Pulse Pressure Variation Patterns in a Swine Model of Hypovolemia under Spontaneous Breathing vs. Invasive Positive-Pressure Ventilation

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OBJECTIVE: This study was performed to obtain the title of Master in Medicine, Nov/2012–Jul/2013. Improvement in cardiac output after fluid administration is known as fluid responsiveness. A reliable parameter for its evaluation is pulse pressure variation: it has established its utility in predicting volume responsiveness in mechanically ventilated patients.

METHOD: Pulse pressure variation was analyzed in 10 anesthetized male pigs at four different stages: I) normovolemia and spontaneous breathing; II) hypovolemia and spontaneous breathing; III) hypovolemia under mechanical ventilation; and IV) after volume replacement, under mechanical ventilation. Cardiac output, pulmonary artery occlusion pressure, systolic pressure variation, mean arterial pressure, and heart rate were measured at all stages; red blood cell count was determined at stages I, II, and IV.

RESULTS: Mean pulse pressure variation values during hypovolemia with spontaneous breathing (stage II) were significantly higher than at any other stage. After institution of mechanical ventilation, pulse pressure variation values returned to baseline without fluid administration. The lowest values were achieved after volume replacement.

CONCLUSION: Pulse pressure variation values are higher during spontaneous breathing than during mechanical ventilation. Thus, it may be useful for assessment of fluid volume under these conditions, with baseline values as a starting point to which serial measurements should be compared after institution of specific therapy.

KEYWORDS: pulse pressure variation; hypovolemia; swine model; spontaneous breathing.

■ INTRODUCTION

Shock is a syndrome characterized by the inability of the circulatory system to adequately provide oxygen and nutrients to body tissues to meet their metabolic needs. Regardless of its etiology, early and vigorous fluid replacement (except in cardiogenic shock due to left ventricular involvement) should be instituted to reverse hypotension and, consequently, progression to multiple organ dysfunction.[1]

Static and dynamic variables parameters have been developed to guide appropriate volume replacement. Dynamic variables include the pulse pressure variation (ΔPP), the systolic pressure variation (ΔPS), the dynamic range of the vena cava and the aortic flow variation. Static variables for predicting fluid responsiveness include central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and the left and right ventricular end-diastolic volumes. There is no single optimal variable, and all have major limitations.[2-22]

One variable that has been used in recent years for this purpose is ΔPP. During the breathing cycle, the peak and minimum pulse pressures (defined as the difference between systolic and diastolic pressure) are calculated and used to derive the ΔPP, as described below, in methods. A ΔPP >13% discriminates patients that will respond to volume replacement with an increase in cardiac output; those with ΔPP values ≤13% will not exhibit such a response. This parameter thus defines two groups of patients: volume expansion responders and nonresponders.[2-5,23-26]

For any value of arterial distensibility, pulse pressure amplitude is directly related to the left ventricular stroke volume. Thus, changes in arterial pulse pressure essentially reflect left ventricular stroke volume.[24-26]

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

MEDICALEXPRESS 2014;1(6):359-365

The utility of ΔPP is limited in patients with spontaneous ventilation and/or cardiac arrhythmias, in whom its accuracy is reduced. The changes in alveolar and intrapleural pressure during spontaneous ventilation are smaller than the changes induced by positive-pressure mechanical ventilation; thus they are insufficient to alter ventricular preload – and, consequently, left ventricular stroke volume – to an extent measurable by ΔPP. Furthermore, active expiratory movements can change alveolar pressure from one respiratory cycle to another and generate fluctuations in ventricular volumes due to the outflow of blood from the abdomen to the chest during contraction of the diaphragm and abdominal muscles. Cardiac arrhythmias, in turn, can cause fluctuations in ventricular volumes and in cardiac output independently of changes in intrathoracic pressures or blood volume, thus interfering substantially with the accuracy of ΔPP as a marker of blood volume.[2–5,23–26]

In patients undergoing elective procedures with risk of bleeding and without systemic inflammation and/or hemodynamic instability, ΔPP may be useful as an additional parameter for assessment of fluid volume and, more specifically, of fluid responsiveness. Moreover, little is known about the pattern of ΔPP in spontaneous ventilation, and there are no validated ΔPP cutoff values for use in spontaneously breathing patients. Few studies have assessed ΔPP in spontaneous ventilation, and all included patients with systemic inflammation.[27–37]

Within this context, we sought to analyze the ΔPP in swine models of hypovolemia, both during spontaneous breathing and under positive-pressure mechanical ventilation, in the absence of systemic inflammation.

■ MATERIALS AND METHODS

Preparation of animals
The sample comprised 10 male pigs. Before the experiments, the animals were fasted for 12 hours. Pre-anesthetic medication consisted of intramuscular acepromazine maleate 1% (0.1 to 0.25 mg/kg) and midazolam (0.5 mg/kg). After 30 minutes, the animals were placed in the supine position on a V-shaped table, rectal temperature was measured, and continuous ECG monitoring was started to record the heart rate and enable detection of arrhythmias. A left ear vein was cannulated for drug infusion. After orotracheal intubation, the animals were kept on spontaneous ventilation with supplemental O_2 to maintain oxygen saturations above 95%.

Vascular access
The following vessels were dissected and cannulated for measurement of hemodynamic variables: (i) right femoral artery: pigtail catheter into the aortic arch for central blood pressure monitoring; (ii) right femoral vein: Swan-Ganz catheter for pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output monitoring; (iii) left femoral artery: for peripheral blood pressure monitoring; (iv) left femoral vein: for infusion of drugs and fluids.

Measurement and calculation of hemodynamic variables
Cardiac output was measured by the thermodilution technique (Dixtal 2010®); the average of three measurements was considered for analysis. Central blood pressure,

peripheral blood pressure, pulmonary artery pressure, and pulmonary artery occlusion pressure were recorded on a polygraph (TEB SP 32®) for subsequent interpretation, analysis, and manual calculation. Systolic and diastolic blood pressures (both central and peripheral) were measured and pulse pressure calculated as the difference between these two pressures. Peak and minimum systolic blood pressure and pulse pressure values were measured over three different respiratory cycles, as described elsewhere;[23–26] Figure 1 illustrates the procedures. Using these values, ΔPP (peripheral pulse pressure variation) and the central pulse pressure variation (cΔPP) were calculated according to the formula:[23]

ΔPP (%) = 100 × [(peak peripheral pulse pressure − minimum peripheral pulse pressure)/(peak peripheral pulse pressure + minimum peripheral pulse pressure)/2].

cΔPP (%) = 100 × [(peak central pulse pressure − minimum central pulse pressure)/(peak central pulse pressure + minimum central peripheral pulse pressure)/2].

The peripheral systolic pressure variation (ΔPS) and the central systolic pressure variation (cΔPS) were determined using the formula:

ΔPS (%) = 100 × [(peak peripheral systolic pressure − minimum peripheral systolic pressure)/(peak peripheral systolic pressure + minimum peripheral systolic pressure)/2].

cΔPS (%) = 100 × [(peak central systolic pressure − minimum central peripheral systolic pressure)/(peak central systolic pressure + minimum central systolic pressure)/2].

Mean arterial pressure (MAP) was calculated as follows:
MAP (mmHg) = [(2 × diastolic blood pressure) + systolic blood pressure]/3, as shown in Figure 1.

Invasive positive-pressure mechanical ventilation
The animals were ventilated in controlled positive-pressure mode using the following settings (Takaoka CC 500®): tidal volume (V_T) 7 mL/kg, positive end-expiratory pressure (PEEP) 6 mmHg, respiratory rate (RR) 12 bpm, inspiratory-expiratory ratio (I:E) = 1:2, and fraction of inspired oxygen (FiO_2) = 40%.

Induction of hypovolemia and fluid replacement
Hypovolemia was induced by controlled bleeding of 17 mL/kg over a period of 4 minutes. This model was based on a pilot experiment with five animals, which showed that a blood loss of 17 mL/kg is sufficient to reduce blood pressure by 30%. The removed blood was stored in plastic transfusion bags (Fresenius Kabi CompoFlex CPDA-1®) for later reinfusion.

Protocol
Cardiac output, central and peripheral blood pressure, pulmonary arterial pressure, pulmonary artery occlusion pressure and complete blood counts were obtained from all animals according to the following sequence:

Stage I:
- Normovolemia, mild sedation, and spontaneous ventilation;
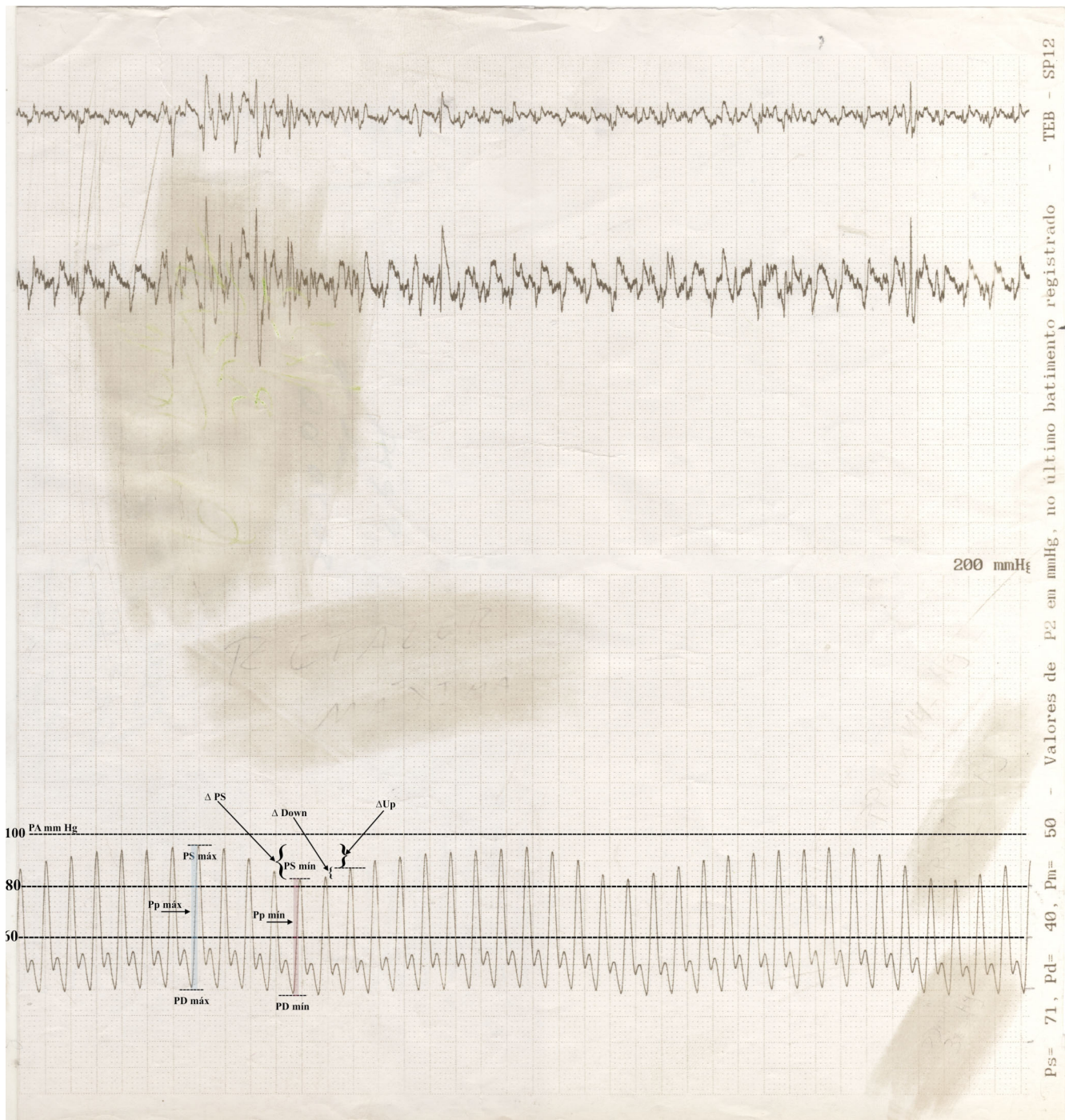- Measurement of hemodynamic variables and complete blood count.

MEDICALEXPRESS 2014;1(6):359-365

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

Figure 1 - Representative example of arterial pressure waveform in a mechanically ventilated animal at stage III of the experiment. PA = systemic arterial pressure; mmHg = millimeters of mercury; ΔPS = systolic pressure variation; PS max = peak systolic pressure; PS min = minimum systolic pressure; PD max = peak diastolic pressure; PD min = minimum diastolic pressure; Pp max = peak pulse pressure; Pp min = minimum pulse pressure.

Stage II:
- Mild sedation and spontaneous ventilation;
- Induction of hypovolemia (controlled bleeding of 17 mL/kg; average bleeding time of 3 minutes and 54 seconds);
- Ten-minute waiting period for hemodynamic stabilization;

- Measurement of hemodynamic variables and complete blood count.
Stage III:
- Hypovolemia, deep sedation with intravenous thiopental sodium (100 mg loading dose and 5-10 mg/kg/hour maintenance dose) and fentanyl (10 mg/kg/hour), and paralysis (pancuronium

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

MEDICALEXPRESS 2014;1(6):359-365

0.2 mg/kg intravenous bolus) to eliminate respiratory activity;
- Institution of mechanical ventilation;
- Ten-minute waiting period for hemodynamic stabilization;
- Measurement of hemodynamic variables.
Stage IV:
- Same level of sedation and mechanical ventilation as stage III;
- Replacement of blood volume withdrawn during stage II (average reinfusion time of 10 minutes);
- Ten-minute waiting period for hemodynamic stabilization;
- Measurement of hemodynamic variables and complete blood count.

Statistical analysis

Means and standard deviations, ranges, and medians were calculated for all numeric variables. Repeated-measures analysis of variance (ANOVA) was used to compare normally distributed means. The Kolmogorov–Smirnov test, Levene's test, and Tukey's and Dunnett's multiple comparisons procedures were used in this analysis. The significance level was set at P < 0.05.

Ethical approval

This study was approved by Ethical Committee of the Universidade Federal de São Paulo. Case number 0318/12.

■ RESULTS

General

The mean body weight of the animals included in this project was 32.8 ± 3.6 kg, and their, mean rectal temperature was 39.5 ± 1.3°C. Table 1 summarizes the mean values of the hemodynamic variables of interest at each stage of the experiment.

Pulse pressure variation (ΔPP)

The mean ΔPP value at the first stage of the experiment was 22.30% ± 15.27%, increasing significantly to 42.27% ± 27.84% (p < 0.046) during stage II (hypovolemia plus spontaneous ventilation). During stage III, ΔPP fell to 21.80% ± 9.63%, a level similar to that of stage I (p > 0.999) and significantly lower compared to stage II (p = 0.039). The lowest ΔPP (10.48% ± 12.55%) was observed in stage IV, with no statistically significant difference compared to stage I (p = 0.372) or III (p = 0.410), but significantly lower than that observed at stage II (p = 0.001). The median ΔPP values showed similar characteristics (Figure 2).

Cardiac output

The initial mean CO value (L/min) was 5.85 ± 1.65. At stage II, CO fell to 4.11 ± 0.52, a value significantly lower than that observed in stage I (p < 0.048). At stage III, this value increased to 5.04 ± 1.19, with no significant difference from stage II (p = 0.248). During the last stage of the experiment, the mean CO value was 8.93 ± 1.99, significantly higher from those observed at stages I (p = 0.009), II (p < 0.001), and III (p = 0.001). The median CO values behaved similarly, as shown in Figure 3.

Pulmonary artery occlusion pressure (PAOP)

The mean PAOP values (mmHg) at each stage of the study were 6.92 ± 2.19, 4.08 ± 2.67, 7.01 ± 2.37, and 9.22 ± 2.15 respectively. There was no statistically significant difference between stages I and II (p = 0.058). At stage III (hypovolemia plus mechanical ventilation, deep sedation, and paralysis), the mean value increased to 7.01 ± 2.37, which was significantly higher than at stage II (p = 0.049). The difference between stages II and IV was also significant (p < 0.001). Comparison between the mean PAOP values at stages III and IV showed no statistically significant difference (p = 0.192).

■ DISCUSSION

The main finding of this study was that mean and median ΔPP values were significantly higher in hypovolemic animals during spontaneous ventilation as compared to the under positive-pressure mechanical ventilation values. The higher mean ΔPP value (42.27% ± 27.84%) observed in stage II (hypovolemia and spontaneous ventilation) is probably related to the variability of tidal volumes in animals at this stage of the experiment. The institution of positive-pressure mechanical ventilation in stage III led to a

Table 1 - Mean values of hemodynamic variables at each stage of the experiment.

Variable	Stage I	Stage II	Stage III	Stage IV	P-value
SBP, mmHg*	136.2 ± 26.54	92.1 ± 22.45	106.9 ± 27.84	134.8 ± 15.36	p < 0.001
DBP, mmHg*	86.1 ± 20.71	57.53 ± 21.76	62.59 ± 23.16	67.13 ± 13.71	p = 0.017
MAP, mmHg*	102.8 ± 21.91	69.05 ± 21.73	77.12 ± 24.53	89.79 ± 12.68	p < 0.003
PAOP, mmHg*	6.92 ± 2.19	4.08 ± 2.67	7.01 ± 2.37	9.22 ± 2.15	p < 0.001
CO, L/min*	5.85 ± 1.65	4.11 ± 0.52	5.04 ± 1.19	8.93 ± 1.99	p < 0.001
HR, bpm*	126.82 ± 23.15	142.21 ± 32.01	169.29 ± 49.31	171.25 ± 39.87	p = 0.001
Hb, g/dL	10.41 ± 0.93	10.28 ± 0.78	n/a	10.55 ± 0.97	p = 0.577
Hct, %	31.80 ± 3.61	31.40 ± 3.06	n/a	32.2 ± 3.71	p = 0.326
ΔPP, %*	22.3 ± 15.27	42.27 ± 27.84	21.8 ± 9.63	10.48 ± 12.55	p = 0.002
cΔPP, %	35.5 ± 35.27	22.4 ± 21.65	12.73 ± 7.09	8.72 ± 7.7	p = 0.067
SPV, %	12 ± 6.42	16.2 ± 9.66	13.78 ± 3.61	13.9 ± 11.57	p = 0.680
cSPV, %	12.4 ± 6.31	13.28 ± 4.71	10.03 ± 3	10.18 ± 4.36	p = 0.372

*P (ANOVA) < 0.05 for differences among the four stages. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PAOP = pulmonary artery occlusion pressure, CO = cardiac output, HR = heart rate, Hb = hemoglobin, Hct = hematocrit, ΔPP = pulse pressure variation, cΔPP = central pulse pressure variation, SPV = systolic pressure variation, cSPV = central systolic pressure variation, L/min = liters per minute, bpm = beats per minute, g/dL = grams per deciliter, mmHg = millimeters of mercury, n/a = not available.
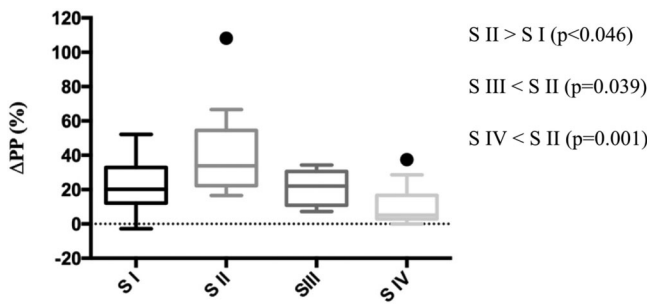
MEDICALEXPRESS 2014;1(6):359-365

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

Figure 2 - Box plot of ΔPP values at each stage of the experiment. ΔPP = pulse pressure variation; • = outlier; S I = stage I; S II = stage II; S III = stage III; S IV = stage IV.
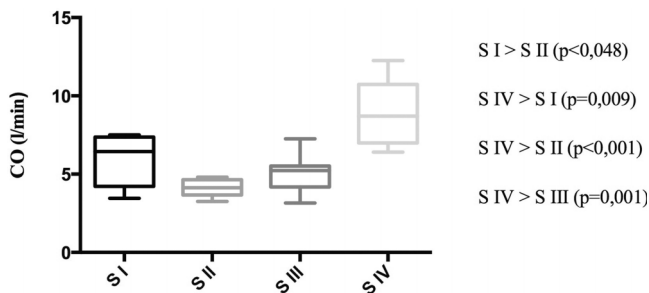

Figure 3 - Box plot of CO values at each stage of the experiment. CO = cardiac output; l/min = liters per minute; S I = stage I; S II = stage II; S III = stage III; S IV = stage IV.

decrease in ΔPP (21.80% ± 9.63%), but the difference in comparison with the preceding stage did not reach statistical significance. This can be explained by the consistency in tidal volumes induced by mechanical ventilation, leading to less marked changes in ventricular volumes as compared with spontaneous ventilation. However, fluid resuscitation during stage IV caused a further decrease in ΔPP (10.48 ± 12.55%), which returned to baseline (normovolemic) values, similar to those found in stage I (22.3% ± 15.27%).

All previous studies that evaluated ΔPP during spontaneous ventilation did so in heterogeneous patient groups, and mostly in the setting of systemic inflammation and/or sepsis.

Heenen et al.[28] analyzed the ability of certain static and dynamic preload parameters to predict fluid responsiveness in 21 patients with various clinical conditions (sepsis, status post cardiac surgery, gastrointestinal bleeding, etc.). Twelve patients were on a face mask and nine were mechanically ventilated on pressure support mode. PAOP, CVP, ΔPP, and inspiratory CVP variation were measured before and after volume expansion with colloids. Responders were defined as patients who exhibited a ≥15% increase in cardiac output from baseline. The ΔPP value at baseline ranged from 0% to 49%, and the median baseline value was 11%. In mechanically ventilated patients, the area under the ROC curve for ΔPP was 0.64 ± 0.26, versus 0.29 ± 0.17 in patients breathing through a face mask (p = 0.25). There were no statistically significant differences in any of the analyzed variables between responders and nonresponders.

Fluid responsiveness was predicted more efficiently by static indices than by dynamic parameters, with areas under the ROC curve of 0.73 ± 0.13 for PAOP versus ΔPP (p < 0.05), 0.69 ± 0.12 for PVC versus ΔPP (p = 0.054), 0.40 ± 0.13 for ΔPP, and 0.53 ± 0.13 for inspiratory changes in PVC (p = not significant in relation to ΔPP). The median value in stage II of our study was 33%, versus 11% in the Heenen et al.[28] investigation. This can be attributed to the greater variation in tidal volume in our sample. Both spontaneous ventilation and spontaneous ventilation with pressure support cause oscillations in tidal volume, a phenomenon that is known to interfere with the interpretation of ΔPP values. In our opinion, the use of pressure support mode and face mask mitigated those oscillations by providing a the tidal volume more constant thus explaining the lower ΔPP values found by Heenen et al.[28] as compared with our sample. In our experiment, we did not stratify animals as fluid responders and nonresponders, but rather the pattern of ΔPP in hypovolemic animals during spontaneous breathing followed by mechanical ventilation and fluid resuscitation. Taking into account the definition of volume responsiveness used by Heenen et al.,[28] all animals in our sample were responders. However, several differences in methodology between the two studies preclude any further comparisons.

In another study, Dahl et al.[31] hypothesized that, during spontaneous breathing, the use of inspiratory and/or expiratory resistors could improve the accuracy of ΔPP and ΔPs in identifying volume responsiveness. Eight anesthetized and spontaneously breathing pigs were subjected to a sequence of 30% hypovolemia, normovolemia, and 20% and 40% hypervolemia. The mean ΔPP values observed in spontaneously breathing animals, during 30% hypovolemia without any resistor, with an inspiratory resistor, with an expiratory resistor, and with a combination of inspiratory and expiratory resistors were 17 ± 5%, 25 ± 6%, 25 ± 6%, and 26 ± 7% respectively. Using a combination of inspiratory and expiratory resistors and a cutoff value of 16%, ΔPP, Dahl et al. study[31] was able to predict fluid responsiveness with 100% sensitivity and 81% specificity. These ΔPP values differ from those found in stage II (hypovolemia and spontaneous ventilation) of our experiment (mean = 42.27%). One explanation for this discrepancy may be the greater degree of hypovolemia in our experiment. In the Dahl et al. study, there were no differences in heart rate or cardiac output between the hypovolemia and normovolemia stages. This leads us to believe that the degree of hypovolemia in their study was not as severe as that induced in our investigation. Moreover, the higher mean ΔPP value (42.27 ± 27.84%) observed in our study may have been due to our non-use of any mechanisms that could have made tidal volumes more constant in spontaneously breathing animals, thus leading to greater variability in ventricular volumes and, consequently, ΔPP values. However, this is precisely what our study sought to evaluate and we should stress that, to the best of our knowledge, this has never been previously described in the literature, namely: the ΔPP value in a setting where tidal volumes were not fixed by mechanical ventilation, sedation, and paralysis and in the absence of a systemic inflammatory response.

Clinical implications

This experiment can contribute to the assessment of patients undergoing elective invasive procedures, in the absence of

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

MEDICALEXPRESS 2014;1(6):359-365

systemic inflammation, in which blood loss poses a concern. Measurement of baseline ΔPP levels before the procedure will enable identification of any changes in this parameter in response to hypovolemia and positive-pressure ventilation. By monitoring these values and the variation thereof, clinicians can evaluate the need for volume replacement.

Limitations

Some limitations of this study are worth noting. The animals were studied without induction of systemic inflammatory response or sepsis, and fluid replacement consisted of reinfusion of the same fluid removed rather than administration of crystalloid; the behavior of the parameters of interest might have been different in the presence of these conditions. Furthermore, we did not use a control group. However, our population of animals exhibited similar clinical conditions, which makes for a homogeneous group. Although we did not evaluate fluid responders and nonresponders volume and did not establish a cutoff value for ΔPP, this study demonstrated the importance of using this variable for the assessment of blood volume in spontaneously breathing patients, alongside other markers of hypovolemia known and employed in routine clinical practice. Measurement of ΔPP at baseline and over time during an elective procedure should be the optimal manner of monitoring this parameter for diagnosis of hypovolemia and response to therapy, as demonstrated by Rooke et al. with regard to systolic pressure variation[34].

■ CONCLUSION

We therefore conclude that ΔPP values are higher in hypovolemic pigs during spontaneous ventilation when compared to those observed under positive-pressure ventilation, and that this parameter may assist in the measurement of blood volume from a baseline with which measurements should be compared serially and after institution of specific therapy in elective procedures performed in the absence of systemic inflammation.

■ RESUMO

OBJETIVO: Este estudo foi realizado para obtenção do título de Mestre em Medicina, Novembro/2012–Julho/2013. A melhoria do débito cardíaco após a administração de fluidos é conhecida como a capacidade de resposta do fluido. Um parâmetro confiável para sua avaliação é a variação da pressão de pulso, cuja utilidade na previsão da capacidade de resposta volêmica em pacientes sob ventilação mecânica é reconhecida.

MÉTODO: A variação de pressão de pulso foi analisada em 10 suínos machos, anestesiados em quatro diferentes estágios: I) normovolemia e respiração espontânea; II) hipovolemia e respiração espontânea; III) hipovolemia sob ventilação mecânica; e IV) após a reposição volêmica, sob ventilação mecânica. O débito cardíaco, a pressão de oclusão da artéria pulmonar, a variação da pressão sistólica, a pressão arterial média e frequência cardíaca foram medidos em todas as fases; a contagem de hemácias foi determinada nas fases I, II e IV.

RESULTADOS: Os valores de variação de pressão de pulso durante a hipovolemia com respiração espontânea (estágio II) foram significativamente maiores do que em qualquer outra fase Após a instituição da ventilação mecânica, os valores de variação de pressão de pulso voltaram ao valor inicial, sem a administração de fluidos. Os valores mais baixos foram obtidos após a reposição.

CONCLUSÃO: Os valores de variação da pressão de pulso são maiores durante a respiração espontânea do que durante a ventilação mecânica. Assim, esse parâmetro pode ser útil para a avaliação do volume de fluido sob estas condições. Os valores da linha de base devem ser tomados como ponto

de partida contra o qual as medições seriadas devem ser comparadas após a instituição da terapêutica específica.

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MEDICALEXPRESS 2014;1(6):359-365

Pulse Pressure Variation in Hypovolemia
Mauricio Macário Rocha et al.

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