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Ultrasound and NICOM in the assessment of fluid responsiveness in patients with mild sepsis in the emergency department: a pilot study

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ABSTRACT

Objective: We investigated whether combining the caval index, assessment of the global contractility of the heart and measurement of stroke volume with Noninvasive Cardiac Output Monitoring (NICOM) can aid in fluid management in the emergency department (ED) in patients with sepsis.

Setting: A prospective observational single-centre pilot study in a tertiary care centre.

Primary and secondary outcomes: Ultrasound was used to assess the caval index, heart contractility and presence of B-lines in the lungs. Cardiac output and stroke volume were monitored with NICOM. Primary outcome was increase in stroke volume after a fluid bolus of 500 mL, while secondary outcome included signs of fluid overload.

Results: We included 37 patients with sepsis who received fluid resuscitation of at least 500 mL saline. The population was divided into patients with a high (>36.5%, n=24) and a low caval index (<36.5%, n=13). We observed a significant increase (p=0.022) in stroke volume after 1000 mL fluid in the high caval index group in contrast to the low caval index group but not after 500 mL of fluid. We did not find a significant association between global contractility of the left ventricle and the response on fluid therapy (p=0.086). No patient showed signs of fluid overload.

Conclusions: Our small pilot study suggests that at least 1000 mL saline is needed to induce a significant response in stroke volume in patients with sepsis and a high caval index. This amount seems to be safe, not leading to the development of fluid overload. Therefore, combining ultrasound and NICOM is feasible and may be valuable tools in the treatment of patients with sepsis in the ED. A larger trial is needed to confirm these results.

Strengths and limitations of this study

- This was a prospective observational pilot study combining multiple modalities for measuring the effect of fluid resuscitation in an important medical condition (sepsis).
- The results of this study give better insight for a larger study ultimately resulting in better personalised treatment of patients with sepsis.
- This was a pilot study with a small study population.
- The majority of patients only suffered from mild sepsis.

INTRODUCTION

Despite several decades of research, assessment of fluid responsiveness remains a challenge in patients with sepsis in the emergency department (ED). An important part in the treatment of sepsis is fluid resuscitation, which ensures effective tissue perfusion.[1] However, both insufficient and overzealous fluid administration are associated with increased complications and mortality.[2–6] Only 50% of patients with sepsis are fluid responsive, defined as an increase in cardiac output or stroke volume after a fluid bolus.[7 8] In these fluid responders, the left ventricle functions on the ascending part of the Frank-Starling curve, meaning that an increase of preload leads to a subsequent rise in stroke volume.[9 10] As soon as the left ventricle functions near the plateau part of the Frank-Starling curve, administration of fluid has only a minimal effect on stroke volume. A fast and non-invasive method to predict fluid responsiveness would be of great help, because in real life invasive monitoring is not readily available in the initial resuscitation of haemodynamic unstable patients in the ED.

A common method to determine the volume status is assessment of the respiratory variation of the inferior caval vein (IVC) using ultrasound (US).[11] A high caval index (CI; relative decrease in IVC diameter during a respiratory cycle) is associated with a

depletion of intravascular volume.[12] Several studies showed that the CI was a reliable and accurate predictor of fluid responsiveness in mechanically ventilated patients in the intensive care.[13 14] However, these findings may not be extrapolated to patients who are breathing spontaneously, because spontaneous respiration influences haemodynamic parameters and cyclic changes of the CI.[15] A recent pilot study performed in our ED with spontaneously breathing patients with shock showed that a low CI reliably predicted the absence of fluid responsiveness which was defined as an increase in blood pressure.[16] US can also be used to get a global impression of the contractility of the heart and for pulmonary fluid overload visible as B-lines in the lungs.[17–19] Combining this with the measurement of the IVC might give a better estimation of who will benefit from more fluid resuscitation as well as identifying patients in whom more fluid resuscitation may be detrimental. Several studies have shown that traditional haemodynamic parameters like blood pressure and cardiac filling pressures cannot assess the effect of a volume bolus accurately.[1 7 8] Traditionally, invasive measurements of haemodynamic indices (like cardiac output and stroke volume) were used but these are not readily available in the ED. An easy and promising alternative method to measure cardiac output non-invasively is with the Noninvasive Cardiac Output Monitoring (NICOM).[20–23]

The purpose of this pilot study was to investigate the feasibility and possible value of the combination of US and NICOM in measuring the effects of fluid resuscitation. This was done by measuring the respiratory variation of the CI, the global contractility of the heart and the assessment of the lungs for fluid overload in patients with sepsis admitted to the ED.

MATERIALS AND METHODS

We have performed a prospective cross-sectional single-centre observational pilot study in the ED of the University Medical Center Groningen. During a 19-week period from February to June 2014, a convenience sample was obtained by screening all patients admitted by the internist or the emergency physician to the ED between 9:00 and 19:00 for sepsis. Sepsis was defined as proved or suspected infection with two or more of the following systemic inflammatory response syndrome criteria: body temperature <36.0°C or >38.3°C, heart rate >90/min, tachypnoea with >20 breaths/minute or arterial carbon dioxide tension <4.3 kPa, leucocytes >12×10^9/L or <4×10^9/L or >10% immature neutrophils.[24 25] Patients were considered to have severe sepsis if there were signs of acute organ failure and septic shock, having a mean arterial pressure (MAP) of <65 mm Hg despite fluid challenge and/or use of vasoactive medication. Patients were included if the attending physician intended to treat with volume resuscitation (minimum of 500 mL <30 min) according to the Surviving Sepsis Campaign treatment goals.[24] We excluded patients who were unable to maintain the supine position for a few minutes. In addition, patients with increased abdominal pressure caused by ascites, pregnancy, a recent abdominal operation, peritoneal dialysis and Kussmaul breathing and patients who were intubated or mechanically ventilated were excluded because these conditions could interfere with the US measurements.

The NICOM is a new technique based on bioreactance, which measures the relative phase shifts of oscillating alternating currents that traverse the thorax and then calculates several haemodynamic indices.[20–23 26 27] Patients with anatomical abnormalities of the thoracic aorta, such as an aorta dissection, aneurysm or vascular prosthesis, were excluded because of the possible influence on measurements with the NICOM.[20] The study was approved by the local Medical Ethical Committee. All patients provided informed consent.

Measurements

At baseline, patient characteristics and vital parameters (systolic and diastolic blood pressure, MAP, heart rate, oxygen saturation and temperature) were recorded (Intellivue MP30 system, Philips, Eindhoven). All US recordings were performed by one investigator, after completing US training in accordance with the emergency US guidelines from the American College of Emergency Physicians (ACEP).[19] The recordings were stored and examined afterwards by two independent experts. The IVC was observed by a subcostal longitudinal view. During a normal respiratory cycle, the minimal (IVCi) and maximal (IVCe) diameters of the IVC were measured. Patients were not instructed on how to breathe. The IVC was measured in a B-mode 2–3 cm distal to the junction of the right atrium.[14 25] US examinations were performed using an abdominal probe (2–6 MHz) from the US machine z.one ultra-convertible US system (Zonare, Mountain View, California, USA). The CI was calculated using the following formula: CI=(IVCe–IVCi)/(IVCe)×100%.[12] A CI of 36.5% was used to differentiate between a low and high CI.[16] The global contractility of the left ventricle was assessed in parasternal, apical and subcostal view with a cardiac probe (2–6 MHz) and was divided in an eyeballing contractility of poor, moderate, good and hypercontractility.[19] Lung US was performed in eight different fields (dividing the frontal chest wall in four different regions on each side) with an abdominal probe (2–6 MHz) scanning for B-lines. More than three B-lines per field at least bilateral was considered a sign of pulmonary oedema.[17]

Protocol

After inclusion, US of heart, lungs and IVC was performed in supine position and subsequently cardiac output and stroke volume were measured with the NICOM. Hereafter, resuscitation with sodium chloride (NaCl) 0.9% was initiated according to the sepsis protocol. Measurements of vital parameters and NICOM were

repeated after every 500 mL of 0.9% NaCl, and US imaging was repeated after infusion of every 1000 mL 0.9% NaCl.

Statistical analysis

Statistical analysis was performed using SPSS PASW-V.20.0. Results are presented as medians with IQR. A p value <0.05 was considered significant. Changes in stroke volume, cardiac output and other vital parameters were assessed using the Wilcoxon signed-rank test. Correlation between the change in stroke volume and the global contractility of the heart was tested using Spearman's correlation coefficient.

RESULTS

During the study period, 932 patients were screened for sepsis, of whom 55 fulfilled the criteria for sepsis. Of these 55 patients, 18 were excluded for the following reasons: no informed consent in 2 patients; 5 patients did not receive fluid resuscitation; adequate NICOM measurements were not possible due to technical reasons in 2 patients; 1 patient was mechanically ventilated; US measurement was impossible due to pain in 2 patients and in 6 patients the US images were inadequate. A total of 37 patients were included in the study, of whom 24 (64.8%) had a high CI. The majority of patients (28 of 37) received a second fluid bolus of 500 mL if indicated by the treating physician, who was not part of the study and was blinded for the CI and NICOM results. Of the nine patients who did not receive a second fluid bolus, four had a low CI. Another three patients had a history of reduced left ventricular function and one patient was hypertensive at baseline explaining why the physician did not order a second fluid bolus. There were no clinical signs of fluid overload. The study population included 34 patients with mild sepsis (91.9%) and 3 patients with severe sepsis (8.1%). The mean length of hospital stay was 12.9 days, and only one patient was admitted to the intensive care for 1 day. The 28-day mortality was 0%. The baseline characteristics are shown in table 1.

There was no significant difference between the low and high CI group in haemodynamic parameters after a fluid bolus of 500 mL 0.9% NaCl. In the low CI, stroke volume changed from 70.5 to 77.2 mL (p=0.116) and in the high CI from 69.0 to 76.5 mL (p=0.097). Stroke volume significantly increased in the high CI group, in contrast to the low CI group (table 2 and figure 1) after a second fluid bolus of 500 mL if indicated by the treating physician. There were no significant changes in heart rate and blood pressure after the fluid bolus of 500 and 1000 mL.

None of the 29 patients showed clinical signs of fluid overload after 1000 mL of fluid administration. US of the lungs was positive for B-lines unilateral in two patients and this was explained by pneumonia. We obtained adequate views of the heart in 31 patients, while in the other 6 patients, arrhythmias complicated the assessment of the global contractility. Of these 31 patients, only 25 received 1000 mL fluid administration. There were no patients with a poor global contractility of the left ventricle, 6 (24%) patients with moderate contractility and 19 (76%) patients with good contractility or hypercontractility. We could not demonstrate an impaired response to fluid therapy in patients with

Table 1 Baseline characteristics of the total group, patients with a low and high caval index

	Total (n=37) (IQR)	Low caval index (n=13) (IQR)	High caval index (n=24) (IQR)
Male	23 (62.2%)	8 (61.5%)	15 (62.5%)
Age (years)	64.0 (43.5–74.5)	50.0 (29.0–67.5)	65.5 (50.8–76.0)
BMI (kg/m^2)	24.4 (20.7–28.4)	25.7 (20.5–27.5)	23.8 (20.8–28.6)
Respiratory rate (breaths/min)	21.0 (18.0–23.0)	22.0 (17.5–23.0)	20.5 (18.0–23.0)
Oxygen saturation (%)	97.0 (95.0–99.0)	97.0 (92.0–99.5)	96.5 (95.3–98.8)
Oxygen supply (L)	0.0 (0.0–0.75)	0.0 (0.0–2.0)	0.0 (0.0–0.0)
Temperature (°C)	38.7 (38.4–39.2)	38.8 (38.6–39.3)	38.6 (38.2–39.1)
Capillary refill time (seconds)	3.0 (2.0–3.5)	3.0 (3.0–3.5)	3.0 (2.0–3.8)
Leucocyten (mmol/L)	9.8 (4.1–14.2)	5.0 (2.6–13.5)	11.4 (6.7–15.4)
Lactate (mmol/L)	1.2 (0.8–1.8)	1.2 (0.6–1.5)	1.3 (0.8–2.7)
Thrombocytes (mmol/L)	208.0 (114.5–260.5)	172.0 (112.5–257.0)	210.5 (116.5–263.3)
Number of SIRS criteria	3.0 (2.0–4.0)	3.0 (3.0–4.0)	3.0 (2.0–3.8)
Systolic blood pressure (mm Hg)	123.0 (101.5–145.0)	123.0 (91.0–152.0)	123.0 (111.3–139.0)
Diastolic blood pressure (mm Hg)	70.0 (59.5–79.5)	70.0 (52.5–84.0)	70.0 (61.5–78.5)
Mean arterial pressure (mm Hg)	88.0 (75.2–101.2)	93.0 (65.3–104.5)	88.0 (79.4–100.5)
Stroke volume (mL)	67.6 (55.6–81.0)	69.2 (53.7–85.9)	67.0 (55.9–76.3)
Cardiac output (L/min)	6.4 (6.0–8.0)	6.4 (6.2–8.5)	6.5 (5.9–7.7)
Heart rate (beats/min)	101.0 (95.5–109.5)	107.0 (99.0–118.0)	100.5 (93.3–106.5)

Values are presented as median with IQR (25.0–75.0).
BMI, body mass index; SIRS, systemic inflammatory response syndrome.

Table 2 Comparison of stroke volume and cardiac output in patients with a low and high caval index after 1000 mL 0.9% NaCl

	Low caval index (n=9)		p Value	High caval index (n=19)		p Value
	Baseline	After 1000 mL		Baseline (CI)	After 1000 mL	
SV (mL)	69.2 (53.7 to 83.2)	55.6 (44.6 to 97.5)	0.953	66.4 (55.6 to 70.3)	77.9 (57.3 to 100.7)	0.022
CO (L/min)	6.4 (6.2 to 8.1)	5.7 (5.2 to 9.0)	0.514	6.4 (5.9 to 7.9)	7.9 (5.5 to 8.9)	0.117

p Value: statistical difference in parameters between baseline and after a fluid bolus of 1000 mL, 0.9% NaCl.
p ΔL-ΔH: statistical difference between a low and high caval index.
CO, cardiac output; NaCl, sodium chloride; SV, stroke volume.

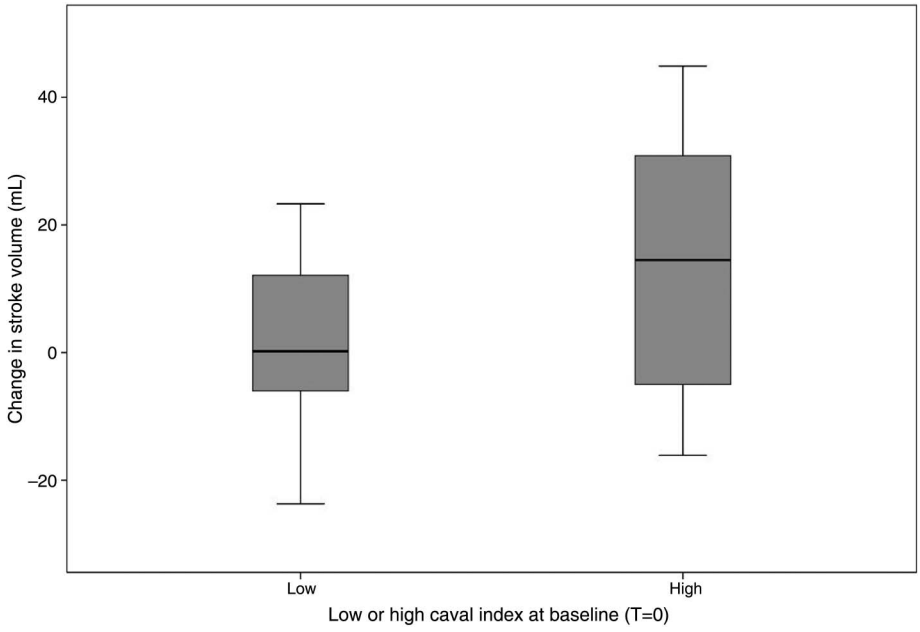

Figure 1 Comparison of stroke volume between patients with a low and high caval index after a fluid bolus of 1000 mL sodium chloride.

moderate versus good contractility or hypercontractility of the left ventricle in this small study group. None of the patients were treated with vasoactive medication.

DISCUSSION

Our results demonstrate that a high CI (>36.5%) is associated with an increase in stroke volume after administration of a fluid bolus of 1000 mL in patients with sepsis in the ED. This is in contrast with the low CI group where no significant rise was observed. Haemodynamic parameters remained equal after a fluid bolus of 500 mL 0.9% NaCl in both groups. This suggests that a minimum of 1000 mL is needed to reach a significant change (>10%) in stroke volume and/or cardiac output in patients with untreated sepsis. This finding slightly contrasts with the observations of previous studies where only 500 mL of fluid was sufficient to increase stroke volume.[27] This definition of a responder (an increase in stroke volume and/or cardiac output of at least 10% after a fluid bolus of 500 mL 0.9% NaCl) might not be suitable in untreated patients with sepsis in the ED, because possibly more fluid is needed to induce a significant response.[20 26 28–30] Multiple studies showed that fluid overload is generally associated with an increase in complications, mortality and a prolonged hospital stay.[2–6] Despite a mean fluid administration of 1439 (±789.2) mL in our study, there were no patients with clinical fluid overload. This suggests that a patient with mild sepsis could receive at least 1000 mL 0.9% NaCl, without developing complications. This is in line with the recent multicentre study of Arnold *et al*[31] demonstrating that although progression to organ dysfunction could not be prevented by fluid resuscitation, therapy was not associated with clinical fluid overload in patients with mild sepsis in the ED. We investigated if the global contractility of the left ventricle was useful in guiding fluid therapy. In our study, which comprised a small group of patients with sepsis, global contractility of the left ventricle was not associated with stroke volume (p=0.086), although we did not include patients with poor contractility. An important limitation of this study was the small study population and in particular the small amount of patients with a low CI, so several changes might be unfairly not significant. This was a pilot study to assess feasibility of a larger prospective study. Combining NICOM and US is non-invasive, patient friendly, can be done in the majority of patients and is easily performed,

so a larger study is feasible. This larger study should also address the validity of NICOM in a larger population with sepsis including septic shock in the ED. Despite our small study population, we were able to demonstrate a significant rise in stroke volume in patients with a high CI after a fluid bolus of 1000 mL. The mean administered amount of fluid therapy in this study was still relatively low (1439 (±789.2) mL) compared with the advised amount of a minimal 2000 mL in the Surviving Sepsis Campaign resuscitation bundles, and compared with other studies where the mean administered fluid was 4981 and 2800 mL, respectively.[24 32 33] Another limitation is the high percentage of patients with mild sepsis, so we cannot predict the response in patients with severe sepsis and septic shock. On the other hand, it is often more clinically obvious that these patients require larger volumes of fluid to optimise haemodynamic parameters. It is for that very reason that in patients with mild sepsis, in whom guiding fluid resuscitation is difficult, a non-invasive tool could be of great value. After completion of our study, the sepsis definitions were changed with the consequence that less patients would have fulfilled the criteria.[34] This will be addressed in a larger study.

In conclusion, the combination of NICOM and US may be of additive value in the management of sepsis and fluid resuscitation. This study suggests that patients with sepsis and a high CI should receive at least 1000 mL of fluid to obtain a sufficient rise in stroke volume without risking complications like fluid overload. Whether the clinical course of patients with mild sepsis improves after fluid resuscitation remains to be elucidated.

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Contributors MO performed data acquisition, data analysis and wrote the manuscript. TJO was involved in the conception, hypothesis delineation and design of the study, as well as coordinated the study and assisted in data analysis and writing the manuscript. MD-H assessed all ultrasound measurements and was involved in revising the manuscript critically. MPMH made substantial contributions to the conception and design of this study and revised the manuscript critically. JJML made substantial contributions to the conception and design of this study and revised the manuscript critically. JCtM was involved in the conception, hypothesis delineation as well as design of the study and revised the manuscript critically. All authors read and approved the final manuscript.

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