Author/s:
Long, E;Duke, T;Oakley, E;O'brien, A;Sheridan, B;Babl, FE

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Long Elliot (Orcid ID: 0000-0003-0225-7953)
OAKLEY ED (Orcid ID: 0000-0002-3712-6200)
Babl Franz (Orcid ID: 0000-0002-1107-2187)

Title

Does respiratory variation of inferior vena cava diameter predict fluid responsiveness in spontaneously ventilating children with sepsis.

Authors

Elliot Long FRACP[1,2,3]

Trevor Duke FCICM[2,3,4]

Ed Oakley FACEM[1,2,3]

Adam O'Brien FACEM[1,2,3]

Bennett Sheridan FCICM[2,3,4,5]

Franz E Babl FRACP[1,2,3]

On behalf of the Pediatric Research in Emergency Departments International Collaborative (PREDICT).

1. Department of Emergency Medicine, The Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, Australia.
2. Murdoch Children's Research Institute, 50 Flemington Road, Parkville, Australia.
3. Department of Pediatrics, Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, Victoria, Australia.
4. Pediatric Intensive Care Unit, The Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, Australia.

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5. Department of Cardiology, The Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, Australia.

Author Contribution

All authors contributed to the study concept and design; acquisition, analysis, and interpretation of data; drafting and revising the manuscript; and agree to be accountable for the accuracy and integrity of the work.

Running Title

Predicting fluid responsiveness in septic children.

Correspondence to

Dr Elliot Long

Department of Emergency Medicine

The Royal Children's Hospital

50 Flemington Road

Parkville, Vic. 3052 Australia

Phone 61 3 9345 6592

Fax 61 3 9345 5938

Email: Elliot.long@rch.org.au

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Abstract

Objective: The intent of fluid bolus therapy is to increase cardiac output and tissue perfusion, yet only 50% of septic children are fluid responsive. We evaluated respiratory variation of inferior vena cava (IVC) diameter as a predictor of fluid responsiveness.

Methods: A prospective observational study in the Emergency Department of The Royal Children's Hospital, Melbourne, Australia. Patients were spontaneously ventilating children treated with fluid bolus therapy for sepsis induced acute circulatory failure. IVC ultrasound was performed prior to fluid bolus therapy. Transthoracic echocardiography was performed prior to, 5 and 60 minutes after fluid bolus therapy. IVC collapsibility index and stroke distance were calculated by a blinded Paediatric Emergency Physician and blinded Paediatric Cardiologist, respectively.

Results: Thirty-nine fluid boluses were recorded in 33 children, 28/39 (72%) of which met criteria for fluid responsiveness at 5 minutes, which was sustained in 2/28 (7%) of initial fluid responders at 60 minutes. Sensitivity and specificity (95% confidence interval) of IVC collapsibility index were 0.44 (0.25 – 0.65) and 0.33 (0.10 – 0.65) with an area under the receiver operator characteristics curve (95% confidence interval) of 0.38 (0.23 - 0.55) at 5 minutes. Test characteristics 60 minutes after fluid bolus administration were not meaningful due to the infrequency of sustained fluid responsiveness in this patient group. There was no significant correlation between IVC collapsibility and fluid responsiveness at 5 or 60 minutes.

Conclusions: IVC collapsibility has poor test characteristics for predicting fluid responsiveness in spontaneously ventilating children with sepsis.

Key Words

Cardiac Output; Child; Fluid Therapy; Observational Study; Sepsis; Vena cava, inferior

Introduction

Fluid bolus therapy (FBT) is the initial recommended treatment for sepsis induced acute circulatory failure (1, 2). The intent of FBT is to increase blood flow to hypo-perfused vital organs by increasing stroke distance and cardiac output (3), where stroke distance is the distance (in cm) that a column of blood is ejected from the heart with each cardiac contraction (4). FBT that does not contribute to increased stroke distance may not be beneficial, and may accumulate in the interstitial space, leading to end-organ oedema and dysfunction (5). Excessive FBT and a positive cumulative net fluid balance have been independently associated with worsening renal function, acute respiratory distress syndrome, prolonged intensive care unit (ICU) and hospital length of stay, and mortality (6-15). Fluid responsiveness, defined as an increase in stroke distance of >10%, can be used to identify patients who may benefit from FBT (16). Fluid un-responsiveness, by comparison, can be used to identify patients who may not benefit from FBT (17). The ability to predict fluid responsiveness may therefore allow FBT to be administered only to those likely to benefit (18).

Respiratory variation of inferior vena cava (IVC) diameter is a non-invasive method for predicting fluid responsiveness based on dynamic heart-lung interactions (19). In spontaneously ventilating patients, negative intrathoracic pressure generated during inspiration leads to infra-diaphragmatic IVC collapse, and positive pressure generated during expiration leads to infra-diaphragmatic IVC distention. The ratio of minimum to maximum IVC diameter in spontaneously ventilating patients is termed the collapsibility index (20).

The aim of this study was to determine the test characteristics of respiratory variation in IVC diameter for predicting fluid responsiveness in spontaneously ventilating children with sepsis induced acute circulatory failure.

Methods

Study Design

The study was designed as a prospective observational cohort study. The study was approved by the hospital institutional review board (The Royal Children's Hospital Human Research and Ethics Committee, approval #33169A) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12614000824662). Written informed consent from parents and / or study participants was obtained prior to enrolment.

Study Setting and Population

The study setting was the Emergency Department (ED) of The Royal Children's Hospital, Melbourne, Australia; a tertiary-level dedicated paediatric hospital with an annual ED census of >90 000 children. Participants were spontaneously ventilating septic children with acute circulatory failure. Inclusion criteria were: clinically suspected sepsis according to international consensus criteria (21), and treating clinician decision to administer FBT (defined as 20ml/kg of 0.9% saline). Exclusion criteria were: underlying uncorrected structural cardiac disease, non-curative goals of therapy, and where the child's family were non-English speaking.

Study Protocol

The study was nested within a larger project examining multiple physiological changes after fluid bolus administration (22). Participants were identified by the Principal Investigator (PI), who performed all sonographic recordings, and has the qualification of Post-Graduate Certificate in Clinical Ultrasound (The University of Melbourne, Australia). IVC ultrasound was performed immediately prior to FBT and images recorded. Echocardiography was performed immediately prior to, 5 minutes after, and 60 minutes after FBT, and images recorded. Recorded IVC images were de-identified, randomized, and interpreted by a Paediatric Emergency Physician with a Diploma in Diagnostic Ultrasound (Australasian Society for Ultrasound in Medicine) blinded to reference standard results and to patient identity. Echocardiographic images were de-identified, randomized, and interpreted by a Paediatric Cardiologist blinded to index test results, patient identity and timing of echocardiogram relative to FBT.

Measurements

The index test was IVC collapsibility index. All sonographic recordings were performed using a Zonare Z.one (Zonare Medical Systems, Mountain View, CA, USA) with a 3-10MHz phased array transducer. Using a subcostal, trans-hepatic longitudinal view including the IVC-right atrial (RA) junction and confluence of the hepatic veins, a 2D cine loop was recorded over 3 respiratory cycles. IVC measurements were taken 1cm caudal to the

confluence of the hepatic veins. IVC collapsibility index was calculated as: (max IVC diameter – min IVC diameter) / maximum IVC diameter x 100 (figure 1).

The reference standard test was change in stroke distance using trans-thoracic echocardiography. An apical 5-chamber view was obtained and used to record stroke distance over 3-5 respiratory cycles using a 3mm pulsed-wave doppler signal gated 1cm proximal to the aortic valve. Fluid responsiveness was defined as an increase in stroke distance of >10% following FBT.

Key Outcome Measures

The primary outcome measures were the test characteristics of IVC collapsibility index as a predictor of fluid responsiveness 5 and 60 minutes after FBT. The secondary outcome measure was the correlation between IVC collapsibility and change in stroke distance 5 and 60 minutes after FBT.

Data Analysis

Assuming a fluid responsiveness rate of 50% at 5 and 60 minutes after FBT (23), and a variance in IVC collapsibility index of +/-12% (10% population variance and 2% measurement variance) (24), as sample size of 35 was required to detect a difference between median IVC collapsibility index in fluid responders and fluid non-responders with $\beta = 0.2$ and a two-tailed $\alpha < 0.05$.

Participants were stratified into fluid responders and non-responders. The difference in median IVC collapsibility index between fluid responders and non-responders calculated using Wilcoxon's signed ranks test. Receiver operator characteristic (ROC) analysis was performed and used to determine optimal cut-off values for sensitivity and specificity at each time point. The correlation between IVC collapsibility and change in stroke distance 5 and 60 minutes after FBT was calculated using Spearman's correlation co-efficient. Intra-observer variability was calculated for IVC collapsibility index and stroke distance using two measurements taken immediately prior to fluid bolus administration by the same observer using the same method, and calculated as the mean difference between measurements with standard deviation (25). Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Role of Funding Organizations

Funding organizations had no role in the design, conduct, or reporting of the study.

Results

Between August 2013 and February 2017, 44 fluid boluses were recorded in 38 participants (6 participants received 2 fluid boluses). Demographic and clinical data were recorded for all participants. Echocardiographic images were un-interpretable in 1 participant, and IVC images un-interpretable in 4, and these images were excluded from analysis, yielding a total of 39 fluid boluses for analysis in 33 participants. Stroke distance was obtained at baseline (n=39), 5 minutes (n=39) and 60 minutes (n=30) after FBT. Stroke distance at 60 minutes

was not recorded in 2 cases due to critical procedures preventing echocardiography and in 7 cases following repeat fluid bolus administration between 5 and 60 minutes. All participants who had the index test (IVC ultrasound) also had the reference standard test (echocardiography).

Participant demographic and outcome data are presented in Table 1. There were no significant differences in demographic data between fluid responders 5 and 60 minutes after FBT. Four participants were receiving heated, humidified, high flow nasal cannula oxygen therapy throughout the study period; none experienced escalation of respiratory support during study investigations. No participants were receiving inotropic support at the time study observations. All included participants were treated based on a presumptive clinical diagnosis of sepsis; two participants had non-infective final (discharge) diagnoses. The overall 28-day mortality was zero.

Primary outcome measurements:

Twenty-eight of thirty-nine (72%) fluid boluses resulted in an increase in stroke distance of >10% 5 minutes after FBT, and these participants were considered fluid responsive. This was sustained in 2/28 (8%) of initial fluid responders 60 minutes after FBT (figure 2). There was no significant difference in IVC collapsibility index between fluid responders and non-responders at 5 and 60 minutes after FBT (Table 2).

Optimal sensitivity and specificity were derived when IVC collapsibility of >57% was used to predict fluid responsiveness to FBT as implied by the stroke distance measured 5 minutes post bolus (Table 3). Using this threshold value, the sensitivity and specificity of IVC collapsibility index (95% CI) at 5 minutes were 0.44 (0.25 – 0.65) and 0.33 (0.10 – 0.65), respectively. The area under the receiver operator characteristics curve (AUROC) for IVC collapsibility index as a predictor of fluid responsiveness was 0.38 (95% confidence interval (CI): 0.23 – 0.55) 5 minutes after FBT. No meaningful test characteristics for IVC collapsibility index 60 minutes after fluid bolus administration could be determined due to the infrequency of sustained fluid responsiveness in this patient group.

Secondary outcome measurements:

The correlation (rho) between IVC collapsibility index and change in stroke distance 5 minutes after FBT was -0.02 (p=0.93), and 60 minutes after FBT was -0.13 (p=0.49).

The mean intra-observer variability (+/- standard deviation) for IVC collapsibility index was 3.6% (+/- 4.2%) and for stroke distance measurement was 0.5% (+/- 1.6%).

Discussion

In spontaneously ventilating septic children, the test characteristics of IVC collapsibility index to predict fluid responsiveness 5 minutes after FBT were poor. Test characteristics after this time were difficult to assess due to the low prevalence of sustained fluid responsiveness.

Respiratory variation in IVC diameter as a predictor of fluid responsiveness has generated considerable interest and controversy in the critical care literature (26, 27). The argument against IVC collapsibility index as a predictor of fluid responsiveness is based on pooled central venous pressure (CVP) data, indicating that CVP and change in CVP with FBT are poor predictors of fluid responsiveness (28). Respiratory variation in IVC diameter occurs in part due to changes in CVP, as well as changes in several additional parameters, including: the magnitude of intrathoracic pressure changes with respiration, venous compliance, and intra-abdominal pressure (29). As such, it is likely that multiple contextual factors influence the degree of respiratory variation in IVC diameter in individual patients. These contextual factors are not easily accounted for in study settings, and may have contributed to the negative results observed in this study.

The accuracy of respiratory variation of IVC diameter to predict fluid responsiveness in children has only been reported in those being mechanically ventilated, and may be significantly different in spontaneously ventilating children. During mechanical ventilation, right atrial pressure is elevated due to increased mean airway pressure (30), and the amplitude of intrathoracic pressure changes can be controlled by maintaining a constant tidal volume (>8ml/kg during the assessment of fluid responsiveness). During spontaneous ventilation, however, lower right atrial pressure and uncontrolled, variable intrathoracic pressure changes with respiration may reduce the accuracy of IVC ultrasound to predict fluid responsiveness (29). The test characteristics of respiratory variation in IVC diameter in mechanically

ventilated children are mixed, with reported AUROC values ranging from 0.37 to 0.85 (31-33). These studies all maintained tidal volumes of 8-10 ml/kg during IVC sonography, reducing one possible source of heterogeneity. All differed, however, in their inclusion criteria, fluid bolus volume and content, their definition of fluid responsiveness, and in their cut-off values for a positive index test. In addition, as a user-dependent test, sonographer characteristics may play a part in explaining the observed heterogeneity between studies.

Multiple studies in spontaneously ventilating adults have reported the accuracy of respiratory variation in IVC diameter as a predictor of fluid responsiveness (34-40), with a pooled AUROC of 0.76 (24). The majority of these studies enrolled mixed patient populations, including those with trauma, dehydration, and post-operative surgical patients. The hemodynamic response to FBT in patients with systemic inflammation may differ from that observed in patients with fluid loss (27); endothelial dysfunction in may significantly influence the rate of fluid shift out of the intravascular compartment and the duration of effect of FBT (41). In addition, the underlying haemodynamic abnormalities and response to treatment differ between septic children and adults, with a higher incidence of septic myocardial dysfunction and “cold shock” in the former, and vaso/venoplegic “warm shock” in the latter (42, 43). The combination of endothelial dysfunction and septic myocardial dysfunction may reduce the magnitude and duration of effect of FBT on stroke distance in children with sepsis (5), and may explain in part the inferior predictive ability of IVC collapsibility found in our study when compared to adult studies involving mixed patient populations.

Intra-observer variability in our study compared favourably to that reported in previous studies (<10% for IVC collapsibility index measurement and <5% for stroke distance measurement) (24).

As the availability and training in point-of-care ultrasound is increases in critical care environments (44), complete sonographic assessment, including echocardiography and lung ultrasound, may provide contextual information aiding the interpretation of respiratory variation in IVC diameter as a predictor of fluid responsiveness. As a test in isolation, however, respiratory variation in IVC diameter seems to have poor test characteristics on which to base clinical decisions regarding fluid resuscitation.

Limitations

The study included a convenience sample of participants, and may have systematically excluded some participant groups. As a pragmatic study, however, the study population was thought to be representative of the spectrum of illness encountered in clinical practice, and had similar characteristics to previous clinical audits using the same inclusion criteria (45). The data from several participants were uninterpretable and excluded from analysis, which may have introduced a source of bias, however the number of uninterpretable images was in keeping with previous studies (35). At the time of participant enrolment, patients had a presumptive clinical diagnosis of sepsis, yet two had non-infective final (discharge) diagnoses. The response to FBT in these patients may have been different to that in patients with systemic inflammation. Confounding by other interventions during the study period was

likely minimal, as no patients had a change in cardio-respiratory support other than fluid bolus administration over the study period.

Conclusions

IVC collapsibility index has poor test characteristics for predicting fluid responsiveness in spontaneously ventilating children with sepsis.

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Competing Interests

None declared

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Table 1. Demographic and outcome data for included participants.

Demographic data	All Participants (n=33)
Age (years), median (IQR[1])	1.5 (0.25 to 3)
Male sex, n(%)	21 (63)
Chronic disease, n(%)	11 (33)
Oncological diagnosis	5 (15)
Cerebral palsy	3 (9)
Other	3 (9)
Outcome data	
ICU admission, n(%)	12 (36)
ICU LOS (hours), median (IQR)	82.5 (50 to 166.5)
Hospital LOS (hours), median (IQR)	90 (48 to 221)
Invasive ventilation[2], n(%)	6 (18)
Inotrope / vasopressor infusion[1], n(%)	4 (12)
Pathogen Identified, n(%)	20 (61)
Virus	8 (24)
Respiratory Syncitial Virus	2 (6)
Enterovirus	2 (6)
Parainfluenza	2 (6)
Human Metapneumovirus	1 (3)
Parechovirus	1 (3)

	5 minutes after fluid bolus therapy	60 minutes after fluid bolus therapy

Bacteria	12 (36)
Staphylococcus aureus	3 (9)
Streptococcus pneumoniae	3 (9)
Streptococcus mitis	2 (6)
Mycoplasma pneumoniae	1 (3)
Coagulase negative staphylococcus	1 (3)
Group A Streptococcus	1 (3)
Escherichia coli	1 (3)
Discharge diagnosis	
Sepsis	9 (27)
Pneumonia / acute lower respiratory tract infection	6 (18)
Meningitis	5 (15)
Viral illness	3 (9)
Bronchiolitis	3 (9)
Febrile neutropaenia	2 (6)
Staphylococcal scalded skin syndrome	1 (3)
Epiglotitis	1 (3)
Colitis	1 (3)
Food protein induced enterocolitis syndrome	1 (3)
Diabetic keto-acidosis	1 (3)

[1]IQR=interquartile range, [2]ventilatory support is reported as the maximal level required during hospital admission.

	Non-responders (n=11)	Responders (n=28)	p	Non-responders (n=26)	Responders (n=2)	p
IVC Collapsibility Index (%), median (IQR)	57 (43 to 67)	57 (25 to 75)	0.37	57 (38 to 71)	0% and 25%	0.18

Table 2. Difference in median IVC collapsibility index between fluid responders and non-responders.
IVC=inferior vena cava, IQR=interquartile range

Table 3. Test characteristics of IVC collapsibility for predicting fluid responsiveness 5 and 60 minutes after fluid bolus therapy.

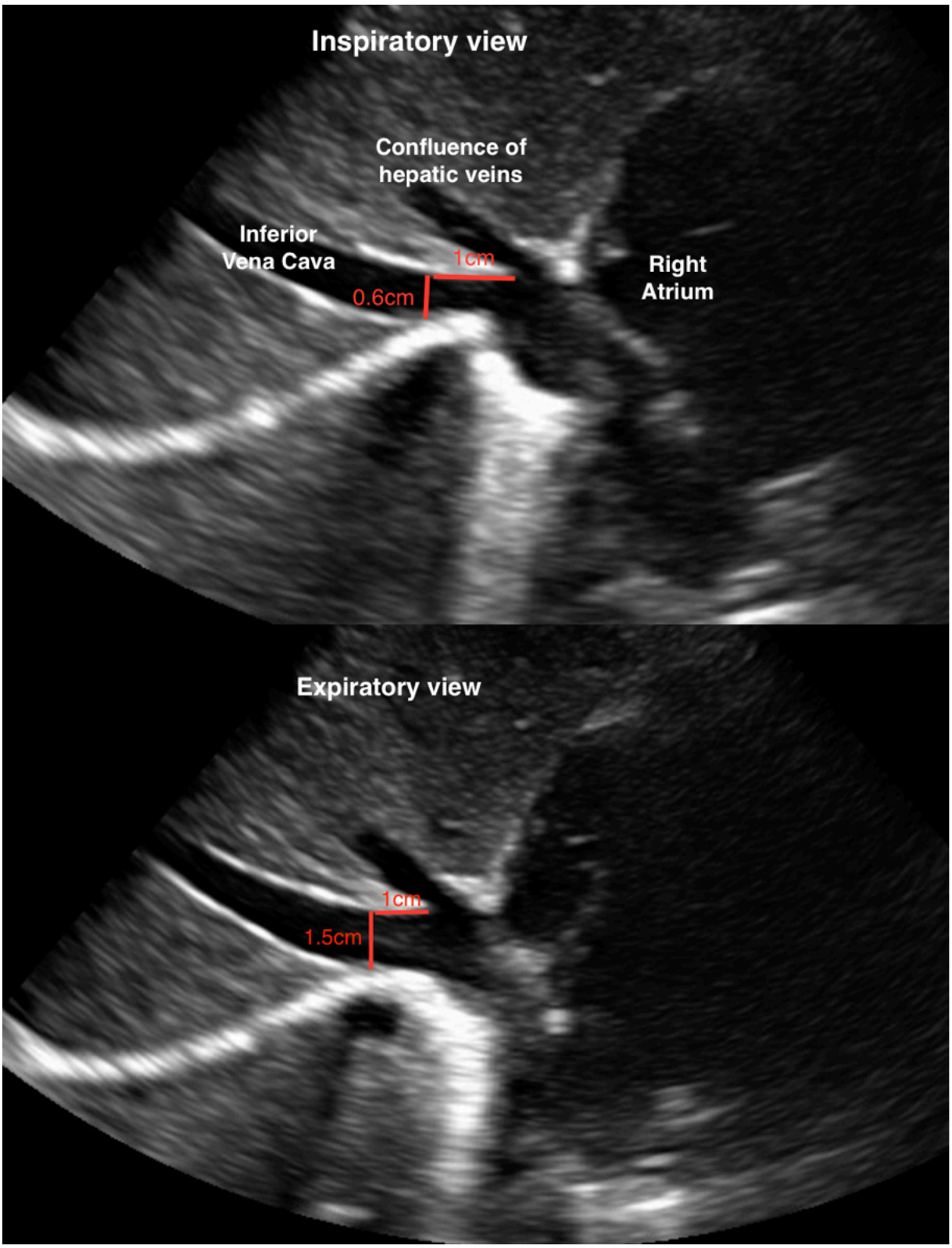
Time of evaluation	No (total)	Fluid responders, n(%)	Threshold IVC collapsibility index (%)	TP	FP	FN	TN	Sens (95% CI)	Spec (95% CI)	AUROC (95% CI)
5 minutes after fluid bolus therapy	39	28 (72)	>57%	12	7	16	4	0.44 (0.25 – 0.65)	0.33 (0.10 – 0.65)	0.38 (0.23 – 0.55)
60 minutes after fluid bolus therapy	28	2 (8)	-	-	-	-	-	-	-	-

IVC=inferior vena cava, TP=true positive, FP=false positive, FN=false negative, TN=true negative, Sens=sensitivity, Spec=specificity, CI=confidence interval, AUROC=area under the receiver operating characteristic curve.

Figure Legends

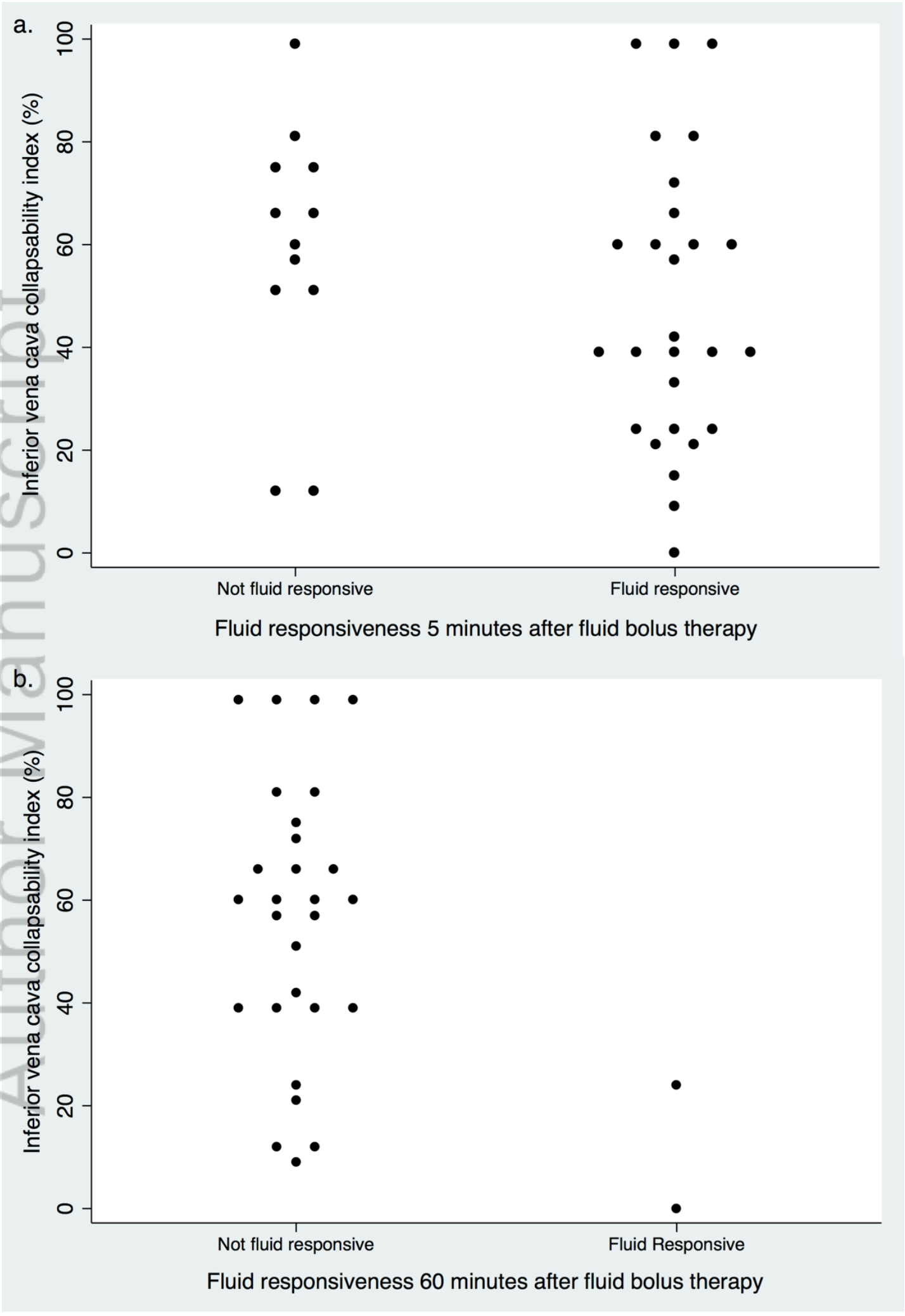
Figure 1. Subcostal, trans-hepatic longitudinal view of the inferior vena cava. Inferior cava collapsibility index was measured 1cm caudal to the confluence of the hepatic veins.

Figure 2. Inferior vena cava collapsibility index in non-fluid responders and fluid responders 5 (a.) and 60 (b.) minutes after fluid bolus therapy.



Inferior vena cava collapsibility index = (max IVC diameter – min IVC diameter) / maximum IVC diameter x 100, (1.5cm-0.6cm)/1.5cm x 100; 60%

IVC EMA r1 fig1.tiff



IVC EMA r1 Fig 2.tiff