Pulse pressure variations to guide fluid therapy in donors: A multicentric echocardiographic observational study

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Abstract

Purpose: Preload responsiveness parameters could be useful in the hemodynamic management of septic shock.
Methods: A multicentric prospective echocardiographic observational study was conducted from March 2009 to August 2011. Clinically brain-dead subjects were included. Pulse pressure variations (ΔPPs) were recorded. Cardiac index, variation of the maximum flow velocity of aortic systolic blood flow, and right ventricular function parameters were evaluated via transthoracic echocardiography. Fluid responsiveness was defined by at least 15% cardiac index increase, 30 minutes after a 500-mL colloid solution infusion. The number of organs harvested was recorded.
Results: Twenty-five subjects were included. Pulse pressure variation could not discriminate responders (n = 15) from nonresponders (n = 10). The best ΔPP threshold (20%) could discriminate responders with a sensitivity of 100% and a specificity of 40%. Variation of the maximum flow velocity of aortic systolic blood flow, tricuspid annular plane systolic excursion, and right ventricle dilation could not discriminate responders from nonresponders. Eighteen subjects underwent organ harvesting. The number of organs harvested was higher in responders (3.5 [3-5]) than in nonresponders (2.5 [2-3]; P = .03).
Conclusions: A ΔPP threshold of 13% is insufficient to guide volume expansion in donors. The best threshold is 20%. Fluid responsiveness monitoring could enhance organ harvesting.

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1. Background

In Western countries, the number of organ donations remains problematic. For example, in France in 2010, 3049 potential donors were recorded, whereas 1476 received organs. Over the same period, 9109 patients were recorded on the national waiting list and 273 patients died owing to a lack of transplant.

In order to enhance the number and function of organs harvested, aggressive donor management strategies have been recommended [1]. Adequately treating a circulatory failure [2] is warranted, but...

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neuroendocrine alterations and cardiopulmonary interactions are complex in brain-dead subjects. In this setting, predicting fluid responsiveness is crucial to avoid fluid overload, which could be detrimental for the lungs but also to avoid hypovolemia, which could impair kidney function [3]. To the best of our knowledge, no data are available in the current literature to guide the attending physician in an attempt to adequately guide the administration of fluids in brain-dead subjects. The preload-dependency principles currently used for hemodynamic management of septic patients [4] have been transposed to organ donors. In this study, the primary end point was to evaluate pulse pressure variations (ΔPPs) as a fluid responsiveness parameter in brain-dead subjects. Secondary end points were to evaluate the variations of the maximum flow velocity of aortic systolic blood flow (ΔVPeak) and right ventricular function, as well as the impact of fluid responsiveness on organ harvesting.

2. Methods

The protocol was approved by the institution ethics committee (Groupe Nantais d’Ethique dans le Domaine de la Santé, Nantes, France). Consent was waived because the protocol was considered as routine practice. This multicenter prospective study was conducted from March 2009 to August 2011 in 3 intensive care units (ICUs): 1 medical ICU (CHG la Roche-sur-Yon, France), 1 neurosurgical ICU (Hospital Laennec, Université Hospital of Nantes, France), and 1 surgical ICU (Hospital Hôtel Dieu, University Hospital of Nantes, France).

2.1. Inclusion criteria

Patients with clinical signs of brain death were eligible for this study: a Glasgow Coma scale score of 3, no brain stem reactivity, age, sex, Simplified Acute Physiology Score II, etiology of brain death, and history of cardiovascular disease were all noted. Brain death confirmation by 2 EEGs or an angiographic brain CT scan and the number of organs harvested were recorded.

2.2. Management of donors

Volume expansion (VE) and the type of hemodynamic monitoring were left to the discretion of the attending physician (see Study Protocol). National recommendations for the management of heart-beating brain-dead donors were edited by the Société Française d’Anesthésie-Réanimation and the Société de Réanimation de Langue Française [7]. The recommendations state that during organ harvesting, norepinephrine should be tapered to sustain a mean arterial pressure (MAP) of 65 mm Hg or greater. In case of diabetes insipidus (defined as a diuresis >4 mL kg⁻¹ h⁻¹ and urine density <1.003 g cm⁻³), 4 mg of desmopressin was administered intravenously. A liberal glycemic control (6-9 mmol/L) was performed in each center. According to French recommendations [7], co-amoxiclav was administered to the donor in case of lung harvesting. Dobutamine was administered when the left ventricular ejection fraction (LVEF) was 40% or less in order to verify the potential reversibility of heart failure. During the study period, Mascia et al [1] demonstrated the usefulness of ventilatory protective strategy, including low tidal volume. We used this ventilatory strategy during the study period in order to increase the number of harvested lungs. Patients with protective ventilation were therefore included because ΔPP has been validated with tidal volume less than 8 mL kg⁻¹ [8].

2.3. Demographic data

Age, sex, Simplified Acute Physiology Score II, etiology of brain death, and history of cardiovascular disease were all noted. Brain death confirmation by 2 EEGs or an angiographic brain CT scan and the number of organs harvested were recorded.

2.4. Study protocol

When the attending physician suspected hypovolemia (systolic arterial pressure (SAP) ≤100 mm Hg, low central venous pressure, excessive diuresis, tachycardia), one of the investigators was contacted. The investigator checked the validity criteria for ΔPP: absence of cardiac arrhythmia, volume-controlled respiratory mode, and inspiratory/expiratory ratio of 1:3 to 1:2. Hemodynamic stability was required over a 15-minute period before performing VE and was defined by a variation of less than 10% in terms of heart rate (HR) and systolic blood pressure. Before VE, the following data were recorded: ΔPP, HR, SAP, MAP, diastolic arterial pressure (DAP), the last hourly diuresis (in mL kg⁻¹ h⁻¹), catecholamine dose (in µg kg⁻¹ min⁻¹), tidal volume (in mL kg⁻¹), and plateau pressure (cm H₂O). Pulse pressure variation was retrieved via automatic calculation in all centers. A TTE examination was then performed.

2.5. Left parasternal long-axis view

The diameter of the left ventricle (LV) aortic chamber, hypertrophy, or end-diastolic dilatation of the LV were recorded. For these latter parameters, the time-motion mode was used. Hypertrophy was defined as an end-diastolic septal thickness of 13 mm or greater [9]. Dilatation was defined as an end-diastolic LV diameter of at least 32 mm m⁻² in women and at least 31 mm m⁻² in men [9].

2.6. Apical 4- and 5-chamber view

Left ventricular ejection fraction was evaluated with the following techniques: visual evaluation and Simpson calculation in the 4-chamber and the 2-chamber views [10]. A pulsed-wave Doppler beam was performed at the mitral valve tips. Mitral inflow Doppler measurements included the following: early (E) and late (A) peak diastolic velocities and the E/A ratio.

Using the 5-chamber view, the velocity time integral (VTI) was computed from the area under the envelope of the pulsed-wave Doppler signal obtained at the level of the aortic annulus. Stroke volume was calculated by the product of the VTI by aortic valve area. Cardiac output (CO) was calculated as the product of stroke volume by HR. The mean of 3 measurements of VTi performed at the end of the inspiratory period was used for CO calculation. Cardiac index (CI) was calculated as the CO/body surface ratio (in L min⁻¹ m⁻²).

An evaluation of right ventricle (RV) function was also performed. Right ventricle dilatation was evaluated through bidimensional echocardiographic measurements by the basis diameter of the RV/basis diameter of the LV ratio. The RV was considered dilated when the ratio was greater than 0.6 [11]. The longitudinal systolic function of the RV was evaluated by the tricuspid annular plane systolic excursion (TAPSE) with a time-motion image of the lateral corner of the tricuspid annulus.

2.7. Echocardiographic parameters of fluid responsiveness

Before VE, ΔVPeak in the 5-chamber view [12] was recorded. After the echocardiographic examination, VE was performed with 500 mL of a colloid solution (Gelfusine 4%, B-Braun® 204 avenue du Maréchal Juin, 92100 Boulogne-Billancourt, France) over a 30-minute period [4]. After VE, HR, SAP, MAP, and DAP were recorded and a second TTE was performed in order to obtain VTI and calculate CO. The study ended after the second TTE.

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Because echocardiography is operator dependent, we carried out an interobserver and intraobserver variability analysis of the most important parameter, aortic VTI because this variable and its change are of critical importance for calculating CO.

Transthoracic echocardiography was performed by 5 trained anesthesiologists or intensivists with approved TTE training and with a daily practice of TTE.

2.8. Primary objective

The primary objective was to assess the performance of ΔPP as a fluid responsiveness parameter in brain-dead subjects. Fluid responsiveness was defined by an increase of CI of at least 15% after VE [4,13]. Patients with CI variations of at least 15% and less than 15% after VE were classified as responders and nonresponders, respectively. In the study by Michard et al [4], a ΔPP of at least 13% accurately predicted preload responsiveness.

2.9. Secondary objective

We aimed to assess the performances of echocardiographic ΔVpeak preload responsiveness index, TAPSE, E/A ratio, and RV dilation. We evaluated the influence of fluid responsiveness on organ harvesting.

2.10. Statistical analysis

All patients enrolled in the study were considered as candidates for receiving VE by the attending physician. Therefore, 100% of the patients could be responders. The number of patients was determined by a power analysis based on an expectation of a 15% change in CO in brain-dead patients, with α = .05 and 1 − β = 0.80. The power calculation yielded a sample size of 25 patients. Accordingly, 25 patients were enrolled, as each patient was his/her own control. Nominal data are expressed as number (%) and continuous data as median (25th-75th percentile). Kolmogorov-Smirnov tests were used to test the normality of continuous variables. Correlations were established between ΔPP and the variation of CI before and after VE and tested using Spearman rank test. A P value less than .05 was considered statistically significant.

The comparison of hemodynamic parameters before VE in responder and nonresponder patients was assessed using a nonparametric Mann-Whitney U test. Receiver operating characteristic (ROC) curves were generated for ΔPP, ΔVpeak, TAPSE, and dilatation of the RV. In order to compute the 95% confidence interval (95% CI) of the area under the curves, we performed 1000-bootstrap resampling and we used the 2.5 and 97.5 percentiles of the bootstrap estimations.

For intraobserver variability, the first operator randomly chose 1 of the 3 aortic VTIs and measured aortic VTI a second time. An interobserver analysis was randomly performed on 15 aortic VTI measurements. Variability was expressed as the mean percent error (ie, the difference between 2 observers divided by the mean of the 2 observed values) for measurements of VTI [12]. Statistical analysis was performed with GraphPad Prism software (GraphPad, San Diego, Calif), and SAS 9.3 was used for ROC curve graphs (SAS, Cary, NC).

3. Results

3.1. Overall population

Our study included 25 brain-dead subjects. Brain death was confirmed in 23 (92%) subjects by a brain angiographic CT scan in 18 (78%) and by 2 EEGs in 5 (22%) subjects. Two subjects were included before brain-death confirmation with CT scan. Data were kept in the analysis, in accordance with our inclusion criteria (clinical diagnosis of brain death). The origin of brain death was traumatic brain injury in 13 patients (52%), subarachnoid haemorrhage in 4 patients (16%), stroke in 6 patients (24%), resuscitated cardiac arrest in 1 patient (4%), and a brain tumor in 1 patient (4%). Demographic and hemodynamic data are summarized in Table 1. All patients were ventilated with a medium tidal volume of 7.2 (6.9-7.8) ml kg\(^{-1}\), a PEEP ranging from 3 to 5 cm H\(_2\)O, and the median plateau pressure of 18 (16-18) cm H\(_2\)O. Visual LVEF was 55% (50%-60%). Left ventricular ejection fraction in the 4-chamber view with a Simpson calculation was 52% (46%-55%; Table 1). At baseline, CI was 2.2 (1.8-3.1) L min\(^{-1}\) m\(^{-2}\). One subject had LV dilation and another subject had HV hypertrophy. Regarding RV parameters, TAPSE was not retrieved in 5 patients for technical reasons. Median values ranged from 2.2 (1.9-2.3) cm (Table 1). Right ventricle dilation was monitored in all patients; 12 subjects (48%) had mild to moderate RV dilation [11], 7 subjects (28%) had severe RV dilation [11], and 6 (24%) subjects had no RV dilation (ratio < 0.6). Twenty subjects received norepinephrine on inclusion with a median dose of 0.3 (0.1-0.5) μg kg\(^{-1}\) min\(^{-1}\). The median diuresis in the hour before inclusion was 2 (1-5) ml kg\(^{-1}\). Five (20%) patients received desmopressin after brain death diagnosis and before inclusion.

3.2. Hemodynamic results

3.2.1. Pulse pressure variation

Pulse pressure variation ranged from 8.5% to 36% (median, 13% [13%-20%]), and there was a significant correlation between baseline ΔPP and the increase of CI (r\(^2\) = 0.19, P = .02; Supplementary data 1). Baseline ΔPP was not different between responders and nonresponders (17 [13–27] vs 14 [12.2-15]. P = .11; Fig. 1). Since the accurate threshold of CI increase to define fluid responsiveness has not been validated with certainty, we performed a sensitivity test by varying the CI increase threshold from 10% to 20%. This led to the reclassification of only 2 subjects as responders and 1 subject as a nonresponder with a 10% and 20% threshold respectively. In this posthoc analysis ΔPP still could not discriminate responders from nonresponders with these different definitions of fluid responsiveness (Supplementary data 2), suggesting that our results do not depend on the definition of fluid responsiveness.

3.2.2. Other echocardiographic parameters

Measurements of ΔVpeak were not available in 3 subjects. The values of ΔVpeak ranged from 5.3% to 36.8% (median, 17.5% [10.7%-27.2%]). The values of ΔVpeak were not different between responders and nonresponders (22.6 [10.9-31.7] vs 14.2 [6.7-25], P = .4; Fig. 1).

Table 1

Demographic and hemodynamic data of brain-dead subjects at the time of inclusion.

<table>
<thead>
<tr>
<th></th>
<th>Brain-dead patients (n = 25)</th>
<th>Nonresponders (n = 10)</th>
<th>Responders (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology of brain death, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>13 (52)</td>
<td>4 (40)</td>
<td>9 (60)</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>4 (16)</td>
<td>2 (20)</td>
<td>5 (33)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (24)</td>
<td>3 (30)</td>
<td>1 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (4)</td>
<td>1 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demography</td>
<td>8 (53)%/7 (47)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: male/female, no. (%)</td>
<td>14 (56)/11 (44)</td>
<td>6 (60)/4 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y), median (IQR)</td>
<td>48 (37-63)</td>
<td>44 (32-63)</td>
<td>48 (37-59)</td>
<td>.9</td>
</tr>
<tr>
<td>SAPS II, median (IQR)</td>
<td>56 (49-64)</td>
<td>54 (47-82)</td>
<td>56 (52-65)</td>
<td>.4</td>
</tr>
<tr>
<td>BMI (kg/m(^2)), median (IQR)</td>
<td>24 (22-26)</td>
<td>24 (21-28)</td>
<td>24 (23-25)</td>
<td>1</td>
</tr>
<tr>
<td>Hemodynamic data at baseline, median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>89 (85-112)</td>
<td>94 (84-109)</td>
<td>105 (87-105)</td>
<td>.3</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>91 (85-98)</td>
<td>92 (85-97)</td>
<td>91 (85-87)</td>
<td>.8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>66 (62-69)</td>
<td>67 (63-71)</td>
<td>65 (61-68)</td>
<td>.4</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>52 (47-58)</td>
<td>54 (51-58)</td>
<td>52 (45-56)</td>
<td>.5</td>
</tr>
<tr>
<td>Norepinephrine (μg kg(^{-1}) min(^{-1}))</td>
<td>0.3 (0.1-0.5)</td>
<td>0.3 (0.3-0.6)</td>
<td>0.2 (0.07-0.4)</td>
<td>.2</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55 (50-60)</td>
<td>55 (51-60)</td>
<td>55 (47-60)</td>
<td>.5</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>2.2 (1.9-2.3)</td>
<td>2.2 (2.1-2.2)</td>
<td>2.2 (1.9-2.4)</td>
<td>.9</td>
</tr>
</tbody>
</table>

Nominal data are expressed as n (%). Continuous data are expressed as median (25th-75th percentile).

BMI indicates body mass index; IQR, interquartile range.

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3.2.3. Right ventricle analysis

The values of TAPSE and RV dilation between responders and nonresponders were not statistically different (2.2 [1.9-2.4] vs 2.2 [2.1-2.2; \( P = .96 \)) and 0.7 [0.5-0.8] vs 0.8 [0.68-0.97; \( P = .10 \)), respectively; Fig. 1).

3.2.4. Receiver operating characteristic curves

Fig. 2 shows ROC curves for \( \Delta PP \), \( \Delta V\text{peak} \), TAPSE, and dilation of the RV. The area under the ROC curve (AUC) for \( \Delta PP \) was 0.69 (95% CI, 0.47-0.88). A \( \Delta PP \) threshold of 13% would predict a successful VE with a sensitivity of 40%, a specificity of 66%, and a Youden test of 6%. With a threshold value of 20%, \( \Delta PP \) would predict preload responsiveness with a sensitivity of 100%, a specificity of 40%, and a Youden test of 40%. In our study, 6 donors had a \( \Delta PP \) at least 20%, and the improvement of CI was significant in this group (\( P = .008 \)) but not among the 19 patients with a baseline \( \Delta PP \) less than 20% (Fig. 3). The AUC for \( \Delta V\text{peak} \) was 0.61 (95% CI, 0.48-0.85). The AUC for TAPSE and RV dilation was 0.49 (95% CI, 0.44-0.80) and 0.7 (95% CI, 0.50-0.91), respectively.

3.2.5. Intraobserver and interobserver variability

Intraobserver variability was 3% (1%-4%). Interobserver variability was 2% (1%-7%).

3.3. Organ harvesting

Among the 25 subjects included, multorgan harvesting procedures were performed in 18 subjects and 7 harvesting were not performed because of refusal by next-of-kin (n = 6) or medical contraindication (n = 1), which led to the harvesting 36 kidneys, 11 livers, 6 hearts, 5 lungs, and 1 pancreas. The mean number of organs harvested was significantly higher in responders than in nonresponders: 3.5 (3-5) and 2.5 (2-3), respectively (\( P = .03 \)). There was a trend toward more organ donation refusal, and procedure withdrawal for medical reasons was higher in the responders group (n = 5) than in the nonresponders (n = 2), but the difference did not reach statistical significance.

4. Discussion

This study aimed to evaluate the ability of \( \Delta PP \) to predict CI increase after VE in brain-dead subjects presenting circulatory failure. Pulse pressure variation with a threshold of 13% was poorly correlated with fluid responsiveness, whereas sensitivity was 100% when the \( \Delta PP \) limit was set to 20%. There was a significant difference in organ harvesting between responders and nonresponders.
suggesting that discriminating these 2 populations could be relevant to improve the number of organs available for transplantation.

Circulatory failure is common and complex in brain-dead donors. The causes of decrease in CI of brain-dead subjects could associate hypovolemia as a consequence of incomplete volume resuscitation or excessive diuresis owing to diabetes insipidus, vascular vasodilation secondary to the loss of central vasomotor tone, decrease of circulating catecholamines after cerebral herniation, and cardiogenic shock secondary to myocardial contusion in case of trauma or myocardial dysfunction after a catecholamine storm. Loss of sympathetic tone could, at least in part, be the consequence of neuroendocrine alterations, which frequently occur after brain death. In a recent study, the authors demonstrated that 87% of donors had adrenal insufficiency and supplementation with hydrocortisone led to a significant reduction in the norepinephrine dose. Therefore, circulatory failure in brain-dead subjects is complex because all of the types of pathophysiological mechanisms described above may be present, each to a variable degree. In the setting of brain death, choosing between fluid therapy and vasopressors may therefore be a challenging issue for the attending physician.

If hypotension occurs, an “easy-to-use” tool should be available to attempt proper administration of VE or vasopressors. In order to guide VE, ΔPP has been proposed in septic patients. A ΔPP of 13% or greater accurately predicted fluid responsiveness in patients presenting a septic shock with a sensitivity of 94% and a specificity of 96%.

Because ΔPP is widely available, it has been used extensively in nonseptic patients and quite naturally in brain-dead subjects. However, to our knowledge, no data evaluating the accuracy of ΔPP during brain death have been published to date. The current results suggest that a ΔPP threshold set at 13% will inaccurately define fluid responsiveness. Increasing the threshold to 20% would be more efficient to detect hypovolemia, but with a poor AUC.

Fluid responsiveness was studied in an observational monocentric 21-donor series. The authors found that fluid responsiveness (defined as ΔPP ≥ 13%) occurred in 48% of donors, which is consistent with our median ΔPP values, although most donors had undergone trauma in our study. Murugan et al. found in a univariate analysis that a ΔPP of 13% or greater was associated with lower organ yield, whereas we found that fluid responsiveness (CI ≥ 15%) was associated with more organ yield. However, in the study by Murugan et al, CI modifications after VE were not studied, thereby avoiding assessment of which donors were truly fluid responders. In our study, we cannot exclude that some fluid unresponsive donors could have received detrimental VE for organs, knowing the side effects of VE such as cardiac dysfunction or inflammatory disorders. Moreover, nonresponder patients could have received detrimental VE before brain death. In such cases, VE could also have been detrimental for organs. However, it should be kept in mind that apart from the hemodynamic status, organ donation depends on several parameters (age, previous medical condition).

The evaluation of RV function was suggested to be important regarding fluid responsiveness evaluation. Mahjoub et al. could discriminate responders from nonresponders by monitoring RV systolic function in 35 patients with septic shock with a sensitivity of 91% and a specificity of 83%. We evaluated RV systolic function, in order to ascertain that a potential ΔPP false positivity could have been the consequence of RV failure. In this setting, Stoica et al. found RV systolic dysfunction in 33 consecutive donors compared with 10 patients undergoing coronary artery surgery. Astonishingly, brain-dead donors experienced an increased stroke volume along with a decreased ejection fraction. These data underline the fact that evaluating systolic RV function is complex because abnormalities are not always correlated with CO alterations. Apart from systolic dysfunction, dilation related with an increased RV afterload can also induce RV failure. The increase of RV afterload leading to RV dilation could be observed after brain death because of neurogenic pulmonary edema, nosocomial pneumonia, or atelectasis. In our study, 76% of the subjects displayed mild to severe RV dilation, but no echocardiographic sign of RV systolic failure (assessed with TAPSE) was recorded. The high incidence of RV...
dilation could therefore explain false positivity and, subsequently, the high overlap of fluid responsiveness between responders and nonresponders. In accordance with these data, Majdof et al. [18] found a trend toward a higher rate of dilated RV in the nonresponder group. Finally, the RV patterns observed after brain death (preserved systolic function and moderate to severe dilation) suggest that RV evaluation is mandatory to rule out false-positive patients [18,27].

Because echocardiographic ΔPpeak has been described as a useful surrogate marker of fluid responsiveness in septic shock [12], we also evaluated this parameter. In 19 patients with septic shock [12], ΔPpeak was higher in responders than in nonresponders. In our study, ΔPpeak was unable to discriminate responders from nonresponders.

Several limitations should be noted. First, echocardiography is an observer-dependent examination. Because a low intravascular and interobserver variability was found regarding the evaluation of CL, low-quality echocardiography cannot be advocated to explain these results. Second, before brain death, patients could have received VE. This could alter fluid responsiveness. Another limit is the rather low tidal volume because the mean tidal volume was less than 8 mL kg−1 of measured body weight. Criteria for initiating VE are required when caring for organ donors. A 13% ΔP threshold has been validated in septic patients as well as in other clinical settings. This was confirmed by the meta-analysis of Marik et al. [8], where a 12.5% ΔP threshold was retrieved. In this meta-analysis [8], some patients received mechanical ventilation with a tidal volume of 8 mL kg−1 or less. This has justified our choice to perform VE with a 13% ΔP threshold in brain-dead donors when using a tidal volume of 8 mL kg−1 or less [1]. The use of low tidal volume could decrease the sensitivity of ΔP to predict fluid responsiveness [28]. However, in a recent study, a low tidal volume did not decrease ΔP sensitivity to predict fluid responsiveness in septic patients [29]. However, despite a low tidal volume, Freitas et al. [29] found a good performance of ΔP to predict fluid responsiveness, probably owing to a high PEEP (10 cm H2O) which could have enabled a good transmission of ventilatory pressure to the circulatory system. Because donors displayed low PEEP (range, 3–5 cm H2O) in the present results, this could have impaired ΔP’s sensitivity and specificity. Also, it should be kept in mind that studies regarding ΔP in patients receiving mechanical ventilation with low tidal volumes (≤8 mL kg−1) exhibited lower thresholds (6.5% [29] or 7% [30]). Our results are the opposite, and only 2 brain-dead subjects had a ΔP less than 10% (see Supplementary data 1; Fig. 1) and only 2 were false negative. A low tidal volume cannot be advocated solely to explain the small rate of false negative for ΔP. Brain-dead donors exhibit a unique hemodynamic pattern, which could be explained by a high incidence of diabetes insipidus and variations in the sympathetic tone and in the neuroendocrine status. All these modifications could alter response to VE. The sample size of our population is rather low. However, according to the central limit theorem [31], the inclusion of 25 patients should enable an accurate description of physiological values. Finally, it should be kept in mind that ΔP is available in few patients in the ICU [32] including maybe brain-dead donors because of a high incidence of nonvalidity criteria. Larger investigations should be performed to validate our findings.

5. Conclusion

Pulse pressure variation should be used with caution in brain-dead subjects during circulatory failure. A higher than previously described threshold value of ΔP (20%) could be considered to discriminate responder and nonresponder subjects. Further studies focusing on fluid responsiveness should be performed in order to verify its potential impact on organ donation. Large prospective studies are mandatory to confirm these results, before modifying bedside practices during donor resuscitation.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2014.03.027.

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