Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated patients

Philippe Vignon[1,2,3], Xavier Repessé*[4], Emmanuelle Bégot*[1,2], Julie Léger[5], Christophe Jacob[6], Koceila Bouferrache[7], Michel Slama[8], Gwenaël Prat[6], Antoine Vieillard-Baron[4,9,10]

*: these two authors participated equally in the study

Running title: Echocardiographic indices and fluid responsiveness

Affiliations:

[1]: Medical-surgical intensive care unit, Limoges University hospital, Limoges, France

[2]: INSERM CIC 1435, Limoges University hospital, Limoges, France

[3]: Faculty of Medicine, University of Limoges, Limoges, France

[4]: Assistance Publique-Hôpitaux de Paris, University hospital Ambroise Paré, intensive care unit, Boulogne-Billancourt, France

[5]: INSERM CIC 1415, Tours University hospital, Tours, France

[6]: Medical intensive care unit, Brest University hospital, Brest, France

[7]: Medical-surgical intensive care unit, Foch hospital, Paris, France

[8]: Medical intensive care unit, Amiens University hospital, Amiens, France

[9]: Faculty of Medicine Paris Ile-de-France Ouest, University of Versailles Saint-Quentin en Yvelines, Saint-Quentin en Yvelines, France

[10]: INSERM U-1018, CESP, Team 5, University of Versailles Saint-Quentin en Yvelines, Villejuif, France

At a glance commentary:

Scientific knowledge on the subject:

Initial validation studies which proposed echocardiographic dynamic parameters to predict fluid responsiveness have validated threshold values in small populations of septic shock patients. These indices of fluid responsiveness have not yet been compared in ventilated patients hemodynamically assessed using echocardiography for acute circulatory failure of whatever cause.

What this study adds to the field:

This study provides evidence that dynamic parameters can be obtained in most patients, but overall are of only moderate diagnostic accuracy in predicting fluid responsiveness in ventilated patients sustaining various types of shock. Respiratory variations of the maximal Doppler velocity in left ventricular outflow tract had the best sensitivity in predicting fluid responsiveness. Respiratory variations of superior vena cava diameter had the best specificity and were of greater diagnostic accuracy than variations of inferior vena cava diameter and pulse pressure, but transesophageal echocardiography is required for their measurement.

Authors' contributions: Philippe Vignon, Michel Slama, Gwenaël Prat, and Antoine Vieillard-Baron designed the study, enrolled patients, performed off-line measurements, participated in data analysis and in drafting the manuscript. Xavier Repessé, Emmanuelle Bégot, Christophe Jacob and Koceila Bouferrache actively participated in patient enrollment and in drafting the manuscript. Julie Léger performed data analysis and participated in drafting the manuscript.

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Address for correspondence: Pr Philippe Vignon, Réanimation Polyvalente, CHU Dupuytren, 2 Ave. Martin Luther King, 87042 Limoges Cedex, France.
Tel: (33) 5 55 05 62 40; Fax: (33) 5 55 05 62 44; E-mail: philippe.vignon@unilim.fr

Abstract

Rationale. Assessment of fluid responsiveness relies on dynamic echocardiographic parameters which have not yet been compared in large cohorts.

Objectives. To determine the diagnostic accuracy of dynamic parameters used to predict fluid responsiveness in ventilated patients with a circulatory failure of any cause.

Methods. In this multicenter prospective study, respiratory variations of superior vena cava diameter (ΔSVC) measured using transesophageal echocardiography, of inferior vena cava diameter (ΔIVC) measured using transthoracic echocardiography, of the maximal Doppler velocity in left ventricular outflow tract (ΔVmaxAo) measured using either approach, and pulse pressure variations (ΔPP) were recorded with the patient in the semi-recumbent position. In each patient, a passive leg raise was performed and an increase of aortic velocity time integral ≥ 10% defined fluid responsiveness.

Measurements and Main Results. Among 540 patients (379 men; age: 65±13 years; SAPSII: 59±18; SOFA: 10±3), 229 exhibited fluid responsiveness (42%). ΔPP, ΔVmaxAo, ΔSVC, and ΔIVC could be measured in 78.5%, 78.0%, 99.6%, and 78.1% of cases, respectively. ΔSVC ≥ 21%, ΔVmaxAo ≥ 10% and ΔIVC ≥ 8% had a sensitivity of 61% (95% confidence intervals: 57-66%), 79% (75-83%) and 55% (50-59%), respectively, and a specificity of 84% (81-87%), 64% (59-69%), and 70% (66-75%), respectively. The area under the Receiver Operating Characteristic curve of ΔSVC was significantly greater than that of ΔIVC (p=0.02) and ΔPP (p=0.01).

Conclusions. ΔVmaxAo had the best sensitivity and ΔSVC the best specificity in predicting fluid responsiveness. ΔSVC had a greater diagnostic accuracy than ΔIVC and ΔPP but its measurement requires transesophageal echocardiography.

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Key words: Fluid therapy, hemodynamic, echocardiography, Doppler ultrasonography

Introduction

Fluid management is a crucial component of acute care in intensive care unit (ICU) patients. Two recent studies emphasized the heterogeneity of practice and the uncommon use of hemodynamic monitoring to evaluate fluid requirements [1,2]. Optimal fluid resuscitation and targeted endpoints frequently remain elusive among front-line intensivists [3]. Prompt correction of symptomatic hypovolemia is intended to improve oxygen delivery to meet metabolic needs, while unnecessary fluid loading may be detrimental in ICU patients [4-7]. Although widely used and currently recommended to guide fluid resuscitation in septic shock patients [8], central venous pressure has major limitations in assessing fluid responsiveness [9,10]. Alternatively, dynamic parameters based on heart-lung interactions have been proposed to predict fluid responsiveness and to reduce unnecessary and potentially detrimental fluid loading [11]. With the spread of critical care echocardiography [12], several echocardiographic indices of fluid responsiveness have been proposed in mechanically ventilated patients [13]. Nevertheless, dynamic parameters used to predict fluid responsiveness, including pulse pressure variation (ΔPP), have numerous limitations which reduce their applicability on clinical grounds [14]. In addition, echocardiographic indices have been derived from fairly small study populations of highly selected septic patients, and have not been compared in a large cohort of consecutive patients with circulatory failure of various causes. Accordingly, we sought to determine the diagnostic accuracy of dynamic parameters in predicting fluid responsiveness in consecutive ventilated patients admitted to the ICU with circulatory failure of any cause. Some of the results of the current study have been reported previously in the form of an abstract [15].

Methods

This prospective, multicenter (4 university hospitals and 1 general hospital in France), descriptive study was approved by the Ethics Committee of Limoges, which waived the need for informed consent. All participating centers have expertise in critical care

echocardiography and use dynamic parameters of fluid responsiveness routinely on clinical grounds.

Patients. From November 2012 to November 2014, sedated patients under mechanical ventilation who required echocardiographic assessment for acute circulatory failure, with an inserted central venous catheter and arterial catheter, were eligible. All patients were perfectly adapted to the ventilator. Acute circulatory failure was defined as [16]: sustained hypotension (systolic blood pressure < 90 mmHg or mean blood pressure < 65 mmHg) and/or the presence of clinical signs of hypoperfusion (e.g., mottled skin, oliguria), metabolic acidosis (pH < 7.35 and base excess < - 5 mmol/L), elevated lactate (> 2 mmol/L) or decreased central venous oxygen saturation ($ScvO_2$ < 70%). Hypotension may not have been present if previously corrected by ongoing vasopressor infusion or in the presence of signs of tissue hypoperfusion at an early stage of compensated circulatory failure [16]. Exclusion criteria were: age < 18 years, pregnancy, amputation or severe lower limb ischemia, and contra-indication to transesophageal echocardiography (TEE) or to a passive leg raise (PLR) maneuver (e.g., elevated intracranial pressure, tamponade, acute aortic dissection).

In each patient, the Simplified Acute Physiological Score (SAPS) II, Sequential Organ Failure Assessment (SOFA), recent surgery, the presence of acute respiratory distress syndrome (ARDS) [17], the cause of circulatory failure [18], and vital status at ICU discharge were recorded. At the time of echocardiographic assessment, we recorded hemodynamic parameters including central venous pressure and ΔPP, respiratory parameters, bladder pressure used as a surrogate of intra-abdominal pressure, and ongoing therapy.

Echocardiography. Transthoracic echocardiography (TTE) and TEE were successively performed with the patient in the semi-recumbent position by experienced intensivists trained in advanced critical care echocardiography [19]. Since circulatory failure was frequently the reason for ICU admission, echocardiography was performed within the first 24 h of ICU stay in 78% of patients. To allow a safe introduction of the esophageal probe, neuromuscular blockade agents were routinely used in these unstable patients as a

standard of care. Each measurement was performed in triplicate and averaged. The following parameters of fluid responsiveness were obtained (supplementary Table E1): respiratory variations of the diameter of superior vena cava (ΔSVC) [20], respiratory variations of the diameter of inferior vena cava (ΔIVC) [21], and respiratory variations of the maximal Doppler velocity in left ventricular outflow tract (ΔVmaxAo) [22]. In addition, left ventricular ejection fraction determined using the monoplane Simpson's rule [23], left ventricular outflow tract velocity-time integral and diameter to calculate left ventricular stroke volume [24], right ventricular and left ventricular end-diastolic area ratio in the long axis view of the heart were measured at end-expiration. Acute cor pulmonale was defined as the conjunction of right ventricular dilatation (i.e., right ventricular and left ventricular end-diastolic area ratio > 0.6) and paradoxical septal motion. ΔIVC was obtained using TTE and ΔSVC using TEE, while other echocardiographic parameters were measured using either approach. Echocardiographic examination was interpreted at the bedside in the presence of the attending physician to guide the patient's resuscitation, according to the standard of care of participating centers.

Identification of fluid responsiveness. Fluid loading was not routinely performed to identify fluid responsiveness to avoid potentially inefficient yet detrimental volume overload in some of our patients with cardiogenic shock or ARDS, but was rather left to the discretion of the attending physician according to the results of hemodynamic assessment. Alternatively, we routinely used PLR to mimic fluid loading, since this maneuver has been shown to induce a reversible venous blood shift from the legs and the splanchnic reservoir to the thoracic compartment which allows accurate identification of fluid responsiveness in ICU patients [25-27]. PLR with the patient in the semi-recumbent position was routinely performed using a previously described technique [28]. At the end of the first minute of PLR, patients were classified as fluid responders when the left ventricular outflow tract velocity-time integral increased by at least 10% compared with baseline [29]. This time lag corresponds to the maximum change in cardiac output following a fluid challenge [30] and to the previously validated PLR maneuver [28].

Statistical analysis.

Since the present study was observational, we did not test any quantitative hypothesis but rather focused on assessing a non-biased sample of patients with acute circulatory failure. Accordingly, we planned to enroll consecutive patients with shock of various causes during a two-year period, which was considered as a time-frame allowing the hemodynamic assessment of a broad cohort representative of the population admitted to the ICU with acute circulatory failure and the use of comparable standards of care. Categorical data were expressed as numbers and percentages, while continuous variables were reported as means ± standard deviations. Fluid responders and non-responders were compared using a t-test or a chi-square test (or Fisher exact test when necessary). A two-tailed p value < 0.05 was considered statistically significant. In 55 randomly selected patients (~10% of study sample size), an experienced investigator repeated measurements of ΔSVC, ΔIVC, ΔVmaxAo and PLR-induced variations of left ventricular outflow tract velocity-time integral, and another experienced investigator performed the same measurements to determine their reproducibility. Three participating sites contributed equally to these serial measurements. Inter- and intra-observer agreements were assessed using the intraclass correlation coefficient [31] and using the Bland-Altman method [32].

A Receiver Operating Characteristic (ROC) curve was constructed to determine the threshold value of each dynamic parameter (ΔPP, ΔSVC, ΔIVC, ΔVmaxAo) yielding the best sensitivity and specificity to identify patients with fluid responsiveness. Patients with non-sinus rhythm were intrinsically not eligible for the measurement of ΔPP and ΔVmaxAo. Derived areas under the curves were compared using the non-parametric approach of DeLong et al. [33] in the subset of patients in whom all four dynamic parameters could have been measured. In patients who received fluid loading based on hemodynamic assessment, an increase of left ventricular stroke volume > 10% defined fluid responsiveness. ROC curves were also constructed in patients who underwent blood volume expansion, in patients without confounding factors known potentially to limit the use of dynamic parameters to predict fluid responsiveness (i.e., sinus rhythm, tidal volume ≥ 8 mL/kg and intra-abdominal

pressure < 12 mmHg), in patients hemodynamically assessed for septic shock, and in patients with hypotension and elevated lactate (> 2 mmol/L) unrelated to cardiogenic or obstructive shock. In addition, the value of each dynamic parameter yielding the highest sensitivity (to minimize false-negative results in a patient sustaining severe shock) and the highest specificity (to minimize the risk of false positives in a patient with severe associated respiratory compromise) was determined in the entire study population and in each of the predefined subsets of patients.

Results

Among the 742 patients screened during the study period, 125 presented with an exclusion criterion, and 77 patients were not studied for other reasons (Figure 1). Finally, 540 patients were studied (379 men; age: 65±13 years; SAPSII: 59±18; SOFA: 10±3), and fluid responsiveness was identified in 229 of them (42%). At study enrollment, patients were predominantly hypotensive or had corrected hypotension on vasopressor support (87%), frequently had lactate > 2 mmol/L (62%), and exhibited clinical or laboratory signs of tissue hypoperfusion in 98% of cases (supplementary Table E2). Overall, 355 patients (66%) had a tidal volume < 8 mL/kg of predicted body weight, 174 patients (32%) had an intra-abdominal pressure ≥ 12 mmHg and 78 patients (14%) had a non-sinus rhythm (Figure 1). A total of 117 patients (22%) presented with ARDS, 135 patients (25%) had undergone recent abdominal surgery and 51 patients (9%) recent thoracic operation (Table 1). The cause of acute circulatory failure was predominantly septic in 295 patients (55%), cardiogenic in 100 patients (18%), and hypovolemic in 81 patients (15%). Patients with fluid responsiveness were less frequently men, had more frequently undergone recent abdominal surgery, and more frequently had hypovolemic shock as opposed to cardiogenic or obstructive shock. Respiratory parameters were not statistically different, whether patients exhibited fluid responsiveness or not. ICU mortality was 40%, irrespective of fluid responsiveness (Table 1).

At the time of echocardiographic assessment, 461 patients (85%) were receiving catecholamines and the mean volume of fluids administered during the preceding 24 hours

was 2.5±2.7 L. Patients with fluid responsiveness exhibited lower systolic and mean blood pressures, lower central venous pressure (9±5 vs. 11±5 mmHg: p=0.0001) and greater ΔPP (13.5±8.5 vs. 9.1±7.4%: p<0.0001) than patients without fluid responsiveness (Table 2). Mean heart rate (105±24 vs. 104±25 bpm: p=0.79), mean lactate level (3.90±3.79 vs. 3.87±3.67 mmol/L: p=0.93), and mean ScvO2 (77±11 vs. 76±12%: p=0.51) were similar whether patients exhibited fluid responsiveness, or not (Table 2). Mean ΔSVC, mean ΔIVC and mean ΔVmaxAo were significantly greater in patients with fluid responsiveness (31±24 vs. 12±15%; 13±14 vs. 8±15%; 15.2±7.4 vs. 9.5±6.5%, respectively; all p<0.001) (Table 2). Patients with fluid responsiveness exhibited significantly lower left ventricular end-diastolic volume (83±34 vs. 95±41 mL: p=0.0002) and left ventricular stroke volume at baseline (48±19 vs. 56±24 mL: p<0.0001). During PLR, mean increase of left ventricular stroke volume was 27±18% in patients with fluid responsiveness, whereas it remained as low as 0.5±6% in their non-responsive counterparts (Table 2). Forty-two patients (8%) exhibited acute cor pulmonale. Intra- and inter-observer reproducibility of measurements of echocardiographic indices used to predict fluid responsiveness were good to excellent, as reflected by intraclass correlation coefficients ranging between 0.79 and 0.98, and 0.75 and 0.95, respectively (supplementary Table E3), and by low values of mean biases according to Bland-Altman representation (supplementary Figure E1).

ΔPP and ΔVmaxAo could not be measured in 78 patients with a non-sinus rhythm and were not obtained in 38 and 41 additional patients, respectively. Overall, ΔPP and ΔVmaxAo were available in 78.5% and 78.0% of patients, respectively, while ΔSVC and ΔIVC could be measured in 99.6% and 78.1% of cases, respectively. ROC curves of dynamic parameters used to predict fluid responsiveness are depicted in Figure 2. Threshold values, sensitivity, specificity and areas under the curves of dynamic parameters are summarized in Table 3. Threshold values to optimize the sensitivity or specificity of dynamic parameters are listed in Table 4. Similar threshold values yielding the best sensitivity and specificity to identify patients with fluid responsiveness were obtained in the subset of 319 patients (59%) in whom all four dynamic parameters could be measured (Figure 3). In these patients, the area under

the curve of ΔSVC was significantly greater than that of ΔIVC (p=0.02) and ΔPP (p=0.01) (Table 3) (Figure 3).

Among the 243 patients (45%) who received fluid loading based on echocardiographic findings, 229 underwent hemodynamic assessment after blood volume expansion. Mean increase of left ventricular stroke volume induced by fluid loading was markedly higher in patients with PLR which was indicative of fluid responsiveness (36±26% [n=161] vs. 5±17% [n=68]: p<0.001). Areas under the curves were similar to those of the entire study population (supplementary Table E4), including in the subset of patients in whom all dynamic parameters could have been measured (supplementary Figure E2). Areas under the curves obtained in patients with sinus rhythm, a tidal volume ≥ 8 mL/kg and an intra-abdominal pressure < 12 mmHg (n=84), and in septic shock patients (n=295) appeared similar to those of the entire study sample (supplementary Table E5), including in the subset of patients with the four dynamic parameters available (supplementary Figure E3). In patients with hypotension and high lactate unrelated to cardiogenic or obstructive shock (n=212), areas under the curves appeared similar to those obtained in the entire study population (Figure 4). With the exception of ΔSVC, the respective threshold values of dynamic parameters providing the best compromise between sensitivity and specificity (Table 5) and threshold values providing optimized sensitivity and specificity (supplementary Table E6) were also similar to those derived from the entire study sample.

Discussion

In the present study which evaluated the largest published cohort of ventilated patients with acute circulatory failure using echocardiography, ΔSVC had a significantly greater area under the curve than ΔPP and ΔIVC in predicting fluid responsiveness, but required TEE. The diagnostic accuracy of dynamic parameters in predicting fluid responsiveness was similar in the subset of patients with sinus rhythm who had a tidal volume ≥ 8 mL/kg and an intra-abdominal pressure < 12 mmHg, in patients with septic shock, and in patients with hypotension and high lactate unrelated to cardiogenic or obstructive shock.

We purposely used PLR to identify fluid responsiveness since routine fluid loading for the sole purpose of the study would not have been ethical in certain of our patients with cardiogenic shock, volume overload or associated ARDS but no echocardiographic sign of fluid responsiveness. In these patients, unnecessary blood volume expansion might have been detrimental [4]. An increase of aortic blood flow ≥ 10% during PLR has a reported sensitivity of 97% and a specificity of 94% in identifying responders to 500 mL fluid loading [29]. In two recent meta-analyses, the area under the curve of PLR for predicting fluid responsiveness in shocked patients was 0.96 and 0.95, respectively [25,26]. Another systematic review recently reported similar diagnostic accuracy and the best threshold value was a PLR-induced increase in cardiac output ≥ 10±2% [27]. In addition, areas under the curves obtained in the subset of our patients who received fluid loading during echocardiographic monitoring were similar to those derived from the entire study population. As a reversible fluid challenge, PLR-induced increase of left ventricular stroke volume at one min fails to predict the long-term effects of fluid loading on hemodynamics since the effects of blood volume expansion disappear 10 min after the infusion [30]. Nevertheless, the same limitation holds true for conventional fluid loading, with the disadvantage of increasing fluid balance. In a recent European survey, PLR was the leading index used to identify fluid responsiveness [1]. In our patients, mean intra-abdominal pressure was markedly lower than 16 mmHg, the threshold value leading to potential false negative results of PLR [34]. Overall, PLR appear to be a valuable alternative to routine fluid loading in determining the presence of fluid responsiveness in our ventilated patients with acute circulatory failure.

Since the present prospective pragmatic study enrolled consecutive ICU patients with acute circulatory failure of various causes, it allowed determination of the feasibility of dynamic parameter measurement. Interestingly, ΔPP and ΔVmaxAo were obtained in approximately 78% of the study population, but in more than 90% of patients with sinus rhythm. ΔSVC could be measured in virtually all ventilated patients, but it requires TEE [20]. In contrast, ΔIVC was obtained in 78% of patients, presumably due to the presence of numerous interferences with TTE image acquisition in our study population, such as recent

abdominal surgery. The reproducibility of echocardiographic dynamic parameters and left ventricular outflow tract velocity-time integral measurement (primary criterion to define fluid responsiveness) underlines the robustness of our results and is in keeping with that reported for two-dimensional and Doppler indices in experienced hands [35,36].

In our patients, ΔVmaxAo yielded the greatest sensitivity in predicting fluid responsiveness, whereas ΔSVC had the highest specificity. Using both dynamic parameters may be clinically relevant in clinical presentations raising the possibility of a false-positive result of ΔVmaxAo, such as the presence of acute cor pulmonale [37]. As previously reported [38], ΔIVC had a lower diagnostic accuracy in identifying fluid responsiveness than ΔSVC in our patients. As recently shown for ΔPP [39], the threshold value of dynamic echocardiographic indices yielding the best compromise between sensitivity and specificity may not adequately identify fluid responsiveness according to specific clinical needs. Since decision making fails to rely on a single binary parameter but rather on convergent findings, the decision to give fluid is not solely based on an isolated value of any dynamic parameter predictive of fluid responsiveness [40]. In our patients, threshold values were globally less than 8% when targeting 90% sensitivity. This range of values is within the reproducibility of echocardiographic dynamic parameter measurement. Accordingly, in shocked patients with persistent clinical or laboratory signs of tissue hypoperfusion, one may argue that a fluid challenge should be performed despite low values of dynamic parameters [41]. In this setting, echocardiography has the major advantage of assessing accurately both the efficacy and tolerance of fluid challenge, and is ideally suited to depict the presence of failing ventricles with associated elevated filling pressures, all information which could help to guide fluid resuscitation [42]. Interestingly, when targeting 90% specificity in patients in whom unnecessary fluid loading would be detrimental, threshold values of echocardiographic dynamic indices are closer to those reported in earlier studies [20,21]. A pragmatic approach would be to perform fluid loading in patients with persistent signs of tissue hypoperfusion and low risk of lung water overload, even in the presence of low respiratory variations of dynamic parameters (< 10%), whereas a strict threshold of 31% for ΔSVC and 18% for both ΔVmaxAo

and ΔIVC should be respected to ascertain the benefit of fluid loading in patients at high-risk of volume overload (e.g., ARDS). In all cases, the front-line intensivist should keep in mind that the identification of fluid responsiveness does not necessarily mean that the patient needs fluid, irrespective of the type and value of used dynamic parameter. This explains why only 161 out of 229 of our patients (70%) with PLR indicating fluid responsiveness did receive fluids. In the remaining patients, the fairly elevated ScvO2 presumably led the attending physicians not to increase cardiac output further by administering fluids [41]. Finally, hemodynamic changes induced by fluid loading are known to result in relatively small effects on tissue perfusion in responders [43].

In the current study, the areas under the curves of dynamic parameters used to identify fluid responsiveness were lower than those reported in initial validation studies. Several factors may have contributed to the lower diagnostic accuracy of dynamic parameters in our patients [14,44,45]. First, pioneer studies included only a small number of selected patients with septic shock [20-22,46], whereas we assessed fluid responsiveness in a large number of ventilated patients with circulatory failure of various causes. Second, the volume deficit was presumably higher in initial studies than in the present cohort, as reflected by markedly higher mean ΔPP (24±9%), ΔVmaxAo (20±6%), ΔSVC (64±17%) and ΔIVC (40±24%) at the time of hemodynamic assessment [20-22,46]. Third, a large proportion of our patients were under protective ventilation with a tidal volume < 8 mL/kg [44]. Surprisingly, ΔPP (and dynamic echocardiographic parameters) failed to have a greater diagnostic accuracy in our patients with sinus rhythm, a tidal volume ≥ 8 mL/kg [44] and an intra-abdominal pressure < 12 mmHg [45]. This may be related to the fact that this subset of patients involved only 16% of our study population. Fourth, the recent abdominal surgery performed in one-fourth of our patients may have reduced the diagnostic accuracy of ΔIVC. In patients with hypotension and high lactate unrelated to cardiogenic or obstructive shock, the diagnostic accuracy of dynamic parameters appeared similar to that of the entire study population. This suggests that our results derived from a large sample are confirmed in a more restricted population of well-defined shocked patients predominantly of septic cause. With the exception of a lower

cut-off value of ΔSVC, threshold values predicting fluid responsiveness were similar when compared to the entire study population. In this subset of patients, the lower prevalence of systemic venous congestion which directly increases the closure pressure of the superior vena cava presumably explains the lower cut-off value of ΔSVC.

The present study has substantial limitations. First, it was not designed to provide an external validation of previously reported studies [20-22,46], since fluid loading was not routinely performed to separate responders from non-responders and the recruitment was not limited to patients with septic shock. In addition, certain factors invalidating ΔPP were not studied [14], including the influence of lung compliance, and the influence of PLR on intra-abdominal pressure could not be assessed since bladder pressure was not measured during the postural change. Nevertheless, the present cohort is the largest reported to date and the data collected in consecutive patients assessed for various types of circulatory failure reflect the intrinsic limitations of dynamic parameters commonly used on clinical grounds. Second, we used Doppler echocardiography to measure left ventricular stroke volume, but this method is not interchangeable with thermodilution [47], a commonly used method to monitor the hemodynamic effects of PLR [27]. Nevertheless, the techniques may be interchangeable in tracking directional changes in cardiac output [47]. Third, the therapeutic impact of the hemodynamic assessment and its potential influence on patient-centered outcomes were purposely not evaluated in this descriptive rather than interventional study. Fourth, our results cannot be extrapolated to patients with spontaneous breathing, but are restricted to the most severely ill ICU patients who require invasive mechanical ventilation. Finally, dynamic parameters of fluid responsiveness were recorded by experienced investigators in centers using advanced critical care echocardiography as a first-line method to assess patients with circulatory failure. This limits the generalizability of our results, as opposed to ΔPP, which is widely available.

Conclusion

In this study describing the largest published series of ventilated patients consecutively assessed using advanced critical care echocardiography for any type of acute circulatory failure, ΔVmaxAo had the highest sensitivity and ΔSVC the highest specificity in identifying fluid responsiveness. ΔSVC had a greater diagnostic accuracy than ΔIVC and ΔPP, but it requires TEE. Since the diagnostic accuracy of dynamic parameters used to predict fluid responsiveness was lower than initially reported, the use of single threshold values which traditionally combine optimized sensitivity and specificity may not be appropriate. Whether a tailored approach relying on distinct cut-off values according to the risk of fluid overload is valid remains to be determined in specific populations of shocked patients.

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Figure legends

Figure 1. Flow chart of the study. *: a single patient may cumulate different criteria.

Figure 2. ROC curves and area under curve of dynamic parameters used to identify fluid responsiveness in ventilated patients with acute circulatory failure. Both the number of patients in whom each dynamic parameter could have been measured and the threshold value yielding the best compromise between sensitivity and specificity are indicated for each hemodynamic parameter. Red curves were constructed from the subset of patients in whom all four dynamic parameters could be measured for comparison.

Figure 3. ROC curves of dynamic parameters obtained in the subset of patients in whom all four indices used to predict fluid responsiveness could have been measured for comparison (n=319). The area under curve of ΔSVC was significantly greater than that of ΔPP and ΔIVC (asterisk).

Figure 4. ROC curves of dynamic parameters obtained in the subset of patients with hypotension and high lactate unrelated to cardiogenic or obstructive shock (n=212). Both the number of patients in whom each dynamic parameter could have been measured and the threshold value yielding the best compromise between sensitivity and specificity are indicated for each hemodynamic parameter. Red curves were constructed from the subset of patients in whom all four dynamic parameters could be measured for comparison.

Table 1: Characteristics of the study population

Parameters	Global population (n=540)	No fluid responsiveness (n=311)	Fluid responsiveness (n=229)	P Value
Patient's characteristics:				
Men (n)	379 (70)	233 (75)	146 (64)	0.005
Age (years)	65±13	65±13	65±14	0.59
SAPSII (ICU admission)	59±18	59±18	58±19	0.58
SOFA (inclusion)	10±3	10±3	10±3	0.17
Death in the ICU (n)	213 (40%)	124 (40%)	89 (39%)	0.81
Medical history:				
Congestive heart failure (n)	108 (20)	68 (22)	40 (18)	0.21
Chronic respiratory insufficiency (n)	77 (14)	47 (15)	30 (13)	0.51
Abdominal surgery (n)	135 (25)	67 (22)	68 (30)	0.03
Thoracic surgery (n)	51 (9)	24 (8)	27 (12)	0.11
ARDS (n)	117 (22)	72 (23)	45 (20)	0.33
Cause of circulatory failure:				< 0.0001
Septic shock (n)	295 (55)	173 (56)	122 (53)	
Cardiogenic shock (n)	100 (18)	73 (23)	27 (12)	
Hypovolemic shock (n)	81 (15)	19 (6)	62 (27)	
Obstructive shock (n)	10 (2)	9 (3)	1 (0.5)	
Anaphylactic shock (n)	4 (1)	3 (1)	1 (0.5)	
Other causes (n)	50 (9)	34 (11)	16 (7)	
Respiratory parameters:				

Tidal volume (mL/kg)	7.7±1.3	7.6±1.3	7.8±1.3	0.13
Plateau pressure (cm H_2O)	19±5	19±5	19±5	0.85
Total positive end-expiratory pressure (cmH_2O)	6±3	6±3	6±3	0.60
Driving pressure (cmH_2O)	13±4	13±4	13±4	0.86
Respiratory rate (cpm)	18±4	18±4	18±4	0.57

Results are expressed as means ± standard deviations. Numbers in brackets are percentages.

Abbreviations: SAPS, Simplified Acute Physiological Score; SOFA, Sepsis-related Organ Failure Assessment; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Table 2: Hemodynamic characteristics at the time of echocardiographic assessment

Parameters	Global population (n=540)	No fluid responsiveness (n=311)	Fluid responsiveness (n=229)	P Value
Hemodynamic parameters:				
Heart rate (bpm)	104±25	104±25	105±24	0.79
Systolic blood pressure (mmHg)	110±25	113±25	107±24	0.007
Diastolic blood pressure (mmHg)	62±14	62±14	61±14	0.20
Mean blood pressure (mmHg)	77±17	79±16	75±16	0.01
Central venous pressure (mmHg)	10±5	11±5	9±5	0.0001
ΔPP (%)	11.0±8.2	9.1±7.4	13.5±8.5	< 0.0001
Intra-abdominal pressure (mmHg)	11±5	10±5	11±5	0.12
Therapy:				
Norepinephrine* (n)	400 (74)	226 (73)	174 (76)	0.39
Epinephrine* (n)	70 (13)	49 (16)	21 (9)	0.02
Fluid loading (L)	2.5±2.7	2.3±2.4	2.8±2.9	0.02
Laboratory findings:				
$ScvO_2$ (%)	77±11	76±12	77±11	0.51
pH	7.28±0.13	7.29±0.14	7.28±0.13	0.78
Lactate (mmol/L)	3.89±3.72	3.87±3.67	3.90±3.79	0.93
Echocardiographic findings:				
ΔSVC (%)	20±21	12±15	31±24	< 0.0001
ΔIVC (%)	10±15	8±15	13±14	< 0.0005
ΔVmaxAo (%)	12.0±7.4	9.5±6.5	15.2±7.4	< 0.0001
Left ventricular end-diastolic volume	90±39	95±41	83±34	0.0002

(mL)				
Left ventricular ejection fraction (%)	49±18	47±18	52±17	0.002
Right ventricular and left ventricular end-diastolic areas ratio in long axis cardiac view	0.68±0.33	0.70±0.34	0.64±0.32	0.07
Acute cor pulmonale	42 (8)	37 (12)	5 (2)	≤ 0.0001
Baseline left ventricular stroke volume (mL)	52±23	56±24	48±19	< 0.0001
PLR-induced left ventricular stroke volume variations (%)	12±18	0.5±6	27±18	< 0.0001

*: a single patient could receive several catecholamines.

Abbreviations: ΔPP, pulse pressure variations; ΔSVC, respiratory variations of the diameter of superior vena cava; ΔIVC, respiratory variations of the diameter of inferior vena cava; ΔVmaxAo, respiratory variations of the maximal Doppler velocity in left ventricular outflow tract; PLR, passive leg raise.

Numbers in brackets are percentages.

Table 3: Diagnostic capability of dynamic parameters measured in ventilated patients with acute circulatory failure to predict fluid responsiveness

Dynamic parameters	Threshold value	Sensitivity (95% CI)	Specificity (95% CI)	Area under the curve
Study population (n=540):				
ΔPP (n=424)	≥ 11%	58% (53-62)	72% (68-76)	0.675
ΔVmaxAo (n=421)	≥ 10%	79% (75-83)	64% (59-69)	0.752
ΔSVC (n=538)	≥ 21%	61% (57-66)	84% (81-87)	0.755
ΔIVC (n=422)	≥ 8%	55% (50-59)	70% (66-75)	0.635
Subset of patients with all dynamic parameters available (n=319)				
ΔPP	≥ 11%	55% (49-60)	73% (68-78)	0.657
ΔVmaxAo	≥ 9.4%	78% (74-83)	60% (55-66)	0.720
ΔSVC	≥ 21%	63% (58-68)	81% (77-86)	0.742*∂
ΔIVC	≥ 13%	44% (39-49)	85% (81-89)	0.653

Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of the maximal Doppler velocity in left ventricular outflow tract; ΔSVC, respiratory variations of the diameter of superior vena cava; ΔIVC, respiratory variations of the diameter of inferior vena cava.

*: p = 0.01 vs. ΔPP; ∂: p = 0.02 vs. ΔIVC

Table 4: Threshold values of dynamic parameters to predict fluid responsiveness according to optimized sensitivity or specificity in ventilated patients with acute circulatory failure (n=540)

Dynamic parameters	Threshold value for optimized sensitivity	Optimized sensitivity (associated specificity)	Threshold value for optimized specificity	Optimized specificity (associated sensitivity)
ΔPP (n=424)	4%	92% (19%)	18%	89% (28%)
ΔVmaxAo (n=421)	7%	90% (39%)	18%	90% (29%)
ΔSVC (n=538)	4%	89% (25%)	31%	90% (43%)
ΔIVC (n=422)	3%	74% (36%)	18%	90% (28%)

Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of the maximal Doppler velocity in left ventricular outflow tract; ΔSVC, respiratory variations of the diameter of superior vena cava; ΔIVC, respiratory variations of the diameter of inferior vena cava.

Table 5: Diagnostic capability of dynamic parameters to predict fluid responsiveness in ventilated patients with hypotension and high lactate unrelated to cardiogenic or obstructive shock (n=212)

Dynamic parameters	Threshold value	Sensitivity (95% CI)	Specificity (95% CI)	Area under the curve
ΔPP (n=164)	≥ 11%	71% (64-78)	70% (63-77)	0.740
ΔVmaxAo (n=162)	≥ 13%	71% (64-78)	80% (74-86)	0.794
ΔSVC (n=211)	≥ 13%	79% (74-85)	73% (67-79)	0.783
ΔIVC (n=156)	≥ 8%	57% (50-65)	69% (62-76)	0.608

Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of the maximal Doppler velocity in left ventricular outflow tract; ΔSVC, respiratory variations of the diameter of superior vena cava; ΔIVC, respiratory variations of the diameter of inferior vena cava.

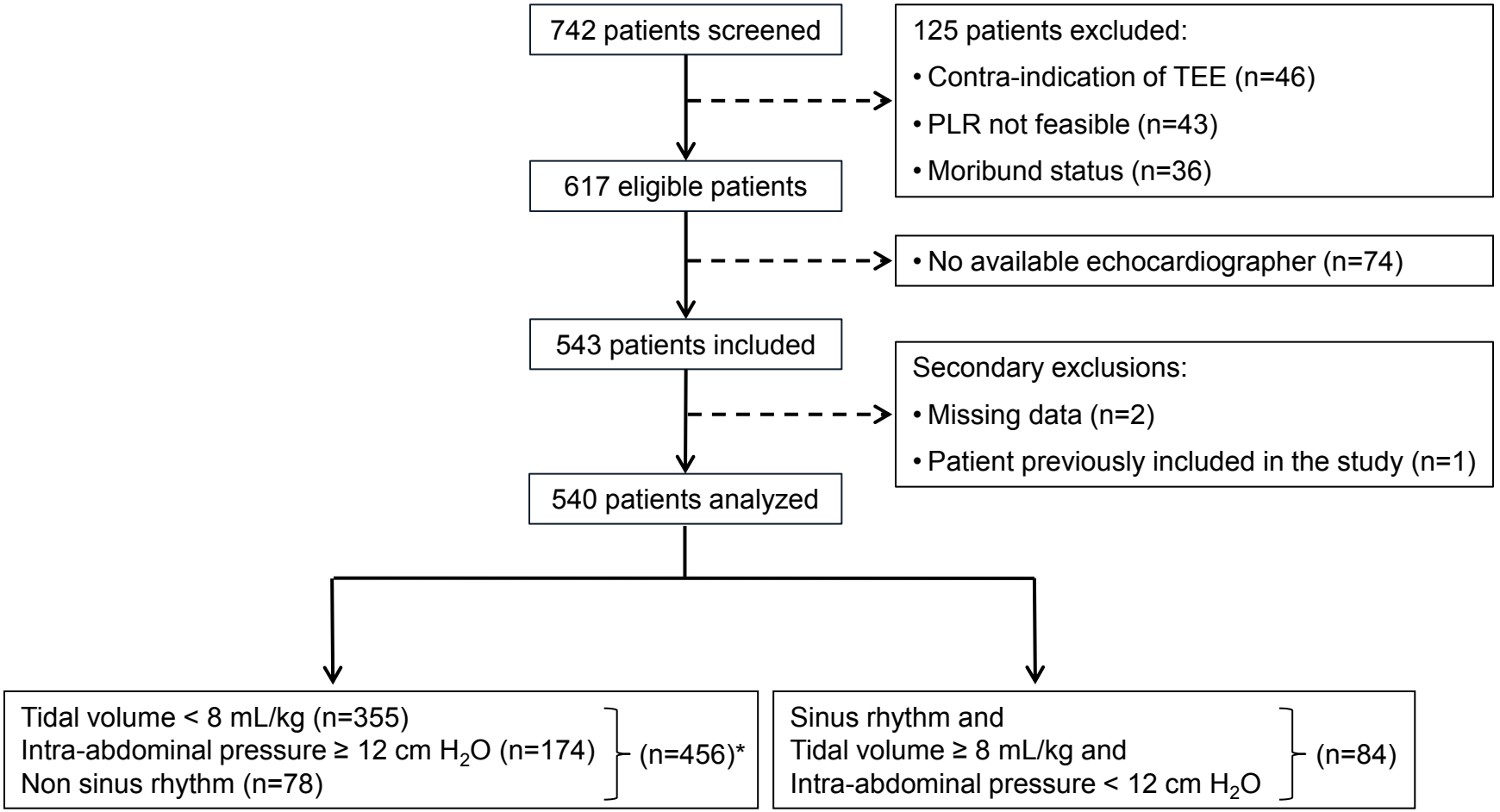

742 patients screened
125 patients excluded:
• Contra-indication of TEE (n=46)
• PLR not feasible (n=43)
• Moribund status (n=36)
617 eligible patients
• No available echocardiographer (n=74)
543 patients included
Secondary exclusions:
• Missing data (n=2)
• Patient previously included in the study (n=1)
540 patients analyzed
Tidal volume < 8 mL/kg (n=355)
Intra-abdominal pressure ≥ 12 cm H_2O (n=174)
Non sinus rhythm (n=78)
(n=456)*
Sinus rhythm and
Tidal volume ≥ 8 mL/kg and
Intra-abdominal pressure < 12 cm H_2O
(n=84)

Figure 1

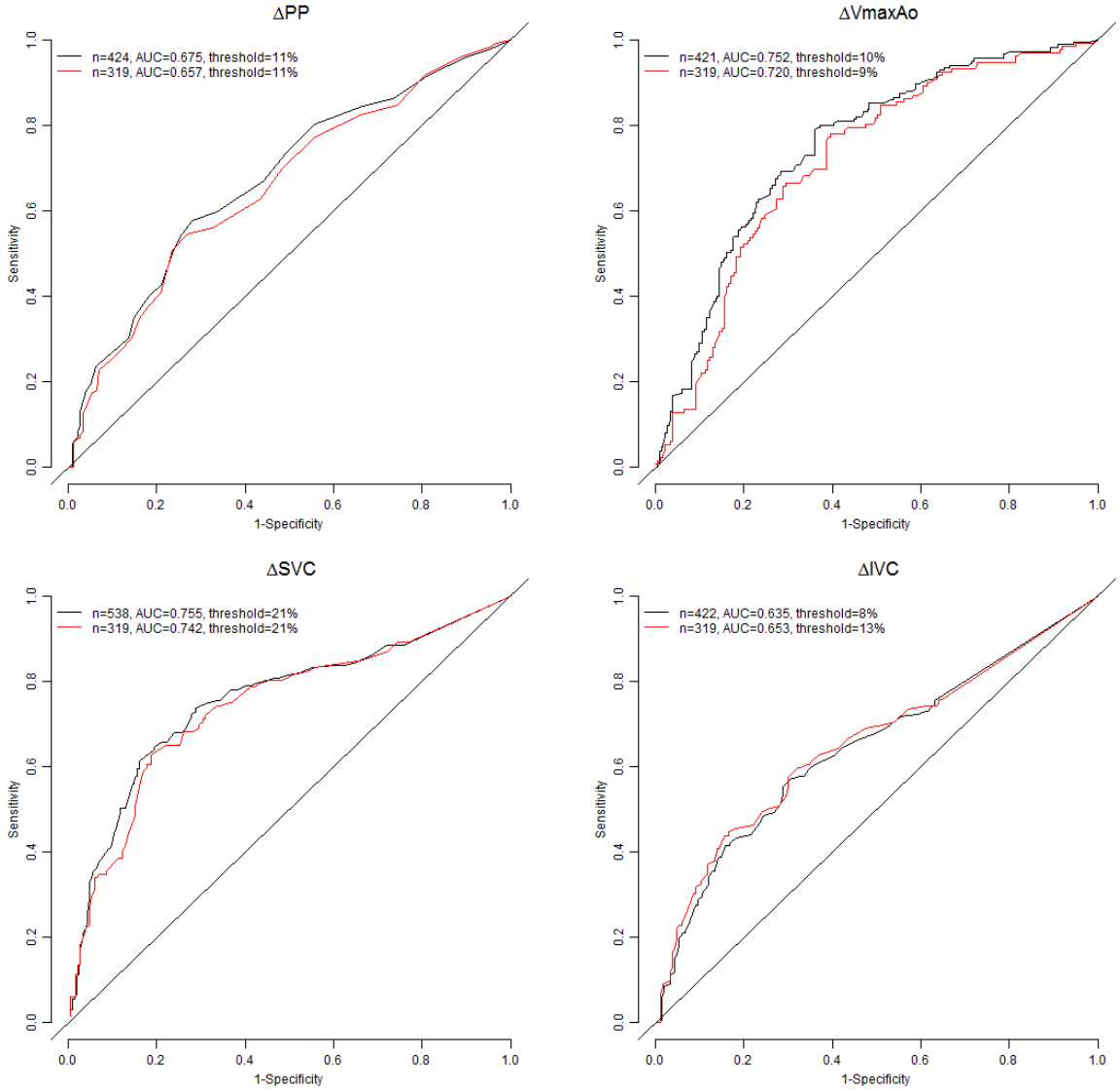

ΔPP
n=424, AUC=0.675, threshold=11%
n=319, AUC=0.657, threshold=11%
ΔVmaxAo
n=421, AUC=0.752, threshold=10%
n=319, AUC=0.720, threshold=9%
ΔSVC
n=538, AUC=0.755, threshold=21%
n=319, AUC=0.742, threshold=21%
ΔIVC
n=422, AUC=0.635, threshold=8%
n=319, AUC=0.653, threshold=13%
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 2

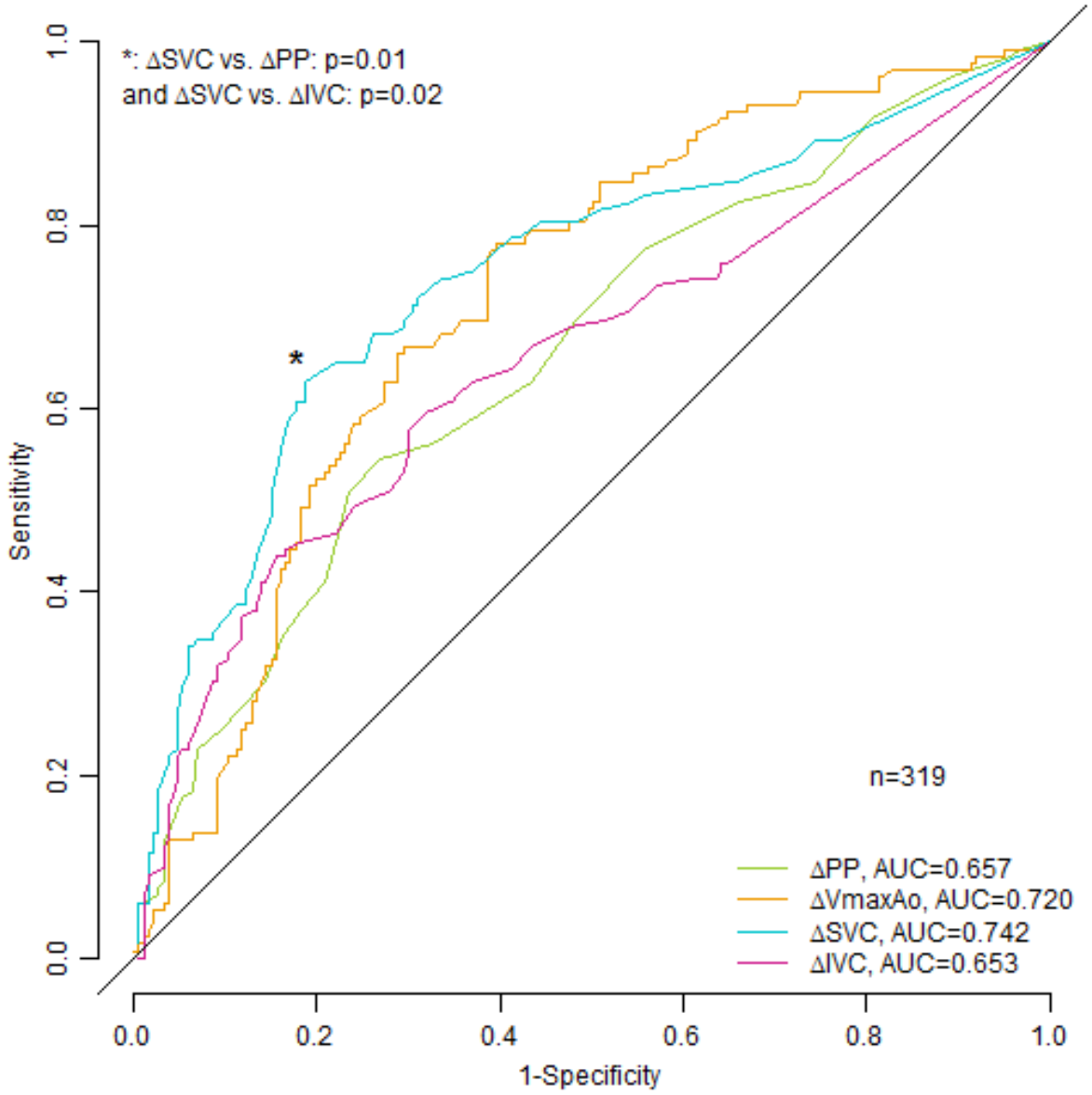

*: ΔSVC vs. ΔPP: p=0.01
and ΔSVC vs. ΔIVC: p=0.02
*
n=319
ΔPP, AUC=0.657
ΔVmaxAo, AUC=0.720
ΔSVC, AUC=0.742
ΔIVC, AUC=0.653
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 3

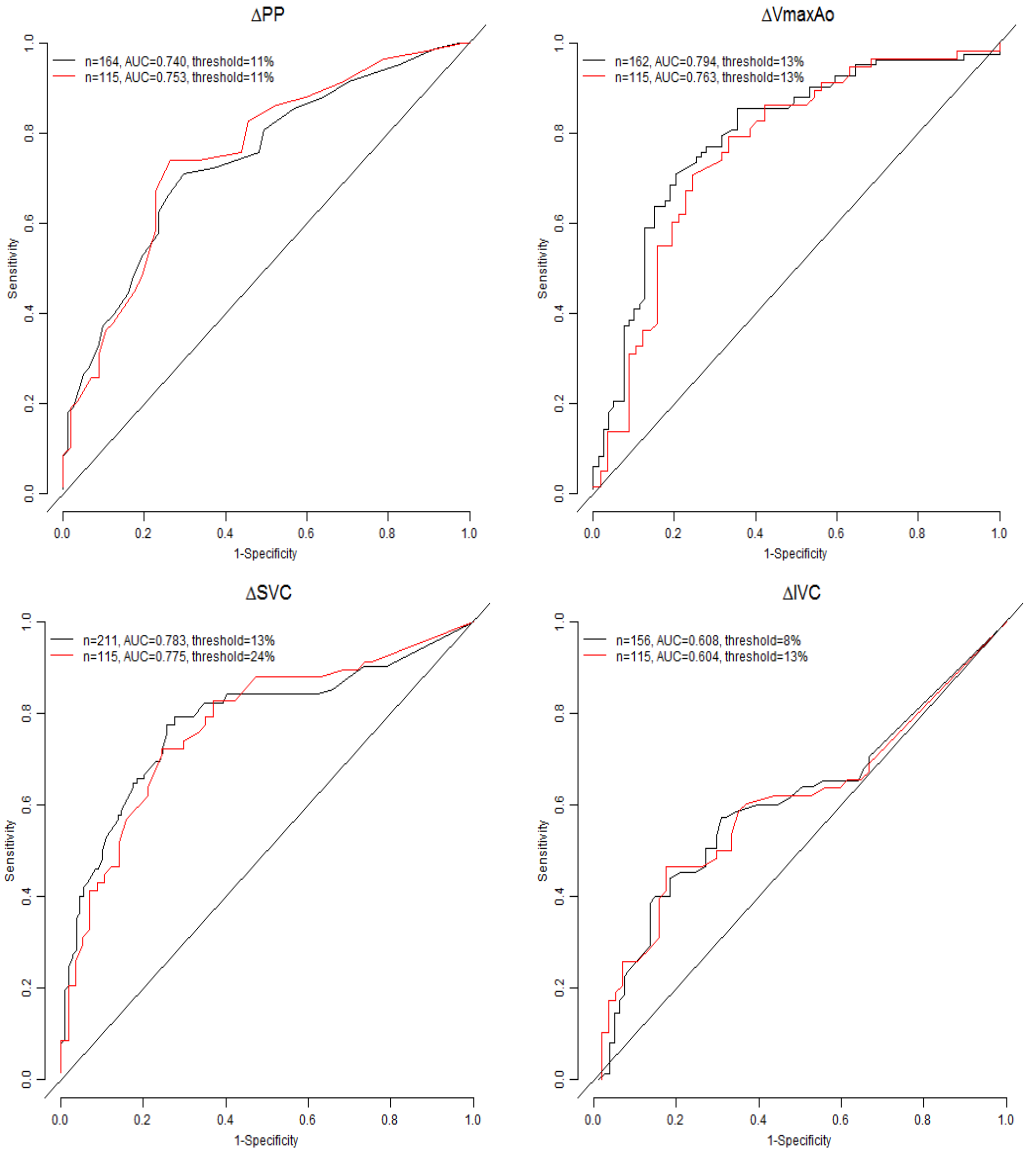

ΔPP
n=164, AUC=0.740, threshold=11%
n=115, AUC=0.753, threshold=11%
ΔVmaxAo
n=162, AUC=0.794, threshold=13%
n=115, AUC=0.763, threshold=13%
ΔSVC
n=211, AUC=0.783, threshold=13%
n=115, AUC=0.775, threshold=24%
ΔIVC
n=156, AUC=0.608, threshold=8%
n=115, AUC=0.604, threshold=13%
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 4

Online Data Supplement

Comparison of echocardiographic indices used to predict fluid responsiveness in ventilated patients

Philippe Vignon, Xavier Repessé, Emmanuelle Bégot, Julie Léger, Christophe Jacob, Koceila Boufferache, Michel Slama, Gwenaël Prat, Antoine Vieillard-Baron

Supplementary figure legends

Figure E1: Blant-Altman representation of measurements of dynamic echocardiographic parameters and of the criterion used to define fluid responsiveness when performed by two independent observers and repeatedly by the same observer to determine their reproducibility.

Figure E2: ROC curves and area under the curves (AUC) obtained in patients who where hemodynamically assessed prior to and after a fluid loading (n=137) (please refer to supplementary Table E4).

Figure E3: ROC curves and area under the curves (AUC) obtained in patients without confounding factors known to limit the value of dynamic parameters to predict fluid responsiveness (n=62) and in patients with septic shock (n=177).

Supplementary Table E1: Dynamic echocardiographic parameters described to predict fluid responsiveness in ventilated patients*

Dynamic parameters (%)	Formulae	Patients* (n)	Threshold (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ΔSVC [20]	(Dmax at expiration - Dmin at insufflation) / Dmax at expiration	66	36%	90%	100%	-	-
ΔIVC [21]	(Dmax at insufflation - Dmin at expiration) / Dmin at expiration	20	18%	90%	90%	-	-
ΔVmaxAo [22]	Vmax at insufflation – Vmin at expiration / (Vmax + Vmin / 2)	19	12%	100%	89%	91%	100%

*: all patients included in initial studies had septic shock.

Abbreviations: ΔSVC, respiratory variations of the diameter of the superior vena cava, or “collapsibility index”; ΔIVC, respiratory variations of the diameter of the inferior vena cava, or “distensibility index”; ΔVmaxAo, respiratory variations of left ventricular outflow tract maximal Doppler velocity; PPV, Positive predictive value; NPV, Negative predictive value.

Supplementary Table E2: Inclusion criteria met by the patients enrolled in the study cohort

Inclusion criteria (%)	All patients (n=540)	Non hypotensive patients (n=68)
Hypotension*	472 (87)	-
Clinical or biological signs of tissue hypoperfusion:	530 (98)	68 (100.0)
Cold extremities or mottled skin	375 (71)	52 (77)
Oliguria < 0.5 mL/kg/h over at least one hour	360 (68)	44 (65)
pH < 7.35 and base excess < -5 mmol/L	329 (62)	39 (57)
Elevated lactate > 2 mmol/L	323 (62)	47 (69)
SvcO2 < 70%	85 (16)	16 (24)
Number of clinical of biological signs of tissue hypoperfusion:		
1	91 (17)	8 (12)
2	129 (24)	15 (22)
3	144 (27)	24 (35)
4	139 (26)	17 (25)
5	27 (5)	4 (6)

*: or corrected hypotension by ongoing vasopressor support

Numbers into brackets are percentages.

Supplementary Table E3: Intraclass correlation coefficients of echocardiographic parameters measured to define and predict fluid responsiveness in ventilated patients

Dynamic parameters	Inter-observer	Intra-observer
Left ventricular outflow tract Doppler velocity-time integral before and after PLR	0.932 (0.886-0.960)	0.978 (0.972-0.987)
ΔSVC [20]	0.947 (0.912-0.969)	0.949 (0.914-0.970)
ΔIVC [21]	0.940 (0.895-0.966)	0.979 (0.963-0.988)
ΔVmaxAo [22]	0.745 (0.590-0.847)	0.786 (0.651-0.873)

Numbers into brackets are 95% confidence intervals

Abbreviations: PLR, passive leg raise; ; ΔSVC, respiratory variations of the diameter of superior vena cava; ΔIVC, respiratory variations of the diameter of the inferior vena cava; ΔVmaxAo, respiratory variations of left ventricular outflow tract maximal Doppler velocity.

Supplementary Table E4: Diagnostic capability of dynamic parameters to predict fluid responsiveness in ventilated patients with acute circulatory failure who were hemodynamically assessed prior to and after a fluid loading (n=229)*

Dynamic parameters	Threshold value	Sensitivity (95% CI)	Specificity (95% CI)	Area under the curve
ΔPP (n=191)	≥ 10%	71% (65-77)	57% (50-64)	0.657
ΔVmaxAo (n=194)	≥ 10%	81% (75-86)	56% (49-63)	0.705
ΔSVC (n=228)	≥ 19%	78% (72-83)	73% (67-78)	0.763
ΔIVC (n=159)	≥ 16%	40% (32-47)	83% (77-88)	0.567

Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of left ventricular outflow tract maximal Doppler velocity; ΔSVC, respiratory variations of the diameter of the superior vena cava; ΔIVC, respiratory variations of the diameter of the inferior vena cava.

*: Please refer to supplementary Figure E2 for ROC curves built in the subset of patients in whom all dynamic parameters could have been obtained.

Supplementary Table E5: Diagnostic capability of dynamic parameters to predict fluid responsiveness in two subsets of ventilated patients with circulatory failure*

Dynamic parameters	Threshold value	Sensitivity (95% CI)	Specificity (95% CI)	Area under the curve
Patients in sinus rhythm with a tidal volume ≥ 8 mL/kg and intra-abdominal pressure < 12 mmHg (n=84):				
ΔPP (n=81)	≥ 11%	69% (59-79)	61% (50-72)	0.661
ΔVmaxAo (n=74)	≥ 14%	58% (46-69)	78% (69-88)	0.689
ΔSVC (n=84)	≥ 21%	75% (66-84)	67% (57-77)	0.714
ΔIVC (n=72)	≥ 5%	63% (52-75)	60% (48-71)	0.600
Patients with septic shock (n=295)				
ΔPP (n=230)	≥ 12%	54% (47-60)	73% (68-79)	0.651
ΔVmaxAo (n=226)	≥ 11%	65% (59-72)	75% (69-81)	0.731

ΔSVC (n=294)	≥ 13%	71% (66-77)	72% (67-77)	0.739
ΔIVC (n=236)	≥ 8%	53% (46-59)	74% (68-79)	0.630

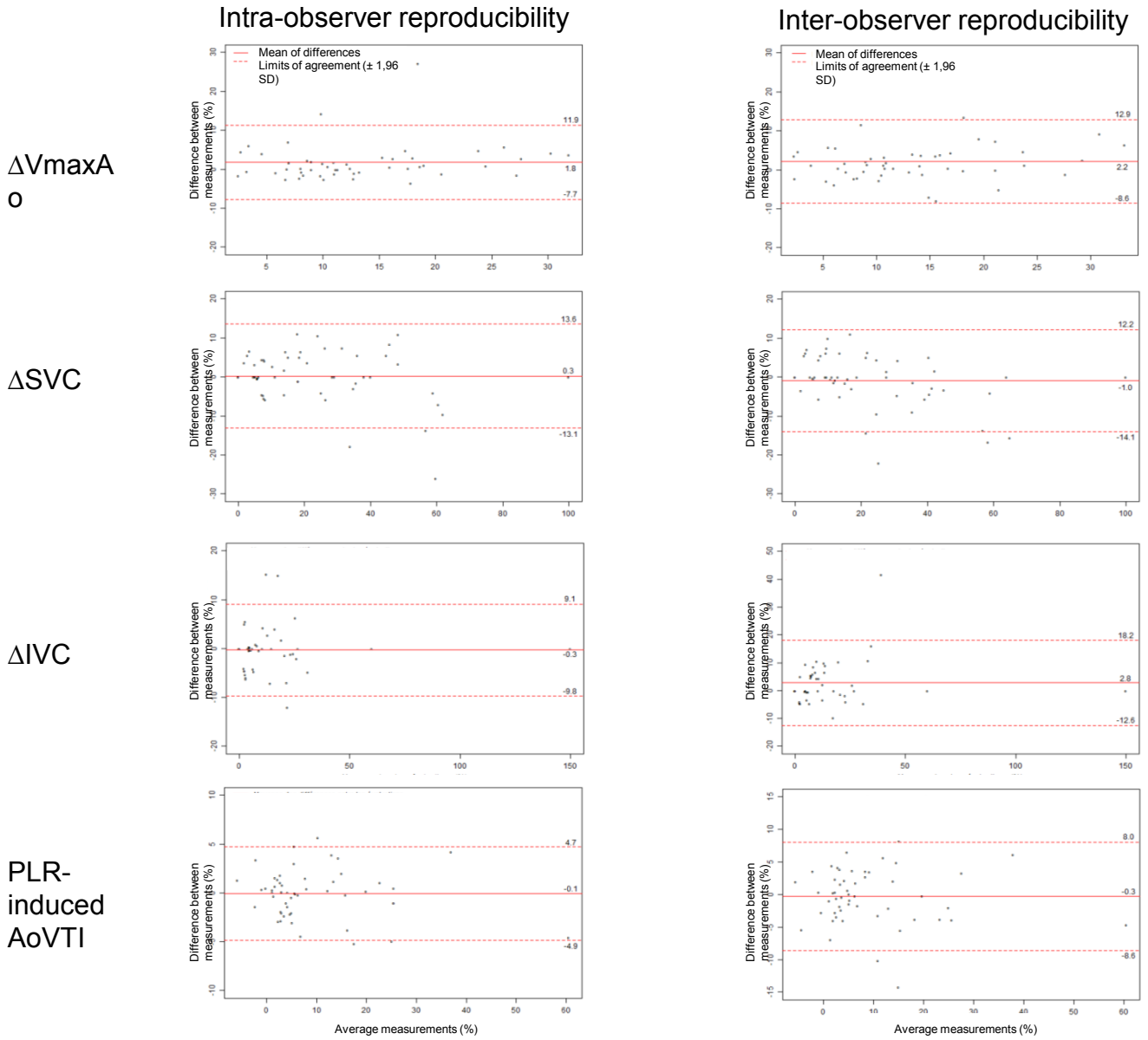
Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of left ventricular outflow tract maximal Doppler velocity; ΔSVC, respiratory variations of the diameter of the superior vena cava; ΔIVC, respiratory variations of the diameter of the inferior vena cava.

*: please refer to supplementary Figure E3 for ROC curves built in the subset of patients in whom all dynamic parameters could have been obtained.

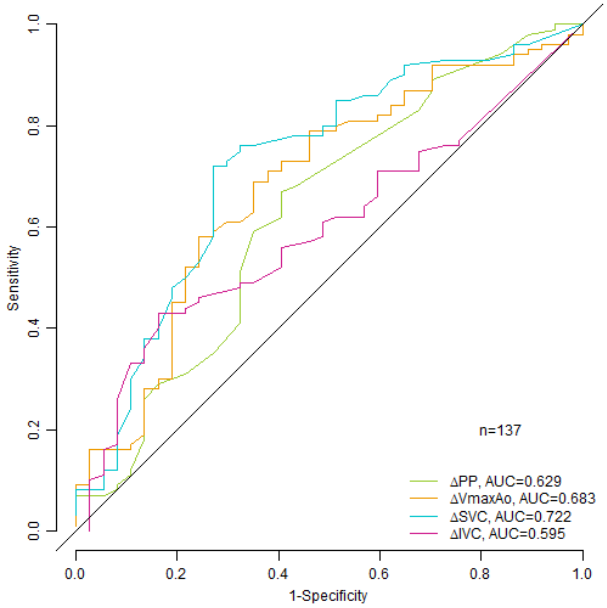
Table E6: Threshold values of dynamic parameters to predict fluid responsiveness according to optimized sensitivity or specificity in hypotensive patients with high lactate unrelated to cardiogenic or obstructive shock (n=212)

Dynamic parameters	Threshold value for optimized sensitivity	Optimized sensitivity (associated specificity)	Threshold value for optimized specificity	Optimized specificity (associated sensitivity)
ΔPP (n=164)	5%	92% (30%)	19%	90% (37%)
ΔVmaxAo (n=162)	7%	90% (42%)	18%	90% (39%)
ΔSVC (n=211)	4%	90% (22%)	31%	90% (48%)
ΔIVC (n=156)	3%	71% (33%)	21%	90% (24%)

Abbreviations: ΔPP, pulse pressure variations; ΔVmaxAo, respiratory variations of left ventricular outflow tract maximal Doppler velocity; ΔSVC, respiratory variations of the diameter of the superior vena cava; ΔIVC, respiratory variations of the diameter of the inferior vena cava.

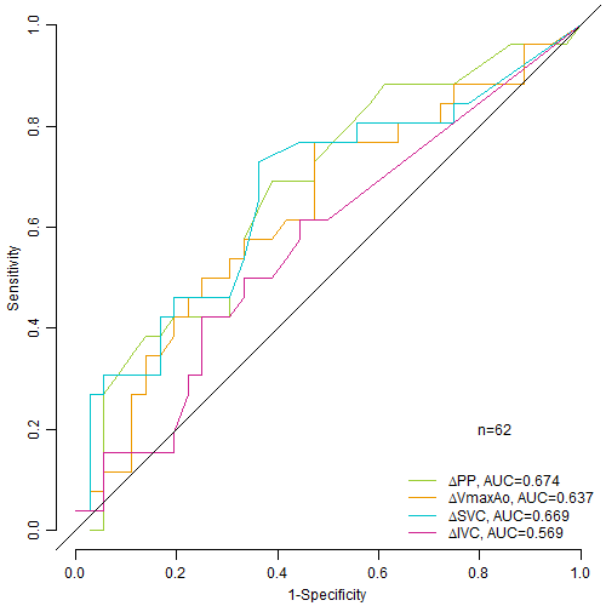


Supplementary Figure E1

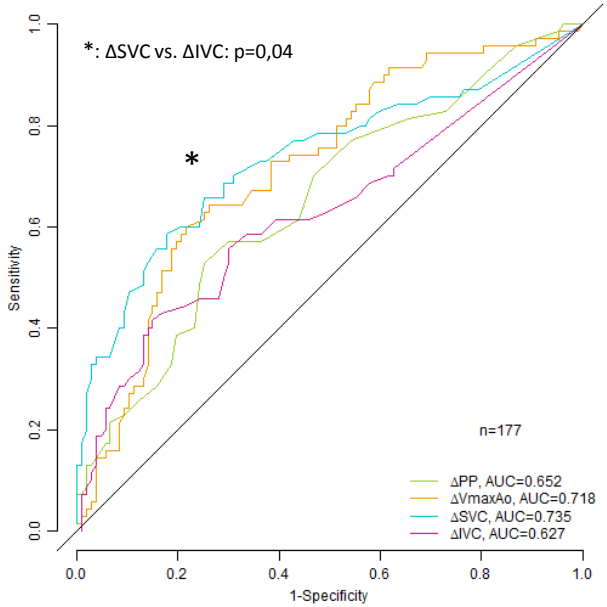


Supplementary Figure E2

Patients in sinus rythm with a tidal volume ≥ 8 mL/kg and an intra-abdominal pressure < 12 mmHg (n=62)



Patients with a septic shock (n=177)



Supplementary Figure E3