Ultrasound assessment of central venous pressure: A systematic review and meta-analysis

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Abstract
Background Ultrasound is increasingly relied upon to estimate central venous pressure (CVP) in the echocardiography lab and using point-of-care systems in the intensive care unit and the emergency department. However, there is uncertainty regarding the diagnostic accuracy of ultrasound-based parameters as reported in diverse studies.

Methods A systematic review was performed by searching MEDLINE, EMBASE, and the Cochrane Database for studies evaluating ultrasound-based indicators of filling pressures in relation to catheterization-based CVP. Studies were screened for predefined inclusion criteria and rated for quality by duplicate observers. Standardized correlation coefficients for each ultrasound-based indicator were meta-analyzed using a random effects model.

Results 3949 articles were screened and 64 met the criteria for inclusion. Inferior vena cava (IVC) diameter was assessed in 34 study measures and the pooled standardized correlation with invasive CVP was 0.74 (95% CI 0.63 to 0.84). IVC collapsibility was assessed in 20 study measures and the pooled standardized correlation with invasive CVP was -0.57 (95% CI -0.70 to -0.44). Tricuspid E/Ep was assessed in 6 study measures and the pooled standardized correlation with invasive CVP was 0.59 (95% CI 0.26 to 0.93). IVC parameters but not E/Ep remained correlated with CVP in mechanically ventilated patients, including cardiac surgery patients. Results were similar in studies featuring non-traditional users and cardiac specialists.

Conclusions Echocardiographic IVC diameter, collapsibility, and tricuspid E/Ep ratio are significantly correlated with invasive CVP, albeit with important heterogeneity between studies. Most of these indicators are equally valid when applied in ventilated patients and by non-traditional users.

Introduction
Volume assessment is a fundamental component of the clinical exam in the office, ward, and critical care settings. Classical teaching has relied on the physical examination of the jugular venous pressure waveform (JVP), although its modest sensitivity of 33% and inter-observer reliability have increasingly led to the use of other tools (1–3). Invasive methods to assess the JVP, namely, the central venous pressure (CVP), require expertise in installation and interpretation, have inherent risks related to its invasiveness, and can be time consuming (1–3). Although controversial in its utility to predict volume
responsiveness, the invasive determination of CVP remains the gold standard in measuring venous filling pressures (4,5).

Non-invasive determination of CVP was pioneered by echocardiographers and largely based on assessment of the inferior vena cava (IVC) using ultrasound systems in the echocardiography lab. Recently, point of care ultrasound systems have been developed and transformed the way physicians in critical care settings evaluate volume status. Newer techniques including 2-dimensional (2D) ultrasonography of the jugular and subclavian veins and Doppler interrogation of the right ventricle have been reported to be useful, although results have been inconsistent (particularly in mechanically ventilated patients) and day-to-day practice continues to rely on basic techniques of IVC size and collapsibility.

Thus, we performed a systematic review and meta-analysis of the ultrasound assessment of CVP to analyze which techniques provides the most accurate assessment of right atrial pressure in both mechanically ventilated and spontaneously breathing adult patients.

Methods
A systematic review was performed, searching Ovid MEDLINE(1946-), Ovid EMBASE(1974-), and the Cochrane Database using the search string: (Ultrasound OR Ultrasonography OR Echocardiogram OR Echocardiography OR Echocardiographic OR Doppler) AND ("Central venous pressure" OR "Right atrial pressure" OR "Jugular venous pressure" OR "Fluid status" OR "Volume status" OR "Filling pressure"). References from retrieved manuscripts were scanned for additional articles. English language studies using echocardiography and point of care ultrasound systems in the humans were included between 1980-2017.

Eligible articles were identified through two phases. In the first phase, two authors (JL, AW, or JD) independently reviewed the titles and abstracts of all retrieved bibliographic records for potential inclusion. In the second phase, full texts of the selected articles were retrieved and two authors independently reviewed and selected studies that met the inclusion criteria. Studies were included if right atrial pressure was estimated by ultrasound and directly compared to invasive CVP measured with a fluid filled catheter. Inclusion criteria included prospective and cross-sectional studies of adult
(>=18 years of age) human patients, on spontaneous or mechanical ventilation, directly comparing absolute or dichotomized CVP using a fluid filled catheter to bedside 2D TTE or TEE of right atrial pressure, with or without Doppler. Exclusion criteria were studies focusing on congenital, retrospective studies, duplicate studies, and absence of comparison to the invasive CVP reference standard.

Patient characteristics, primary diagnosis, clinical setting, time between ultrasound and invasive measurement, and breathing status (mechanical ventilation or spontaneous breathing) were extracted from the original full text manuscripts. Echocardiographic parameters were recorded as continuous measures with their mean and standard deviation in the normal CVP and abnormal CVP groups, and as binary measures when dichotomized according to a given cut-point. For each parameter, correlation coefficients were extracted and transformed using Fisher’s Z-transformation, and then meta-analyzed using a random effects model (STATA version 15). Meta-analyses were performed for all patients combined and subsequently for the spontaneously ventilated and mechanically ventilated subgroups. Heterogeneity was assessed with the I-squared statistic.

Quality of each study was independently analyzed by two authors (J.L, J.D or A.W) using the QUADAS-2 questionnaire for systematic reviews (6). Seven parameters (patient selection bias, patient selection applicability, index test (ultrasound) risk of bias, index test applicability, reference test (invasive CVP) risk of bias, and risk of bias due to timing were scored on a scale from 1 to 3; with 1 indicating low risk of bias, 2 indicating moderate risk, and 3 indicating high risk. Aggregate scores were averaged between the two reviewers. A score of 7-10 was defined as high quality, 11-14 as intermediate, and >14 as low.

Results
A total of 3949 articles were screened, 159 were identified for full-text review, and 64 met the prespecified selection criteria and were included in our analysis. The 29 studies (representing 34 measures) that reported on IVC size are shown in Table 1, the 19 studies (representing 20 measures) that reported on IVC collapsibility are shown in Table 2, and the 21 studies (representing 27 measures) that reported on right ventricular Doppler or tissue Doppler measures or peripheral vein
measures are shown in Table 3 (these are not mutually exclusive as studies often reported on more than a single measure). In all studies, the reference standard was invasively measured CVP, generally performed within 0.5-1 hours from the time of the echocardiographic assessment. The quality of the studies assessed was high with the exception of 10 studies with intermediate ratings (13,33,34,45,49,56,57) and 3 studies with low ratings (20).

For IVC diameter as a continuous measure, 32 study measures were pooled and 2 study measures were not pooled because the R value was not available(15,63). The pooled standardized correlation with invasive CVP was 0.74 (95% CI 0.63 to 0.84) with significant heterogeneity across studies (I-squared 77.6%, P<0.01) (Figure 2). The correlation was similar in mechanically ventilated patients (0.79, 95% CI 0.61 to 0.97) than non-ventilated patients (0.70, 95% CI 0.57 to 0.83).

For IVC collapsibility as a continuous measure, 17 studies were pooled and 2 studies were not pooled because the R value was not available(15,63). The pooled standardized correlation with invasive CVP was -0.57 (95% CI -0.70 to -0.44) (Figure 3). The correlation was similar in mechanically ventilated patients (-0.56, 95% CI -0.77 to -0.34) than non-ventilated patients (-0.57, 95% CI -0.69 to -0.46), with significant heterogeneity in the former (I-squared 88.6%, P<0.01) but not the latter (I-squared 36.9%, P=0.135).

Among non-IVC parameters, only E/Ep was reported in at least 3 studies and thus was analyzed. This ratio represents the Doppler-measured trans-tricuspid inflow velocity divided by the tissue Doppler-measured lateral tricuspid annular velocity. For E/Ep as a continuous measure, 10 studies were included in the analysis. The pooled standardized correlation with invasive CVP was 0.62 (95% CI 0.24 to 0.99) with significant heterogeneity across studies (I-squared 92.7%, P<0.01) (Figure 4). The correlation was lower and not statistically significant in mechanically ventilated patients (0.39, 95% CI -0.57 to 1.34) whereas it was statistically significant in non-ventilated patients (0.71, 95% CI 0.25 to 1.17).

The subgroup of cardiac surgery patients was assessed in 8 studies (10,27,44,70) with a total of 547 patients. The 2 high quality studies (10,27) used the IVC diameter in mechanically ventilated patients and had correlation coefficients of 0.81 and 0.86 respectively. The subgroup of non-traditional users
(NTU) was assessed in 15 studies, with the majority including both spontaneous and mechanically ventilated patients having a primary diagnosis of sepsis or respiratory failure. In these studies, the correlation coefficients were in keeping with the overall trends observed, ranging from 0.49 to 0.81 for IVC diameter, -0.32 to -0.40 for IVC collapsibility, and 0.62 to 0.84 for peripheral vein measures. Finally, Table 4 depicts the diagnostic performance of binary cut-points for echocardiographic parameters used in certain studies, wherein sensitivity ranged from 47-92% and specificity ranged from 72-100% for the various ultrasound parameters.

Discussion
Our meta-analysis encompassing a representative sample of patients and physician users has shown that ultrasound-based estimates of CVP are moderately correlated with invasive measures. In an undifferentiated population, the IVC diameter is the most highly correlated, followed by E/Ep, and lastly IVC collapsibility. The IVC diameter was similarly correlated in ventilated and non-ventilated patients, while the other parameters performed less well in ventilated patients. Given these findings, and the relative ease of measuring the IVC diameter, it is reasonable to utilize IVC diameter as the starting point to determine volume status if invasive monitoring is not warranted or available.

The findings of our meta-analysis demonstrate that the tricuspid E/Ep ratio is a promising parameter. E/Ep performed with moderate correlation in the non-ventilated group of patients. The performance of this test in mechanically ventilated group remains an unknown due the inclusion of only 2 studies in this subgroup of patients and requires further study. Possible reasons for low adoption of this parameter include the technical challenges inherent to performing this test, and the requirement of specialized ultrasound systems capable of performing Doppler and tissue Doppler measurements (which initial point of care ultrasound systems did not uniformly support). As the field of ultrasound continues to evolve from technological and pedagogical perspectives, a larger number of trained users will be equipped to implement the E/Ep and other advanced measures for the estimation of CVP.

Mechanically ventilated patients deserve special attention as they are a challenging subgroup of patients to study, and estimation of filling pressures is likely to be of great clinical relevance. In
mechanically ventilated patients, the increased intrathoracic pressure exceeds intraabdominal pressures causing the IVC diameter to be larger than in spontaneously breathing patients. Despite this, the IVC diameter is still positively correlated with RAP (71). Moreover, insufflation during a passive mechanical ventilator-induced breath causes dilation rather than collapse of the IVC (71), rendering an opposite and less predictable correlation with RAP. In our study, the IVC diameter had the highest correlation and the narrowest CI of all the ultrasound measures evaluated, while IVC collapsibility had a reduced correlation with a wide CI, and the E/Ep had a non-significant correlation but included only 2 studies (44). Further study will be required before recommending IVC collapsibility or E/Ep in this group of patients.

Given the expanding interest and use of ultrasound by diverse practitioners, ultrasound-based assessment of CVP in no longer restricted to the cardiologist trained in echocardiography. Accordingly, the proportion of studies with non-traditional users was notable (30%). These studies generally focused on basic measures such as IVC diameter and reported correlation coefficients in line with those reported by traditional users. These data support the continued dissemination of echocardiographic training among non-traditional users in the intensive care unit, internal medicine, emergency medicine, and other fields.

Current guidelines from the ASE (72) are in line with the data currently covered in our systematic review and meta-analysis. Most of the studies included a dichotomization of CVP of > 10 mmHg corresponding with an IVC collapsibility > 40-50%. There was some discordance with IVC diameter, in that 3 out of 10 studies had significantly lower IVC diameter cut-off(17,25), but overall most studies had an IVC diameter corresponding to current recommendations.

First, the studies that were identified and reviewed evaluated the accuracy of ultrasound parameters in isolation and did not compare various combinations of parameters which may lead to greater diagnostic accuracy. Second, specific factors may interfere with the reliable use of IVC and right heart parameters as surrogates of CVP: these include tricuspid valve disease, etiology of right heart disease, pericardial disease, and atrial fibrillation. We could not determine presence or absence of these parameters from the published studies.
Finally, although it is important to understand how well ultrasound measures correlate to an invasive CVP, perhaps the more important question to be answered is how well ultrasound measures correlate to volume responsiveness.

Conclusions
Non-invasive ultrasound assessment of the IVC can be effectively performed at the bedside to estimate CVP and can be performed by cardiologists and non-traditional users across a broad spectrum of patients, including those on mechanical ventilation. Assessment of other parameters such as E/Ep may be complementary if confirmed in additional studies, provided that the expertise and equipment is in place to acquire them. The observed heterogeneity in the studies reviewed highlights the need for further high-quality studies with adequately powered sample sizes to be performed, comparing different parameters and testing the value of an integrated multi-parameter approach for estimating CVP.

Declarations

Ethics approval and consent to participate
This systematic review and meta-analysis did not acquire any primary patient data. All data was sourced from other studies. As such, ethics approval was not required to proceed with this study.

Consent for publication
All authors consent to publication of this manuscript.

Availability of data and materials
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Competing interests
None declared.

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**Authors’ contributions**

JD, JL and AW were responsible for the screening, selection and analysis of articles. JD, JL and JA were responsible for drafting the manuscript. All authors critically reviewed the manuscript. JL and JA were responsible for study design and conception. DJ and LR provided expert guidance for interpretation and generalizability of the results. JA was responsible for the statistical methods and analysis. All authors read and approved the final manuscript.

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Tables
Table 1: Characteristics of Studies Reporting IVC Size
Table 2: Characteristics of Studies Reporting IVC Collapsibility

| Authors        | Year | Setting | U/S modality | User | # Patients | Age | Primary diagnosis | Intubated | CS | Delay | R value | Quality Score | Quality Rating |
|----------------|------|---------|---------------|------|------------|-----|-------------------|-----------|----|-------|---------|----------------|----------------|
| Peicker ME     | 2013 | ICU     | POC           | NTU  | 65         | 59  | Sepsis            | No        | No | 0.98  | -0.40   | 9.5            | High           |
| Patel AI       | 2011 | ICU     | TTE           | Card | 45         | 53  | Sepsis            | No        | No | 0.98  | -0.49   | 10             | High           |
| Veldhuis O     | 2010 | ER      | POC           | NTU  | 73         | 63  | NA                | No        | No | 0.96  | 0.25    | 9.5            | High           |
| Slaats SM      | 2009 | ICU     | POC           | NTU  | 101        | 58  | Surgical          | No        | No | 0.98  | -0.32   | 8              | High           |
| Blaise JE      | 2009 | ICU     | HMUS          | Card | 71         | 50  | NA                | No        | 1h | 0.98  | 8.5     | 8              | High           |
| Brennan JM     | 2007 | Card    | TTE           | Card | 91         | 50  | CHF               | No        | 1h | 0.98  | 10       | 8              | High           |
| Brennan JM     | 2005 | Card    | TTE           | Card | 91         | 50  | CHF               | No        | 1h | 0.98  | 10       | 8              | High           |
| Lee SL         | 2004 | ICU     | TTE           | Card | 150        | 54  | CHF               | No        | No | 0.98  | 8.5     | 8              | High           |
| Lee SL         | 2004 | ICU     | TTE           | Card | 150        | 54  | CHF               | No        | No | 0.98  | 8.5     | 8              | High           |

Table 3: Characteristics of Studies Reporting Non-IVC Parameters

| Authors        | Year | Setting | U/S modality | User | # Patients | Age | Primary diagnosis | Intubated | CS | Delay | R value | Quality Score | Quality Rating |
|----------------|------|---------|---------------|------|------------|-----|-------------------|-----------|----|-------|---------|----------------|----------------|
| Karalabeys S   | 2015 | ER      | POC           | NTU  | 65         | 67  | NA                | No        | No | 0.98  | 10       | 8              | High           |
| Karalabeys S   | 2015 | ER      | POC           | NTU  | 65         | 67  | NA                | No        | No | 0.98  | 10       | 8              | High           |

Note: (1) inspirat (end-inspiration); (2) at subphrenic level (end-inspiration); (3) at supra-ileac level (end-inspiration) (4) end-inspiration; (5) end-inspiration; TTE: Transesophageal Echo; TEE: Transesophageal Echo; HMUS: Hand-Held Ultrasound; POC: POC; CUSP: Custom Ultrasound Pressure system; CS: Cardiac Surgery; RF: Respiratory Failure; NTU: Non-traditional user, defined as Non-Cardio-trained. Cardiac; Cardiologist, or cardiac sonographer. Anholt: Anesthesiologist
Table 4: Characteristics of Studies Reporting Binary IVC Parameters

| Authors | Year | Setting | U/S Modality | User | # Patients | Primary Diagnoses | Intubated | CS | Daily | R Value | Quality Score | Quality Rating |
|---------|------|---------|--------------|------|------------|-------------------|-----------|----|--------|---------|---------------|---------------|
| Trivedi NS | 2004 | TTE | Cardiac | 75 | Yes | 56 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Malhotra S | 2007 | TTE | Cardiac | 50 | Yes | 60 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Patel AI | 2011 | TTE | Cardiac | 100 | Yes | 65 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Mehta A | 2007 | TTE | Cardiac | 50 | Yes | 60 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Khosla S | 2007 | TTE | Cardiac | 50 | Yes | 60 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Patel A | 2011 | TTE | Cardiac | 100 | Yes | 65 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Mehta A | 2007 | TTE | Cardiac | 50 | Yes | 60 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |
| Khosla S | 2007 | TTE | Cardiac | 50 | Yes | 60 | CHF, N/A | No | No | 0.5 | 0.09 | 9 | 10 |

Figures
Figure 1
Flow Diagram
### Figure 2

Forest Plot for Echocardiographic IVC Diameter and Invasive CVP
Figure 3

Forest Plot for Echocardiographic IVC Collapsibility and Invasive CVP
Figure 4

Forest Plot for Echocardiographic E/Ep Ratio and Invasive CVP