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End-Expiratory Occlusion Test Predicts Fluid Responsiveness in Patients With Protective Ventilation in the Operating Room

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BACKGROUND: End-expiratory occlusion test (EEOT) has been proposed to predict fluid responsiveness in mechanically ventilated intensive care unit patients. The utility of this test during low-tidal-volume ventilation remains uncertain. This study aimed to determine whether hemodynamic variations induced by EEOT could predict the effect of volume expansion in patients with protective ventilation in the operating room.

METHODS: Forty-one patients undergoing neurosurgery were included. Stroke volume and pulse pressure variations were continuously recorded using pulse contour analysis before and immediately after a 30-second EEOT and after volume expansion (250 mL saline 0.9% given over 10 minutes). Patients with an increase in stroke volume ≥ 10% after volume expansion were defined as responders.

RESULTS: Twenty patients were responders to fluid administration. EEOT induced a significant increase in stroke volume, which was correlated with the stroke volume changes induced by volume expansion ($r^2 = 0.55$, $P < .0001$). A 5% increase in stroke volume during EEOT discriminated responders to volume expansion with a sensitivity of 100% (95% confidence interval [CI], 83%–100%), a specificity of 81% (95% CI, 58%–95%), a positive predictive value of 84% (95% CI, 64%–96%), and a negative predictive value of 100% (95% CI, 80%–100%). The gray zone ranged from 4% to 8%, including 17% of patients. The best pulse pressure variation threshold was 9%, with a sensitivity of 60% (95% CI, 36%–81%) and specificity of 86% (95% CI, 64%–97%). The area under the receiver operating characteristics curve generated for changes in stroke volume induced by EEOT (0.91, 95% CI, 0.81–1.00) was significantly higher than the one obtained for pulse pressure variations (0.75, 95% CI, 0.60–0.90); $P < .05$.

CONCLUSIONS: Changes in stroke volume index induced by EEOT can predict fluid responsiveness in patients with protective ventilation in the operating room. This test may have potential applications. (Anesth Analg 2017;125:1889–95)

Perioperative hypovolemia and hypervolemia increase morbidity and length of hospital stay.[1,2] Volume expansion (VE) is frequently used as the first therapeutic line when patients present low blood pressure, tachycardia, and oliguria. However, only 30% to 50% of fluid challenges will lead to an increase in stroke volume (SV).[3–5] Since many years, several studies have investigated the way to predict the hemodynamic effects of VE.[6] Dynamic variables derived from heart–lung interaction are the most studied. Among them, respiratory-induced pulse pressure variations (PPVs) have been extensively studied in mechanically ventilated patients both in the operating room (OR) and in the intensive care unit (ICU).[4,5] The main limitations for their clinical use are the need for a tidal volume of at least 8 mL/kg and a driving pressure higher than 20 cm H_2O.[7,8] Several studies done both in the ICU and in the OR demonstrated that protective ventilation with low tidal volume (6–8 mL/kg of ideal body weight) is associated with a better outcome.[9–11] Consequently, PPVs and surrogates became less usable.

Several years ago, Monnet et al[12] proposed a new test (end-expiratory occlusion test [EEOT]) to predict fluid responsiveness. During mechanical ventilation, the inspiratory phase increases intrathoracic pressure and decreases venous return. EEOT prevents any variation in intrathoracic pressure. This leads to an increase in venous return, cardiac preload, and SV in preload-responsive patients. Conflicting results concerning the ability of EEOT to predict fluid responsiveness have been published. On the one hand, some studies demonstrated that EEOT was able to predict fluid responsiveness in mechanically ventilated patients in the ICU, even in the presence of these conditions: low-tidal-volume ventilation, acute respiratory distress syndrome, or arrhythmia.[12,13] On the other hand, Myatra et al[14] found that EEOT was accurate to predict fluid responsiveness only in ICU patients ventilated with tidal volume of 8 mL/kg of ideal body weight but not in those ventilated with lower tidal volume (6 mL/kg of ideal body weight). In another study performed in the OR, Guinot et al[15] found that changes in SV during an EEOT was not informative on preload responsiveness in patients

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receiving protective ventilation. Discussions about methodological aspects of this study were also published (cardiac output monitoring and type of ventilator used).[16] Thus, this test still raises questions in the context of low tidal volume and the use of an anesthesia ventilator.

This study aimed to evaluate the ability of EEOT (performed automatically with an anesthesia ventilator) to predict fluid responsiveness and to compare the abilities of EEOT and PPV, in patients ventilated with tidal volume less than 8 mL/kg in the OR.

METHODS

Patients

This prospective, single-center study was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France N°DC2016/129). Between May and October 2016, 41 nonconsecutive patients were included after oral informed consent. Inclusion criteria were availability of the investigator, patients older than 18 years, scheduled for neurosurgery, and equipped with radial artery catheter and cardiac output monitor. Exclusion criteria were preoperative lung disease, intracranial hypertension, left ventricular ejection fraction below 50%, arrhythmia, suspected right ventricular dysfunction, obesity (body mass index >40 or <15 kg/m^2), and use of vasopressors or inotropes before and during anesthesia. Patients were also excluded if the target-controlled infusion of remifentanil and/or propofol was modified during the study period.

Perioperative Management

Standard monitoring included noninvasive blood pressure, heart rate, peripheral oxygen saturation, and continuous electrocardiography. After preoxygenation, all patients received propofol and remifentanil anesthesia (target-controlled infusion).[17–19] Following tracheal intubation, patient's lungs were ventilated with a mixture of air/oxygen using volume-control mode. Tidal volume was set between 6 and 8 mL/kg of ideal body weight and positive end-expiratory pressure was set between 3 and 5 cm H_2O (Felix, Taema, Anthony, France). Peripheral oxygen saturation was maintained above 96% and respiratory rate was adjusted to maintain end-tidal carbon dioxide concentration between 30 and 35 mm Hg. The inspiratory to expiratory ratio was set to 1/2.

Hemodynamic Monitoring

All patients were equipped with a radial artery catheter inserted just after the induction of anesthesia (Vygon, Ecouen, France) for mean arterial pressure (MAP), PPVs, and stroke volume index (SVI) monitoring (ProAQT, Pulsion Medical Systems, Feldkirchen, Germany). An "autocalibration" (allowing an estimation of initial cardiac output with a proprietary algorithm) was performed at baseline 1, baseline 2, and after VE. Cardiac index was determined beat-to-beat by pulse contour analysis.

Study Design

Measurements were performed in the supine position, after induction of anesthesia, before skin incision, and after hemodynamic stability (defined as changes in MAP less than 10% during 5 minutes). Four sets of measurements including heart rate, MAP, pulse pressure (PP), PPV, and SVI were recorded at baseline (baseline 1), at the end of a 30-second EEOT, ie, 1 minute after releasing the EEOT (baseline 2), and 1 to 3 minutes after the end of the fluid challenge (250 mL saline 0.9% infused during 10 minutes immediately after baseline 2) (VE). During the EEOT, the absence of spontaneous breathing effort was confirmed by 2 investigators through visual examination of respiratory curves.

Statistical Analysis

Data are expressed as median (25–75% interquartile range) or mean ± standard deviation where appropriate. Thirty-eight patients were necessary to show an area under the receiver operating characteristics (ROC) curve ≥ 0.75 (type I error of 5% and type II error of 20%). The ROC curves were compared using the DeLong test.[20] Response to VE was defined as an increase in SVI ≥ 10%.[21,22]

Normality of the distribution was tested using d'Agostino-Pearson test. The effects of EEOT and VE on hemodynamic parameters were analyzed using Student paired *t* test. The relationship between changes in SV induced by EEOT (ΔSV-EEOT) and changes in SV induced by VE (ΔSV-VE) was tested using linear correlation. The intraclass correlation between SV, PP, and PPV measurements at the 2 baseline steps was measured using the random-effects models.[23]

ROC curves were generated for ΔSV-EEOT, changes in PP induced by EEOT (ΔPP-EEOT) and PPV, and were compared. Best threshold values were identified using the Youden index (specificity + sensitivity − 1). To avoid the binary response provided by ROC curves and to take into account the existence of an overlap between responders and nonresponders, a gray zone was determined for ΔSV-EEOT, ΔSV-PP, and PPV. Briefly, the gray-zone approach proposes a low cutoff value that excludes positive fluid challenge in 90% of patients, whereas a high cutoff value predicts positive fluid challenge in 90% of cases.[24–26] Statistical analysis was performed using Medcalc (software 11.6; Ostend, Mariakerke, Belgium) and NCSS 8 (NCSS, LLC, Kaysville, Utah). A *P* value of <.05 was considered to be statistically significant.

RESULTS

Patients' Characteristics

The main characteristics of the study population (n = 41) are shown in Table 1. Twenty were responders to VE and 21 were not. Hemodynamic variables are shown in Table 2.

Hemodynamic Changes During EEOT and Volume Expansion

The intraclass correlation between SV, PPV, and PP measurements at the 2 baseline steps were 0.99 (95% confidence interval [CI], 0.99–1.00), 0.98 (95% CI, 0.96–0.99), and 0.93 (95% CI, 0.87–0.97), respectively. Individual values of percentage changes in SV induced by EEOT and values of PPV in responders and nonresponders are shown in Figure 1. EEOT induced an increase in SV in both responders and nonresponders.

Relationship Between Changes in Stroke Volume Induced by EEOT and Changes in Stroke Volume Induced by Volume Expansion

ΔSV-EEOT and ΔSV-VE were closely correlated: $r^2 = 0.55$, $P < .0001$ (Figure 2).

Table 1. Main Characteristics of Nonresponders (n = 21) and Responders (n = 20)

Characteristics	Nonresponders n = 20	Responders n = 21
Age (y)	54 ± 14	55 ± 16
Sex, M/F (n)	7/14	12/8
Height (cm)	167 ± 9	169 ± 9
Weight (kg)	68 ± 13	69 ± 12
Ideal body weight (kg)	61 ± 13	63 ± 7
Tidal volume (mL)	415 ± 54	436 ± 41
Tidal volume (mL/kg of ideal body weight) (min to max)	6.8 ± 0.5 (6.1 to 7.8)	6.9 ± 0.6(5.4 t o 8.2)
Respiratory rate (cycles/min)	13 ± 2	13 ± 1
Positive end-expiratory pressure (cm H_2O)	5 [5–5]	5 [5–5]
F_{IO_2} (%)	47 ± 6	46 ± 7
Driving pressure (cm H_2O)	13 ± 2	12 ± 2
Compliance of the respiratory system (mL/cm H_2O)	38 ± 10	40 ± 10
Creatinine (mmol/L)	70 ± 18	79 ± 20
Hemoglobin (dg/L)	13.6 ± 1.2	13.9 ± 1.0
Surgery (n)		
Cerebral tumor	19	16
Pituitary adenoma	1	3
Cortectomy	0	2

Values are mean ± SD or median (percentile 25–75) or number (n) or compliance of the respiratory system = tidal volume/driving pressure. Driving pressure = plateau pressure – positive end-expiratory pressure. Patients were considered responders if stroke volume increased by ≥10% after 250 mL intravascular volume expansion.

Abbreviations: F, female; F_{IO_2}, inspired oxygen fraction; M, male.

Table 2. Hemodynamic Variables at Baseline, and the End of End-Expiratory Occlusion Test, Before Volume Expansion and After Volume Expansion in Responders (n = 20) and Nonresponders (n = 21)

	Baseline 1	EEOT	P1	Baseline 2	After VE	P2
Heart rate (bpm)						
Responders	62 ± 11	64 ± 17	0.39	61 ± 11	60 ± 10	0.37
Nonresponders	67 ± 11	65 ± 11	0.04	65 ± 11	64 ± 11	0.12
Mean arterial pressure (mm Hg)						
Responders	70 ± 13	70 ± 14	0.95	69 ± 13	70 ± 15	0.45
Nonresponders	71 ± 9	72 ± 12	0.40	71 ± 8	71 ± 11	0.49
Pulse pressure (mm Hg)						
Responders	44 ± 10	48 ± 14	0.16	45 ± 11	48 ± 12	0.0052
Nonresponders	51 ± 13	50 ± 13	0.49	51 ± 12[a]	51 ± 14	0.33
Stroke volume (mL)						
Responders	68 ± 13	74 ± 13	<0.0001	67 ± 13	79 ± 14	<0.0001
Nonresponders	71 ± 16	73 ± 16	0.0004	71 ± 16[a]	72 ± 16	0.04
PPV (%)						
Responders	11 ± 4	–	–	10 ± 4[a]	6 ± 3	<0.0001
Nonresponders	8 ± 3	–	–	7 ± 3	6 ± 3	0.24

Values are mean ± SD. Patients were considered responders if stroke volume increased by ≥10% after 250 mL intravascular volume expansion.

Abbreviations: after VE, measurements immediately after volume expansion (250 mL saline); baseline 1, before end-expiratory occlusion test (EEOT); baseline 2, measurements 1 min after releasing the EEOT; EEOT, measurements at the end of 30-sec end-expiratory occlusion test; P1, comparison between baseline 1 and EEOT; P2: comparison between baseline 2 and after VE; PPVs, pulse pressure variations.

[a]$P < .05$ between responders and nonresponders at baseline 2.

Prediction of Fluid Responsiveness

The abilities of ΔSV-EEOT, ΔPP-EEOT, and PPV to predict fluid responsiveness are shown in Table 3. The area under the ROC curve generated for changes in SV induced by EEOT (0.91, 95% CI, 0.81–1.00) was significantly higher than those generated for changes in PP induced by EEOT (0.62, 95% CI, 0.44–0.80, $P = .003$) and PPV (0.75, 95% CI, 0.60–0.90, $P = .02$) (Figure 3).

DISCUSSION

This study, performed in patients ventilated with a tidal volume less than 8 mL/kg in the OR, demonstrates that (i) a 5% increase in SV during an EEOT is able to predict fluid responsiveness with good positive and negative predictive values, (ii) EEOT is better than PPV for predicting the hemodynamic effects of VE, and (iii) changes in PP induced by an EEOT is not accurate to predict fluid responsiveness.

The hemodynamic effects of mechanical ventilation have been extensively described. Briefly, inspiration induces an increase in intrathoracic pressure, impeding venous return and squeezing the intra-alveolar pulmonary vessels.[27] The result is a decrease in ventricular preload. End-expiratory occlusion, which is commonly used to monitor intrinsic positive end-expiratory pressure, stops the effects of mechanical ventilation. EEOT leads to an increase in right ventricular preload and in right ventricular SV. After blood pulmonary transit, the increase in right ventricular SV induces an increase in left ventricular filling and left ventricular SV. When the heart operates on the steep portion of the Frank-Starling curve, the hemodynamic effects of EEOT are significant because slight changes in right ventricular preload induced by EEOT can lead to substantial changes in SV. Conversely, when ventricles operate on the flat portion of the Frank-Starling curve, hemodynamic effects of EEOT are small.

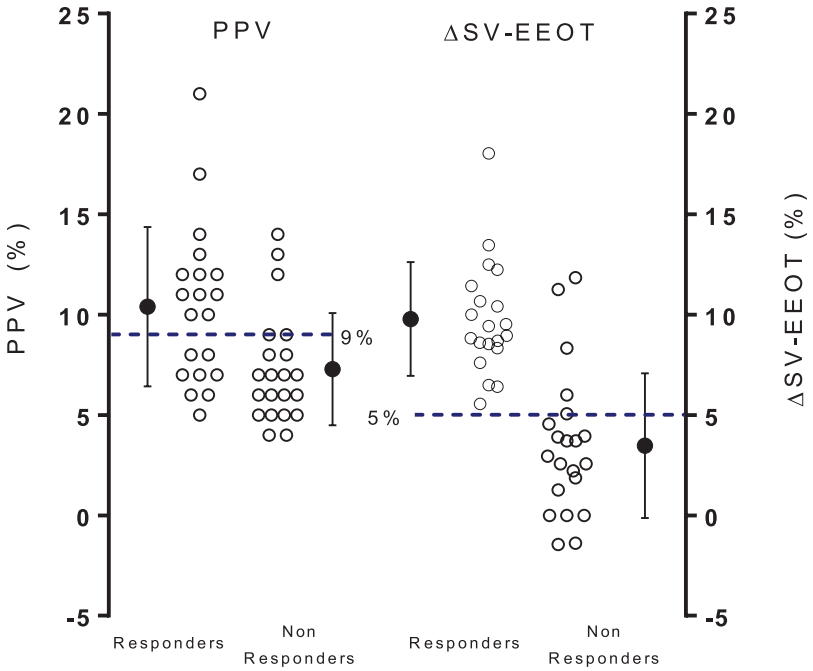

Figure 1. Individual values with mean and standard deviation of percentage changes in stroke volume induced by end-expiratory occlusion test and pulse pressure variations in responders and nonresponders. Responders were defined as an increase in stroke volume ≥ 10% from baseline 2 after 250 mL infusion of saline 0.9%. ΔSV-EEOT indicates changes in stroke volume induced by end-expiratory occlusion test; PPVs, pulse pressure variations.

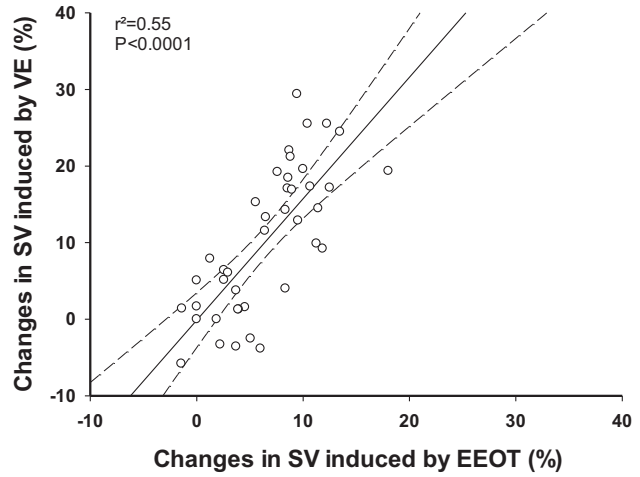

Figure 2. Relationship between percentage changes in stroke volume induced by end-expiratory occlusion test and changes in stroke volume induced by volume expansion. EEOT indicates end-expiratory occlusion test; SV, stroke volume; VE, volume expansion, 250 mL saline 0.9%.

Monnet et al[12] were the first to evaluate the ability of EEOT to predict fluid responsiveness in mechanically ventilated patients. Their first study included 34 ICU patients suffering from acute circulatory failure. Mean tidal volume was 6.8 mL/kg in both responders and nonresponders. Cardiac index was monitored using calibrated pulse contour (PiCCO, Pulsion Medical System). This work demonstrated that changes in cardiac index and changes in PP during an EEOT was as able as changes in cardiac index during passive leg raising test to predict fluid responsiveness.[12] The area under the ROC curves remained high even in patients suffering from cardiac arrhythmia or moderate spontaneous breathing activity. Another study published by the same team showed that acute respiratory distress syndrome and/or low compliance of the respiratory system did not affect the good accuracy of this test.[13]

More recently, Myatra et al[14] demonstrated in 20 ICU patients that EEOT was accurate to predict fluid responsiveness in these patients ventilated with a tidal volume of 8 mL/kg of ideal body weight but not in those ventilated with a lower tidal volume (6 mL/kg of ideal body weight). The main difference between this study and ours is that we used a higher tidal volume (6.9 vs 6.0 mL/kg) and that our patients presented significantly higher compliance of the respiratory system (40 vs 30 mL/cm H_2O).

Only one study performed in the OR has been published. Guinot et al[15] included 42 patients and found that hemodynamic effects of EEOT were not able to predict fluid responsiveness. In this study, the mean tidal volume was 8.2 mL/kg. The driving pressure and compliance of the respiratory system were not displayed. From our point of view, at least 2 factors are needed to interpret the hemodynamic effects of an EEOT. The first element is the cardiac output monitor. The device should be able to track changes in cardiac output, rapidly and precisely in real time. In this study, we used pulse contour analysis without calibration. Even if the absolute value of cardiac output may be inaccurate under specific conditions, this algorithm is able to detect changes in cardiac output related to changes in preload.[28,29] The second element is the necessity to have a ventilator able to provide end-expiratory occlusion. While all recent ICU ventilators offer this possibility (especially for intrinsic positive end-expiratory pressure monitoring), most anesthesia ventilators are not yet equipped with this function. Having the automatic EEOT in all OR ventilators would have made our findings more broadly applicable in today's ORs. Hence, many companies are working to provide automatic EEOT in anesthesia ventilators. In this study, we used one of the ventilators that provide this possibility (Felix, Taema).

Other studies investigating the specific impact of tidal volume, driving pressure, and compliance of the respiratory system on the accuracy of EEOT are warranted.

Table 3. Ability to Predict an Increase in Stroke Volume ≥10% After Infusion of 250 mL Saline Over 10 Min

Index	Best Threshold (%)	Gray Zone (%)	Patients Whose Measurements Were in the Gray Zone (%)	AUROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Youden Index J	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
ΔSV-EEOT	>5	4–8	17	0.91 (0.81–1.00)	100 (83–100)	81 (58–95)	0.81	84 (64–96)	100 (80–100)
ΔPP-EEOT	>1	−10 to 5	61	0.62 (0.44–0.80)	55 (32–77)	71 (48–89)	0.26	65 (39–86)	61 (39–80)
PPV	>9	5–12	76	0.75 (0.60–0.90)	60 (36–81)	86 (64–97)	0.47	81 (53–96)	68 (47–85)

Best threshold value was determined using Youden index (J = sensitivity + specificity − 1).

Abbreviations: ΔPP-EEOT, changes in mean arterial pressure induced by end-expiratory occlusion test; ΔSV-EEOT, changes in stroke volume induced by end-expiratory occlusion test; AUROC, area under the receiver operating characteristics curves; CI, confidence interval; PPVs, pulse pressure variations.

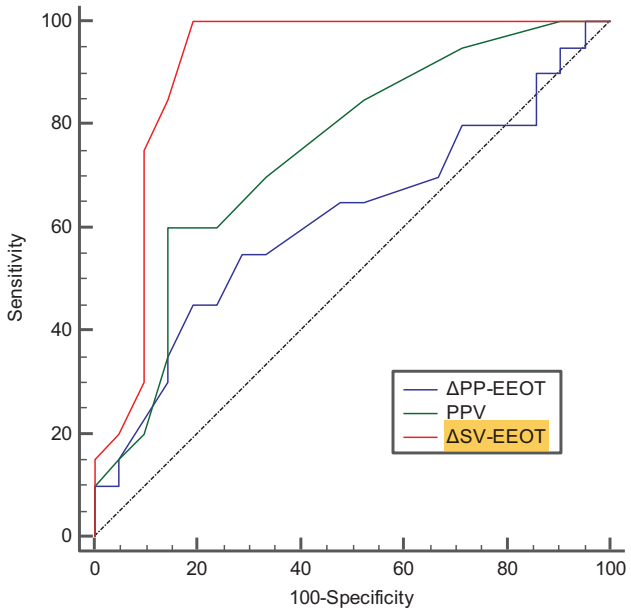

Figure 3. Receiver operating characteristics curves generated for ΔSV-EEOT, ΔPP-EEOT, and PPV showing the ability to predict the effect of a 250 mL volume expansion given over 10 minutes. Responders were defined as an increase in stroke volume ≥10% from baseline 2 after 250 mL infusion of saline 0.9%. ΔPP-EEOT indicates changes in pulse pressure induced by end-expiratory occlusion test; ΔSV-EEOT, changes in stroke volume induced by end-expiratory occlusion test; PPVs, pulse pressure variations.

Ventilatory management of ICU patients has changed drastically in the past 15 years,[11,30] with the use of low tidal volume and moderate to high levels of positive end-expiratory pressure. Several recent studies demonstrated that such protective ventilation strategy was also beneficial for patients.[9,10,31] Hemodynamic optimization using dynamic indices in the OR seems attractive,[32] but the use of protective ventilation would preclude their uses. Furthermore, the PPV gray zone is much larger than that of ΔSV-EEOT.

Fluid Challenge

We decided to perform a VE of 250 mL (and not 500 mL) during 10 minutes for many reasons. Many studies demonstrated that the effects of VE are maximal at the beginning of the fluid administration. This is the cornerstone of the minifluid challenge approach.[33] To avoid unnecessary fluid administration, many authors proposed to titrate fluid with "only" 200–250 mL. This approach has been proposed during intraoperative goal-directed fluid therapy with positive results.[21,34–36] European and French guidelines recommend to titrate VE with bolus of 200–250 mL.[23,37] More recently, consensus statement on perioperative fluid management (using this approach) within an enhanced recovery pathway for colorectal surgery have been published by the American Society for Enhanced Recovery and Perioperative Quality Initiative.[38,39] We assessed the effects of VE 1 to 3 minutes after the end of fluid challenge. This is supported by a recent recommendation and a recent study analyzing the pharmacodynamics a fluid challenge.[40]

We defined 2 groups of patients: responders and nonresponders according to the changes in SV (<10% or 10%). Such approach is questionable because of the potential loss of information when continuous variables are treated as binary.[41] However, categorization of continuous variables is common in clinical research and converting continuous variable data to 2 groups (eg, dichotomizing responders and nonresponders) is the most common approach. Even if such simplification is gained at some cost, grouping may help in data presentation and mostly in providing individuals with or without an attribute, such as being responder or nonresponder patients.

Our study presents some limitations. First, we included a small number of highly selected patients (supine position, neurosurgery, lack of cardiac dysfunction and/or arrhythmia, etc). Our results require validation in a larger population of more heterogeneous patients. Second, cardiac output was monitored using PP analysis without external calibration. Even if this may have impacted the absolute value of SV, this device is able to track rapid changes in SV induced by changes in preload.[12,28,29] Third, we performed an EEOT during 30 seconds and not during 15 seconds as previously described. We made this choice because the ventilator was designed to perform 30-second pause. We assume that extending time pause may have sensitized the test and possibly led to more observations of SV increase as attested by 4 false positives and zero false negative. Finally, patients received protective ventilation with mean tidal volume of about 7 mL/kg of ideal body weight (min = 5.4 mL/kg and max = 8.2 mL/kg); thus, we cannot extrapolate our results in patients ventilated with very low tidal volume.

To conclude, our study demonstrated that an increase in SV of at least 5% induced by a 30-second EEOT can detect fluid responsiveness with good positive and negative predictive values in patients mechanically ventilated with tidal volume less than 8 mL/kg in the OR.

DISCLOSURES

Name: Matthieu Biais, MD, PhD.

Contribution: This author helped design the study, collect the data, perform statistical analysis, and write the manuscript.

Conflicts of Interest: M. Biais received honoraria from Edwards Lifescience and Pulsion Medical System for lecturers.
Name: Mathilde Larghi, MD.
Contribution: This author helped analyze the data and write the manuscript.
Conflicts of Interest: None.
Name: Jeremy Henriot, MD.
Contribution: This author helped analyze the data and write the manuscript.
Conflicts of Interest: None.
Name: Hugues de Courson, MD.
Contribution: This author helped analyze the data and write the manuscript.
Conflicts of Interest: None.
Name: Musa Sesay, MD.
Contribution: This author helped analyze the data and write the manuscript.
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Name: Karine Nouette-Gaulain, MD, PhD.
Contribution: This author helped analyze the data and correct the manuscript.
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