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Role of carotid corrected flow time and peak velocity variation in predicting fluid responsiveness: a systematic review and meta-analysis

Running title:
Carotid ultrasound in predicting fluid responsiveness

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Contributions:
DS and MM: the conception and design of the study, acquisition of studies for review
DS, BG and PV: analysis and interpretation of data
BW and TJ: Literature search
DS: drafting the article and revising it critically for important intellectual content, final approval
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Role of carotid corrected flow time and peak velocity variation in predicting fluid responsiveness: a systematic review and meta-analysis

Running title: Carotid ultrasound in predicting fluid responsiveness
Abstract

Background: Over a period, it was realized that dynamic parameters are more suitable as compared to static parameters in predicting fluid responsiveness. Still, most of these techniques require special equipment and are still minimally invasive. So, attention has recently been focused on the use of carotid artery ultrasound parameters like carotid corrected flow time (FTc), and peak velocity variation (ΔV peak).

Methods: We searched PubMed and EMBASE databases for articles studying the diagnostic accuracy of FTc or ΔV peak in predicting fluid responsiveness. Two independent authors performed the search and selected studies published up to May 2022. Studies were analysed based on inclusion and exclusion criteria with Rayyan (Rayyan Systems Inc. 2022).

Results: We selected 10 (n=438) studies which fulfilled the inclusion criteria. Studies were divided in those studying FTc and those involving assessment of ΔV peak. Five studies (six data sets) assessed FTc. The pooled sensitivity of FTc was 0.758, specificity was 0.883. The SROC curve for FTc had an area under the curve (AUC) of 0.9092 with a Q value of 0.8412. Seven studies that calculated ΔVpeak. The pooled sensitivity for ΔVpeak was 0.828, specificity was 0.805. The SROC curve had an AUC of 0.8941 with a Q value of 0.8250.

Conclusions: Our meta-analysis has shown that both carotid corrected flow time and peak velocity variation are useful in predicting fluid responsiveness in anaesthesia and critical care settings with good specificity and sensitivity.

Keywords: Carotid artery; Ultrasonography; Doppler; Echocardiography; Cardiac output; Physiological Monitoring.
Introduction

Adequate preload is a prerequisite for a decent cardiac output and is an important determinant of patient outcome in anaesthesia and critical care. The patient is considered fluid responsive when cardiac output increases in response to increasing preload [1,2]. Initially, we relied on static markers like central venous and pulmonary artery pressure to determine the fluid responsiveness. However, their reliability has been questioned now [3]. Over a period, it was realized that dynamic markers like pulse pressure variation (PPV), stroke volume variation (SVV) etc., are more suitable as compared to static paraments in predicting fluid responsiveness [4].

Still, all these dynamic determinants of fluid responsiveness have some or other limitations. Most of these techniques require special equipment or devices that are expensive. These techniques are still minimally invasive. PPV and SVV require arterial cannulation and/or central line insertion, which has its own complications [5]. Others, like transoesophageal echocardiography (TEE), require the patient to be completely sedated and relaxed. Also, the patient's movements, like turning, might displace the TEE probe. So, attention has recently been focused on the use of carotid artery ultrasound parameters. Of these, carotid corrected flow time (FTc), and peak velocity variation (ΔV peak) are the most studied. FTc is the duration of left ventricular ejection measured on a systolic pulse waveform at the start of the upstroke to the incisural notch [6]. It is corrected to heart rate using Wodey's or Bazett's formula or other similar methods [7]. ΔV peak is the change in the height of carotid pulse upstroke with respiratory variations.

The use of carotid ultrasound derived FTc and ΔV peak has certain advantages. They do not require any specific equipment. It can be studied with bedside using ultrasound in M mode. Further, this technique is completely non-invasive. The ultrasound is performed at the neck level, which remains assessable during most thoracic and abdominal surgeries. Further these parameters are useful even at low tidal volume (TV) of 6 ml/kg or in spontaneously breathing patients, unlike other dynamic
markers (like PPV) which require mechanical ventilation with a TV of at least 8 ml/kg to accurately predict fluid responsiveness. However, the carotid artery derived parameters may not be reliable markers in presence of significant carotid artery stenosis (> 50%). Also, in head and neck surgeries, carotid artery site may be difficult to access.

Various studies have been done to assess the applicability of these parameters in determining fluid responsiveness. These studies have used diverse patient populations, small sample sizes and different cut offs to identify fluid responders. So, the authors did this systematic review and meta-analysis to the ability of carotid ultrasound-derived corrected flow time and/or peak velocity variation in accurately predicting fluid responsiveness.

**Objective**

This systemic review aims to determine the accuracy of corrected flow time (FTc) and peak velocity variation (ΔV peak) in predicting fluid responsiveness in different clinical scenarios in adult patients under anaesthesia or critical care.
Materials and Methods

For our systematic review we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement [8]. We registered our protocol with PROSPERO, I.D. no. CRD42022334313 on 03/06/2022. Since no humans were directly involved in our study, so no institutional ethical clearance was obtained for this study.

Search strategy

For our systemic review, we searched PubMed and Embase databases for clinical trials up to May 2022. The search terms were 'carotid' and 'corrected' and 'flow' and 'time' for the first search and 'carotid' and 'peak' and 'velocity' and 'variation' for the second search.

Study selection

We analysed the studies based on the following inclusion and exclusion criteria.

Inclusion criteria:

1. Must involve adult human patients in anaesthesia and critical care settings.
2. Must involve ultrasound assessment of carotid FTc and/or ∆V peak in relation to fluid responsiveness.
3. Carotid ultrasound assessment should be done by a person well versed with the technique.
4. Had clearly defined criteria to determine fluid responders that involved a cardiac output or stroke volume-based method to assess fluid responsiveness.
5. Should provide a cut-off value, sensitivity, specificity and area under the receiver operating characteristic curve for investigated intervention.

Exclusion criteria:
1. Studies not involving human participants (i.e., animal studies, in vitro studies).
2. Studies involving children
3. Language of article other than English
4. Full text is not available online (conference abstracts etc.).
5. Studies not related to fluid responsiveness.
6. Not involving assessment of corrected flow time (FTc) and/or peak velocity variation (ΔV peak) to assess fluid responsiveness.
7. No clearly defined criteria to determine fluid responders.

Two independent authors (DS and MM) analysed all the abstracts, and if found acceptable full texts of the articles were analysed in a blinded manner to identify articles for inclusion in the meta-analysis. Any disagreement was decided by discussion.

**Data extraction and quality assessment**

Data was extracted to Rayyan (Rayyan Systems Inc. 2022). After removing duplicates and unrelated studies, full texts of the remaining studies were obtained. After selecting studies based on inclusion and exclusion criteria, data from these was presented in a Microsoft Excel sheet (Microsoft Corp., USA). From each study, we extracted data regarding author, title, year of publication, number of participants, population type (mechanical/spontaneous ventilation, medical condition), carotid ultrasound parameter analysed, reference methods to check fluid responsiveness, criteria for fluid responsiveness, number of fluid responders and results. For quality assessment, we used Quality Assessment of Diagnostic Accuracy Studies version 2 [9]. Two independent authors (DS and MM) analysed all the data, and any disagreement was decided by discussion.
Statistical analysis

We divided the studies into two separate groups, i.e., those analysing change in FTc or ΔV peak. For statistical analysis, we used Meta-DiSc® (version 1.4, XI Cochrane Colloquium, Barcelona, Spain). We used the Spearman correlation coefficient of sensitivity and 1-specificity log, to estimate heterogeneity due to the threshold effect. Heterogeneity due to the non-threshold effect was estimated by $I^2$ test. An $I^2$ of less than or equal to 25%, 50% and 75% pointed to low, moderate, and high heterogeneity respectively. In presence of heterogeneity, a random effect model was used for further analysis. From each study, we calculated true positive (TP), false positive (FP), false negative (FN) and true negative (TN) data for the index parameter. Then pooled sensitivity, specificity, negative likelihood ratio and positive likelihood ratio were determined with 95% confidence intervals. For each parameter, a SROC (Summary receiver operating characteristic) curve was generated, and a Q value was calculated. Publication bias was evaluated by Egger's and Begg's test with MedCalc statistical software (version 20.110, MedCalc software ltd.)
Results

Study identification, screening, and inclusion
For the first search, i.e., 'carotid' and 'corrected' and 'flow' and 'time', we got 221 articles on PubMed and 193 results on Embase. For 'carotid' and 'peak' and 'velocity' and 'variation', we got 139 articles on PubMed and 131 articles on Embase. So, in total, we found 684 articles (Figure 1). Out of the 684 articles, 181 duplicate records were removed. The remaining 503 abstracts were screened based on inclusion and exclusion criteria. 470 studies were excluded. Of the remaining 33 studies, 12 were excluded as the full text was not available online, 04 articles were not in the English language, 05 studies had no predefined criteria for fluid responsiveness, and in 02 studies, the assessment was done by novice investigators. So, we were able to include 10 studies for our analysis.

These 10 studies together enrolled 438 patients and involved 478 assessments of fluid responsiveness. Of these, 264 (55.23%) were fluid responsive (Table 1). For ease of analysis, we divided the studies based on the parameter analysed, i.e., FTc or ∆Vpeak. We got five studies (and six data sets), that investigated FTc. One study by Jung S et al.10, used two different formulae to determine FTc. So, it was taken as two different studies, and both data sets (at physiological tidal volume of 6 ml/kg) were included (Supplementary Table 1). Similarly, we got seven studies that evaluated ∆Vpeak (Supplementary Table 2). From sensitivity and specificity data, we calculated true positives, false positives, false negatives, and true negatives for each study (Supplementary Table 1, 2).

Quality assessment
For quality assessment of the included studies, we used QUADAS-2 (Table 2). Most studies did not describe how sample patients were selected, i.e., consecutively or randomly. In a study by Soliman et al. [11] and Ibara-Estrada et al. [12], the criteria for septic shock were not clearly defined. Pace et al. [13] did not explain if both observers performed all the ultrasounds and for how many
examinations the third expert was called. Kimura et al. [14] and Xu et al. [15] did not assess the interobserver reproducibility. Kimura et al. [14] did not exclude patients with significant carotid artery stenosis. In Kimura et al. [14] and Jung et al. [10] study, cardiac output monitoring was done by the Vigileo-FloTrac™ system, which may be affected by changes in systemic vascular resistance. Barjaktarevic et al. [15] used a NICOM™ study to assess the fluid responsiveness. Also, they did not define the type of shock and did not mention excluding patients with carotid artery stenosis.

Meta-analysis of FTc

Five studies (six data sets) assessed FTc. Spearman correlation coefficient was 0.928 with a p-value of 0.008. So, there was a positive correlation between sensitivity and (1-selfspecificity) and heterogeneity due to a threshold effect. The pooled sensitivity of FTc was 0.758 [95% confidence interval (CI): 0.684 -0.823] with an I² value of 44.6% (Figure 2A). That was suggestive of low to moderate heterogeneity due to the non-threshold effect. Pooled specificity was 0.883 (95% CI: 0.818 - 0.930) with an I² value of 2.8% (Figure 2B) suggesting low heterogeneity. So, we used a random effect model for our analysis. Pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) was 5.769 (95% CI: 3.676 - 9.054), 0.297 (95% CI: 0.226 - 0.390), 28.130 (95% CI: 13.803 - 57.327) respectively. I² value for PLR, NLR, DOR was 0.0%. The SROC curve for FTc had an area under the curve (AUC) of 0.9092 with a Q value of 0.8412 (Figure 3A). For publication bias, we calculated standard error using 95% confidence intervals and used these along with AUC values for assessment. There was no publication bias when assessed by Egger’s (p value 0.4217) and Begg’s test (p value 0.3476).

Meta-analysis of ∆Vpeak

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Seven studies that calculated $\Delta V_{\text{peak}}$, were considered for analysis. Spearman correlation coefficient was 0.464 (p-value= 0.294), suggestive of the inability to reject the null hypothesis and no threshold effect. The pooled sensitivity for $\Delta V_{\text{peak}}$ was 0.828 (95% CI: 0.763 - 0.881) with an $I^2$ value of 0 % (Figure 4A). Pooled specificity was 0.805 (95% CI: 0.736 - 0.864), and an $I^2$ value of 50.5%, suggesting moderate heterogeneity (Figure 4B). So, in this case also the random effect model was applied. Pooled PLR, NLR and DOR was 4.128 (95% CI: 2.588 - 6.586), 0.220 (95% CI: 0.158 - 0.308), 20.847 (95% CI: 11.436 - 38.004) respectively. $I^2$ value for PLR, NLR, DOR was 42.7%, 0%, and 0% respectively. The SROC curve had an AUC of 0.8941 with a Q value of 0.8250 (Figure 3B).

The study by Pace R et al [13] only gave a p value (0.001) with AUC and not standard error. We calculated the standard error for p value from an article by Altman DG et al. [16] The standard error came to be very low, of 0.0221 and on analysis showed publication bias by Edger's test (p value 0.0061) but not on Begg's test (p value 0.0985). However, since the actual standard error was not known, on the exclusion of that study, both Edger's (p value 0.1379) and Begg's test (p value 0.3476) showed no publication bias.

**Subgroup analysis**

Studies examining FTc provided either an absolute value [10,17-18] or a percentage change [14] or absolute change [15] in FTc, as a cut off. So, we performed a subgroup analysis of studies analysing absolute value of FTc. Spearman correlation coefficient was 0.8 (p value = 0.200). The pooled sensitivity was 0.76 [95% CI: 0.66 -0.85] with an $I^2$ value of 0.0%. Pooled specificity was 0.87 (95% CI: 0.80 - 0.930) with an $I^2$ value of 0.0%. Pooled PLR, NLR and DOR was 5.57 (95% CI: 3.676 - 9.17), 0.28 (95% CI: 0.19 - 0.42), 23.60 (95% CI: 10.72 - 51.9) respectively. $I^2$ value for PLR, NLR, DOR was 0.0%. The SROC curve for FTc subgroup had an AUC of 0.8902 with a Q value of 0.8209.
Discussion

This study found that carotid ultrasound derived FTc and $\Delta V$ peak could be useful in predicting fluid responsiveness in anaesthesia and critical care patients. Though mild to moderate heterogeneity was noted based on $I^2$ values, both the parameters were shown to predict fluid responsiveness with good sensitivity and specificity. A subgroup analysis was also performed with studies using an absolute cut-off value of FTc. It was found to predict fluid responsiveness with sensitivity of 0.76 [95% CI: 0.66 - 0.85] and specificity of 0.87 (95% CI: 0.80 - 0.930), $I^2$ value of 0.0%.

Assessment of fluid responsiveness is of great value in critically ill patients and patients undergoing major surgical procedures. Though we have gradually shifted from static parameters (like central venous pressure, pulmonary capillary wedge pressure) to dynamic parameters (like pulse pressure variation, stroke volume variations, inferior vena-cava collapsibility etc.), there are certain limitations to the use of these techniques in clinical practice [19]. So, in recent times there has been considerable interest in using carotid ultrasound for predicting fluid responsiveness [7,10-15, 17,18, 20-22]. These papers studied carotid corrected flow time [7, 10, 14, 15, 17, 18, 22] changes in peak velocity [11-13, 17, 18, 20, 21] or carotid blood flow [22] to predict fluid responsiveness. Since most of the available studies used carotid corrected flow time or changes in peak velocity, we decided to use those two parameters for our systematic review and meta-analysis.

A study by Abbasi et al. [23] showed that novice sonologists were unable to determine fluid responsiveness using based on changes in FTc or carotid blood flow. Another study [24] showed that $\Delta V$peak was also unable to predict fluid responsiveness when used by novice sonologists. So, some level of expertise might be required to correctly evaluate the carotid ultrasound derived FTc and $\Delta V$peak to determine fluid responsiveness. Therefore, in our meta-analysis we included only studies which had some experts for performing and interpreting carotid ultrasound findings.
Studies using carotid corrected flow time have used either Bazett's [10,18] or Wodey's [10, 14-15, 17] formulas for assessing FTc. Bazett's formula is calculated by dividing the flow time with square root of cycle time while Wodey's formula gives FTc as measured flow time + [1.25 (heart rate – 60]. Wodey’s formula had been shown to be better than Bazett’s formula as the latter was still affected by heart rate in certain situations [25]. However, most of the studies calculating FTc by either formula had found it to be reliable indicator of fluid responsiveness. Jung et al [10] had used both the formulas (FTcB: Bazett’s, FTcW: Wodey’s) for calculating FTc in mechanically ventilated patients and found both to predict fluid responsiveness with high sensitivity (FTcB: 68.8 (41.3-89.0) and FTcW: 87.5 (61.7-98.4) and specificity (FTcB: 95.0 (75.1-99.9) and FTcW: 80.0 (56.3-94.3) at 6 mL/kg tidal volume. We have included all the studies calculating FTc by either Bazett’s or Wodey’s formula to predict fluid responsiveness. We found a pooled sensitivity of 0.758 and a pooled specificity of 0.883 with moderate to low heterogeneity. The SROC curve had an AUC of 0.9092 with a Q value of 0.8412, which suggests that, as per available evidence, FTc can be a good predictor of fluid responsiveness in both mechanically ventilated [10,14] and spontaneously breathing [17,18] patients.

Further, studies had used either an absolute value of FTc or a change in FTc after fluid challenge, as mentioned above. So, we have performed a subgroup analysis including only studies that had used an absolute value of FTc as a cut-off. In the subgroup analysis, we got a pooled sensitivity of 0.76 and specificity of 0.87 with I² value of 0.0 %. That showed decent sensitivity and specificity with no heterogeneity. Subgroup analysis with either absolute or percentage change of FTc could not be done as one study was there in each case.

We also analysed studies using ΔVpeak for assessing fluid responsiveness [11-13,17,18,20,21]. All the studies included in our analysis had used a percentage change in ΔVpeak, though the cut off values varied among the studies. Cut-off for ΔVpeak was 9.1% n studies by Xu et al. [17] and Kim et al. [18] and as high as 26% in the study by Soliman et al. [11]. We calculated the pooled sensitivity of 0.828
and pooled specificity of 0.805 (95% CI: 0.736 - 0.864), with no to moderate heterogeneity. Our findings suggested that ΔVpeak can be a good predictor for assessing fluid responsiveness. Similar findings were in a meta-analysis by Yao et al [26]. They had used four studies assessing carotid ΔVpeak [12,21,27 28] in their analysis. They found that ΔVpeak from both carotid and brachial artery can be used to predict fluid responsiveness. However, carotid ΔVpeak had more diagnostic value than one from brachial artery.

A systematic review by Beier et al. [29] examined the role of carotid ultrasound in predicting fluid responsiveness among adults. The authors could not do a meta-analysis due to considerable heterogeneity among studies. They found that carotid corrected flow time and peak velocity variation were the most frequently assessed parameters, with the latter being the most well-defined parameter reported at that time. They further concluded that carotid ultrasound derived parameters could be useful in predicting fluid responsiveness in conjunction with clinical data. We have also found that both FTc and ΔVpeak could predict fluid responsiveness.

**Limitations**

Though we took great care in examining all available studies, our meta-analysis had some limitations. Firstly, we included studies in the English language only. That resulted in the exclusion of certain studies [27,28] that could have provided valuable data for our analysis. However, this was done to prevent misinterpretation of findings presented in those studies. Secondly, only two carotid artery parameters, i.e., FTc and ΔVpeak were analysed. Our analysis did not consider other parameters like carotid blood flow and carotid artery diameter. That was done because studies testing carotid blood flow and carotid artery diameter for predicting fluid responsiveness were limited. So, we restricted our analysis to FTc and ΔVpeak only. Lastly, our findings showed mild to moderate heterogeneity in both FTc and ΔVpeak. The absence of a uniform cut-off value and the use of different criteria for
assessing the same variable further added to the problem. So, further studies are required to improve the diagnostic value of carotid ultrasound in defining fluid responsiveness.

**Conclusion**

Our meta-analysis has shown that both carotid corrected flow time and peak velocity variation can be useful in predicting fluid responsiveness in anaesthesia and critical care settings with good specificity and sensitivity. However, there was lack of a uniform cut off value for both the parameters and so, further studies are required to establish more consistent cut-off values and improve both parameters' diagnostic accuracy.
References


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Table 2: Quality assessment with QUADAS-2

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<td>Song</td>
<td>2014</td>
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</table>

? High: May be high
**Fig. 1.** PRISMA flow diagram.

* PubMed = 221 + 139; Embase = 193 + 131. So, in total we found 684 articles.

**No automation tools were used.**
Fig. 2. Pooled sensitivity (A) and specificity (B) of carotid corrected flow time in diagnosing fluid responsiveness.
Fig. 3. SROC curve for carotid corrected flow time (A) and peak velocity variation (B).
Fig. 4. Pooled sensitivity (A) and specificity (B) of carotid peak velocity variation in diagnosing fluid responsiveness.