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Uncalibrated Stroke Volume Variations Are Able to Predict the Hemodynamic Effects of Positive End-Expiratory Pressure in Patients with Acute Lung Injury or Acute Respiratory Distress Syndrome after Liver Transplantation

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Background: **Positive end-expiratory pressure (PEEP) may reduce cardiac output and total hepatic blood flow after liver transplantation. Pulse pressure variation is useful in predicting the PEEP-induced decrease in cardiac output. The aim of the study was to examine the relationships between stroke volume variations (SVV) obtained with the Vigileo monitor (Edwards Lifesciences, Irvine, CA), and the hemodynamic effects of PEEP.**

Methods: **Over 2 yr, patients presenting an acute lung injury or an acute respiratory distress syndrome in the 72 h after liver transplantation were prospectively enrolled. Patients were monitored with a pulmonary artery catheter (stroke volume) and with the Vigileo system (stroke volume and SVV). Measurements were performed in duplicate, first during zero end-expiratory pressure and then 10 min after the addition of 10 cm H_2O PEEP.**

Results: **Twenty-six patients were included. Six patients were excluded from analysis. On PEEP, SVV and pulse pressure variation increased significantly and stroke volume decreased significantly. PEEP-induced changes in stroke volume measured by pulmonary artery catheter were significantly correlated with SVV ($r^2 = 0.69$; $P < 0.001$) and pulse pressure variation on zero end-expiratory pressure ($r^2 = 0.66$, $P < 0.001$). PEEP-induced decrease in stroke volume measured by pulmonary artery catheter ≥ 15% was predicted by an SVV > 7% (sensitivity = 100%, specificity = 80%) and by a pulse pressure variation > 8% (sensitivity = 80%, specificity = 100%). PEEP-induced changes in stroke volume measured by pulmonary artery catheter and Vigileo device were correlated ($r^2 = 0.51$, $P < 0.005$).**

Conclusions: **SVV obtained with Vigileo monitor is useful to predict decrease in stroke volume induced by PEEP. Moreover, this device is able to track changes in stroke volume induced by PEEP.**

LIVER transplantation is a complex operation that may involve substantial blood loss, massive transfusion, and large fluid shifts. A significant portion of patients nowadays are extubated early.[1] However, pulmonary complications are known to contribute significantly to morbidity and mortality.[2] The most frequent are pleural effusion, atelectasis, pulmonary edema, pneumonia, sepsis, transfusion-related acute lung injury (ALI), reperfusion syndrome, and hepatic-lung syndrome.[2–4]

The use of positive end-expiratory pressure (PEEP) is an established component of the mechanical ventilatory support for ALI and acute respiratory distress syndrome (ARDS).[5–7] However, application of PEEP may reduce cardiac output and influence its distribution.[8–12] Marked reduction of either total hepatic blood flow and portal venous blood flow has been reported in various experimental models, but the results are controversial.[9,10,13,14] Kiefer *et al.* demonstrated that changes in PEEP do not influence splanchnic perfusion, unless accompanied by change in cardiac output.[14]

Positive pressure ventilation induces cyclic changes in left ventricular stroke volume (SV) that are mainly related to the expiratory decrease in left ventricular preload because of the inspiratory decrease in right ventricular filling and ejection.[15] The decrease in mean cardiac output induced by PEEP shares the same mechanisms. Michard *et al.* demonstrated strong relationships between respiratory changes in arterial pulse pressure (pulse pressure variation [PPV]) and the effects of PEEP on cardiac output in ventilated patients.[16] More recently, it has been demonstrated in an animal model that PEEP induced an increase in stroke volume variations (SVV).[17]

The recently introduced Vigileo monitor (Vigileo; FloTrac; Edwards Lifesciences, Irvine, CA), which allows continuous cardiac output and SVV monitoring, is based on the analysis of the systemic arterial pressure wave and does not require pulmonary artery catheterization or external calibration.[18–20] It has been recently shown that SVV obtained with this device is accurate in predicting fluid responsiveness.[21–23]

The primary end point of this study was to examine the relationships between SVV obtained with the Vigileo/FloTrac system and the hemodynamic effects of PEEP in patients with ALI or ARDS in the 72 h after liver transplantation. The secondary end points were to identify a SVV and PPV threshold to predict a 15% PEEP-induced decrease in stroke volume (SV), examine the relationships between PPV and SVV before and after the application of PEEP, and evaluate the ability of the Vigileo system to detect change in SV induced by PEEP.

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Materials and Methods

Patients

We conducted a prospective and single-center study. After approval by the local Ethics Committee (*Comité de Protection des Personnes Sud-Ouest et Outre Mer III*, Bordeaux, France) and obtaining written informed consent, patients presenting ALI or ARDS in the 72 h after a liver transplantation between March 2006 and March 2008 in our institution were consecutively included. ALI or ARDS were diagnosed using the American-European Consensus Conference on ARDS criteria: Acute onset, bilateral infiltrates on chest x-ray, pulmonary artery occlusion pressure < 18 mmHg, and P_{AO_2}/fraction of inspired oxygen (FIO_2) < 300 for ALI and < 200 for ARDS.[6]

All patients had to be hemodynamically stable as defined by a variation in heart rate, blood pressure, and cardiac output of less than 10% over the 15-min period before starting the protocol. Exclusion criteria were as follows: Patients younger than 18 yr, arrhythmias, body mass index greater than 40 kg/m^2 or less than 15 kg/m^2, hepatopulmonary syndrome, significant valvular heart disease, intracardiac shunt, spontaneous breathing activity, left ventricular ejection fraction less than 50% at zero end-expiratory pressure (ZEEP), and any contraindication to the use of PEEP.

Hemodynamic Monitoring

Pulmonary Artery Catheter. All patients were preoperatively equipped with a pulmonary artery catheter (CCOmbo, 744HF75, 7.5 French, Edwards Lifesciences) inserted *via* the left subclavian vein through an introducer (M3L9FHSI, 9 French, Edwards Lifesciences). This was connected to the Vigilance monitor (Edwards Lifesciences) for semicontinuous cardiac output and SV monitoring (SV-PAC). The position of the catheter was confirmed by pressure curves, δ-pulmonary artery occlusion pressure (PAOP)/δ-pulmonary artery pressure ratio as previously described[24] and postoperatively by chest x-ray. Central venous pressure and pulmonary artery pressure were monitored continuously. The STAT mode displayed cardiac output values determined within the previous 60 s and was averaged over three consecutive measurements. The plausibility of every temperature curve was judged visually on the attached monitor, and a difference of less than 10% between the measurements was considered appropriate. The mean values of three consecutive determinations were used for statistical analysis. If cardiac output changed by more than 15%, five measurements were performed and the highest and lowest were rejected. Hemodynamic management of the patients was guided by the pulmonary artery catheter.

Vigileo Monitor

A 3 French, 8-cm–long arterial catheter (115.09, Vygon, Ecouen, France) was inserted in the left radial artery. A dedicated transducer (FloTrac) was connected to the radial arterial line on one side and to the Vigileo system on the other side. The system enables the continuous monitoring of arterial pressure, cardiac output, SV, and SVV by pulse contour analysis. This system needs no calibration and provides continuous cardiac output measurements from the arterial pressure wave. The Vigileo system analyzes the pressure waveform 100 times per second over 20 s, capturing 2000 data points for analysis, and performs its calculations on the most recent 20 s of data. The device calculates SV (SV-Vigileo) as $k \times$ pulsatility, where pulsatility is the SD of arterial pressure over a 20-s interval, and k is a factor quantifying arterial compliance and vascular resistance. k is derived from a multivariate regression model including Langewouter's aortic compliance,[25] mean arterial pressure, variance, skewness, and kurtosis of the pressure curve. The rate of adjustment of k is 1 min (Vigileo software 1.07; Edwards Lifesciences). SVV is calculated as the variation of beat-to-beat SV from the mean value during the most recent 20 s data: SVV = (SVmax – SVmin)/SVmean.

Echocardiographic Measurements

Doppler echocardiography was performed by the same operator using an ultrasound device (EnVisor C; Philips, Eindhoven, The Netherlands) equipped with a phased array transthoracic probe (2.5 megahertz).

Left ventricular ejection fraction was measured using Simpson's biplane method from the apical two- and four-chamber views.

Acute Cor Pulmonale. The echographic pattern of acute cor pulmonale associates right ventricular enlargement, heralded by a right/left ventricular area ratio at end-diastole > 0.6 on a four-chamber view, and systolic septal dyskinesia on a short-axis view.[26]

Calculation of PPV

Pulse pressure was defined as the difference between systolic and diastolic arterial blood pressure. Maximal (Pulse Pressure max) and minimal (Pulse Pressure min) values were determined over the same respiratory cycle. PPV was then calculated as PPV = (Pulse Pressure max - Pulse Pressure min)/[(Pulse Pressure max + Pulse Pressure min)/2], as previously described. PPV was evaluated in triplicate over each of three consecutive respiratory cycles. The mean values of the three determinations were used for statistical analysis.[27] PPV and SVV measurements were coincident.

Pressure Measurements

Central venous pressure, mean pulmonary arterial pressure, and mean arterial pressure were recorded continuously. PAOP was determined at the end of expiration and averaged from three consecutive respiratory cycles.

Mechanical Ventilation

All patients were intubated and sedated with propofol and sufentanil to ensure that there was no evidence of spontaneous breathing effort (identified by clinical examination and visual examination of respiratory curves). All patients received mechanical ventilation in a volume-controlled mode with a tidal volume of 6-7 ml/kg and an inspiratory/expiratory ratio of 1/2-1/1. The respiratory rate was adjusted to maintain an arterial carbon dioxide pressure of less than 45–50 mmHg.

The total PEEP and the plateau pressure (Pplat) were measured using an end-expiratory and end-inspiratory occlusion maneuver of 5 s. Tidal volume (Vt) was measured by means of the ventilator transducer.

Study Protocol

Measurements were performed in duplicate, first 10 min after 0 cm H_2O PEEP (ZEEP) and then 10 min after the addition of 10 cm H_2O PEEP. If Pplat was greater than 28 cm H_2O at PEEP, Vt was decreased to obtain a Pplat $\leq$ 28 cm H_2O. Cardiac output and SV measured by Vigileo and by pulmonary artery catheter, SVV, PPV, central venous pressure, PAOP, mean pulmonary arterial pressure, mean arterial pressure, and heart rate were simultaneously measured. Fluid administration and dosage of inotropic and vasopressive drugs were held constant.

Statistical Analysis

Results were expressed as median (25–75% interquartile range), unless stated otherwise. The effects of PEEP were assessed using Wilcoxon's nonparametric test. Correlations were tested using the Spearman rank test. Hemodynamic parameters on ZEEP in patients with good or poor tolerance were compared with a nonparametric Mann–Whitney *U* test. Assuming that a 15% change in SV was required for clinical significance and to cope with the intrinsic variability of SV measurements, patients were separated into Good Tolerance or Poor Tolerance groups according to a decrease in SV-PAC $<$ 15% or $\geq$ 15% after the application of PEEP, respectively.[28,29] Receiver operating characteristic curves were generated for SVV and PPV, varying the discriminating threshold of each parameter. The areas under the receiver operating characteristic curves ($\pm$ SE) were calculated for each parameter and compared.[30] The relationship between changes in SV-PAC and SV-Vigileo after the PEEP introduction was evaluated using a Spearman correlation. A *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using Statview for Windows, version 5 (SAS Institute, Cary, NC) and MedCalc software 8.1.1.0 (MedCalc Software, Mariakerke, Belgium).

Table 1. Main Characteristics of Patients

Characteristics	
Age (years)	50 (42–57)
Height (cm)	171 (167–176)
Weight (kg)	66 (60–74)
Body mass index (kg/m^2)	23 (21–26)
Sex, F/M (n)	5/15
Liver diseases	
—Alcoholic cirrhosis (n)	10
—HCV cirrhosis (n)	6
—HBV cirrhosis (n)	3
—Wilson (n)	1
Child-Pugh classification (A/B/C)	3/11/6
MELD score	16 (8–20)
Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.44 (0.15–0.70)
Vt (ml/kg)	6.8 (6.4–6.9)
Respiratory rate (min)	16 (15–18)
Crs,st (ml/cm H_2O)	32 (29–34)
P_{AO_2}/FIO_2	140 (106–187)
ALI/ARDS (n)	5/15

Values are median (percentile 25–75) or number (n).

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; Crs,st = static compliance of respiratory system; FIO2 = fraction of inspired oxygen; HBV = hepatitis B virus; HCV = hepatitis C virus; MELD = Model for End-stage Liver Disease; P_{AO_2} = partial arterial oxygen pressure; Vt = tidal volume.

Results

Patients

During the study protocol, 69 liver transplantations were performed. Twenty-six patients (38%) presented ALI (n = 10) or ARDS (n = 16) in the 72 h after liver transplantation.

Six patients were excluded from analysis for arrhythmia during the protocol (n = 1) or difficulties in transthoracic echographic image analysis (n = 5). The main characteristics of the 20 patients studied are listed in table 1. The etiologies of ALI or ARDS were bacterial pneumonia (n = 11), sepsis (n = 4), and massive transfusion (n = 5). Hemodynamic parameters on ZEEP and PEEP are presented in table 2.

Data on ZEEP

On ZEEP, SVV correlated with PPV (r^2 = 0.59; $P <$ 0.001) and with PAOP (r^2 = 0.21; P = 0.048), but not with central venous pressure (r^2 = 0.12; P = 0.13), Vt (r^2 = 0.01; P = 0.64), and static compliance of the respiratory system (r^2 = 0.15; P = 0.09).

Data with PEEP

Pplat was $\leq$ 28 cm H_2O in all patients at PEEP, and no decrease in Vt was necessary. PEEP induced a significant decrease in cardiac output and SV (table 2). SVV and PPV were significantly higher during ventilation with PEEP. PEEP-induced changes in SV-PAC were significantly correlated with SVV on ZEEP (r^2 = 0.69; $P <$ 0.001) (fig. 1) and with PEEP-induced changes in SVV (r^2 = 0.37; $P <$ 0.005). PEEP-induced changes in

Table 2. Effects of Positive End-Expiratory Pressure on Hemodynamic Variables

	ZEEP	PEEP	*P* Value
HR (min)	76 (68–84)	81 (74–90)	< 0.001
MAP (mmHg)	95 (81–104)	84 (71–94)	< 0.001
CVP (mmHg)	7 (4–10)	8 (7–10)	< 0.005
MPAP (mmHg)	22 (18–23)	24 (22–26)	< 0.001
PAOP (mmHg)	10 (8–12)	13 (12–16)	< 0.001
CO-PAC (l/min)	6.3 (5.5–8.2)	5.8 (5.2–6.9)	< 0.005
CO-Vigileo (l/min)	6.2 (5.5–7.7)	5.6 (5.2–6.7)	< 0.005
SV-PAC (ml)	86 (76–99)	72 (63–83)	< 0.001
SV-Vigileo (ml)	82 (75–96)	70 (63–90)	< 0.001
SVR (dyne · s^{-1} · cm^{-5})	899 (796–1233)	917 (718–1235)	NS
LVEF (%)	62 (55–71)	58 (55–68)	NS
SVV (%)	9 (6–13)	15 (8–20)	< 0.005
PPV (%)	6 (3-14)	15 (8-25)	< 0.001

Values are median (percentile 25–75).

CO-PAC = cardiac output obtained with pulmonary artery catheter; CO-Vigileo = cardiac output obtained with Vigileo system (Edwards Lifesciences, Irvine, CA); CVP = central venous pressure; HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NS = not significant; PAOP = pulmonary artery occlusion pressure; PEEP= positive end-expiratory pressure; PPV = pulse pressure variation; SV-PAC = stroke volume obtained with pulmonary artery catheter; SV-Vigileo = stroke volume obtained with Vigileo system; SVR = systemic vascular resistance; SVV = stroke volume variation; ZEEP= zero end-expiratory pressure.

All patients received norepinephrine, while none received dobutamine, epinephrine, or vasopressin.

SV-PAC also correlated with PPV on ZEEP ($r^2 = 0.66$; $P < 0.001$) (fig. 2) and with PEEP-induced changes in PPV ($r^2 = 0.31$; $P < 0.05$). On PEEP, SVV and PPV were correlated ($r^2 = 0.65$; $P < 0.001$). The left ventricular ejection fraction was not different between PEEP and ZEEP (table 2). No patients presented echographic pattern of acute cor pulmonale.

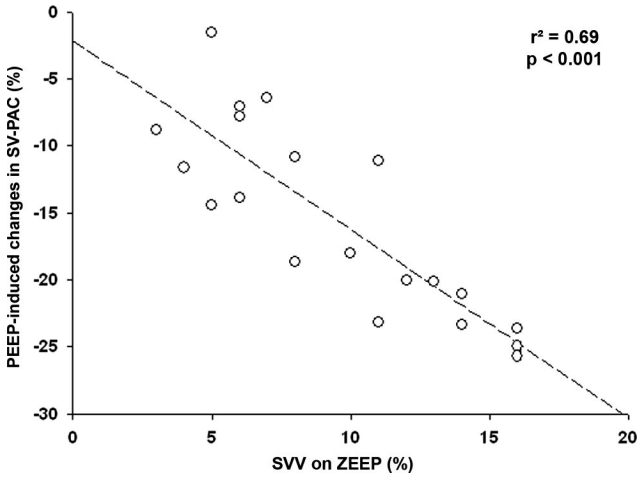

Fig. 1. Correlation between stroke volume variation (SVV) on zero end-expiratory pressure (ZEEP) and positive end-expiratory pressure (PEEP)-induced changes in stroke volume obtained by pulmonary artery catheter (SV-PAC).

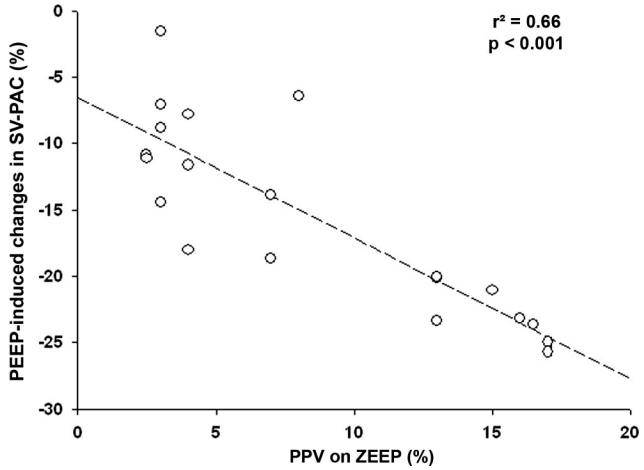

Fig. 2. Correlation between pulse pressure variation (PPV) on zero end-expiratory pressure (ZEEP) and the positive end-expiratory pressure (PEEP)-induced changes in stroke volume obtained by pulmonary artery catheter (SV-PAC).

Ability of SVV and PPV to Predict Decrease in SV Induced by PEEP

After the application of PEEP, 10 patients presented a decrease in SV-PAC ≥ 15% (table 3). Cardiac output measured by pulmonary artery catheter decreased from 6.2 (5.7–8.3) l/min to 6.0 (5.3–8.0) l/min in the Good Tolerance group ($P < 0.05$) and from 6.6 (5.2–8.2) l/min from 5.6 (4.7–6.7) l/min in the Poor Tolerance group ($P = 0.005$). Before PEEP application, a SVV threshold value > 7% predicted a decrease in SV-PAC ≥ 15% with a sensitivity of 100% (69–100) and a specificity of 80%

Table 3. Hemodynamic Variables on Zero End-Expiratory Pressure in Patients with Good or Poor Tolerance to Positive End-Expiratory Pressure Introduction

	Good Tolerance (n = 10)	Poor Tolerance (n = 10)	*P* Value
HR (min)	77 (68–88)	74 (68–81)	NS
MAP (mmHg)	99 (88–106)	91 (80–99)	NS
CVP (mmHg)	10 (7–12)	4 (3–7)	< 0.005
MPAP (mmHg)	21 (18–23)	22 (18–23	NS
PAOP (mmHg)	10 (10–12)	8 (7–12)	NS
CO-PAC (l/min)	6.2 (5.7–8.3)	6.6 (5.2–8.2)	NS
CO-Vigileo (l/min)	6.3 (5.5–7.8)	6.1 (5.5–7.5)	NS
SV-PAC (ml)	91 (76–102)	86 (76–94)	NS
SV-Vigileo (ml)	88 (77–97)	80 (73–95)	NS
SVR (dyne · s^{-1} · cm^{-5})	962 (772–1,194)	899 (819–1,345)	NS
SVV (%)	6 (5–7)	14 (11–16)	< 0.005
PPV (%)	3 (3–4)	14 (13–17)	< 0.005

Good or poor tolerance was defined as a decrease in stroke volume obtained with pulmonary artery catheter < 15% or ≥ 15%, respectively, after positive end-expiratory pressure introduction. Values are median (percentile 25–75).

CO-PAC = cardiac output obtained with pulmonary artery catheter; CO-Vigileo = cardiac output obtained with Vigileo system (Edwards Lifesciences, Irvine, CA); CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NS = not significant; PAOP = pulmonary artery occlusion pressure; PPV = pulse pressure variation; SV-PAC = stroke volume obtained with pulmonary artery catheter; SV-Vigileo = stroke volume obtained with Vigileo system; SVR = systemic vascular resistance; SVV = stroke volume variation.

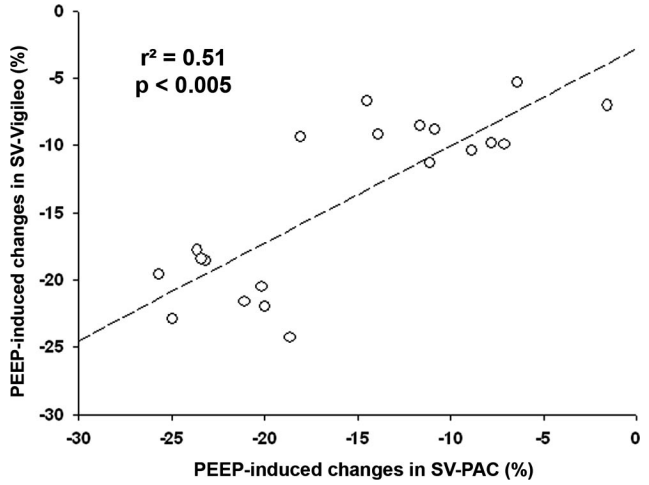

Fig. 3. Correlation between positive end-expiratory pressure (PEEP)-induced changes in stroke volume obtained with pulmonary artery catheter (SV-PAC) and with the Vigileo system (Edwards Lifesciences, Irvine, CA) (SV-Vigileo).

(45–97), while a PPV threshold value > 8% predicted a decrease in SV-PAC ≥ 15% with a sensitivity of 80% (44–97) and a specificity of 100% (69–100). There was no statistical difference between the area under the receiver operating characteristic curve generated for SVV or PPV, respectively, 0.970 and 0.955 (not shown).

SV Comparison

Values of SV-PAC and SV-Vigileo are shown in table 2. After the introduction of PEEP, the percentage change in SV-PAC correlated with the percentage change in SV-Vigileo ($r^2 = 0.51$; $P < 0.005$) (fig. 3). Good and poor tolerance classification was similar using SV-PAC or SV-Vigileo in 19 patients (95%). Only one patient was classified as having poor tolerance using SV-PAC and good tolerance using SV-Vigileo.

Discussion

Our study shows that SVV obtained with the Vigileo system is able to predict a PEEP-induced decrease in stroke volume in patients with ALI after liver transplantation. Mechanical ventilation and PEEP induce cyclic changes in intrathoracic and transpulmonary pressure[31,32] that transiently affect left ventricular preload, resulting in cyclic changes in SV. These cyclic changes in SV can be evaluated by the cyclic changes in arterial pressure such as pulse pressure, and by SVV. These parameters are known to predict fluid responsiveness in mechanically ventilated patients.[21,23,27,33] It has also been shown that changes in arterial pulse pressure are useful in predicting and assessing the hemodynamic effects of PEEP.[16] Our study demonstrates that another evaluation of cyclic changes in arterial pressure as SVV is useful to predict the decrease in SV induced by PEEP.

Pulse pressure depends on left ventricular stroke volume and on arterial compliance. Assuming that the arterial compliance is constant over a single mechanical breath, respiratory variations in pulse pressure closely reflect the respiratory variations in left ventricular stroke volume during the respiratory cycle.[34] Respiratory variations in stroke volume may be measured directly close to the heart (by echocardiography, for example) or calculated using the arterial waveform analysis or pulse contour techniques.

In the present study, we used a new device to monitor SVV. The Vigileo is a system for monitoring SV, cardiac output, and SVV continuously using the radial arterial pressure wave, and does not require calibration with another method.

Our results may be surprising because we found that uncalibrated SVV is able to predict a decrease in cardiac output induced by PEEP, and that the Vigileo device is able to track changes in cardiac output induced by PEEP in a study population (liver transplantation) in which this monitor may underestimate cardiac output.[18] The accuracy of the Vigileo device to assess cardiac output has been tested in numerous settings with various results.[18,19,35–37] During cardiac surgery and using the second-generation device, Mayer *et al.* showed a good agreement with intermittent pulmonary artery thermodilution.[36] In contrast, it seems that the Vigileo device does not accurately determine cardiac output absolute values in the event of profound systemic vasodilation (septic shock or liver transplantation) and in unstable patients.[18,35,37] In the present study, patients received significant vasopressor support but presented normal systemic vascular resistance (899 [796–1,233] dyne · s^{-1} · cm^{-5} at ZEEP) and were hemodynamically stable (defined by a variation in heart rate, blood pressure, and cardiac output of less than 10% over the 15-min period before starting the protocol). Furthermore, three studies found that the SVV obtained by the Vigileo system was able to predict fluid responsiveness during cardiac surgery and liver transplantation.[21–23] SVV is not based on SV or cardiac output absolute values, but on their relative change over the respiratory cycle. Thus, it was not surprising to find an accurate ability of SVV to predict fluid responsiveness, even if the absolute cardiac output was different from the gold standard. Finally, it has been shown that the Vigileo system is able to track changes in cardiac output when systemic vascular resistance was constant, whereas this was not the case when there were changes in systemic vascular resistance.[21,37,38] In the present study, systemic vascular resistance was not significantly different at PEEP and on ZEEP.

Management of ALI or ARDS after liver transplantation is a dilemma. On one hand, preserving satisfactory total hepatic and portal venous blood flow is extremely important, because any reduction in graft perfusion may dramatically compromise its function. On the other

hand, severe hypoxemia can also damage the graft. It has been demonstrated that low levels of cardiac index and oxygen delivery after liver transplantation make patients more prone to organ failure and death.[39] Conversely, normal graft function early after liver transplantation is a pivotal predictor of patient outcome, and is important in the prevention of multiple organ dysfunction syndrome.[40] Several experimental studies reported marked and consistent reductions in total splanchnic blood flow and portal venous blood flow in response to PEEP, and a similar reduction in cardiac output.[41–44] Furthermore, in patients undergoing laparotomy or after polytrauma, PEEP reduced portal venous flow in parallel with a decrease in cardiac output.[45–47] In contrast, two studies demonstrated that the PEEP-induced reduction in portal and total hepatic blood flow was corrected after normalizing the cardiac output by fluid administration.[42,44] Kiefer *et al.* demonstrated that PEEP by itself did not have a consistent effect on splanchnic blood flow and metabolism when cardiac output remained stable. Saner *et al.* showed similar results in 39 living-donor liver transplant patients. PEEP up to 10 millibar did not induce any decrease in cardiac index and did not impair liver outflow.[48] This emphasizes the need for predictive factors of PEEP-induced decrease in cardiac output to select patients who could benefit from fluid administration before the introduction of PEEP.

No patient presented echocardiographic acute cor pulmonale. The ventilatory strategy with a high level of PEEP produced a significant increase in pulmonary vascular resistance and a marked decrease in cardiac output.[26,49,50] These phenomena may cause acute cor pulmonale, and may be responsible for an increase in values of dynamic indices such as PPV or SVV. Indeed, in patients with acute cor pulmonale with a dilated right ventricle and paradoxical septal movement, cyclic increases in right ventricular afterload induced by positive pressure ventilation can also induce stroke volume variations.[51,52]

In the present study, PEEP induced an increase in SVV and in PPV, and these changes were strongly correlated with the PEEP-induced change in SV. These results are in accordance with previous findings.[16,17,53,54] Increasing pleural pressure by PEEP may push heart function to the left on the Franck-Starling curve, thereby decreasing preload. This produces a greater decrease in cardiac output in preload-sensitive patients. However, other mechanisms can explain the PEEP-induced changes in cardiac output. Indeed, PEEP may induce an additional increase in right ventricle afterload during insufflations,[50] or a decrease in right ventricle afterload secondary to an improvement in functional residual capacity and/or a decrease in hypoxic pulmonary vasoconstriction.[12]

Before PEEP application, an SVV threshold value $> 7\%$ and a PPV threshold value $> 8\%$ predicted a decrease in SV $\geq 15\%$ on PEEP (10 cm H_2O). It has already been shown that SVV and PPV are very sensitive indices of fluid responsiveness.[27,33] Three studies evaluating the ability of the SVV obtained by the Vigileo system to predict fluid responsiveness found thresholds of 9.6 and 10%.[21–23] In these studies, patients were ventilated using a volume-controlled mode with a tidal volume of 8–10 ml/kg. In the present study, patients were ventilated with low tidal volume (6-7 ml/kg), and it has been shown that PPV and SVV values are affected by the depth of tidal volume.[55,56] Furthermore, all patients in our study received norepinephrine before PEEP introduction. Nouira *et al.* showed in an experimental study in six dogs that norepinephrine could significantly reduce the value of PPV.[57] Our findings confirm that if norepinephrine may affect the absolute value of PPV, it does not affect its clinical value as a predictor of hemodynamic effects of PEEP.

In our study, the left ventricular ejection fraction was not significantly decreased by PEEP. While the effect of PEEP on left ventricular contractility has generated much controversy, most studies failed to demonstrate any decrease in left ventricular function on PEEP.[12]

In the present study, patients were defined as having good tolerance if the SV decreased less than 15% after the application of PEEP, and as having poor tolerance if not. This threshold was chosen because according to Stetz *et al.*,[29] we assumed that a 15% change in SV was needed for clinical significance, and because this threshold is often used to define responders and nonresponders after volume expansion.[58]

Pplat was less than 28 cm H_2O in all patients at PEEP. We did not need to reduce Vt. Vt and respiratory rate remained constant at ZEEP and PEEP in all patients. This could be because of the low Vt used at ZEEP, and because static compliance of the respiratory system was not very decreased.

This study has some limitations. First, the low number of subjects limits the interpretation of the results. Second, we excluded patients with arrhythmias and/or spontaneous breathing activity, because dynamic indices such as SVV or PPV are ineffective in these cases. We also excluded patients with left ventricular ejection fraction less than 50% at ZEEP. Therefore, our results cannot be extrapolated in these specific patients. Third, the respiratory setting (respiratory rate, Vt, and inspiratory/expiratory ratio) was standardized but was not exactly the same in all patients. Patients were ventilated with a Vt that ranged from 6-7 ml/kg, a respiratory rate that ranged from 15–20/min, and an inspiratory/expiratory ratio that ranged from 1/2–1/1. These may interfere in the interpretation of our results. Fourth, we used PEEP = 0 as a control setting. This may be doubtful, because large series of mechanically ventilated patients have shown that few patients are ventilated with ZEEP. However, there are few data concerning ventilation strategies in patients with ARDS or ALI after liver transplantation.

Fifth, PAOP was measured at the end of the expiration and was not corrected for the transmission of intraalveolar pressure to the capillaries. This could have introduced interferences in PAOP measurements, particularly in ventilation with PEEP. Finally, patients who presented a significant decrease in SV on PEEP did not receive fluid loading (PEEP was stopped). In the absence of acute cor pulmonale, fluid loading might increase cardiac output, but the study cannot answer this question.

In conclusion, our study suggests that, in mechanically ventilated patients with ALI or ARDS after liver transplantation, uncalibrated SVV obtained with a minimally invasive device is useful to predict SV decrease induced by PEEP, and that SV-Vigileo is able to track changes in SV induced by PEEP.

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