

Respiratory induced dynamic variations of stroke volume and its surrogates as predictors of fluid responsiveness: applicability in the early stages of specific critical states

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Abstract Respiratory induced dynamic variations of stroke volume and its surrogates are very sensitive and specific predictors of fluid responsiveness, but their use as targets for volume management can be limited. In a recent study, limiting factors were present in 53 % of surgical patients with inserted arterial line. In the intensive care unit (ICU) population the frequency is presumably higher, but the real prevalence is unknown. Our goal was to study the feasibility of dynamic variations guided initial volume resuscitation in specific critical states. We have performed a 5 year retrospective evaluation of patients admitted with diagnosis sepsis, polytrauma, after high risk surgery or cardiac arrest. Occurrence of major (sedation, mandatory ventilation and tidal volume, open chest and arrhythmias) and minor limiting factors (PEEP level, use of vasopressors and presence of arterial catheter) was screened within the first 24 h after admission. In the study period 1296 patients were

hospitalized in our ICU with severe sepsis ($n = 242$), polytrauma ($n = 561$), after high risk surgery ($n = 351$) or cardiac arrest ($n = 141$). From these patients 549 (42.4 %) fulfilled all major criteria for applicability of dynamic variations. In our evaluation only limited number of patients admitted for polytrauma (51 %), sepsis (37 %), after cardiac arrest (39 %) or surgical procedure (33 %) fulfil all the major criteria for use of dynamic variations at the ICU admission. The prevalence was similar in patients with shock. Occurrence of minor factors can pose further bias in evaluation of these patients. General use of dynamic variations guided protocols for initial resuscitations seems not universally applicable.

Keywords Hemodynamics · Dynamic variations · Fluid responsiveness

1 Introduction

Hemodynamic instability due to inadequate fluid loading is often encountered in the early stages of specific critical illness [1]. Adequate initial volume resuscitation is still considered to be the cornerstone of therapy for patients with sepsis, after trauma, high-risk surgery and cardiac arrest. Surprisingly, filling pressures are still recommended as targets for volume loading [2, 3] even though they were proved to be inferior to other parameters [4]. Respiratory induced dynamic variation (DV) of stroke volume and its pressure or flow surrogates are more sensitive and specific than other static parameters [5] and an initial resuscitation protocol based on DV may facilitate the fluid management of patients admitted to intensive care units (ICU). Similar protocols were tested in the intraoperative setting [6–8] mostly with positive results. In the ICU population a DV

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based fluid resuscitation protocol was never tested in humans. Possible explanation for this disproportion lies in frequency of limiting factors. The SOS acronym proposed by Michard [9] states the three most important limitations: spontaneous breathing or use of small tidal volumes, open chest conditions and sustained arrhythmias. Additionally, some other factors may affect the predictive and best cut-off value. Maguire and colleagues [10] published recently an analysis of the DV applicability (both invasive and non-invasive) during 1 year period in anaesthesia procedures performed in their centre. Occurrence of these limitations is probably more frequent in the ICU than intraoperatively, but their real prevalence in critical care patients is unknown. We hypothesize, that including respiratory induced dynamic variation of stroke volume or its pressure surrogates as target of initial fluid resuscitation protocols would enable more accurate and precise treatment than filling pressures. However, number of their limitations could severely impinge the widespread application of such protocol. Aim of this study was to assess the prevalence of the DV limitations in the early stages of specific critical states in order to evaluate the feasibility of their use as a target variable for initial resuscitation protocol.

2 Method

The study was performed as a retrospective evaluation of patients admitted to the eleven-bed ICU of Anaesthesia and Intensive Care Medicine department of Charles University Hospital Plzen, Czech Republic during the 5-years period from January 1st 2006 to December 31st 2010. The study was approved by the local ethics committee of the University Hospital. Due to its retrospective nature the informed consent was not deemed necessary. The data entered in the hospital database (WinMedicalc, Medicalc software s.r.o., Plzen, Czech rep.) were used for the analysis, paper charts and data files were screened in case of missing electronic data.

2.1 Disease groups characteristics and definition

According to admitting diagnosis patients belonging to four specific groups were included in the evaluation (sepsis/systemic inflammatory response, trauma, postoperative and post-cardiac-arrest). All of these states may be accompanied by a central hypovolemia and initial fluid resuscitation is proposed by different authors or international guidelines. Patients included in the sepsis group had to fulfil the Surviving Sepsis Campaign guidelines definition of sepsis or systemic inflammatory response syndrome [2]. As no patients without organ dysfunction were admitted to the ICU, the group consists only of patients

with severe sepsis or septic shock. Patients suffering from multiple trauma involving at least two organ systems were included in the trauma group. Those admitted after elective or emergency (non-trauma) surgeries were considered for the postoperative group. Trauma victims undergoing emergency surgical procedure were included into the trauma group to avoid duplicates. Finally, any patients admitted for the reason of cardiac arrest of any origin were included in the post-CPR group. In all defined groups patients with signs of organ malperfusion or shock were identified and evaluated as a subgroup, because the fluid resuscitation protocol might be of utmost importance for these patients. Due to the study retrospective nature a group of criteria for evaluation of shock/malperfusion was used: extreme serum lactate values (above 4 mmol/l) or increase in serum lactate in the first 24 h, oxygen saturation in the upper vena cava below 65 % or its decrease during the study period and use of high dose vasopressors. Those with clinical diagnosis of shock of any origin (traumatic, hypovolemic, septic etc.) at admission were also assigned into this subgroup.

Besides named disease states also other patients were managed by our department during the study period. Totally 1029 cases were not included into predefined groups: in 249 patients the reason for admission was acute intoxication, 79 and 327 patients were admitted for pain and palliative treatment and in 374 cases were stated other reasons (airway patency management, neurologic disorders etc.). Usually, these patients do not suffer from acute hemodynamic instability and intravascular expansion is not deemed necessary or meaningful.

2.2 Limitations screening

The following factors were screened in the whole period of the first 24 h after admission based on regular (2–3 times a day) and *ad hoc* clinical examinations (in case of sudden changes in the state of patient): level of the sedation, hemodynamic profile, ventilator mode and setting. The hemodynamic profile was screened for presence of arterial line (A-line), heart rhythm and rate, use of vasoactive agents. The heart rhythm was deemed regular when it was stated in the examinations, in case of controversy the ECG curve was extracted from the documentation. The ventilation was noted as controlled according to described ventilator setting (volume or pressure controlled mode) and no spontaneous breathing efforts were mentioned in the examination. Sedation as a prerequisite for mandatory ventilation, regular heart rhythm and controlled ventilation with tidal volume above 8 ml/kg were considered as major permitting factors. The non-inserted arterial line, use of vasopressors and PEEP >10 cm H₂O were marked as minor (potential

Table 1 Patients population characteristic

	Overall N = 1296	Sepsis N = 243 (18.8 %)*	Postoperative N = 351 (27.1 %)*	Trauma N = 561 (43.3 %)*	Post-CPR N = 141 (10.9 %)*
ICU Mortality	171 (13.2 %)	56 (23 %)	39 (11.1. %)	37 (6.6 %)	39 (27.7 %)
ICU length of stay	5 (2–11)	8 (4–19)	3 (1–6)	5 (2–13)	7 (3–11)
Age	49.9 ± 20.5	56.8 ± 17.8	60.2 ± 17.8	37.4 ± 17.5	62.1 ± 14.8
APACHE II	20.4 ± 8.6	22.1 ± 9	21 ± 7.3	16 ± 7.6	28.1 ± 6.9
SOFA	8.2 ± 3.9	9.9 ± 4.1	7.6 ± 3.6	7 ± 3.9	10.1 ± 2.2

APACHE II acute physiology and chronic health evaluation score 2nd version, *SOFA* Sequential Organ Failure Assessment Score, *Post-CPR* patients after cardiac arrest

* percentage of the overall population, all others are displayed as percentage within the group

confounding) factors. In addition signs of increased intraabdominal pressure were evaluated.

2.3 Statistic analysis

All data are presented as absolute and percentage of the population within named group or within the whole population accordingly. The usual descriptive statistic measures were used, including testing for normality by Kolmogorov-Smirnoff test. Patient characteristics are given in the mean ± significant difference. All calculations were done with the MedCalc software version 12.2.1 (Broekstraat 52, 9030 Mariakerke, Belgium).

3 Results

During the evaluated 5-years period 1296 patients with named diagnoses were admitted to our ICU. The group distribution and basic patients' characteristics are given in Table 1. After excluding all the major limitations (Fig. 1) the use of dynamic variables was considered as possible in 549 patients (42.4 %). Within these patients further minor limiting factors occurred: 58 (10.6 %) were without A-line, 357 (65 %) received vasopressor treatment and 245 (44.6 %) had the PEEP >10 cm H₂O.

Occurrence of limiting factors differed substantially among the groups (Table 2). The ventilator setting was the most frequent condition. The irregular heart rhythm limited substantially the possible use in the post-CPR group. Use of vasopressors as potentially confounding factor was very common among the septic patients and those after cardiac arrest (post-CPR). Due to overlap of named conditions the final number of patients with possible use of dynamic predictors reached 33 % in the postoperative population, 37 % in septic and 39 % in post-CPR patients and finally 51.3 % in the trauma group (Fig. 1).

In 853 (65.8 %) patients signs of tissue malperfusion or shock were observed. More of these patients were sedated

with mandatory ventilation (95.1 and 92.5 % respectively), but the final proportion of patients where DV might be useful according to the robust criteria was similar to the overall population (Fig. 1). All of shock patients were on vasopressors and all had inserted A-line.

4 Discussion

Guiding initial volume resuscitation in many critical states is often very difficult and many parameters have been proposed to serve this purpose. However none of them fulfils all the desired features: being sensitive and specific, with a clear cut-off value, easily obtained (preferentially noninvasively), without major intra- and interobserver variability and always applicable. Dynamic variations fit into most of them except the last one. In our retrospective evaluation only 42 % of patients admitted for sepsis, trauma, postoperative or post-cardiac arrest syndrome fulfil all these robust major criteria. Further on, in many of these patients other limitations (for instance high PEEP level or use of high doses of vasopressors or increased intraabdominal pressure) can decrease the sensitivity or specificity of the parameter or change the optimal cut-off value. The results of our study support the notion that DV suffer substantial number of limiting factors in the ICU. That limits their role as simply-to-use protocolised goal for the initial volume resuscitation.

Many factors interfere with the heart–lung interactions, but three of them preclude their use (named major in our paper): irregular heart rhythm, open chest conditions and mandatory ventilation with tidal volume bellow 8 ml/kg [9]. Open chest conditions are very rare in the non-cardiosurgical ICUs and no such case was observed in our population. We have observed a regular heart rhythm in 91.9 % of patients. Similar prevalence of sustained arrhythmias was referred by other authors: between 15 and 19 % in the overall population [11] and 5–6 % in trauma victims [12]. Evaluation of the applicability during

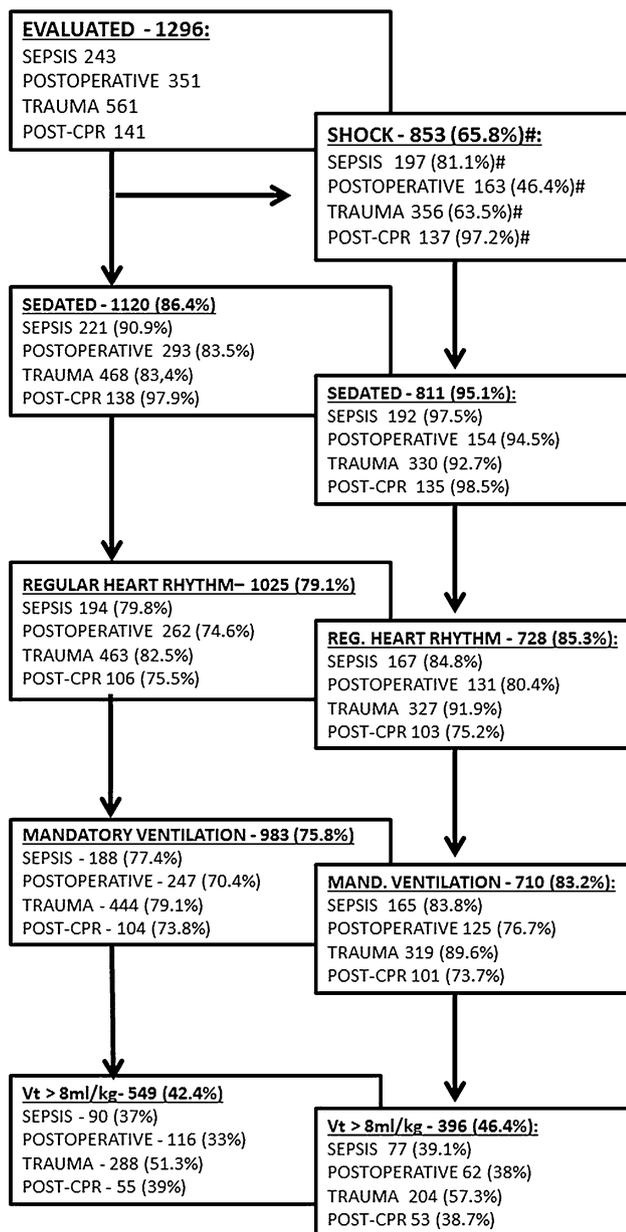


Fig. 1 Prevalence of major limiting factors within specific ICU populations. #—Percentage of patients with shock calculated from the evaluated population; *Post-CPR* patients after cardiac arrest, *Vt* tidal volume

the initial volume resuscitation was the goal of our study. This is why only first 24 h after admission were assessed and possible later arrhythmia development could reason this difference. Contrary, underestimation could occur due to retrospective evaluation. Patients with limited number of premature beats (less than 10/min) are often considered regular during the clinical assessment. We have extracted ECG strips from most of our patients but the usual length comprises 10–15 s, so these irregularities could have been missed as well. These nonfrequent premature beats hardly

affect the patient, but can severely impinge the calculation of dynamic predictors. This potential limitation may be overcome by an inconvenient manual calculation or by the novel proprietary algorithm (SVVxtra) which is able to restore a hypothetical regularity [13].

In contrast to perioperative setting a high proportion of patients receive only limited sedation in the ICU and their breathing activity is not fully abolished. Even though we consider our definition of mandatory ventilation quite robust and further supported by screening for the prerequisite factor of the deep sedation some bias may exist. A short period of mandatory ventilation was observed in most of patients (87.2 %) within the first 24 h in order to establish vascular accesses and start the appropriate treatment. During such periods the use of DV for volume resuscitation seems feasible; however 45.6 % of these patients were ventilated with tidal volumes below 8 ml/kg (6.7 ± 1 ml/kg). In the others, mostly trauma patients, 9.5 ± 1.4 ml/kg was delivered. A substantial trend towards using low *Vt* may be seen throughout the study period (38 % in 2006 vs. 58 % in 2010). The recommendations to use low *Vt* in all mechanically ventilated patients [14] severely affect the possible DV use. Some recent findings show that DV may be used in assessment of fluid responsiveness among patients with *Vt* between 6 and 8 ml/kg [15, 16]. But data regarding resulting change in threshold value, sensitivity and specificity are still limited.

The use of DV in patients with acute respiratory distress syndrome is not recommended [17] due to low tidal volumes delivered, diminished lung compliance and high PEEP levels. The protective ventilation with low *Vt* was used in all patients with any stage of acute lung injury within the study period (defined as $\text{PaO}_2/\text{FiO}_2$ lower than 300 mmHg with bilateral infiltrates as is our common practice). The influence of the PEEP is still unclear showing both decreased [18] or maintained accuracy [19]. High levels of PEEP can induce increase in right ventricle afterload mimicking the preload induced changes and may play a major role in these observations. However, high PEEP levels were used by some authors with maintained DV predictive potential [20, 21] and we consider PEEP to be more confounding than contraindicating factor. In the previous study by Maguire [10] PEEP >5 cm H_2O was used as a potential limitation. We concluded that the level of 10 cm H_2O is more appropriate for the ICU population and allowing the use of dynamic predictors [19]. The respiratory rate and resulting heart–lung interaction frequency could also affect the predictive value of dynamic variables. The cut-off value of 3.6 for heart-to-breath rate ratio was proposed recently [22]. In our population we have observed increased breath rates only in patients with lung protective ventilation. In these patients the DV are already unreliable due to low tidal volume and high PEEP. In

Table 2 Incidence of permitting and limiting factors within populations

	Sepsis (n = 243)	Postoperative (n = 351)	Trauma (n = 561)	Post-CPR (n = 141)	Overall (n = 1296)
Sedated	215 (88.5 %)	283 (80.6 %)	451 (80.4 %)	135 (95.7 %)	1084 (83.6 %)
Regular heart rhythm	215 (88.5 %)	316 (90 %)	552 (98.4 %)	108 (76.7 %)	1191 (91.9 %)
Ventilated	215 (88.5 %)	275 (78.3 %)	447 (79.7 %)	135 (95.7 %)	1073 (82.8 %)
Vt > 8 ml/kg	102 (47.4 %)*	131 (47.6 %)*	288 (64.4 %)*	64 (47.4 %)*	585 (54.5 %)*
PEEP ≤ 10cmH ₂ O	75 (34.9 %)*	177 (64.4 %)*	233 (52.1 %)*	83 (61.5 %)*	568 (52.9 %)*
Vasopressors	186 (76.5 %)	187 (53.3 %)	268 (47.8 %)	124 (87.9 %)	765 (59 %)
A-line	220 (90.5 %)	258 (73.5 %)	437 (77.9 %)	135 (95.7 %)	1050 (81 %)

* percentage value calculated from the number of mandatory ventilated patients only; Bold typed—major limitations

Post-CPR patients after cardiac arrest, Vt tidal volume, PEEP positive end-expiratory pressure, A-line arterial catheter inserted

global, the ventilator setting is the major condition affecting the possible use of dynamic variations in the ICU. From the whole population of 1296 patients only 334 (25.8 %) patients fulfilled all ventilation dependent criteria.

There are two important conditions affecting the accuracy and predictive value of dynamic variations we were unable to assess accurately among our population. Firstly, the prevalence of right heart failure or pulmonary hypertension are unknown as admitting echocardiography was not performed on a regular basis in our institution in studied period. Secondly, increased intraabdominal pressures (IAP) might impact venous return, right heart afterload and heart lung interactions and so affect the accuracy and optimal threshold of dynamic variations. According to data published by Malbrain et al. [23] occurrence of periods of increased IAP occur in almost 50 % of critically ill patients. These temporary elevations may be missed when only clinical examinations are performed. Routine measurements of IAP were not performed in absence of clinical signs in most of our patients. According to abdominal examination and admitting diagnosis in 59 % an increase of IAP is not probable, in other 39 % temporary intraabdominal hypertension (defined as IAP max above 12 mmHg) cannot be excluded. However, influence of these small increases of IAP on the dynamic variations in humans seems to have limited impact [24]. Levels observed to affect the DV were far higher (above 20 or 25 mmHg [25, 26]). In 10 % of our patients (almost exclusively intrabdominal sepsis or postoperative cases) the abdominal compartment syndrome was suspected and IAP measured. The incidence is similar to data published by Malbrain et al. [23] and also the mean IAP value (20 ± 8 mmHg) was comparable. It seems that intraabdominal hypertension might pose important limitation in about 10 % of patients.

Finally the use of vasopressors was also described as a potentially confounding factor for the use of DV based on

systolic pressure and those obtained noninvasively [27]. Most of septic and post-CPR patients were on catecholamine during the first 24-h after admission. In trauma victims and postoperative group the percentage was lower but still comprising more than 50 %. Non-invasive (plethysmographic) dynamic variations (pulsatility variability index) are seldom used in patients with severe hemodynamic disturbances and peripheral vasoconstriction. Two novel devices (ccNexfin, Edwards Lifesciences, Irvine, CA. and CNAP, CNSystems, Graz, Austria) are nowadays available enabling a totally non-invasive continuous beat-to-beat assessment of arterial pressure and hence providing the calculation of pulse pressure variation. The validation of these devices for use in hemodynamically unstable patients is still limited, but in some clinical scenarios they possess the potential to help start fluid resuscitation earlier on, before invasive measures are instituted, or even replace them in some very rare cases. Therefore, we considered both the use of catecholamines and the presence of the A-line as factors potentially limiting or better confounding.

Due to its retrospective nature and used time window our study has some considerable limitations. The referred prevalence might be both under- or overestimated when it was not observed prospectively and no efforts were actually done to measure the DV in many cases. In part of our patients treatment adaptations might allow the DV use in case of need and hence further increase the proportion of patients where DV were applicable. Also, our evaluation was limited on the first 24 h after admission what is generally considered to be the optimal time for initial volume resuscitation in terms of early delivered goal directed therapy. But even within this time the conditions can change vigorously. The later occurrence of conditions allowing the use of DV (for instance sinus rhythm recurrence due to volume substitution etc.) cannot be excluded from our data. However, the frequency of these situations will be rather small. Contrary, after the initial

stabilization the number of limiting factors will rapidly increase with reoccurrence of the spontaneous breathing pattern. Furthermore, to indicate volume expansion in patients after some days spent on ICU with relapse of hemodynamic instability is too complex for a simple algorithm and parameter. The transferability of our results to other ICUs should be also discussed. The proportion of patients suitable for the use of DV will differ according to treated population. We tried to avoid this limitation by studying different diagnosis-subgroups separately. But even within these subgroups the prevalence can differ according to disease severity and local protocols of care. We have observed high APACHE II and SOFA scores among our population and also the initial treatment including sedation and mandatory ventilation could be considered rather aggressive. As a result, the proportion of patients suitable for the use of DV for fluid responsiveness assessment would probably even decrease in less severe patients managed with less aggressive approach. Finally, conditions can vary considerably during the initial phase of the selected critical states allowing using the variations time to time, but will not allow using them as protocol goals.

It is important to note, that in some cases the use of dynamic variations is possible even in presence of named limitations or outside studied diagnoses. We have included only patients with specific conditions into the analysis leaving 1029 patients with critical states of other origin (i.e. intoxication with sedatives, epileptic state). Fluid depletion may be present among these patients, but no general rule of fluid resuscitation exists and it is usually not considered to be the therapy cornerstone. Of course in individual cases the use of DV might be of value, but possibly not as a general measure as might be the case in studied critical states. However, even among patients of studied diagnoses the individual use of DV in presence of its limitation might be possible. High values of DV may indicate hypovolemia even in patients with low tidal volume, increased abdominal pressure or even spontaneous breathing [28]. However, it is hard to define an exact cut-off or target value. Also the sensitivity and specificity is usually decreased under these circumstances preventing further protocolised use. Canesson et al. [29] proposed recently to use of a grey zone approach for the interpretation of DV. According to these experts, lower thresholds could be used in patients with low risk of fluid overload (high sensitivity needed). And opposite, higher thresholds fit better for those with lower tolerance to fluids (high specificity needed). Application of rigorous criteria for applicability of DV, as we did, denotes a population with preserved high sensitivity and specificity. On the other side, among these patients (42 % of critical patients and 46 % of patients with shock in our study population) the DV are definitely useful when minor

limitations are accounted. This should be reflected by our monitoring and treatment decisions in order not to underuse the contemporary best measure of fluid responsiveness assessment. In other patients the dynamic variations might be used too, but it would be very difficult to utilize them as universal targets without risk of maltreatment. In these patients other measures for prediction of fluid responsiveness should help in the decision as for instance passive leg raising or end of expiratory occlusion recently proposed by the group of Monnet and Teboul [30, 31].

5 Conclusions

In our evaluation only limited number of patients admitted for multiple trauma (51 %), sepsis (37 %), after cardiac arrest (39 %) or surgical procedure (33 %) fulfil all the major criteria for the dynamic variations use at the ICU admission. The proportion was similar among patients with shock. Occurrence of minor factors can pose further bias in evaluation of these patients. The use of respiratory induced dynamic variations for individual assessment is not precluded by our findings, but universal, initial volume resuscitation protocol based presumably on dynamic variations seems not to be widely applicable.

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Conflict of interest JB received lecturing fees by Edwards Lifesciences Inc.; all other authors declare no conflict of interests.

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