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Assessment of corrected flow time in carotid artery via point-of-care ultrasonography: Reference values and the influential factors

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ABSTRACT

Objective: Assessment of Corrected Flow Time (FTc) in carotid artery has been suggested recently as a measure of intravascular volume status. This study aimed to determine the reference values of FTc in carotid artery in a normal population.

Methods: A total number of 142 healthy volunteers (73 females and 69 males) with a mean age of 36.65 ± 10.52 years were included.

Results: The mean FTc in carotid artery was 325.18 ± 22.15 $ms^{0.5}$. The mean value of FTc differed significantly between females and males both before and after passive leg raise (PLR) (330.18 ± 21.61 $ms^{0.5}$ vs. 319.88 ± 21.62, $P = 0.005$ before PLR, and 336.89 ± 22.95 $ms^{0.5}$ vs. 326.51 ± 21.21, $P = 0.006$ after PLR).

Conclusion: This study would potentially pave the way to determine clinically significant cutoff points in order to assess the diagnostic accuracy of FTc in predicting intravascular volume status and fluid therapy responsiveness.

1. Introduction

There has been an ever-growing interest in point-of-care ultrasonography due to its potential to provide repeated real-time assessment of the same measure at bedside, which is non-invasive, and easy to learn. Several non-invasive modalities to assess volume status via ultrasonography have been introduced [1]. One of the most accepted modalities is the the measurement of corrected flow time (FTc) in thoracic aorta via a non-imaging esophageal Doppler probe having proven to be a reliable predictor of volume status in several studies [2]. FTc is calculated by measuring systolic flow time with the correction of heart rate (HR) (flow time/√cycle time, Bazett's formula) [3] and is known to be proportional to preload and cardiac inotropy as the indices of volume status and cardiac function respectively [4,5]. Even though the measurement of thoracic aorta FTc is limited due to technical difficulties and the need for expert operators, Blehar et al. showed that FTc can be measured in carotid artery with ease and reliability [6]. Moreover, changes in carotid FTc are correlated with both increase [7] and decrease [1,8] in intravascular volumes.

It has recently been shown that there is a direct and significant correlation between FTc in carotid artery and the loss of intravascular volume in a hemodialysis model of volume removal [8]. However, since the measurement of FTc in carotid artery via ultrasonography is a new concept, there is a need to define its normal values. This could contribute to the accurate interpretation of the measurement and facilitate further efforts to define cutoff points needed for the assessment of the diagnostic accuracy of this ultrasound modality. Understanding of these normal values could also make possible the implantation of this new modality in the clinical setting. Hence as the primary outcome, the current study aimed to investigate the normal ranges of FTc and its probable influential factors in healthy adult volunteers. Moreover, since it has been shown that passive leg raise (PLR) with the subject at supine position increases venous return and preload by about 150 ml [9], we measured pre- and post-PLR FTc to investigate, as a secondary outcome, if such small amounts of change in intravascular volume are detectable by FTc.

2. Materials and methods

2.1. Study design and setting

The current cross-sectional study aiming to determine the normal range of FTc in the carotid artery in the normal population was conducted between August and September 2015 at the emergency department of a university-affiliated hospital. The ethics committee of the university reviewed and approved the process of this study. The aim and process of

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the study were explained to all participants and they were requested to submit signed informed consents. Prior to the commencement of the study, a pilot study was performed on 20 patients (13 male and 7 female) to determine the necessary values for the calculation of minimum sample size and the reliability of measurements. These patients were not included in the current study.

2.2. Participants

Healthy individuals aged 18 or higher who were selected randomly from the hospital employee list were included. Individuals who were unwilling to participate, showed signs and symptoms of dehydration (tachycardia, low blood pressure, dry mouth or skin, tiredness, extreme thirst, sunken eyes, and altered mental status), had a previous medical history of hypertension, cardiovascular or renal disorders, diabetes mellitus, cardiovascular events, blood transfusion 3 months prior to the study or a positive drug history of vasopressor agents were excluded. We also excluded cases where the assessment of FTc encountered technical difficulties, mainly the presence of atherosclerotic plaques.

2.3. Outcomes and data collection

The primary outcome of the study was the measurement of FTc in the carotid artery, as well as the probable associations between subjects' characteristics and FTc. The secondary outcome was the difference between pre- and post-PLR FTc. Prior to measurements, subjects underwent a thorough past medical and drug history-taking, and a brief physical examination. Then, patients were asked to remain in a comfortable position of their own choice for several minutes before the measurement of HR, BP and FTc. All measurements were then performed in supine position. In order to make subjects more comfortable, measurements were performed in the subjects' own workplaces, investigators did not wear white coats, and a female nurse was present as chaperone during the evaluation of female subjects.

2.4. Ultrasonography modality

A portable ultrasound device (SonoScape S6, SonoScape, Shenzhen, China) was deployed with a linear array ultrasound transducer, model L743, with a characteristic frequency range of 5–10 MHz. Measurement of FTc was performed before and after a PLR of 45 degrees for 60 s [10] with patients in supine position, with no object placed beneath their heads and with their beds at the level of horizon. In all cases, the ultrasound evaluation of FTc was performed by assessing right common carotid artery at the level of the lower border of thyroid cartilage as previously described by Blehar et al. [7], with an angle of insonation between 60 and 72 degrees. Real-time measurement of FTc was performed by an attending emergency medicine physician. All images were saved and measurements were performed again in a blind fashion using electronic calipers by the first operator as well as another attending physician of emergency medicine in order to evaluate intra- and inter-observer reliability of calculating FTc via ultrasonography. Since the differences in the measurements were below 5 $ms^{0.5}$, which is below the precision level of the measurements (10 $ms^{0.5}$), all reported results are those observed by the first operator in real-time.

Digital recording was performed on long axis B-mode imaging of carotid arteries by spectral Doppler waveform tracing with the correction of angle. The ultrasound parameters, such as Nyquist limit and wall filter were set at the default setting of the device. It should be noted that none of these factors affect the duration of the cycle, and hence the measurement of FTc. The measurement of FTc in all cases was performed with ease and no underlying condition, such as calcification, which could potentially affect the observed measurements. FTc was calculated as flow time/$\sqrt{}$cycle time (Fig. 1) by assessing a single cycle after several consecutive cycles were stable and of acceptable quality [4,7]. Considering this equation, FTc has units of milliseconds $(ms)^{0.5}$ which to the best of our knowledge has been mentioned as ms either by mistake or for simplification in all previous studies.

2.5. Statistical analysis

To investigate normal values of FTc, a minimum sample size of 24 cases was calculated with an alpha of 0.05, a standard deviation (SD) of 25 $ms^{0.5}$ obtained from a pilot study on 20 cases, and an absolute error or precision of 10 $ms^{0.5}$[11]. For the investigation of probable differences between pre- and post-PLR FTc, a minimum sample size of 49 cases was calculated with an alpha of 0.05 and a power of 0.8, an SD of 25 $ms^{0.5}$, and an absolute error or precision of 10 $ms^{0.5}$ [12]. Using *interclass correlation coefficient* test, Cronbach's alpha of 0.99 and 0.98 were calculated for intra- and inter-observer reliabilities respectively. Data were analyzed using *statistical package* for the Social Sciences (SPSS) for Windows, Version 17.0. (SPSS Inc., Chicago, USA). In order to examine the normality of distribution of quantitative variables, normal Q-Q Plots and Shapiro-Wilk test of normality were deployed. Quantitative variables are presented as mean ± SD (95% confidence interval, 95% CI). Categorical variables are presented as numbers (%). Independent *t*-test was used to examine the statistical significance of the differences observed in quantitative variables between two groups of males and females, and paired *t*-test for pre- and post-PLR quantitative variables. Pearson Correlation test was deployed to investigate the probable association between FTc and quantitative variables of age, HR and MAP. A forward selection model of multiple linear regression analysis was performed to investigate the probable independent factors that could significantly predict FTc. The level of statistical significance for *P* value was considered <0.05.

3. Results

3.1. Participants' characteristics

A total number of 152 cases, including 78 females (51.3%) and 74 males (48.7%), were screened for eligibility to be included in the study. Of these, 6 cases (3.9%), including 4 female and 2 male cases, were excluded due to their unwillingness to participate as well as 4 cases (2.6%), including 1 female and 3 male cases, on account of the presence of atherosclerotic plaques in carotid artery. None of the remaining subjects were excluded due to the presence of an underlying disease or drug history of agents that could possibly affect the blood pressure or other measures of the cardiovascular system. At last, a total number of 142 individuals, including 73 females, (51.4%) and 69 males, (48.6%) were included in the final data analysis. The mean age of the patients was 36.65 ± 10.52 years. Participants' demographic data are presented in Table 1.

3.2. Normal range of FTc

The mean FTc in carotid artery was 325.18 ± 22.15 (95% CI = 321.51 to 328.82) $ms^{0.5}$ before PLR and 331.85 ± 22.65 (95% CI = 328.37 to 336.05) $ms^{0.5}$ after PLR ($P < 0.001$). The FTc range for 2-sigma, 4-sigma, and 6-sigma were 309.20–345.50, 286.55–377.15, and 263.90–399.80 respectively, which included 60.6%, 95.1%, and 99.3% of individuals. After PLR, FTc increased in 103 cases (67.8%). Table 2 presents the distribution of FTc. The mean changes in FTc after PLR were 6.66 ± 19.89 (95% CI = 3.41 to 10.11) $ms^{0.5}$ or in other words, FTc changed by a mean of 2.2% ± 6.6% (95% CI = 1.2% to 3.2%). In our pilot study, which its results are not included in the current study, we did also measure FTc in both carotids, in 12 out of the 20 cases, both before and after PLR, in order to investigate the possibility of any difference between FTc measurements in the right or left side. There was no statistically significant difference in the mean FTc in right vs. left carotid arteries (313.5 ± 15.05 [95% CI = 305.34 to 321.75] $ms^{0.5}$ vs. 313.25 ± 16.31 [95% CI = 304.67 to 322.67] $ms^{0.5}$, $P = 0.676$, for the