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L'index de collapsibilité de la veine cave inférieure comme marqueur prédictif de la réponse au remplissage chez les patients en ventilation spontanée : une étude prospective de validation

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Avertissement

TABLE DES MATIERES

LISTE DES ABREVIATIONS 1
RESUME 2
ABSTRACT 3
INTRODUCTION 4
METHODS 5
TRIAL DESIGN 5
PATIENTS 5
DATA COLLECTION 5
STUDY PROTOCOL 6
ECHOGRAPHY RECORDINGS 7
SAMPLE SIZE CALCULATION 8
STATISTICS 8
RESULTS 10
DISCUSSION 15
CONCLUSION 20
REFERENCES 21
APPENDIX 25

LISTE DES ABREVIATIONS

BMI : indice de masse corporelle

BP : pression buccale en ventilation non-standardisée (BP-ns) ou standardisée (BP-st)

cIVC : indice de collapsibilité de la veine cave inférieure en ventilation non-standardisée (cIVC-ns) ou standardisée (cIVC-st)

eIVC : diamètre expiratoire de la veine cave inférieure

FR : réponse au remplissage

HFNO : oxygénation nasale à haut débit

IAP : pression intra-abdominale

ICU : unité de soins intensifs

iIVC : diamètre inspiratoire de la veine cave inférieure

IVC : veine cave inférieure

LVEF : fraction d'éjection du ventricule gauche

LVOT : chambre de chasse du ventricule gauche

PLR : lever de jambes passif

SAPS : *simplified acute physiologic score*

SOFA : *sequential organ failure assessment*

VTI : intégrale temps-vitesse

ΔVTI : variation de l'intégrale temps-vitesse mesurée au niveau de la chambre de chasse du ventricule gauche, induite par une épreuve de lever de jambes passif

RESUME

Rationnel : Dans une étude de dérivation menée au sein de patients en ventilation spontanée admis en réanimation, des valeurs d'indice de collapsibilité de la veine cave inférieure (cIVC) supérieures ou égales à 33% en ventilation non standardisée ou 44% lors d'une inspiration standardisée permettaient de prédire une réponse au remplissage avec de bonnes performances statistiques.
Cette cohorte de validation avait pour but de valider prospectivement ces seuils.

Méthodes : Cette étude prospective monocentrique a été conduite chez des patients en ventilation spontanée, admis en réanimation au sein de l'hôpital universitaire de Lille. Les mesures échographiques de la veine cave inférieure étaient réalisées à 4cm en amont de son abouchement dans l'oreillette droite, durant une inspiration non-standardisée (cIVC-ns) puis standardisée (cIVC-st). Le test de référence pour prédire la réponse au remplissage était une augmentation supérieure ou égale à 10% de l'intégrale temps-vitesse du flux aortique induite par une épreuve de lever de jambes passif.

Résultats : Parmi les 61 patients inclus, 38 (62%) étaient répondeurs au remplissage. La valeur médiane du *simplified acute physiologic score II* était de 26 (23 ; 33). La durée moyenne d'hospitalisation en réanimation avant l'inclusion était de 6 jours (3 ; 11). Aucun patient n'était intubé, 28 (46%) étaient sous oxygène et 6 (10%) nécessitaient un recours à la noradrénaline au moment de l'inclusion.
A l'état basal, cIVC-ns et cIVC-st étaient significativement plus importants chez les patients répondeurs que non répondeurs. Une valeur de cIVC-ns supérieure ou égale à 33% permettait de prédire une réponse au remplissage avec une sensibilité de 84,2% et une spécificité de 82,6%.
Une valeur de cIVC-st supérieure ou égale à 44% permettait de prédire une réponse au remplissage avec une sensibilité de 94,3% et une spécificité de 87,0%.
Ces seuils permettaient de classer correctement 86,2% des patients pour cIVC-ns et 91,4% pour cIVC-st (p=0,18).

Conclusion : cIVC est un outil non-invasif efficace pour prédire la réponse au remplissage chez les patients de réanimation en ventilation spontanée. En cas de valeur basse lors d'une inspiration non standardisée, une inspiration standardisée doit être réalisée car elle permet d'accroître les performances de cet indice.

Mots clés : Veine cave inférieure, Réponse au remplissage, Précharge dépendance, Fluides, Hémodynamique, Echographie, Index de collapsibilité, Ventilation spontanée, Lever de jambes passif, Variations respiratoires, Inspiration standardisée

ABSTRACT

Background: In a derivation study among spontaneously breathing patients admitted in the intensive care unit (ICU), a collapsibility index of the inferior vena cava (cIVC) superior or equal to 33% under unstandardized breathing or 44% during a standardized inspiration was proven to be able to predict fluid responsiveness with good accuracy.
The present validation cohort aimed to prospectively validate these thresholds.

Methods: This monocentric prospective study was conducted in spontaneously breathing patients hospitalized in the ICU of the Lille university hospital. cIVC was measured by ultrasound at 4 cm from its abutment in the right atrium, during non-standardized (cIVC-ns) and standardized inspiration (cIVC-st).
The reference test to define fluid responsiveness was an increase superior or equal to 10% of the time-velocity integral of aortic flow induced by a passive leg raising test.

Results: Among the 61 patients, 38 (62.2%) were fluid responsive. Median simplified acute physiologic score II was 26 (23; 33). Median ICU length of stay before inclusion was of 6 days (3; 11). At the time of inclusion, 28 patients (45.9%) required oxygenation, none were intubated, and 6 (9.8%) were on vasopressors.
At baseline, cIVC-ns and cIVC-st were significantly higher in fluid responsive than in fluid-unresponsive patients.
When cIVC-ns was superior or equal to 33%, fluid responsiveness was predicted with a sensitivity of 84.2% and a specificity of 82.6%.
When cIVC-st was superior or equal to 44%, fluid responsiveness was predicted with a sensitivity of 94.3% and a specificity of 87.0%.
These thresholds allowed to correctly classify 86.2% of the patients for cIVC-ns, compared to 91.4% for cIVC-st (p=0.18).

Conclusion: cIVC is a useful non-invasive test to predict fluid responsiveness in spontaneously breathing patients, admitted in ICUs. If its value is low under unstandardized breathing, then a standardized inspiration should be performed, as it allows better classification of the patients.

Keywords: Inferior vena cava, Fluids, Fluid responsiveness, Preload dependence, Hemodynamic, Ultrasound, Collapsibility index, Spontaneous breathing, Passive leg raising, Respiratory variations, Standardized inspiration

INTRODUCTION

Volume expansion is one of the most frequent therapies in intensive care, with the aim of increasing cardiac output and tissue oxygenation [1,2], in order to improve the prognosis of patients [3]. However, fluid responsiveness (FR), defined as a rise in cardiac output in response to vascular filling, is found in only 50 to 70% of patients hospitalized in intensive care units (ICU) [4,5]. In addition, while the optimal amount of fluids to administer is difficult to determine, insufficient or excessive blood volume is detrimental to the prognosis of patients [6,7]. Therefore, it is necessary to predict the interest of initiating, continuing or interrupting fluid administration.

Several dynamic indices have been proposed [5,8], but they are not widely used in the ICUs, notably because of their technical nature and their need for invasive monitoring [9]. Moreover, most of these tests are not validated in spontaneously breathing patients [10,11].
Ultrasound assessment of the collapsibility index of inferior vena cava (cIVC; IVC) is a non-invasive, rapid and repeatable tool that has been proposed to predict FR in these patients [12–14]. But, to date, its use has been limited by contradictory data in the literature [15,16]. However, these studies used heterogeneous measurement methods, notably in terms of ultrasonographic views and measurement sites of the IVC. Conversely, the recent use of ventilatory maneuvers has shown to improve the accuracy of non-invasive tests, by artificially enhancing the cyclic changes in intrathoracic and transpulmonary pressures [17,18].

For these purposes, our team has previously shown : on the one hand that the measurement of cIVC was the most reliable in a longitudinal bidimensional mode, at 4cm from its abutment in the right atrium, and that, on the other hand, the use of a standardized and easily achievable inspiration improved the accuracy of cIVC [19–22]. In a derivation cohort, optimal cIVC thresholds were defined to predict FR : namely ≥ 33% in non-standardized inspiration (cIVC-ns) and ≥ 44% in standardized inspiration (cIVC-st) [22].

The present validation cohort aimed to prospectively validate these cIVC thresholds to predict FR in ICU patients breathing spontaneously.

METHODS

TRIAL DESIGN

This was a prospective, monocentric and observational validation study, registered under the number NCT03780660 on ClinicalTrials.gov. It was conducted in 6 ICUs of the Lille university hospital. Inclusions were performed from February 2019 to April 2021, after the ethical approval from the ethic comity of Ile de France in October 2018 (n° 2018-A01449-46). Written consent was obtained from the patient, after written and oral information regarding the objectives of the study and the course of the experiment.

PATIENTS

Inclusion criteria were as follows: patients aged 18 years or older, admitted in one of the participating ICUs, spontaneously breathing without mechanical ventilation or tracheostomy, and equipped with a bladder catheter suitable to measure intra-abdominal pressure (IAP).

Exclusion criteria comprised refusal to participate to the study, lack of national French health insurance, legal incapacity, pregnancy [23], active exhalation, need for urgent hemodynamic treatment during the protocol, or impossibility to assess FR via a PLR, meaning in the event of intracranial hypertension, lower limb amputation, high-grade aortic insufficiency, echogenicity unsuitable to measure the left ventricle outflow tract (LVOT) velocity-time integral (VTI) or intra-abdominal hypertension, defined as an IAP >16 mm Hg [24–27].

For IAP pressure measurement, we connected the bladder catheter to a pressure transducer, itself connected to a Philips Intellivue MP50 monitor (Philips Medical System, Germany). Bladder was emptied and the tubing was clamped. We then filled it with 50mL of 0.9% saline serum, in a sterile way. Zero setting was set at the pubis level. IAP was measured at end expiration in the supine position, with the transducer zeroed at the level where the midaxillary line crosses the iliac crest, as recommended [27].

DATA COLLECTION

Demographic and clinical data were collected prospectively and included age, sex, body mass index (BMI), medical and surgical history, prognostic scores calculated on the day of inclusion in

the study (simplified acute physiology score (SAPS) II [28]; sequential organ failure assessment (SOFA) score [29], and Charlson comorbidity index [30]), length of stay in ICU at the time of inclusion, or presence of clinical signs of hypoperfusion : mottled skin, hypotension (systolic arterial pressure < 90mm Hg or a decrease of 40 mm Hg in a previously hypertensive patient), tachycardia (heart rate ≥ 100 /min) and oliguria (urine output < 0.5 mL/kg/h over one hour or more).

STUDY PROTOCOL

The course of the protocol is described in **Figure 1.**

Buccal pressure (BP) was recorded with a manometer MP101 (0 ± 100 mm H_2O) (KIMO instrument, Montpon, France) during non-standardized (BP-ns) and standardized inspiration (BP-st), as described before [20]. A depression greater than 3 mm H_2O during inspiration defined a standardized inspiration, based on a study conducted by our team showing that this threshold was both easily achievable in ICU patients and sufficient to improve the performance of cIVC to predict FR [19,20].

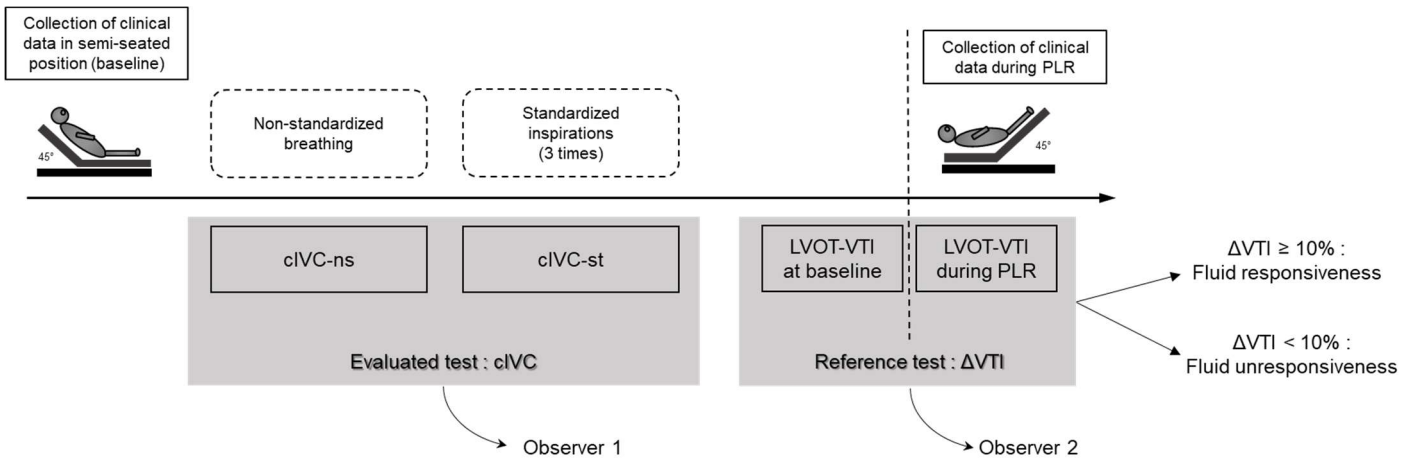

Figure 1. Course of the experiment

Patients were monitored continuously throughout the inclusion period. Vital constants were measured at 45° (baseline), and during the passive leg raising (PLR) maneuver.

The experiment consisted in breathing normally for 30 seconds through a device measuring buccal pressure, each of these respiratory cycles corresponding to unstandardized breathing. Then the patient was asked to perform a standardized inspiration, which consisted in a deep, continuous and brief (< 5 seconds) inspiration, generating a depression greater than -3 mm H_2O. This was repeated 3 times. Collapsibility of inferior vena cava (IVC) was recorded under non-standardized (cIVC-ns) and standardized (cIVC-st) inspirations.

A first left ventricular outflow tract velocity-time integral (LVOT-VTI) was recorded in semi-seated position. We then performed a PLR maneuver, which consisted in the inclination of the trunk to 0°, with an angle being kept at 45° with the lower limbs. Recordings of the new LVOT-VTI were achieved within two minutes of the start of the PLR. This allowed the future computation of the variation of the LVOT-VTI induced by the PLR (ΔVTI), our gold-standard test to assess fluid responsiveness (FR).

ECHOGRAPHY RECORDINGS

The echocardiography recordings were performed using a Vivid S5 ultrasound machine (General Electric, Solingen, Germany) equipped with a trans-thoracic probe. All observers were trained to echocardiography [31].

The IVC recordings were done in a semi-recumbent position, in a sub-xyphoid, long-axis view, using the two-dimensional mode, as described previously [22]. Interest was focused on visualizing the largest possible IVC diameter, in an attempt to obtain the most centered vessel section in the sagittal plane during the whole respiratory cycle. The IVC measurements were remotely performed, after anonymization, using the EchoPAC PC Software (General Electric Healthcare, Chicago, USA). They were performed by an operator, different from the one who measured the ΔVTI. Minimum inspiratory (iIVC) and end-expiratory (eIVC) diameters of the IVC were measured perpendicular to the IVC wall, from the trailing edge to the leading edge of the anterior and posterior wall respectively. Measurements were performed at 4 cm from the termination of the IVC in the right atrium, this being the most optimal location, as previously demonstrated [22]. IVC diameters were measured during unstandardized and standardized respiratory cycles. The mean of three measurements was used to calculate cIVC, as follows: cIVC (%) = (eIVC – iIVC) / eIVC.

The LVOT-VTI recordings were performed with pulsed Doppler, in a 5-cavity view. They were performed by a first observer just before, and then within 2 minutes of the PLR. Recordings were stored digitally and anonymized. The measurements were performed secondarily, by another observer, blinded from clinical data and IVC measurements. The LVOT-VTI were obtained in trans-thoracic view, by measuring the area under the Doppler velocity curve of the sub-aortic blood flow during systole. Values were averaged over fifteen consecutive cardiac cycles. A PLR maneuver was performed as a self-fluid challenge. PLR-induced change in LVOT-VTI (ΔVTI) was calculated as follows: ΔVTI (%) = 100* (LVOT-VTI during PLR – LVOT-VTI at baseline) / LVOT-VTI at baseline. A 10% increase in LVOT-VTI due to PLR defined FR [10,32–35]. Regarding the threshold, we used a value of 10% because it was shown to be sufficient to be clinically relevant, as long as both LVOT-VTIs are measured by the same observer [11,34–

36]. Additionally, the intra-observer variability for the measurement of ΔVTI in our previous study was 3.5%, hence more than twice lower than 10% [22].

SAMPLE SIZE CALCULATION

Considering an H0 hypothesis defining a theoretical area under the curve (AUC) of 0.7 (an AUC less than 0.7 corresponding to insufficient predictive power), an H1 hypothesis equivalent to the previously obtained AUC of 0.89 [20], a percentage of FR patients in the target population estimated at 40%, an α risk of 5% (2-sided test), and a β risk of 10%, the number of patients required to demonstrate a significant difference was 68 patients.

STATISTICS

Categorical variables were expressed as numbers (percentages), and continuous variables as median (interquartile range), according to normality. Normality was checked graphically and using Shapiro-Wilk test.

Comparisons of patients' characteristics according to FR were performed using Chi-square test or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. Diagnostic values (and their 95% confidence intervals) of the published optimal thresholds of cIVC-ns (namely cIVC-ns ≥ 33%) and cIVC-st (namely cIVC-st ≥ 44%) to predict FR were evaluated by calculating sensibility, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio [22]. Well-classified rates of these thresholds were compared between standardized and non-standardized measures using McNemar' test. On top of this single-threshold analysis, we also designed a gray-zone approach. To do so, we used thresholds of cIVC-ns and cIVC-st previously identified for having a sensitivity and a specificity to predict FR above 90% (respectively for the lower and the upper threshold); these thresholds were cIVC-ns ≥ 14% and cIVC-ns ≥ 33% on the one hand and cIVC-st ≥ 35% and cIVC-st ≥ 44% on the other hand [22]. A cIVC under the lower threshold was expected to indicate a patient being fluid unresponsive. A cIVC above the upper threshold was expected to indicate a patient being fluid responsive. A cIVC comprised between the two thresholds would be inconclusive concerning the fluid responsiveness. We then calculated the well-classified rates

using these thresholds. Scatterplot diagrams were produced to provide visual representations of the designed gray-zones.

Correlations between cIVC-ns and cIVC-st on the one hand, and IAP or ΔVTI on the other hand were assessed by calculating the Spearman's rank correlation coefficients.

Intra and inter-observer (between 3 observers) reliability for cIVC-st were evaluated by calculating the intraclass correlation coefficient.

All statistical tests were performed at the two-tailed α level of 0.05 using SAS software, release 9.4 (SAS Institute, Cary, NC).

RESULTS

Of the 90 patients screened, 68 patients constituted the enrolled population. After exclusion of 7 patients, 61 patients were finally included (**Figure 2**).

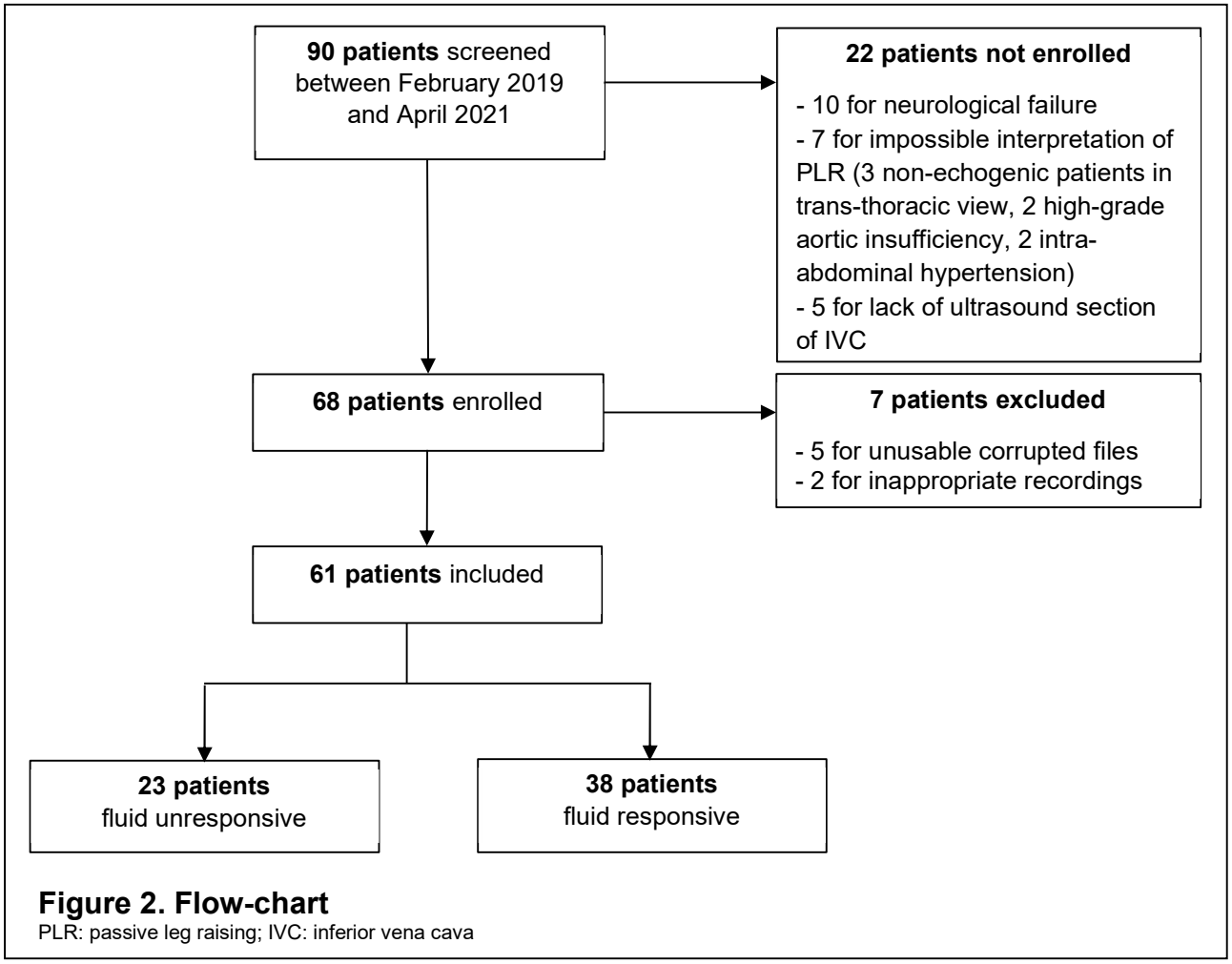

Figure 2. Flow-chart
PLR: passive leg raising; IVC: inferior vena cava

The overall characteristics at baseline are described in **Table 1**, according to FR status. 33 patients (54.1%) were men. The median body mass index (BMI) was 25.8 (23.0; 33.2). Median ICU stay before inclusion was of 6 days (3; 11). The median age was 62 years (50; 72). The median SAPS II score was 26 (23; 33). 10 patients (16.4%) had atrial fibrillation in their past history. The reason for admission was medical in 46 cases (75.4%), with a statistically significant difference between the fluid unresponsive group (56.5%) and the fluid responsive group (86.8%) (p=0.008).

Oxygenation was needed in 28 patients (45.9%), including 22 patients (78.6%) with low flow nasal canula and 6 (21.4%) with high flow nasal oxygen (HFNO) therapy.

Median IAP was 9.5 mm Hg (6.0; 12.2) and did not differ significantly between the two groups (p=0.051). IAP was not correlated with cIVC-ns (p=0.15) or cIVC-st (p=0.26).

Measurements of cIVC-st were obtained in 58 patients (95.1%). Standardized inspiration resulted in a median BP-st significantly lower than BP-ns (-7.5 versus -1.8 mm H_2O; p<0.001). BP-ns was lower than -3 mm H_2O in 19 of the 49 patients (38.8%) for whom the values were recorded.

Table 1. Clinical data in fluid responsive and fluid unresponsive patients at baseline

General data	Fluid unresponsive patients (n=23)	Fluid responsive patients (n=38)	*p* value
Characteristics			
Men	13 (56.5)	20 (52.6)	0.77
Age (years)	60 (45; 73)	62 (51; 69)	0.8
Length of stay (days)	5 (2; 9)	6 (4; 13)	0.29
Admission for medical reason	13 (56.5)	33 (86.8)	**0.008**
Medical history			
BMI (kg/m²)	27.5 (24.5; 37.4)	24.5 (22.6; 30.5)	0.065
Arterial hypertension	12 (52.2)	17 (44.7)	0.57
Chronic left heart failure	2 (8.7)	4 (10.5)	NA
Chronic right heart failure	3 (13.0)	1 (2.6)	NA
Supra-ventricular arythmia	18 (78.3)	33 (86.8)	NA
Obliterative arteriopathy of the lower limbs	3 (13.0)	4 (10.5)	NA
Chronic obstructive pulmonary disease	7 (30.4)	5 (13.2)	0.18
Pulmonary hypertension	2 (8.7)	3 (7.9)	NA
Pulmonary embolism	1 (4.3)	3 (7.9)	NA
Prognostic scores			
SAPS II	26 (17; 38)	26 (21; 29)	0.41
SOFA	4 (1; 6)	3 (1; 5)	0.93
Charlson comorbidity Index	3 (0; 5)	2 (0; 4)	0.41
Signs of hypoperfusion	12 (52.2)	16 (42.1)	0.44
Mottling	2 (8.7)	4 (10.5)	NA
Tachycardia	5 (21.7)	3 (7.9)	0.54
Hypotension	2 (8.7)	1 (2.6)	NA
Oliguria	5 (21.7)	11 (28.9)	0.14
Norepinephrine†	3 (13)	3 (8)	NA
Respiratory variables			
Oxygenation	9 (39.1)	19 (50.0)	0.41
including HFNO	1 (11.1)	5 (26.3)	NA
Respiratory rate (per minute)	23 (18; 26)	21 (18; 24)	0.33
BP-ns (mm H_2O)	-1.8 (-6.5; -0.5)	-1.8 (-4.0; -0.5)	0.57
BP-st (mm H_2O)	-6.7 (-12.6; -4.2)	-7.6 (-11.3; -4.6)	0.96

BMI: body mass index; BP: buccal pressure under unstandardized breathing (BP-ns) and standardized inspiration (BP-st); HFNO: High-flow nasal oxygen; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment.
† Norepinephrine was the only vasoconstrictor used during the study. Doses of the corresponding patients were: 0.2; 0.26 and 0.7µg/kg/min in the fluid unresponsive group and 0.16; 0.18 and 0.25µg/kg/min in the fluid responsive group.
Values are expressed as count (%) or median and interquartile range (25th; 75th percentiles).

Main hemodynamic variables at baseline and during PLR are listed in **Table 2**. Thirty-eight patients (62%) were fluid responsive, with a mean ΔVTI of 15.2% (12.5; 21.3), compared to a mean ΔVTI of 2.5% (0.2; 8.3) in fluid unresponsive patients (p<0.001).

Table 2. Hemodynamic parameters at baseline and during passive leg raising (PLR) in fluid responsive and unresponsive patients

Hemodynamic parameters	Fluid unresponsive patients (n=23)	Fluid responsive patients (n=38)	*p* value
LVEF>50%, n (%)			
45°	20 (87)	33 (92)	NA
Pulse pressure (mm Hg)			
45°	55 (46; 68)	50 (41; 66)	0.59
Per-PLR	56 (48; 67)	54 (45; 75)	0.81
Systolic arterial pressure (mm Hg)			
45°	123 (111; 135)	126 (108; 138)	0,93
Per-PLR	118 (111; 137)	126 (108; 140)	0.48
Diastolic arterial pressure (mm Hg)			
45°	61 (58; 70)	69 (60; 76)	0.21
Per-PLR	59 (55; 68)	66 (60; 71)	0.17
Mean arterial pressure (mm Hg)			
45°	76 (70; 92)	88 (77; 94)	0.13
Per-PLR	79 (70; 86)	83 (75; 93)	0.24
Heart rate (beats/min)			
45°	83 (76; 93)	89 (79; 95)	0.34
Per-PLR	84 (75; 98)	88 (79; 97)	0.31
LVOT-VTI (cm)			
45°	20.9 (18.2; 24.1)	18.6 (16.4; 21.4)	0.063
Per-PLR	20.9 (18.2; 26.4)	21.5 (19.1; 25.4)	0.77
cIVC (%), at 45°			
cIVC-ns	7.5 (4.2; 19.7)	56.3 (38.0; 70.0)	**<0.001**
cIVC-st	18.4 (6.5; 26.4)	61.1 (52.4; 75.7)	**<0.001**

PLR: passive leg raising; LVEF: left ventricular ejection fraction; LVOT-VTI: left ventricular outflow tract velocity-time integral; ΔVTI: PLR-induced change in the LVOT-VTI; cIVC: collapsibility index of the IVC under unstandardized inspiration (cIVC-ns) and standardized inspiration (cIVC-st); IVC, inferior vena cava.
Values are expressed as count (%) or median and interquartile range (25th; 75th percentiles).

At baseline, cIVC-ns and cIVC-st were significantly higher in fluid responsive than in fluid-unresponsive patients, and were positively correlated with ΔVTI (r = 0.58 and 0.56 respectively; p<0.001) (**Figure 3**).

Sensitivity and specificity to predict FR were respectively of 84.2% and 82.6% for a cIVC-ns ≥ 33% and of 94.3% and 87% for a cIVC-st ≥ 44% (**Table 3**). These thresholds allowed to correctly classify 86.2% of the patients for cIVC-ns, compared to 91.4% for cIVC-st, with no significant difference (p=0.18). Standardization of the inspiration allowed a decrease in false

positive patients compared to unstandardized inspiration (respectively 3 patients versus 4), as well as in false negative patients (respectively 2 patients versus 6). Personal data of the false positive and false negative patients can be found in **Appendix 1**.

The gray-zone approach of cIVC-st revealed 2 (5.7%) false-negative patients below the 35% threshold, 3 (13.0%) false-positive above the 44% threshold, and 1 patient (1.7%) in the gray-zone (**Figure 4**). It thus allowed a correct classification of 89.7% patients, compared to 79.3% for cIVC-ns (using thresholds of 14% and 33%), this difference being statistically significative (p=0.034).

Inter-observer agreement for cIVC was 0.87 (0.57; 0.98). The 3 intra-observer agreements were 0.92; 0.97 and 0.98.

Table 3. Accuracy of the previously defined thresholds for predicting fluid responsiveness

		TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	PV+ (%)	PV- (%)	LR+	LR-
cIVC-ns	>14%†	36	8	15	2						
	≥33%†°	32	4	19	6	84 [69; 94]	83 [61; 95]	89 [74; 97]	75 [55; 91]	5 [2; 12]	0.2 [0.1; 0.4]
cIVC-st	>35%†	33	4	19	2						
	≥44%†°	33	3	20	2	94 [81; 99]	87 [66; 97]	92 [78; 98]	91 [71; 99]	7 [3; 21]	0.1 [0.0; 0.3]

Diagnostic values were reported with their 95% confidence intervals.
cIVC-ns: collapsibility index of the IVC under unstandardized breathing (cIVC-ns) and standardized inspiration(cIVC-st); IVC: inferior vena cava.
TP: true positive; FP: false positive; TN: true negative; FN: false negative. Values are given as numbers of patients.
PV+: positive predictive value; PV-: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio
Measurements were obtained in 61 patients for the unstandardized inspiration and in 58 patients for the standardized inspiration.
° previous single optimal threshold.
† thresholds of the gray-zone approach, having previously a sensitivity ≥ 90% and a specificity ≥ 90% [22].

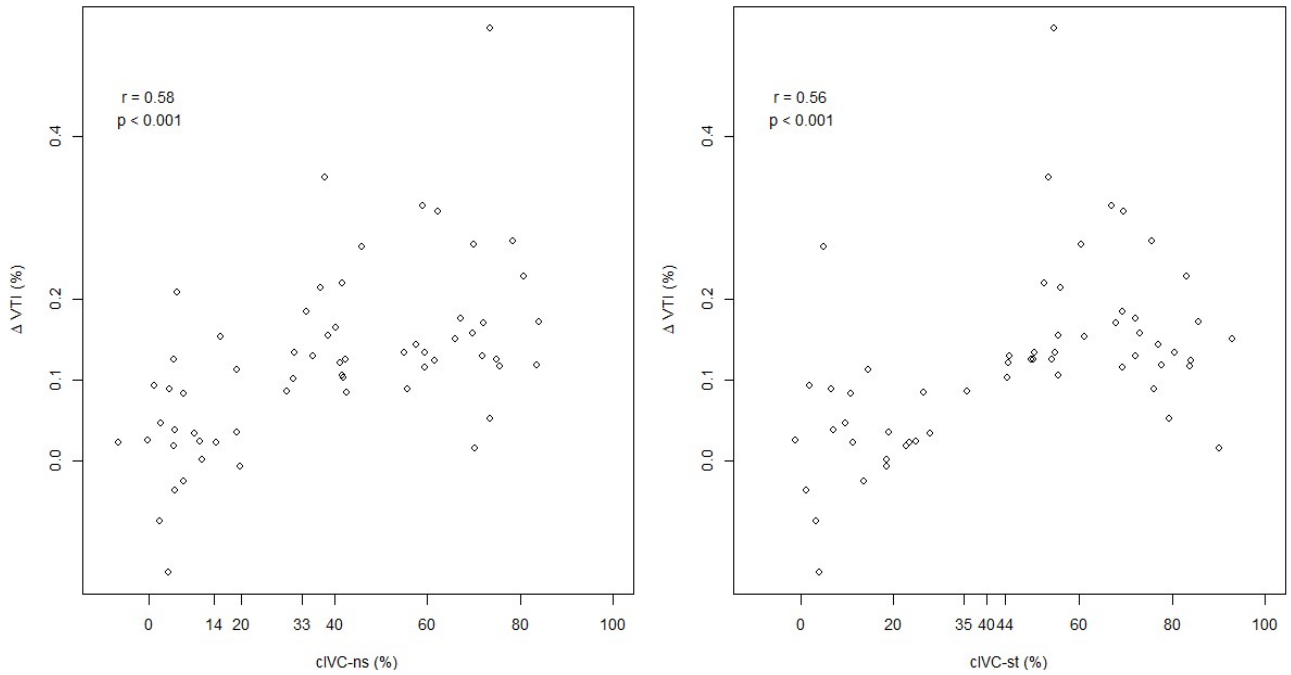

Figure 3. Correlation between passive leg raising induced changes in the velocity-time integral of the left ventricle outflow track (∆VTI) and the collapsibility index of inferior vena cava under unstandardized breathing (cIVC-ns) and standardized inspiration (cIVC-st).

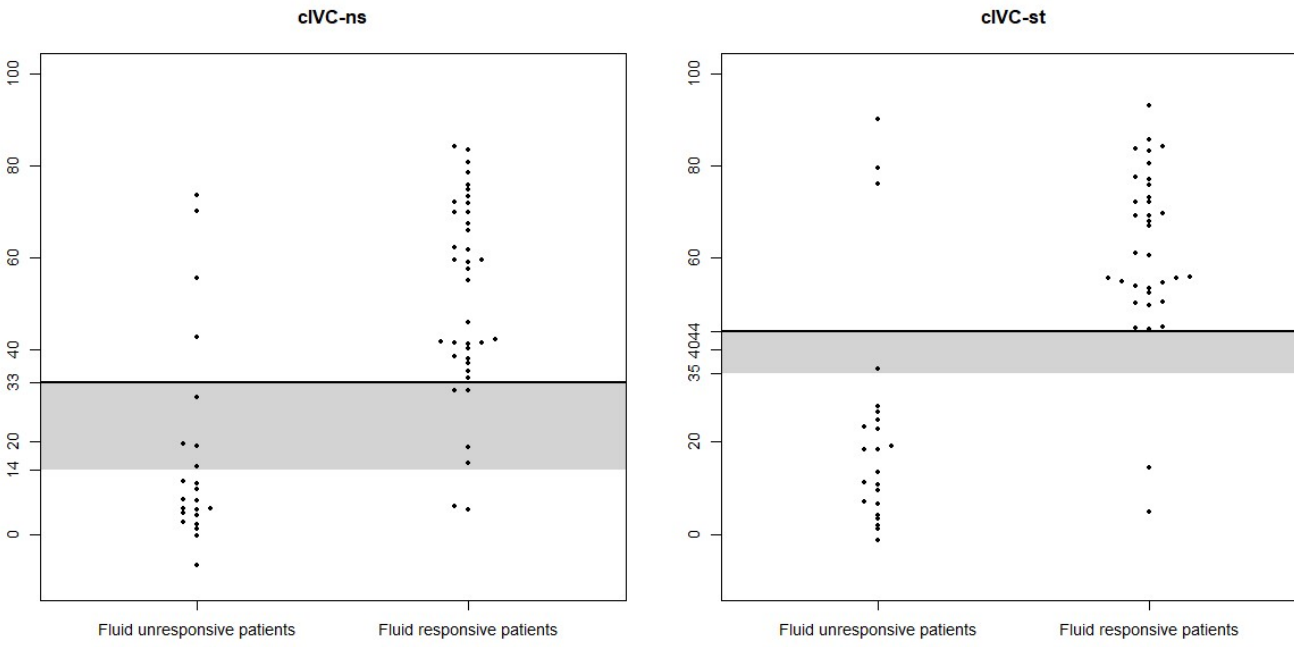

Figure 4. Scatterplot of individual values for the collapsibility index of inferior vena cava under unstandardized breathing (cIVC-ns) and standardized inspiration (cIVC-st)

Black lines show the optimal thresholds. Gray rectangles represent the cIVC gray-zone, using the predefined thresholds. The values on the ordinate axis correspond to the cIVC, expressed in %.

DISCUSSION

Our study prospectively validates previously proposed thresholds of cIVC to predict FR in spontaneously breathing patients [22].

A threshold of cIVC-st ≥ 44% had a sensitivity of 94.3%, a specificity of 87% and allowed to correctly classify 91.4% of the patients. Interestingly, the negative likelihood ratio was 0.1; such a low value grants confidence in excluding FR if cIVC-st is below this threshold. In terms of clinical application, we propose to use these robust cIVC-st thresholds in the first place, even during non-standardized inspiration. As so, in the event of an hypoperfusion, if cIVC-ns is superior or equal to 44%, the patient would likely benefit from fluid expansion, without any need for a deeper inhalation. Conversely, if cIVC-ns is inferior to 44%, then a standardized inspiration should be performed. If cIVC-st becomes superior or equal to 44%, FR is highly probable. If cIVC-st is under 35%, FR is unlikely. If cIVC-st remains between 35% and 44%, the test is not conclusive by itself and other data should be taken into account before decision is made (**Figure 5**).

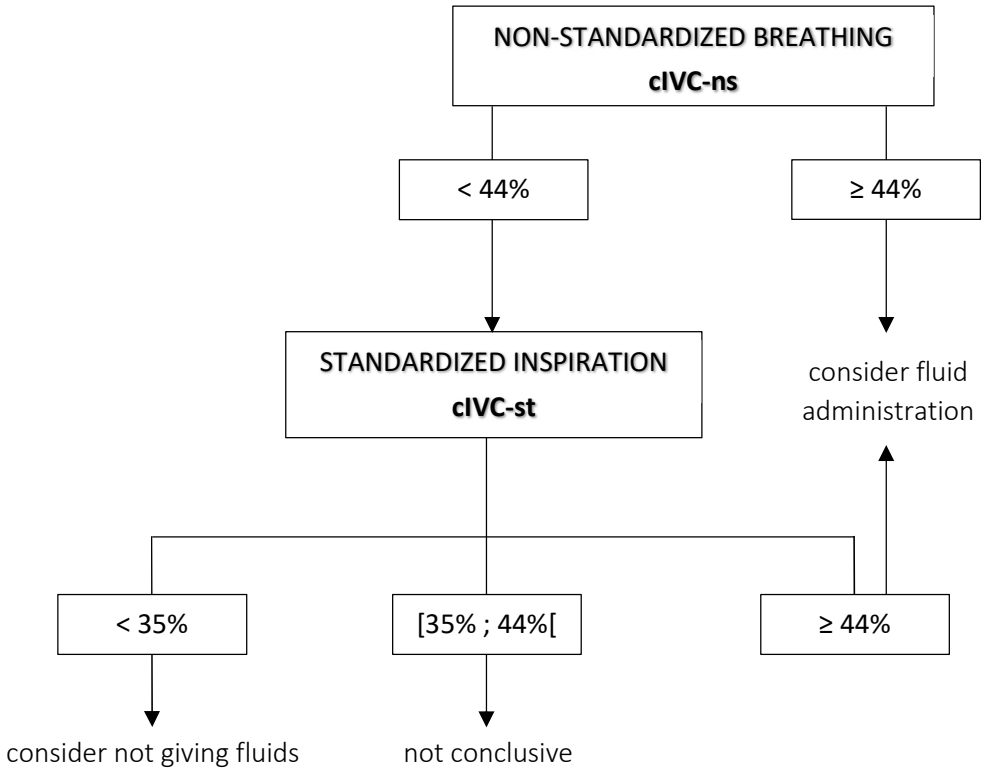

Figure 5. Proposal of an algorithm using the collapsibility of the inferior vena cava to guide fluid administration in a patient presenting with hypoperfusion

cIVC: collapsibility index of the IVC under unstandardized breathing (cIVC-ns) and standardized inspiration (cIVC-st).

However, it is noteworthy that the present results remain accurate only if measurements of IVC diameters are performed as follows: in the sub-xyphoid long-axis view, using the two-dimensional mode, perpendicular to the IVC wall, and 4cm before its termination into the right atrium [22]. Unlike transverse incidence and/or time-motion measurements, long-axis view in two-dimensional mode helps to measure the inspiration and expiration diameters at the same site. This minimizes the bias due to the caudal movement of the IVC, averaged at 21.7 mm during quiet inspiration [37]. In our opinion, even if these conditions are constraints, they ensure improved reproducibility of the measurements. This is evidenced by our inter-observer reliability, which is better than previously reported in two-dimensional mode, with an intraclass correlation coefficient of 0.87 compared to 0.58 in the study of Fields *et al.* [38]. A rigorous standardization of IVC measurement should help limit cIVC variability from one observer to another. This should make the use of cIVC possible even for less experienced clinicians. It should also ensure the comparability between different measures made at different time of the day by different physicians. Therefore, standardization compensates for the non-continuous character of the measurement of the cIVC, by allowing to have a follow-up of the values.

Concerning the three false positive results of cIVC-st, explanation does not come from an excessive inhalation. Indeed, these patients also reached the threshold of 44% in unstandardized inspiration, with BP-ns values comprised between -0.1 and -9.0 mm H_2O (**Appendix 1**).
Interestingly, in two of the three false positive patients, we noticed a visual oscillation in the IVC diameter, at basal state, independently from respiration. Of note, this was also reported in at least seven other patients, who were all fluid responsive. Cardiac induced variations of IVC diameters have been recently studied thanks to automated IVC edge-to-edge tracking system [39]. They could induce a collapsibility of the IVC of 11% in expiration and 13.8% in inspiration [40]. Additionally, in the latter study, the cardiac oscillations seemed to increase in patients with lower central venous pressure, which is in line with their presence among mostly fluid responsive patients in our study. In the present study, when such oscillations occurred, we chose to measure the lowest possible IVC diameters in both inspiration and expiration. Not measuring diameters at the end of diastole might have impaired the diagnostic accuracy of cIVC but it improves its clinical

feasibility. However, standardizing the measure of cIVC on the different phases of the cardiac cycle, by simultaneously recording a real-time electrocardiogram, could provide greater information. Of note, a delay has been reported between the electrocardiogram events and subsequent IVC pulsation; the end-diastolic diameter of the IVC actually being witnessed during ventricular (electrical) systole [41].

From a clinical point of view, false positive patients are of concern to the physician because they might be exposed to unnecessary volume expansion. However, as discussed previously, in these patients, the crossing point between venous return and cardiac function would likely be situated at the junction between the ascending and the flat section of the Frank-Starling curve. Consequently, in the event of a volume expansion, the heart of these patients would shift to the plateau portion. Thereafter, those patients would become true negatives, if re-assessed before a second volume expansion. Accordingly, every false positive cIVC-st in a previous study led to non-compliant IVC after volume expansion [20]; fluid administration would therefore be stopped, limiting the risk of fluid overload. In our study, we could have tested this hypothesis by measuring cIVC during the PLR. PLR could have induced a decrease in cIVC, as shown before [42]. Unfortunately, this could not be performed with sufficient precision due to the transient hemodynamic effects of the PLR (1-2 minutes). Since we prioritized the evaluation of the VTI during PLR, measurement of cIVC during PLR might have been performed too late, after the end of the volume expansion induced by PLR.

Among the 2 false negative results of cIVC-st, one patient did not reach a BP-st below the -3 mm H_2O threshold. Importantly, the key message is to ensure that the patients perform a deep enough inspiration, to avoid as much false negative as possible. Additionally, chest wall breathing has been shown to induce a lower cIVC than diaphragmatic inspirations [43,44]. We did not measure diaphragmatic excursion, nor asked patients to breathe in a specific manner. Even though, we could hypothesize than an exclusive chest wall inspiration could have been involved in our false negative patients.

With regards to unstandardized breathing, our data confirms that cIVC-ns remains less accurate than cIVC-st. This difference was statistically significative concerning the gray-zone-

approach (p=0.03), but not for the single-threshold analysis (p=0.18), unlike the derivation study. One explanation could be that our patients were included in a later stage of their hospitalization or were less severely ill than in the derivation study. Length of stay wasn't collected in the derivation study, but the SAPS II score was lower in our study : 26 (19; 32) than in the derivation study : 34 (24; 42) [22]. This could have led to better respiratory performances in our patients, at basal state. As so, the unstandardized breathing in our study resulted in lower BP-ns levels than those of the derivation study : -1.8 mm H_2O (-4.0; -0.5) versus -0.5 mm H_2O (-1.0; 0.0) [22]. This could explain the better sensitivity of cIVC-ns to predict FR in our study compared to previous data in ICU, reporting lower sensitivities, ranging from 31% to 76% [20,45–47]. Moreover, the fact that patients may have inhaled more deeply during unstandardized breathing could also explain the lower improvement secondary to standardization of the inspiration than in the derivation study. Indeed, 38% of the patients reached the -3 mm H_2O threshold in unstandardized inspiration, thus realizing an unexpected standardized inspiration. Of note, our median value of BP-st level was also inferior: -7.5 mm H_2O (-12.4; -4.2) in our study, compared to -6.0 (-7.0; -5.0) in the derivation study; but this difference seems to be driven mostly by the extreme negative values of the first interquartile, which differ more than the median itself.

Concerning the gray-zone approach, the percentage of correctly classified patients is less important than with the single-threshold approach: respectively 79.3% versus 86.2% for cIVC-ns and 89.7% versus 91.4% for cIVC-st. This decrease in the number of well classified patients is however expected, since patients in the gray-zone are considered as not classified. Conversely, the main purpose of gray-zone is to decrease the number of false negatives. The scatterplot shows that the gray-zone approach of cIVC-ns reduces the number of false negatives from 6 patients to 2 patients, which *in fine*, will lead to a desired increase of the negative predictive value [21]. On the other hand, the gray-zone approach of cIVC-st does not reduce the number of false negatives. However, this does not seem to be due to the inappropriateness of the thresholds defined in the derivation study, but to the extremely low cIVC-st values of these two false negative patients (5% and 14%).

The main strength of our study lies in the prospective collection of the data. Secondly, we chose the ΔVTI induced by the PLR as our primary endpoint. On the one hand, because PLR allows a self-filling, therefore avoiding the risk of an inadequate volume expansion. On the other hand, because it has been validated as an accurate test to predict FR in spontaneously breathing patients [32,33,48]. Additionally, the measurement of ΔVTI was performed by an external observer, blinded of the cIVC and of the clinical patient's status. Thirdly, in comparison to the derivation study, we included patients regardless of their reason for admission to the ICU, and not just in case of sepsis anymore.

Finally, the median BMI of our patients was 25.8 (23.0; 33.2); with 13 patients (21%) being overweight and 20 (33%) being obese. Thus, cIVC seems to be applicable to such a population, in which concerns have been raised [49,50].

There are some limitations in our study that the reader should be aware of. Firstly, due to the inclusion criteria, our patients were not severely ill: they were not be intubated and only 10% received intravenous vasopressors. Therefore, the results should be more directly applicable in emergency or intermediate care departments. Still, we show that cIVC remains an interesting tool in the ICU after the initial resuscitation, as median length of hospitalization in ICU before the inclusion was of 6 days.

Secondly, ultrasonographic view of the IVC could not be obtained in 5 (8%) patients, which is in line with the previous studies, estimating this occurrence between 5% and 18% of spontaneous breathing patients [19,20,38,51,52].

Thirdly, our results cannot be applied to the excluded patients, notably for active exhalation. Similarly, none of our patients suffered from known significative tricuspid regurgitation or acute right heart failure, which limits extrapolation to such patients. Of note, our results can be applied to patients for whom PLR would be contra-indicated, as this tool was not used to determine FR in the derivation study. Therefore, cIVC constitutes a complementary test to the PLR, which could be performed when the latter is not interpretable [50].

Fourthly, we are facing the usual limitations of the diagnostic tests in spontaneously breathing patients: necessary cooperation from the patient, limited interpretation in the event of a high

respiratory rate or a diaphragmatic dysfunction, etc. However, if we recommend the inspiration to be deep enough, we also highlight that it should still remain easily achievable. This is why we used the method described by Préau *et al.*, as it seems easier than other methods previously proposed, such as Valsalva or inspiration lasting above five seconds [19]. This makes it suitable for application even in our ICU patients, including those requiring HFNO. Indeed, if only 9.8% patients required HFNO in our study, this percentage reached 19% in the derivation study [50].

CONCLUSION

Our study confirms prospectively that cIVC is a useful non-invasive test to predict FR in spontaneously breathing patients, admitted in ICUs.

If the result remains unclear under unstandardized breathing, then a standardized inspiration should be performed, as it allows better classification of the patients.

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APPENDIX

Appendix 1. Personal data of false positive and false negative patients

	BP-ns (mm H_2O)	BP-st (mm H_2O)	ΔVTI (%)	cIVC-ns (%)	cIVC-st (%)	IAP (mm Hg)
FP 1	-0.1	-1.5	5.3	73	79	13
FP 2	-9.0	-11.3	8.9	56	76	12
FP 3	-6.0	-30.5	1.5	70	90	12
FN 1	-0.5	-2.8	26.4	46	5	4
FN 2	-0.1	-6.0	11.3	19	14	16

FP: false positive; FN: false negative; BP: buccal pressure under unstandardized inspiration (BP-ns) and standardized inspiration (BP-st); ΔVTI: change in the left ventricular outflow tract velocity-time integral induced by the passive leg raising; IVC, inferior vena cava; cIVC: collapsibility index of the IVC under unstandardized inspiration (cIVC-ns) and standardized inspiration (cIVC-st); IAP: intra-abdominal pressure
Recordings in FN 1 showed *a posteriori* arguments for possible truncated inferior vena cava under unstandardized inspiration.

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Date de soutenance : 13/10/2022

Titre de la thèse : L'index de collapsibilité de la veine cave inférieure comme marqueur prédictif de la réponse au remplissage chez les patients en ventilation spontanée : une étude prospective de validation

Thèse - Médecine - Lille 2022

Cadre de classement : médecine intensive – réanimation

DES + FST/option : médecine intensive – réanimation

Mots-clés : Veine cave inférieure, Réponse au remplissage, Précharge dépendance, Fluides, Hémodynamique, Echographie, Index de collapsibilité, Ventilation spontanée, Lever de jambes passif, Variations respiratoires, Inspiration standardisée

Rationnel : Dans une étude de dérivation menée au sein de patients en ventilation spontanée admis en réanimation, des valeurs d'indice de collapsibilité de la veine cave inférieure (cIVC) supérieures ou égales à 33% en ventilation non-standardisée ou 44% lors d'une inspiration standardisée permettaient de prédire une réponse au remplissage avec de bonnes performances statistiques.
Cette cohorte de validation avait pour but de valider prospectivement ces seuils.

Méthodes : Cette étude prospective monocentrique a été conduite chez des patients en ventilation spontanée, admis en réanimation au sein de l'hôpital universitaire de Lille. Les mesures échographiques de la veine cave inférieure étaient réalisées à 4cm en amont de son abouchement dans l'oreillette droite, durant une inspiration non-standardisée (cIVC-ns) puis standardisée (cIVC-st). Le test de référence pour prédire la réponse au remplissage était une augmentation supérieure ou égale à 10% de l'intégrale temps-vitesse du flux aortique induite par une épreuve de lever de jambes passif.

Résultats : Parmi les 61 patients inclus, 38 (62%) étaient répondeurs au remplissage. La valeur médiane du *simplified acute physiologic score II* était de 26 (23 ; 33). La durée moyenne d'hospitalisation en réanimation avant l'inclusion était de 6 jours (3 ; 11). Aucun patient n'était intubé, 28 (46%) étaient sous oxygène et 6 (10%) nécessitaient un recours à la noradrénaline au moment de l'inclusion.
A l'état basal, cIVC-ns et cIVC-st étaient significativement plus importants chez les patients répondeurs que non répondeurs. Une valeur de cIVC-ns supérieure ou égale à 33% permettait de prédire une réponse au remplissage avec une sensibilité de 84,2% et une spécificité de 82,6%.
Une valeur de cIVC-st supérieure ou égale à 44% permettait de prédire une réponse au remplissage avec une sensibilité de 94,3% et une spécificité de 87,0%.
Ces seuils permettaient de classer correctement 86,2% des patients pour cIVC-ns et 91,4% pour cIVC-st (p=0,18).

Conclusion : cIVC est un outil non-invasif efficace pour prédire la réponse au remplissage chez les patients de réanimation en ventilation spontanée. En cas de valeur basse lors d'une inspiration non-standardisée, une inspiration standardisée doit être réalisée car elle permet d'accroître les performances de cet indice.

<u>Composition du Jury</u> :

Président : Pr Raphaël FAVORY
Assesseurs : Dr Mouhamed MOUSSA, Dr Arthur DURAND
Directeur de thèse : Pr Sébastien PREAU