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Change in end-tidal carbon dioxide outperforms other surrogates for change in cardiac output during fluid challenge

K. Lakhal[1,*], M. A. Nay[2], T. Kamel[3], B. Lortat-Jacob[4], S. Ehrmann[2], B. Rozec[1] and T. Boulain[3]

[1]Réanimation chirurgicale polyvalente, service d'anesthésie-réanimation, Hôpital Laënnec, Centre Hospitalier Universitaire, Nantes, France, [2]Service de réanimation polyvalente, CHRU de Tours, Tours, France, [3]Service de réanimation médicale, Hôpital La Source, centre hospitalier régional, avenue de l'Hôpital, Orléans, France and [4]Réanimation chirurgicale polyvalente, service d'anesthésie-réanimation, Hôpital Bichat-Claude Bernard, assistance publique-hôpitaux de Paris, France

*Corresponding author. E-mail: lakhal_karim@yahoo.fr

Abstract

Background. During fluid challenge, volume expansion (VE)-induced increase in cardiac output ($\Delta_{VE}CO$) is seldom measured.
Methods. In patients with shock undergoing strictly controlled mechanical ventilation and receiving VE, we assessed minimally invasive surrogates for $\Delta_{VE}CO$ (by transthoracic echocardiography): fluid-induced increases in end-tidal carbon dioxide ($\Delta_{VE}E'_{CO_2}$); pulse ($\Delta_{VE}PP$), systolic ($\Delta_{VE}SBP$), and mean systemic blood pressure ($\Delta_{VE}MBP$); and femoral artery Doppler flow ($\Delta_{VE}FemFlow$). In the absence of arrhythmia, fluid-induced decrease in heart rate ($\Delta_{VE}HR$) and in pulse pressure respiratory variation ($\Delta_{VE}PPV$) were also evaluated. Areas under the receiver operating characteristic curves (AUC_{ROC}s) reflect the ability to identify a response to VE ($\Delta_{VE}CO \geq 15\%$).
Results. In 86 patients, $\Delta_{VE}E'_{CO_2}$ had an AUC_{ROC}=0.82 [interquartile range 0.73–0.90], significantly higher than the AUC_{ROC} for $\Delta_{VE}PP$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, and $\Delta_{VE}FemFlow$ (AUC_{ROC}=0.61–0.65, all $P<0.05$). A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) had good positive (5.0 [2.6–9.8]) and fair negative (0.29 [0.2–0.5]) likelihood ratios. The 16 patients with arrhythmia had similar relationships between $\Delta_{VE}E'_{CO_2}$ and $\Delta_{VE}CO$ to patients with regular rhythm (r^2=0.23 in both subgroups). In 60 patients with no arrhythmia, $\Delta_{VE}E'_{CO_2}$ (AUC_{ROC}=0.84 [0.72–0.92]) outperformed $\Delta_{VE}HR$ (AUC_{ROC}=0.52 [0.39–0.66], $P<0.05$) and tended to outperform $\Delta_{VE}PPV$ (AUC_{ROC}=0.73 [0.60–0.84], P=0.21). In the 45 patients with no arrhythmia and receiving ventilation with tidal volume <8 ml kg^{-1}, $\Delta_{VE}E'_{CO_2}$ performed better than $\Delta_{VE}PPV$, with AUC_{ROC}=0.86 [0.72–0.95] *vs* 0.66 [0.49–0.80], P=0.02.
Conclusions. $\Delta_{VE}E'_{CO_2}$ outperformed $\Delta_{VE}PP$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, $\Delta_{VE}FemFlow$, and $\Delta_{VE}HR$ and, during protective ventilation, arrhythmia, or both, it also outperformed $\Delta_{VE}PPV$. A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) indicated a likely response to VE.

Key words: arterial pressure/physiology; blood pressure determination; capnography; echocardiography, doppler; E'_{CO_2}; fluid therapy; heart rate; hypovolaemia; pulse pressure variation; intermittent positive-pressure ventilation; ultrasonography, doppler

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Editor's key points

- Volume expansion is used to improve cardiac filling and output, but changes in cardiac output are infrequently measured owing to costs, invasiveness, and poor reliability of available monitors.
- Change in end-tidal CO_2 was evaluated as a non-invasive surrogate measure of cardiac output in mechanically ventilated intensive care unit patients and compared with other surrogate measures.
- Change in end-tidal CO_2 outperformed other minimally invasive indices of fluid responsiveness in mechanically ventilated patients with shock.

During acute circulatory failure, volume expansion (VE) is often the first-line therapy[1] to increase cardiac output (CO). But either insufficient[2] or overzealous VE[3] can negatively impact patient outcome. Therefore, rational administration of fluids requires reliable identification of patients in whom VE genuinely increases CO. Prediction of fluid responsiveness is not always possible,[4 5] and most intensivists opt for administering VE and assessing its effects.[1 6] This fluid challenge strategy requires ensuring that CO has genuinely increased before considering further VE.[7 8] However, CO measurements are seldom used to guide VE.[1 6] Indeed, the use of CO measuring devices is usually limited by their cost, an unfavourable risk–benefit balance (for indwelling devices), the lack of reliability of some non-invasive devices for tracking changes in CO, the lack of expertise of some users, and pathophysiological barriers.[9] As surrogates for VE-induced increases in CO ($\Delta_{VE}CO$), indices such as increases in systolic, mean, and pulse systemic arterial blood pressure ($\Delta_{VE}SBP$, $\Delta_{VE}MBP$, and $\Delta_{VE}PP$, respectively) or decreases in heart rate ($\Delta_{VE}HR$) are often used,[1] but poorly reflect the CO response to VE.[10 11]

The VE-induced change in end-tidal carbon dioxide ($\Delta_{VE}E'_{CO_2}$) could be a surrogate for $\Delta_{VE}CO$. The amount of exhaled carbon dioxide (CO_2) depends on CO_2 production by the body, its delivery by pulmonary blood flow (CO), and its elimination by alveolar ventilation.[12] If during VE alveolar ventilation is kept unchanged, as during fully controlled ventilation, and if CO_2 production is relatively constant, then $\Delta_{VE}E'_{CO_2}$ would reflect $\Delta_{VE}CO$.[13 14] Contrary to indices and devices using beat-to-beat analysis, $\Delta_{VE}E'_{CO_2}$ should not be limited by cardiac arrhythmias. Doppler measurement of VE-induced increases in femoral artery flow ($\Delta_{VE}FemFlow$) could also be appealing;[15] arterial Doppler is a non-invasive, easily learned technique,[16] not limited by poor transthoracic insonation, and measures a flow rather than a pressure. In patients with an arterial catheter, pulse pressure respiratory variation (PPV) was initially proposed for prediction of fluid responsiveness rather than for the assessment of the effects of a fluid challenge.[17] Nonetheless, VE-induced decreases in PPV ($\Delta_{VE}PPV$) might be helpful in the absence of inspiratory efforts or arrhythmias.[4]

These indices ($\Delta_{VE}E'_{CO_2}$, $\Delta_{VE}FemFlow$, and $\Delta_{VE}PPV$) have rarely been evaluated to assess fluid responsiveness and have never been compared. We compared $\Delta_{VE}E'_{CO_2}$, $\Delta_{VE}FemFlow$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, $\Delta_{VE}PP$, and when applicable, $\Delta_{VE}PPV$ and $\Delta_{VE}HR$, as surrogates for $\Delta_{VE}CO$ to to identify intensive care unit patients who have responded to VE in mechanically ventilated intensive care unit (ICU) patients.

Methods

Ethics

The ethics board of the French Intensive Care Society (SRLF 13-14) approved the study design and waived the need for prior and written consent because the study procedures fulfilled the criteria of a non-interventional study as defined by French law.[18] Patients' next of kin and the patients themselves (if they regained capacity) were informed of their right to refuse use of the data. The French Advisory Board on Medical Research Data Processing (CCTIRS, 14-167) and the French Personal Data Protection Authority (CNIL, DR-2015-215) also approved the study design.[19]

Setting

Patients from three French ICUs were included: the surgical ICU of Laënnec University Hospital, Nantes, medical ICU of Tours University Hospital, and medical ICU of Orléans Hospital.

Patients

Adult patients were included in this prospective study if they met the following criteria: (i) they already had an arterial catheter; (ii) they were receiving strictly controlled mechanical ventilation; (iii) their systemic arterial blood pressure (BP) was stable throughout 5 min [no change in vasoactive drug dosage and no significant (>10%) variation in mean BP]; (iv) the attending physician prescribed VE; and (v) at least one of the following criteria suggested circulatory shock:[20] hypotension (invasive systolic BP <90 mm Hg, mean BP <65 mm Hg, or both), oliguria (<0.5 ml kg^{-1} h^{-1}) considered to be related to circulatory failure, arterial lactate >2.5 mmol $litre^{-1}$, skin mottling, or drug infusion of a vasopressor, inotrope, or both.

Patients were not included if pregnant or with obvious contraindication for femoral Doppler. Patients were excluded in the event of poor thoracic insonation, study protocol-induced discomfort, need for urgent therapy, or significant change in minute ventilation (arbitrary cut-off of 0.2 litres min^{-1}).

Measurements

Arterial blood pressure (BP)

Before and after VE, we averaged three intra-arterial measurements of BP (at 30 s intervals) displayed via an Intellivue™ MP70 monitor (Philips Medical Systems, Best, The Netherlands) connected to a pressure transducer (T100209A; Edwards Lifesciences, Irvine, CA, USA) zeroed at the level of the mid-axillary line. Heart rate was collected in a similar manner. In instances of arrhythmia, defined as atrial fibrillation/flutter or more than one extrasystole per six cardiac cycles, five rather than three measurements were averaged. For PPV analysis, the definition for arrhythmia was more stringent, as follows: if, during 60 s, neither arrhythmia (no extrasystole) nor inspiratory efforts were detected, PPV (automatically displayed on the MP70 monitor) was collected once, 'at a glance'.

Cardiac output

Echographic measurements [Vivid S6™ or Vivid i™ (GE Healthcare, Wauwatosa, WI, USA) or Epiq 5™ (Philips, Andover, MA, USA)] were made by board-certified investigators. The velocity–time integral (VTI) of subaortic flow was computed on an apical five-chamber view using pulse Doppler.

$$CO\ (litres\ min^{-1}) = heart\ rate \times subaortic\ VTI \times (subaortic\ diameter)^2 \times \pi/4.$$

$$\Delta_{VE}CO(\%) = (CO\ before - CO\ after\ VE)/CO\ before\ VE.$$