous breathing activity[12]. In alternative, it might be reasonable to increase for a brief period the support level to reach a $V_T \geq 8$ ml without causing new-onset asynchrony. When patient-ventilator asynchronies occur, other manoeuvres, such as passive leg raising, are necessary to decide whether or not infuse fluids (Figure 2).

Our study has some limitations deserving discussion. First, we neither measured esophageal pressure, nor assessed caval vein collapsibility to ascertain the relative contribution of spontaneous inspiratory effort and ventilator assistance on intrathoracic pressure and venous return. Second, because the sole visual inspection of flow and airway pressure waveforms may lead to underestimating the rate of asynchrony during PSV [16], we cannot exclude that unrecognized asynchronies occurred, leading to improper inclusion of some patients in the Synch group. Considering that IT would affect right ventricular filling in consequence of the modification of the intrathoracic pressure, it is reasonable to consider minimal or even absent the hemodynamic effect of unrecognized ITs that determine scanty variations of expiratory flow and airway pressure [16]. Third, although cardiac output assessment

by PRAM® and by thermodilution were shown to have a good agreement in ICU septic patients receiving vasopressors [60], the value of PRAM® in estimating cardiac output has been questioned in a study comparing this device with transthoracic ecocardiography [61], which reports percents of error and concordance both exceeding the limits of precision proposed by Critcheley et al [62]. In another study not including PRAM®, however, no device under evaluation passed the tresholds proposed by Critcheley et al [38]. Important, the percent of error actually does not influence the ability of a device to trace a trend [63], as it is the case for the changes in cardiac output determined by the fluid challenge in the present study.

Conclusions

In patients receiving partial ventilatory assistance in PSV, patient-ventilator asynchrony significantly affects PPV prediction of fluid responsiveness. PPV performance is very high in synchronous patients with $V_T \geq 8$ ml/kg. If confirmed by larger clinical studies, these findings have the potential to expand the rate of ICU patients for whom this dynamic index could be utilized to guide fluid resuscitation.

Tables

Table 1. Patients characteristics at enrolment.

	Synch (n =27)	Asynch (n =27)
General characteristics		
AGE (yr)	60 ± 16	63 ± 16
Gender (M/F)	17/10	15/12
Body mass index (Kg/m^2)	26 ± 3.4	26 ± 6.0
SAPS II	52 ± 10	49 ± 10
pH	7.40 ± 0.06	7.38 ± 0.08
Temperature (C^0)	37.0 ± 0.6	37.1 ± 0.5
RASS score	-3.3 ± 0.9	-2.7 ± 1.3
Hemodynamics		
CI ($L/min/m^2$)	2.9 ± 1.0	2.9 ± 0.9
MAP (mmHg)	68 ± 15	71 ± 12
HR (breaths/min)	93 ± 18	91 ± 20
PPV (%)	14.4 ± 11.9	13.6 ± 7.7
Lactates (mM/L)	1.7 ± 1.1	1.6 ± 1.1
Ventilator settings		
PEEP (cmH_20)	5.9 ± 1.1	5.6 ± 1.1
Pressure Support (cmH_20)	10.8 ± 1.3	10.7 ± 1.7
V_T (mL/Kg ideal body weight)	7.5 ± 1.6	7.3 ± 1.9
PaO_2/FiO_2 (ratio)	294 ± 70	253 ± 60
RR (breaths/min)	13.5 ± 3.0	15.8 ± 6.0
HR/RR ratio	7.3 ± 2.5	6.5 ± 3.4
Vasoactive agents. n; (µg Kg^{-1} min^{-1})		
Norepinephrine	13; (0.17 ± 0.1)	15; (0.23 ± 0.1)
Dopamine	7; (6.8 ± 1.0)	10; (5.7 ± 2.0)
Epinephrine	1; (0.07 ± 0.0)	1; (0.05 ± 0.0)
Dobutamine	5; (5.7 ± 3.5)	0; (0)
Acute circulatory failure origin. n; (%)		
Sepsis / Septic Shock	12 (44)	10 (37)
Postoperative	7 (26)	9 (33)
Trauma	3 (11)	3 (11)
Cardiogenic	3 (11)	2 (7.5)
Haemorrhagic	1 (4)	2 (7.5)
Subarachnoid haemorrhage	1 (4)	1 (4)

Data are expressed as mean ± standard deviation, unless otherwise specified.

n, number of patients; SAPS, simplified acute physiology score; RASS, Richmond Agitation Sedation Scale; CI, cardiac index; MAP, mean arterial pressure; HR, heart rate; PPV, pulse pressure variation; PEEP, positive end expiratory pressure; V_T Tidal Volume; PaO_2/FiO_2, arterial

partial pressure of oxygen/fraction of inspired oxygen, RR, respiratory rate.

Table 2. Hemodynamic effects of the fluid challenge in responders (CI ≥15%) and non-responders.

	Pre-fluid challenge	Post-fluid challenge	p value
CI (L/min/ m^{-2})			
Responders	2.63 ± 0.83	3.39 ± 1.01	<0.001
Non-responders	3.17 ± 0.95	3.16 ± 0.92	0.88
SVI (mL/ m^{-2})			
Responders	29.0 ± 13.1	37.8 ± 15.3	<0.001
Non-responders	37.3 ± 16.0	37.5 ± 16.4	0.22
PPV (%)			
Responders	18.6 ± 12.2	11.2 ± 8.0	<0.01
Non-responders	10.6 ± 6.0	9.2 ± 6.6	0.28
MAP (mmHg)			
Responders	71.8 ± 12.0	78.8 ± 12.1	< 0.001
Non-responders	68.1± 14.4	71.4 ± 14.3	< 0.001
HR (beats/min)			
Responders	96 ± 13	95 ± 15	0.31
Non-responders	88 ± 21	88 ± 19	0.50
CVP (mmHg)			
Responders	9.4 ± 2.9	9.6 ± 3.2	0.74
Non-responders	10.0 ± 3.9	11.5 ± 4.5	<0.05

Data are expressed as means ± standard deviation. Responders, n = 23, non-responders, n =31. CI, cardiac index; SVI, stroke volume index; PPV, pulse pressure variation; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure.

FIGURES

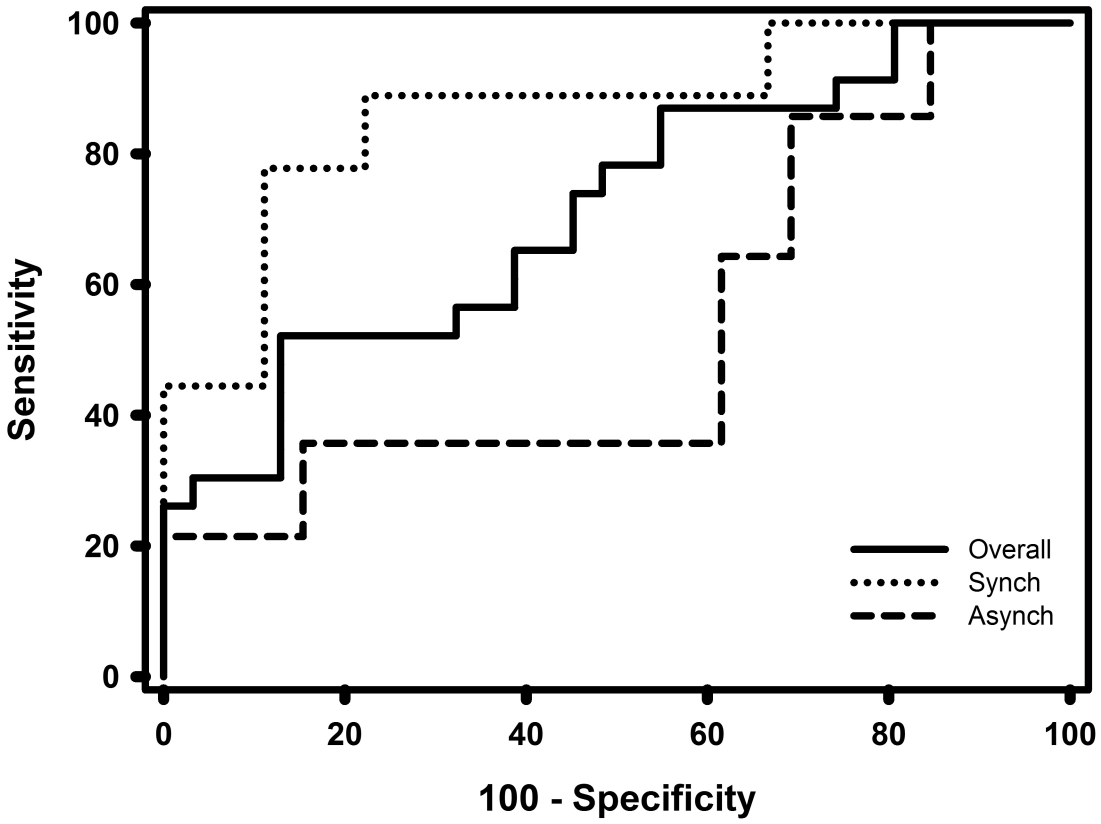

Figure 1. Receiving Operator Curve (ROC) of the groups of synchronous (n=27) and asynchronous (n=27) patients, and of the overall population (n=54).

Receiving Operator Curves comparing Pulse Pressure Variation ability to discriminate fluid responders (CI increase ≥ 15%) and non-responders of synchronous (dotted line) and asynchronous (dashed line) patients, and of the overall population (solid line).

Synch: group of patients with no asynchrony; Asynch: group of patients with asynchronies exceeding 10% of the total breaths.

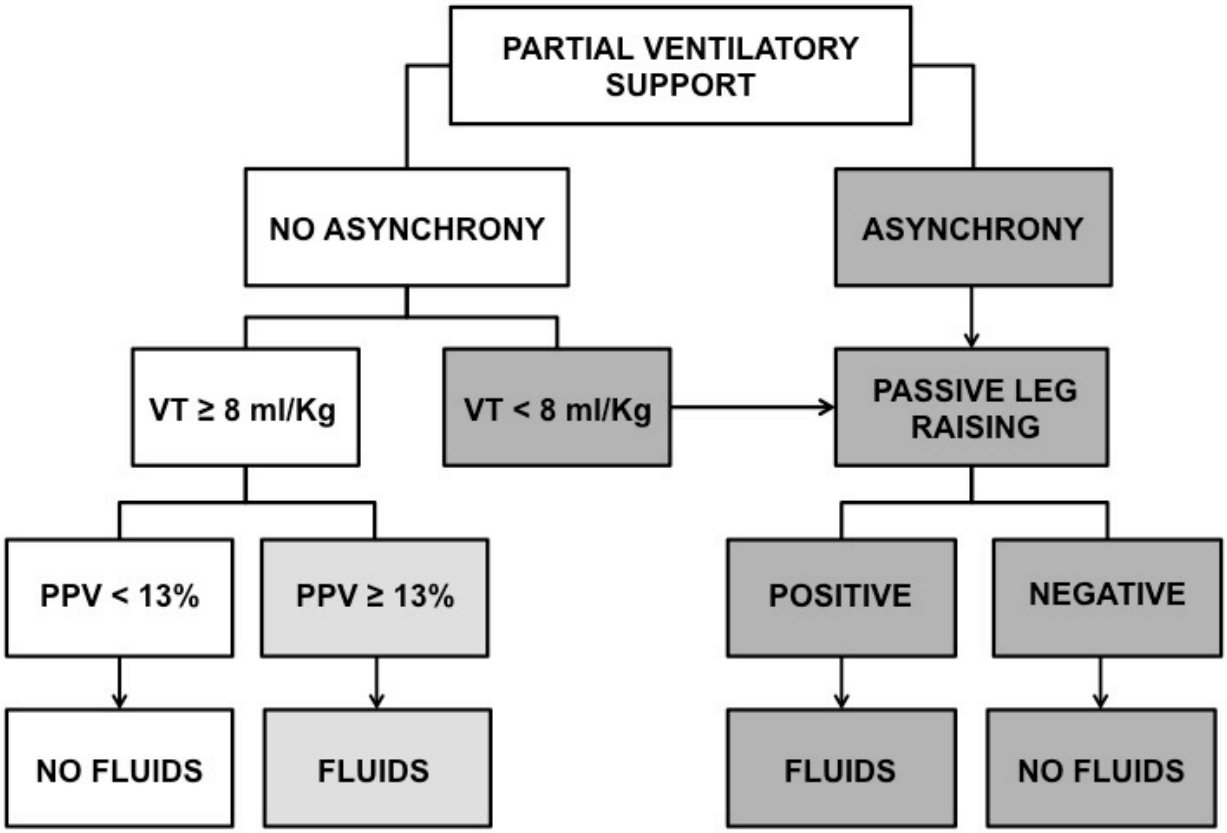

Figure 2. Algorithm for fluid resuscitation during partial ventilatory support.

Based on the rate of correct classification, an algorithm is proposed for the management of fluid resuscitation in patients receiving partial ventilatory support. Conditions where PPV is inadequate to predict of fluid responsiveness and other manoeuvres, such as passive leg raising, are indicated are labelled in medium grey. On the opposite, the white labels characterize the conditions in which PPV can be utilized to predict fluid responsiveness. Light grey indicates 100% correct classification, but in a very small sample of patients. See text for further details.

V_T, tidal volume; PPV, pulse pressure variation.

Trans-thoracic echocardiographic assessment of cardiac output in mechanically ventilated critically ill patients by ICU physicians.

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Introduction

Assessment of Cardiac Output (CO) may help managing patients with impaired hemodynamics in the Emergency and Intensive Care Unit (ICU) and facilitating prompt and proper treatment. Right heart catheterization through the pulmonary artery catheter[25] is considered a cornerstone of CO estimation[26] and a guiding treatment in severely unstable patients requiring cardiovascular support[27, 28]. Its extensive application, however, did not prove to effectively reduce mortality in a general population of ICU patients[23, 29, 30, 32]. Furthermore, although the rate of PAC side effects and complications is relatively low[34], the invasiveness of this technique limits its use. As a matter of fact, the use of PAC is nowadays overall declining and advised only for the most complex and severe cases[23, 35, 36]. Recent years have seen the increased availability of less-invasive devices providing, in association with other hemodynamic variables, surrogate CO estimates[37-39]. Invasiveness, complexity, technical limitations and costs of these devices, however, have never been weighted against the clinical benefit, and indications and proper timing of application remain unclear[30]. The use of transthoracic echocardiography[36] or measurement of CO has been recommended in patients with clinical evidence of left ventricular failure and persistent shock despite adequate fluid resuscitation[64].

TTE was proposed decades ago as a means to obtain a non-invasive snapshot determination of CO (CO_{TTE})[43]. When performed by TTE experienced cardiologists, CO_{TTE} showed, compared to CO assessed by PAC (CO_{PAC}), to provide a reliable CO estimation in clinically stable patients with chronic heart failure[45]. Some case series published in the mid-nineties indicated the potentials of the echocardiographic technique also in critically ill patients[65, 66]. In spite of these positive initial reports, however, these investigations were neither followed by other studies nor by diffuse clinical application, likely because of the problematic attainment of immediate availability of TTE experienced cardiologists in the emergency and ICU settings[67]. Recent work, however, showed that emergency and ICU physicians can proficiently perform basic TTE examinations following a relatively brief training

in image acquisition and interpretation[67, 68], with the advantage of prompt TTE availability and possibility of repeated examinations in order to evaluate the response to therapeutic interventions[69].

Aim of this study is to evaluate feasibility, reproducibility and accuracy (compared to the gold standard CO_{PAC}) of CO_{TTE} assessed by two non-cardiologist intensivists, in mechanically ventilated critical patients.

Methods

The study was conducted between June 2011 and September 2011 in the 14-bed ICU of a University Hospital, in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for this study (Ethical Committee N° CE44/11) was provided by the Institutional ethics committee of the Maggiore della Carità University Hospital on 25 March 2011. We considered eligible any ICU patient ≥ 18 years with the PAC already in place for clinical purposes. Patients were excluded 1) *a priori*, because of a) arrhythmias or b) known moderate or severe aortic valve disease, or 2) during TTE assessment, for a) inadequate acoustic window, b) detection of unknown moderate or severe aortic valve disease, c) detection of unknown moderate or severe tricuspid valve regurgitation.

TTE was performed by two ICU physicians who received a basic training (TTE 3-hour course followed by 6-hour hands-on) by an ultrasound expert cardiologist, focused on standard echocardiographic views and identification of gross ventricular and valvular pathologic findings. Additionally, they underwent a specific training focused on continuous and pulsatile Doppler, and velocity-time integral (VTI) determination (5-hour course followed by 6-hour hands-on). Before the study was initiated, they both performed a minimum of 25 successfully tutored TTE evaluations, including VTI assessment. For each patient, CO_{PAC} was determined with a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) as the average of three consecutive thermodilution measurements (IntelliVue MX700, Philips, Netherlands) by the attending physician. Immediately after CO_{PAC} assessment, the two investigators, blinded to each other and to the CO_{PAC} values, sequentially performed TTE with the portable device in use in the ICU (MyLab 30 CV, Esaote, Italy), according to a predetermined random sequence. Both CO_{PAC} and CO_{TTE} were determined with the patient in supine or semi-recumbent position. CO_{TTE} was obtained through the left ventricular outflow tract (LVOT) method, according to the technique originally proposed by Dubin et al.[42]. Briefly, the LVOT was measured in systole from the parasternal long axis view just below the insertion of the

aortic cusps, and the area was then calculated according to the formula πr^2 (Figure 1a). Three measurements were averaged. The velocity of LVOT flow was measured by pulsed-wave Doppler from the apical 5-chamber view. The sample volume was positioned in the middle of the outflow tract immediately below the aortic cusps and the time velocity integrals, recorded over 5 consecutive cardiac cycles, were digitized using the leading edge convention (Figure 1b). CO was then automatically calculated, according to the formula *VTI x LVOT area x HR*, where VTI is velocity-time integral, LVOT is left ventricular outflow tract cross-sectional area, and HR indicates the average of the instantaneous heart rate of 5 consecutive cardiac cycles

We assessed both inter-observer agreement and correlation between TTE and PAC. The Pearson correlation was used to evaluate the agreement of the CO_{TTE} values obtained by the two operators for each patient. A correlation coefficient >0.8 with $p<0.05$ was considered to indicate adequate reproducibility. Moreover, Cohen's K was also calculated, as indicated when comparing the same measurement performed by two or more operators. We performed Bland and Altman analysis by plotting for each patient the difference between CO_{PAC} values and corresponding CO_{TTE} measurements (average of the determinations by the two ICU physicians)[70]. We further calculated the limits of agreement between the two techniques, as proposed by Critchley et al.[71]. According to the same authors, we assessed TTE agreement with the reference CO_{PAC} using the concordant correlation coefficient (ρ_c), which also allows determining accuracy, through the bias correction factor [60], and precision, through the Pearson correlation coefficient (ρ)[71].

Results

During the four-month study period, 25 patients of 289 admitted to the ICU, met the inclusion criteria. Of these 25 patients, two were excluded *a priori* (one for high ventricular rate atrial fibrillation and one for known severe aortic stenosis), while three (one with partial left pneumothorax following thoracic surgery and two with severe chronic obstructive pulmonary disease) because of inadequate acoustic window, as stated by both operators. Therefore, 20 patients (80%) were included in the analysis. All patients underwent volume-targeted controlled mechanical ventilation with positive end-expiratory pressure (PEEP) ranging between 5 and 20 cmH_2O, and received continuous sedative infusion. Inotropes and/or vasopressors were administered to all patients for treatment of hemodynamic instability associated with cardiogenic shock (5 patients), acute respiratory distress syndrome[72] (7 patients) and septic shock (8 patients) (Table 1).

Table 2 displays for each patient, from left to right, the individual CO_{TTE} determinations by each operator, the average of these two values, and the corresponding CO_{PAC} measurements. The r-value of the correlation between CO_{TTE} determinations by the two operators was 0.987 and the Cohen's K 0.840, indicating good inter-observer reproducibility.

Figure 2 depicts Bland and Altman plot of the differences between CO_{PAC} and CO_{TTE}, this latter being the average of the values obtained by the two operators. The predicted limit of agreement was 11%, definitely below the 30% threshold identified by Critchley et al. to define acceptable agreement[71]. The value of ρ_c was 0.994, also indicating excellent agreement between the two techniques, the mean difference being as small as 0.02 L/min. Accuracy [60] and precision (ρ) were 0.999 and 0.994, respectively.

Discussion

We found that in mechanically ventilated ICU patients CO_{TTE} 1) is feasible in the majority of patients, 2) has a high inter-observer reproducibility, and 3) quite accurately estimates CO, as compared to the gold standard CO_{PAC}.

The use of PAC is currently markedly reduced[23, 32, 34, 36]. Specific indications for PAC monitoring in ICU remain the diagnosis and treatment of acute right ventricular failure and pulmonary hypertension[35, 36], and weaning failure of cardiac origin[35]. PAC also remains indicated for ICU patients with severe heart failure, requiring inotropic, vasopressor, and/or vasodilator therapy[36]. Less complex ICU patients without any of the aforementioned indications for PAC monitoring, however, may experience hemodynamic instability. In these patients, a snapshot non-invasive CO assessment would be valuable to properly choose between fluids and inotropic or vasoactive agents.

TTE has gained ground in ICU and is nowadays considered a valuable tool to assess left ventricular function even when performed by intensivists with a relatively brief training[67, 73]; furthermore, some consider TTE first-line approach for initial assessment of hemodynamic failure in ICU[74]. In keeping with some case series published almost two decades ago reporting TTE to accurately estimate CO when performed by experienced cardiologists[65, 66], our results indicate that TTE offers the possibility to achieve satisfactory CO estimation in mechanically ventilated patients for whom the use of PAC or other forms of less-invasive monitoring is neither feasible or strictly indicated. Worth remarking, our results were obtained by intensivists after a relatively brief training, extending to mechanically ventilated ICU patients the findings of a previous study where CO_{TTE} was determined by two Emergency physicians, who had previously received a 20-hour training by an expert cardiac sonographer, in non-critical patients[73]. While in this prior study the CO_{TTE} values determined by the two Emergency physicians were compared with those obtained by two certified cardiac sonographers[73], in our study we compare CO_{TTE} directly with the gold standard CO_{PAC}.

Although an adequate training is considered essential for a successful TTE-based clinical decision making[69], there is little agreement on the number of cardiac ultrasound examinations to be performed by ICU physicians before achieving an appropriate training[69, 75]. A core curriculum and necessary training elements for ICU physicians have been proposed by Mazraeshahi et al.[76], who consider 10 to 20 successful interrogations adequate to achieve procedural competency on most of the aortic pathologies[76]. In the present study, the two ICU physicians involved received a specific training for LVOT and VTI determination including a minimum of 25 tutored successful evaluations. In keeping with previous work, our results indicate this quite limited specific training to be adequate to perform a limited-scope goal-directed TTE, such as quantitative CO determination[73].

Although CO_{TTE} determination has been successfully applied in non-ICU patients with chronic atrial fibrillation[45], we preferred to exclude patients with arrhythmias to avoid interference due to remarkable variations between consecutive systolic stroke volumes. We also excluded patients with aortic valvular diseases, which may impair the quantitative analysis of Doppler velocity consequent to changes in the spatial profile of blood flow instantaneous velocity. In addition to arrhythmias, making arduous obtaining a representative mean VTI, and aortic valve disease, hampering the quantitative analysis of Doppler velocity, the applicability of TTE to estimate CO in critical patients can be restricted by difficult achievement of adequate acoustic window, consequent to supine position, mechanical ventilation and lung and/or chest wall alterations. Notwithstanding these technical limitations, CO_{TTE} was feasible in the vast majority of our mechanically ventilated patients, as both observers were able to determine it in 80% of the patients. Remarkable, CO_{TTE} was feasible also in 5 patients with PEEP ≥15 cmH_2O. Our data confirm those of recent reports. In 55 ICU patients with shock receiving mechanical ventilation, Bergenzaun et al. obtained acceptable TTE images in more than 90% of the examinations[77]. Amiel et al. in 94 ICU patients, 63% of whom were mechanically ventilated, found left ventricle ejection fraction impossible to determine in 10 individuals only[78]. Dinh et al. were able to determine LVOT, VTI, and CO in 97 of 100 non-critically ill patients in an Emergency Department[73].

It may be argued that the importance of our study is limited by the relatively small number of patients. It should be considered, however, that for the purposes of our investigation a sample of 14 patients would be sufficient to obtain a correlation coefficient of 0.8 with a power of 0.95 and an alpha error of 0.05. Since we included in the data analysis 20 patients and obtained much higher r-values, the risk of type II error is very unlikely.

In addition, CO_{TTE} has intrinsic limitations, such as not allowing direct estimation of fluid responsiveness and need for repeated measures when the hemodynamic profile varies. Although for the purpose of the study we included only ICU patients with severely unstable hemodynamics requiring invasive monitoring, we believe TTE should not be considered for replacement of PAC or other forms of continuous monitoring in the most severe patients, but rather as a mean to extend CO assessment to hypotensive patient for whom hemodynamic monitoring is unfeasible, unavailable, not strictly indicated or temporarily contraindicated. Importantly, as hemodynamic monitoring does not guarantee *per se* improved outcomes unless part of an appropriate therapeutic plan, likewise CO_{TTE} should also be utilized within a specific scheme of treatment for hemodynamic instability[34].

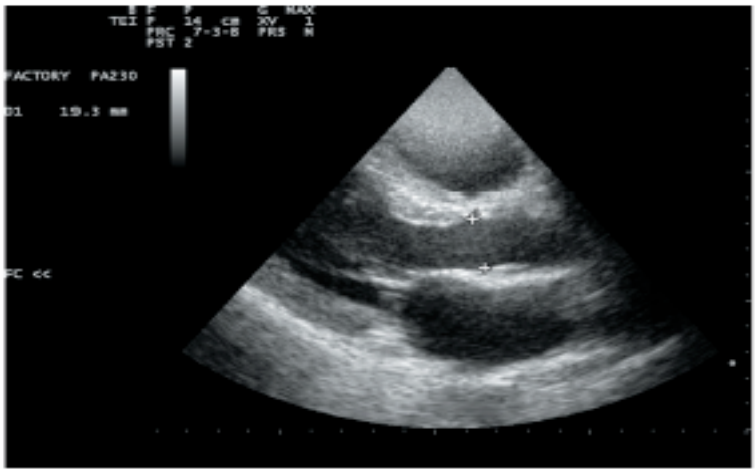
Conclusions

TTE performed by non- cardiologist ICU physicians allows a quick, reproducible, accurate, and inexpensive snapshot CO assessment in the majority of mechanically ventilated ICU patients.

Figures

Figure 1

a)



b)

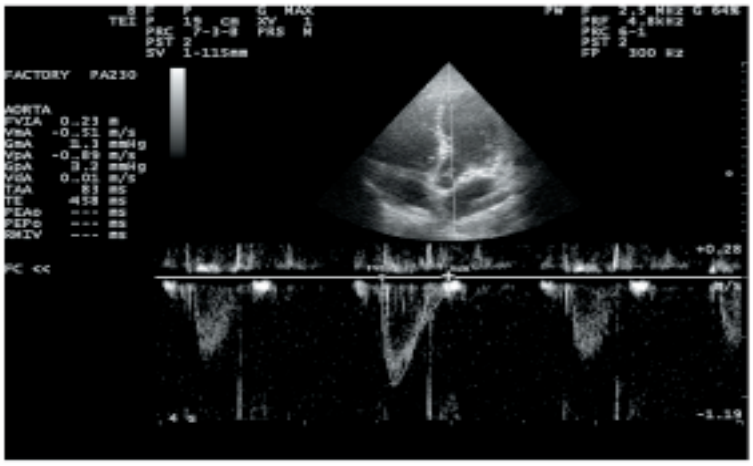


Figure 1. Echocardiographic measurements from one representative patient.

The figure shows: a) measurement of LVOT diameter at aortic valve cusps through a parasternal long-axis view and b) measurement of VTI using the apical 5-chamber view. LVOT, left ventricular outflow tract .VTI, velocity-time integral.

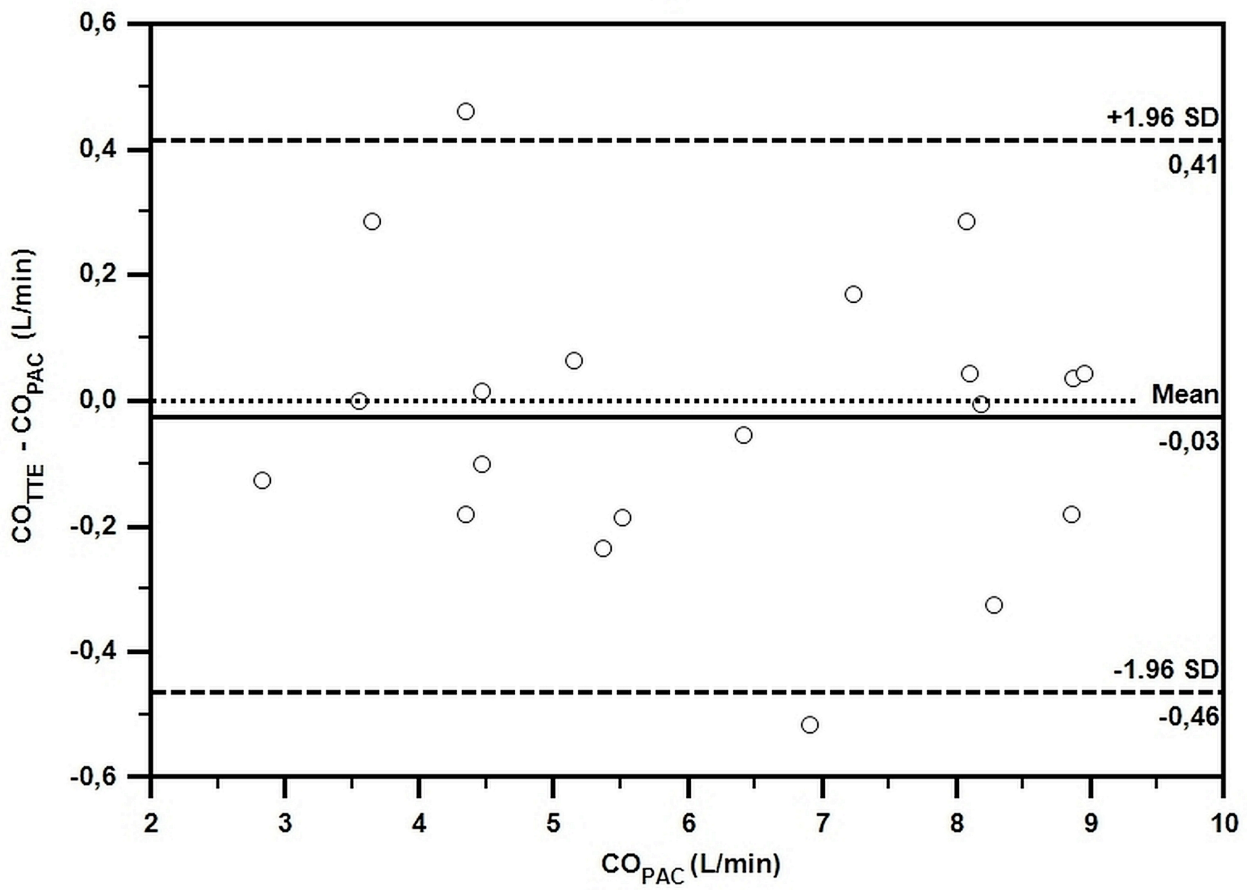


Figure 2. Bland and Altman plot of the differences between CO_{TTE} and CO_{PAC}.

CO_{TTE} values are obtained averaging the determinations of the two observers.

CO_{TTE}, Cardiac Output determined with Trans-thoracic Echocardiography. CO_{PAC}, Cardiac Output determined with the Pulmonary Artery Catheter. SD, Standard Deviation.

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