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Predictor of fluid responsiveness in the 'grey zone': augmented pulse pressure variation through a temporary increase in tidal volume

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Abstract

Background: Pulse pressure variation (PPV) is widely used as a predictor of fluid responsiveness. However, a previous study has suggested a 'grey zone' between 9 and 13% in which PPV would be inconclusive to predict fluid responsiveness. Considering PPV is based on cardiopulmonary interactions, we evaluated whether an augmented PPV using a temporary increase in tidal volume (V_T) from 8 to 12 ml kg^{-1} has the predictability for fluid responsiveness in patients within the grey zone.

Methods: Adult patients requiring general anaesthesia were enrolled. During the period when PPV was within the range of 9–13%, haemodynamic variables such as stroke volume index (SVI) and PPV with an 8 ml kg^{-1} tidal volume ventilation (PPV8) were obtained before and after volume expansion (6 ml kg^{-1}) under mechanical ventilation. Augmented PPV induced by 2-min ventilation with a V_T of 12 ml kg^{-1} (PPV12) was also recorded immediately before volume loading. The patients whose SVI increased ≥10% after volume expansion were considered responders.

Results: In 38 enrolled patients, 20 were responders. Receiver operating characteristic curve analysis showed PPV12 had an excellent predictability for fluid responsiveness {area under the curve [AUC]=0.935 [95% confidence interval (CI) 0.805–0.989]; sensitivity 95%; specificity 72%; $P<0.0001$}. The optimal threshold for PPV12 was >17%. However, PPV8 failed to show significant predictability [AUC=0.668 (95% CI 0.497–0.812); sensitivity 65%; specificity 61%; $P=0.06$].

Conclusion: In mechanically ventilated patients, our augmented PPV successfully predicted fluid responsiveness in the previously suggested grey zone.

Clinical trial registration: ClinicalTrials.gov, NCT02653469.

Key words: cardiovascular system; effects; fluid therapy; heart; cardiac output; monitoring; intraoperative

In mechanically ventilated patients, pulse pressure variation (PPV) is generally accepted as the most accurate predictor for fluid responsiveness.[1–3] The accuracy and optimal threshold of PPV for discriminating fluid responsiveness have been proven in many studies using receiver operating characteristic (ROC) curve analysis. However, the ROC approach has unavoidable limitations since it artificially dichotomizes a continuous variable into a binary statistical index and this binary approach is not always an adequate representation of the clinical reality.[4–6]

To address this binary constraint in the ROC curve approach, recent studies have posed the possible existence of an inconclusive zone (grey zone) where the accuracy of PPV is not precise

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Editor's key points

- Pulse pressure variation (PPV) is used as a predictor of fluid responsiveness, but a PPV between 9 and 13% might not be useful.
- The authors studied whether an augmented PPV using a temporary increase in tidal volume (V_T) from 8 to 12 ml kg^{-1} has predictability for fluid responsiveness.
- Augmentation of PPV by an increase in V_T might be useful in predicting fluid responsiveness.

enough to predict fluid responsiveness.[5 7–10] A multicentre study demonstrated that PPV between 9 and 13% was uncertain for predicting fluid responsiveness during general anaesthesia in one-quarter of patients.[7] In addition, a recent study reported a broader range of the grey zone (4–17%) in 62% of ventilated patients in an intensive care unit (ICU).[8] Although the real range of the grey zone for PPV remains to be evaluated,[9] precise assessment of fluid responsiveness in patients within this uncertain area is essential. However, to our knowledge, there is no specific strategy to increase the predictability of PPV for fluid responsiveness in patients within the grey zone.

Because PPV is calculated from the heart–lung interaction, various factors that affect lung mechanics, including tidal volume (V_T), thoracic wall compliance, and intrathoracic or intra-abdominal pressure, could also influence PPV values.[11–15] Among these factors, the effect of V_T has been widely studied in various studies in which the PPV value was increased and its predictability for fluid responsiveness was improved when applying higher V_T ventilation.[11 12 16 17] Therefore, we hypothesized that a temporary increase in V_T from 8 to 12 ml kg^{-1} would improve the predictability of PPV for fluid responsiveness in this inconclusive zone. The aim of our study was to investigate whether augmented PPV using a temporary increase in V_T can predict fluid responsiveness in patients within the previously suggested grey zone.[7]

Methods

Study design and patient population

After approval from our institutional review board (SMC 2015-06-015) and obtaining written informed consents, adult patients undergoing elective open laparotomy surgery were enrolled from September 2015 to February 2016. We also registered this prospective and observational study at ClinicalTrials.gov (NCT02653469). Exclusion criteria were patients with preoperative cardiac arrhythmia, moderate to severe valvular heart disease, preoperative left ventricular ejection fraction <40%, right ventricular dysfunction, intracardiac shunts, moderate to severe chronic obstructive pulmonary disease, preoperative need of inotropics, moderate to severe renal or liver disease, acute lung injury, coexisting open thorax condition, severe bradycardia, and spontaneous breathing.

Anaesthesia

After arriving at the operating theatre, our routine monitoring devices, including pulse oximetry, non-invasive arterial pressure, and three-lead ECG, were applied to the patients. Anaesthesia was induced with propofol 4–5 μg ml^{-1} and remifentanil 2–5 ng ml^{-1} at the effect site, using target-controlled infusion pumps. Rocuronium (0.6–0.8 mg kg^{-1}) was used to achieve neuromuscular block. Following endotracheal intubation, mechanical ventilation with a V_T of 8 ml kg^{-1} of the ideal body weight,[18] a fraction of inspired oxygen ($F_{I_{O_2}}$) of 0.5, and an *I:E* ratio of 1:2 with or without minimal PEEP (≤5 cm H_2O) was initiated. Respiratory rate (RR) was adjusted to maintain the value of end-tidal carbon dioxide between 35 and 40 mm Hg. To target the bispectral index score between 40 and 60, anaesthesia was maintained with continuous infusion of propofol and remifentanil. During surgery, intermittent bolus doses of rocuronium (10 mg or 0.15 mg/kg i.v. bolus) were injected to maintain a train-of-four count of less than two for adequate muscle relaxation.

Haemodynamic monitoring

A radial arterial catheter was placed and a pressure transducer was zeroed to an ambient pressure at the mid-axillary level. After connecting the arterial catheter to the FloTrac device (Edwards Lifesciences, Irvine, CA, USA), arterial pressure waveforms were simultaneously sent to the IntelliVue MP70 monitor (Philips Medical Systems, Böblingen, Germany) and the EV1000 monitor (Edwards Lifesciences). Through continuous beat detection and analysis, the EV1000 monitor showed stroke volume (SV), stroke volume index (SVI), and stroke volume variation (SVV) continuously without calibration. The IntelliVue MP70 monitor also displayed the automatically calculated PPV in real time using previously described algorithms.[19 20]

Study protocol

Fluid infusion was adjusted to maintain a PPV between 9 and 13%. When the patient's PPV was in the grey zone (between 9 and 13%), baseline haemodynamic and respiratory variables including cardiac index, SV, SVI, heart rate (HR), mean arterial pressure (MAP), SVV, RR, peak airway pressure, plateau airway pressure, PEEP level, and PPV with an 8 ml kg^{-1} tidal volume ventilation (PPV8) were recorded. After baseline measurement, V_T was increased from 8 ml kg^{-1} to 12 ml kg^{-1} of ideal body weight for 2 min and RR was adjusted to maintain constant minute ventilation. During the last minute of high V_T ventilation, the above-mentioned haemodynamic variables, including PPV with a 12 ml kg^{-1} tidal volume ventilation (PPV12), were recorded. After these two baseline haemodynamic measurements, volume expansion was performed for 10 min using an infusion of balanced crystalloid solution (6 ml kg^{-1} of ideal body weight). The same haemodynamic parameters were measured under ventilation with a V_T of 8 ml kg^{-1} 5 min after volume loading. All parameters were recorded in a stable haemodynamic state without using inotropes or vasopressors. To determine PPV and SVV values, at least three consecutive measures were averaged. The patients were excluded from analysis if their PPV failed to enter the grey zone (9–13%) in spite of adequate fluid management or if haemodynamic instability requiring immediate treatment developed.

Statistical analysis

Statistical analysis was performed using MedCalc 15.6.1 (MedCalc Software, Ostend, Belgium) and SPSS 22.0 (IBM, Armonk, NY, USA). Data are presented as mean (SD), median [interquartile range (IQR)], or number of patients (%). Student's *t*-test or Mann-Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical data were