Arterial waveform-analysis is of limited value in daily clinical practice in the intensive care unit

Louise Inkeri Hennings, Nicolai Haase, Ulf Gøttrup Pedersen & Anders Perner

ABSTRACT

INTRODUCTION: It is difficult to identify the patients who will respond to fluid therapy, but the arterial waveform-derived variables have reasonably predictive values for fluid responsiveness. However, the patient must fulfil a number of prerequisites for these variables to be valid. We assessed the proportion of intensive care unit (ICU) patients with shock who at the time of resuscitation fulfilled the prerequisites for using the arterial waveform-derived variables.

METHODS: This was a prospective cohort study performed at six ICUs. The study included consecutive adult patients with shock (20 patients per ICU) who received fluid resuscitation on the first day of shock. The fulfilment or not of the prerequisites (sedation, sinus rhythm and controlled ventilation with tidal volumes > 7 ml/kg) was registered at the time of the first fluid resuscitation episode and at fluid resuscitation episodes during the following days.

RESULTS: A total of 119 patients with a median age of 68 years (interquartile range: 56-76 years) were included. At the time of the first fluid resuscitation, 82% (95% confidence interval (CI): 74-87) of the patients had sinus rhythm, 77% (95% CI: 69-84) were sedated, 55% (95% CI: 46-65) were on controlled ventilation and 50% (95% CI: 39-61) received tidal volumes of more than 7 ml/kg. Only 23% (95% CI: 14-33) of the patients fulfilled all four prerequisites.

CONCLUSIONS: Less than a quarter of the ICU patients with shock fulfilled all the prerequisites for the use of arterial waveform-derived variables to predict fluid responsiveness. Thus, these variables may be of limited use during resuscitation in the ICU.

FUNDING: none.

TRIAL REGISTRATION: not relevant.

During recent years, functional markers of hypovolaemia obtained from changes in the arterial waveform have gained substantial attention as diagnostic tests for hypovolaemia. In clinical studies, hypovolaemia is defined by fluid responsiveness [1-3]. The physiological background for these functional markers is that the changes in plural pressure during positive pressure ventilation change preload. If stroke volume is preload-dependent, then positive pressure ventilation will reduce stroke volume. During continuous ventilation, these changes can be assessed by the arterial waveform-derived variables, which include systolic pressure variation, stroke volume variation and pulse pressure variation. These functional diagnostic tests have been shown to be superior to static markers such as central venous pressure and pulmonary artery occlusion pressure in predicting fluid responsiveness [2, 4-7].

However, the prerequisites of sedation, sinus rhythm and controlled ventilation with tidal volumes of more than 7 ml/kg needed for the arterial waveform-derived variables to be valid may limit their use in the intensive care unit (ICU) [1, 8-11]. Therefore, the aim of this study was to describe the proportion of ICU patients with shock who fulfilled the prerequisites for using the arterial waveform-derived variables during fluid resuscitation.

METHODS

We did a multicentre, prospective cohort study in 6 ICUs (five general and one cardio-thoracic ICU), two in a university hospital, three in teaching hospitals and one in a regional hospital. Patients were included over a three-month period during which the participating ICU included 20 consecutive patients aged 18 years or above who had any type of shock (receiving vasopressor or inotropic agents as infusion) and were treated with fluids for resuscitation (0.9% NaCl, Ringer's solutions or colloids). We registered the fulfilment of the prerequisites for sedation, i.e. sinus rhythm and controlled ventilation with tidal volumes > 7 ml/kg. Data were collected from patient charts including demographics and circulatory status, vasoactive medications, ventilator settings, sedation and fluid treatment at the time of each fluid resuscitation episode until Day 5.

Statistics

Continuous variables were expressed as medians with interquartile ranges (IQR) and categorical variables as proportions with exact binomial 95% confidence intervals (CI). The numbers of surgical and medical patients fulfilling the prerequisites were compared using the chi-squared test. Statistical analyses were performed using SAS (Statistical Analysis System) software version 9.1.3.

Trial registration: not relevant.

ORIGINAL ARTICLE

Department of Intensive Care, Rigshospitalet, Denmark

Dan Med J 2015;62(9):A5136

TABLE 1

Patient characteristics.

Patients, n	119
Age, yrs, median (IQR)	68 (56-75)
Gender, male/female, n (%)	78 (66)/41 (34)
Type of patient, n (%)	
Medical	61 (51)
Surgical	58 (49)
Type of shock, n (%)	
Septic	88 (74)
Hypovolaemic	9 (8)
Cardiogenic	16 (13)
Neurogenic	0
Obstructive	5 (4)
Anaphylactic	0
Unclear	2 (2)

IQR = interquartile range.

TABLE 2

Characteristics at the time of the first fluid resuscitation episode (N = 119)[a].

Circulatory parameters	
Heart rate, beats/min, median (IQR) (n = 115)	100 (83-114)
Sinus rhythm, n (%)	92 (82)
MAP, mmHg, median (IQR) (n = 113)	67 (60-73)
Lactate, mmol/l, median (IQR) (n = 115)	2.5 (1.5-4.4)
CVP, mmHg, median (IQR) (n = 22)	12 (10-15)
$ScvO_2$, %, median (IQR) (n = 35)	69 (64-79)
Cardiac index, l/min./m^2, median (IQR) (n = 9)	2.6 (2.4-3.4)
Vasoactives, µg/kg/min., median (IQR)	
Norepinephrine (n = 108)	0.12 (0.06-0.20)
Dopamin (n = 15)	4 (3-6)
Epinephrine (n = 9)	0.10 (0.07-0.20)
Dobutamine (n = 6)	8 (5-10)
Ventilator settings, n (%)	
Invasive ventilation	92 (77)
Controlled ventilation	66 (55)
Spontaneous breathing activity	58 (52)
Modes, n (%)	
PRVC	62 (52)
PC	4 (3)
CPAP	4 (3)
PS	28 (24)
FiO_2, %, median (IQR) (n = 93)	60 (40-80)
Tidal volume	
Ml (n = 90)	527 (441-638)
Ml/kg (n = 85)	7.0 (5.8-8.4)
RF, per min. (n = 92)	16 (14-20)
PEEP, mmHg (n = 88)	8 (5-10)
Peak pressure, mmHg (n = 58)	24 (19-27)
Sedation given, n (%)	
Propofol	86 (72)
Remifentanil	48 (40)
Midazolam	13 (11)
Fluids given, ml, median (IQR)	
NaCl (n = 70)	2,000 (1,000-2,900)
Ringer's lactate (n = 59)	2,000 (1,000-3,000)
Albumin (n = 29)	500 (250-750)
Dextran 70 (n = 3)	1,000 (500-1,000)
6S trial fluid[b] (n = 20)	1,500 (1,000-1,875)

CPAP = continuous positive airway pressure; CVP = central venous pressure; $Fi0_2$ = fraction of inspired oxygen; IQR = interquartile range MAP = mean arterial pressure; PC = pressure control; PEEP = positive end expiratory pressure; PRVC = pressure regulated volume control; PS = pressure support; RF = respiratory frequency; $ScvO_2$ = central venous oxygen saturation.
a) Where n < N, this is due to missing data.
b) 6S trial fluid was either hydroxyethyl starch 130/0.42 or Ringer's acetate.

RESULTS

A total of 120 patients were evaluated, but one patient did not receive vasopressor or inotropic agents at the time of fluid resuscitation and was therefore excluded. Thus, 119 patients diagnosed with shock and treated with fluid were enrolled; their demographics are shown in **Table 1** and their circulatory variables in **Table 2**.

At the time of the first fluid resuscitation episode, 92 (82%) patients had a sinus rhythm, 92 (77%) were sedated, 66 (55%) were on controlled ventilation and 43 (50%) had tidal volumes exceeding 7 ml/kg. A total of 19 of the 83 patients (23%) with complete data registration regarding sedation, heart rhythm, weight, ventilation settings and mode, fulfilled all four prerequisites at the time of the first fluid resuscitation episode.

In all, 36 patients had missing data for one or more of the prerequisites. This was mainly due to lack of registration on the patient chart. If all these data were categorised as fulfilling the prerequisites (best case scenario), 54 (45%) fulfilled all prerequisites. If the 36 patients with missing data were instead assumed not to fulfil any of the prerequisites (worst case scenario), 19 (16%) fulfilled all prerequisites.

Ten of the 40 surgical patients (25%) with complete data fulfilled all the prerequisites and nine of the 43 medical patients (21%) with complete data fulfilled all the prerequisites (p = 0.70).

From Day 2 of shock until Day 5, the number of patients who fulfilled all four prerequisites at the time of fluid resuscitation had declined from 25% to zero (**Table 3**).

DISCUSSION

This is the first study to assess the proportion of ICU patients with shock fulfilling the prerequisites for the arterial waveform analysis of fluid responsiveness. We found that valid measurements of the arterial waveform-derived variables to predict fluid responsiveness could have been performed only in 23% of the included patients,. In particular, the prerequisites of tidal volumes

TABLE 3

Number of patients fulfilling all the prerequisites at the time of fluid resuscitation on shock, Days 1-5[a].

Day no.	n/N; % (95% CI)
1	19/83; 23 (14-32)
2	13/52; 25 (14-39)
3	8/26; 31 (14-52)
4	1/11; 9 (2-41)
5	0/6

CI = confidence interval.

a) Due to missing data in the patient files for ≥ 1 of the prerequisites, it was only possible to evaluate 83 patients on Day 1. The number of patients dropped from Day 1 through Day 5 because they either no longer fulfilled the inclusion criteria (fluid resuscitation or vasopressor/inotrope infusion) or because they died.

of > 7 ml/kg and controlled ventilation were not fulfilled. This was independent of medical or surgical admission; and over time, the proportion of patients who fulfilled the prerequisites decreased so that on Day 5 none of the patients receiving resuscitation fluid fulfilled all four prerequisites.

Other observations have indicated large proportions of ICU patients not fulfilling the prerequisites at the time of fluid resuscitation. In all, 40% of patients in the 6S trial were not ventilated at the time of inclusion [12]. In the noradrenalin versus dopamine trial, 70% of patients were ventilated at inclusion with mean tidal volumes of 8 ml/kg, and 5% had arrhythmias at this time point [13]. Most likely, a large proportion of patients in these 2 ICU trials in circulatory failure did not fulfil all four prerequisites. In addition, only 4% of patients in one of 26 French ICUs fulfilled all four criteria in a recent one-day point prevalence study [14]. These patients were not diagnosed with shock, nor did they all receive fluid; but considering all of the above observations, it is likely that the majority of ICU patients with shock do not fulfil the prerequisites for the arterial waveform-derived tests to be valid.

The need for accurate circulatory parameters that assess whether a patient will respond to fluid administration or not is highlighted by the fact that in most cohorts only half of ICU patients with shock respond with an increase in cardiac output when given a fluid bolus [11]. The patients who do not respond to fluid will most likely only have side-effects of fluids. These may not be trivial, as an increased positive fluid balance has been associated with increased mortality in patients with septic shock [15].

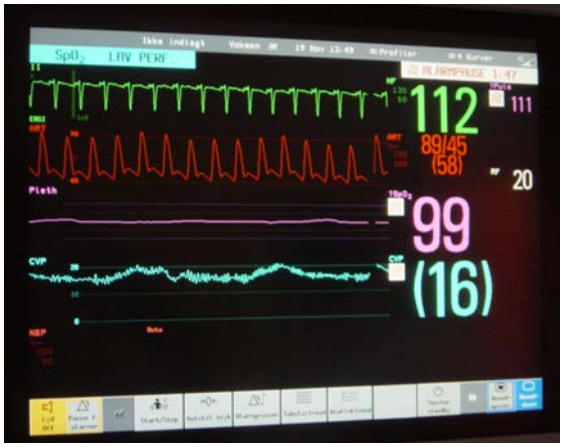
Our data show that other methods are needed to identify fluid responsiveness in ICU patients. Passive leg-raising has recently been suggested as a tool to guide fluid therapy [13]. The test can be done independently of cardiac rhythm and ventilation modus, but to obtain the best predictive value, changes in cardiac output or stroke volume during leg raising should be assessed using continuous measurement [16]. These authors emphasised that no test is perfect and that – at the best – the positive or negative predictive value of passive leg-raising is no more than 90%. Alternatively, a fluid challenge where the stressed volume is increased,
thereby increasing preload, can be used to assess fluid responsiveness. Increased cardiac output will indicate that the patient would benefit from fluid therapy [17]. The obvious caveat with this technique is that fluid needs to be given to assess if the patient responds to fluid.

The strengths of our study include that the patients were included prospectively and consecutively from 6 ICUs in university and non-university hospitals. The ICUs contributed with 20 patients each. Thus, the data were not dominated by those from the larger units. Clinical practice was most likely maintained because clinicians were unaware of the study.

The limitations include that only ICUs from one country participated. Patients were identified prospectively, but data were registered from patient charts, the precision of which is unknown. The lack of registration on the patient charts was the primary cause of missing data; and the prospective nature of our study made it difficult to obtain the missing information. But despite the missing data, the best-worst case analysis supported the result that the majority of ICU patients with shock did not fulfil all prerequisites, not even at the time of the first fluid resuscitation episode.

CONCLUSIONS

We found that less than 25% of patients with shock fulfilled the prerequisites for the arterial waveform-derived variables to be valid in predicting patients who are fluid-responsive at the time of the first fluid resuscitation episode. Thus, the arterial waveform-derived variables may be of limited use in daily clinical practice in the ICU.



Arterial-wave monitor.

CORRESPONDENCE: *Louise Inkeri Hennings*, Intensiv Terapiklinik, 4131, Abdominalcentret, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Denmark. E-mail: louise.inkeri.hennings.01@regionh.dk

ACCEPTED: 23 June 2015

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

ACKNOWLEDGEMENTS: The authors would like to thank the staff of the ICUs at Rigshospitalet (Dept. 4131 and Dept. 4141), Herlev, Hillerød, Holbæk and Bispebjerg Hospitals.

LITERATURE

1. Pinsky MR. Heart-lung interactions. Curr Opin Crit Care 2007;13:528-31.
2. Pinsky MR. Heart lung interactions during mechanical ventilation. Curr Opin Crit Care 2012;18:256-60.
3. Cavallaro F, Sandroni C, Antonelli M. Functional hemodynamic monitoring and dynamic indices of fluid responsiveness. Minerva Anestesiol 2008;74:123-35.
4. Chew MS, Åneman A. Haemodynamic monitoring using arterial waveform analysis. Curr Opin Crit Care 2013;19:234-41.
5. Marik PE. Noninvasive cardiac output monitors: a state-of the-art review. J Cardiothorac Vasc Anesth 2013;27;121-134.
6. Marik PE, Cavallazzi R, Vasu T et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37:2642-7.
7. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. Crit Care Med 2013;41:1774-81.
8. Michard F, Boussat S, Chemla D et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 2000;162:134-8.
9. Perner A, Faber T. Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. Acta Anaesthesiol Scand 2006;50:1068-73.
10. Freitas FG, Bafi AT, Nascente AP et al. Predictive value of pulse pressure variation for fluid responsiveness in septic patients using lung-protective ventilation strategies. Br J Anaesth 2013;110:402-8.
11. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 2000;4:282-9.
12. Perner A, Haase N, Guttormsen AB et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34.
13. De Backer D, Biston P, Devriendt J et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010;362;779-89.
14. Mahjoub Y, Lejenu V, Muller L et al. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observationel multicentre point-prevalence study. Br J Anaesth 2014;112:681-5.
15. Boyd JH, Forbes J, Nakada T et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259-65.
16. Cavallaro F, Sandroni C, Marano C et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. Intensive Care Med 2010;36:1475-83.
17. Perner A, De Backer D. Understanding hypovolaemia. Intensive Care Med 2014;40:613-5.