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ASSESSMENT OF INTER-OBSERVER VARIABILITY, CARDIAC CYCLE AND GENDER INFLUENCE ON CAROTID INTIMA-MEDIA THICKNESS MEASURED USING ULTRASOUND IN HEALTHY ADULTS

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ABSTRACT

Background: Carotid intima-media thickness (cIMT) is a widely utilized non-invasive marker for assessing early atherosclerosis and cardiovascular risk. cIMT is commonly measured using B-mode ultrasound; however, several factors can introduce variability, including the cardiac cycle phase (systole vs. diastole) and inter-observer differences. This study aims to evaluate the inter-observer variability in cIMT measurements and to determine differences in cIMT across genders, cardiac cycle phases, and between contralateral carotid arteries.

Methods: cIMT measurements were obtained using B-mode ultrasound from 50 healthy adults (25 males, 25 females) bilaterally during both systolic and diastolic phases. Two independent operators performed the measurements to assess inter-observer variability using the intraclass correlation coefficient (ICC) and Bland-Altman analysis. Gender differences, cardiac cycle phase effects, and differences between contralateral sides were analyzed using paired t-tests.

Results: A total of 200 cIMT measurements were analyzed. Inter-observer agreement was moderate (ICC = 0.68) with a small bias (-0.02 ± 0.05 mm). Males exhibited significantly higher cIMT than females (mean difference = 0.08 mm, 95% CI 0.07–0.10, $p < 0.001$). No significant differences were found in cIMT between systolic and diastolic phases ($p = 0.51$) or between right and left carotid arteries ($p = 0.70$).

Conclusion: The study demonstrates moderate inter-observer variability in cIMT measurements using B-mode ultrasound. Gender significantly influences cIMT, with males having thicker cIMT compared to females. However, no significant differences were observed between cardiac cycle phases or between contralateral sides of the carotid arteries.

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1. INTRODUCTION

Carotid intima-media thickness (cIMT) is an established surrogate marker for atherosclerosis and cardiovascular risk prediction, widely used in clinical and research settings [1]. Measuring the thickness of the carotid artery wall, specifically the combined intima and media layers, provides a non-invasive method to detect early-stage arterial changes that may precede clinical manifestations of cardiovascular diseases such as myocardial infarction and stroke [2]. In addition , reproducibility of cIMT measurements is crucial, with best results obtained when combining values from both carotid arteries and multiple cardiac cycles [3, 4]. Measurement variability is lowest in the common carotid artery, and consensus on assessment methods is needed [5].

The relationship between cIMT and cardiovascular disease has been well-documented, with increased thickness linked to higher risks of coronary artery disease and cerebrovascular events [6]. However, the clinical utility of cIMT measurements depends heavily on the consistency and accuracy of ultrasound imaging techniques. Various factors, such as operator experience, ultrasound settings, and patient-specific characteristics (e.g., age, gender, and cardiovascular risk factors), can introduce variability into cIMT measurements. Moreover, cardiac cycle phases (systole vs. diastole) and gender differences may also lead to variations in the cIMT [7]. CIMT measurements are most reliable when using automatic or semi-automatic reading methods over a one-centimeter segment, with structured training for sonographers and readers [8].

This study seeks to evaluate the inter-observer variability of cIMT measurements in healthy individual, assessing the impact of the cardiac cycle on these measurements, and investigating gender differences. As the previous data in a healthy adult population are very limited in addressing the inter-observer measurement variations [9]. However, there are various factors associated with the changes in the cIMT and the underlying causes of these association remain unclear [10, 11].

Thus, the findings from this study will contribute to the growing body of literature on cIMT as a diagnostic tool and may inform future protocols for more standardized measurements.

2. METHODS

2.1 Study Design

The prospective observational was approved by the Biomedical Ethics Research Committee of the Faculty of Medicine at King Abdulaziz University . Subject were screened for eligibility and informed written consent was obtained from all participants.

2.2 Eligibility Criteria

Young subjects around age of 20 were selected based on normal health, and lack of cardiovascular conditions or risk factors. These subject were invited through posting an announcement. Sample size were determined according to the practical consideration and availability of participants.

2.3 Technique of Measurement

Ultrasound imaging was performed using a high-frequency linear array transducer with a frequency range of (9-5 MHz) and the ultrasound machine (Philips

EPIQ7) was used for doing the procedure. The depth of acquisition is typically set between 1 to 4 cm which allows for optimal visualization of the common carotid artery, that is relatively superficial and lies just a few centimeters below the skin surface. Approaching the cIMt has been done when the subject is in supine position with their neck extended and supported with a pillow underneath. Each participant underwent bilateral cIMT measurements of the common carotid arteries (CCA) in longitudinal view. The images were obtained using B-mode ultrasound, optimized for maximum resolution, with the focus set on the posterior wall of the CCA 1-2 cm proximal to the carotid bifurcation (Figure 1). The posterior wall was measured in systole and diastole. Two sonographers' operators who have work experience more than three years were independently performed the measurements manually using ImageJ software to assess inter-observer variability.

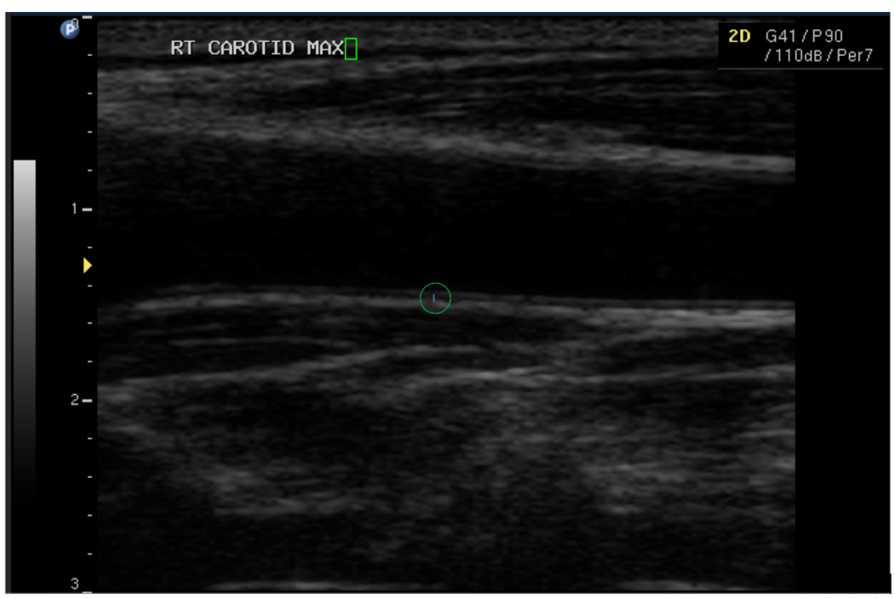

Figure 1 CIMTmeasurement using B-mode ultrasound

2.4 Statistical Analysis

Inter-observer reproducibility and limit of agreement in measuring cIMT between two-operators were assessed using Intraclass correlation coefficient (ICC) and Bland-Altman plot. The ICC estimate values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively [12]. However, intra-operator testing was not performed in this study and will be consider in the design of future studies. T-test was used to determine differences in cIMT between genders (i.e. males vs females), cardiac cycles (i.e. systole vs diastole), and contralateral sides (i.e. right vs left). The level of significance was set at < 0.05. Statistical analysis was performed using IBM SPSS Statistics version 21 (Armonk, NY: IBM Corp) and GraphPad PRISM 7 (La Jolla, CA, USA) were used to create the figures.

3. RESULTS

A total of 200 cIMT measurements were obtained from 50 healthy subjects (males n=25, females n=25) bilaterally in systole and diastole. The age, weight, height, body mass index, blood pressure and heart rate were: 21.04±1.79 years, 65.15.1±18.56 kg, 1.65±0.1 m, 23.58±5.37, systolic blood pressure 127.14±11.49 mmHg and diastolic blood pressure 80.96±9.65 mmHg and 84.8±19 pbm, respectively (Table 1). The mean cIMT measurement is provided in (Table 2).

Participant characteristics are summarized in Table 1.

Table 1 Participant characteristics

Characteristics	**Descriptive statistics (mean±SD)**			**Difference of probability**
	All (n = 50)	Male (n =25)	Female (n = 25)	
Age (years)	21.04±1.79	20.60±2.04	21.48±1.41	p=0.08
Height (m)	1.65±1.08	1.74±0.62	1.56±0.63	p<0.001
Weight (kg)	65.15±18.5	73.26±19.49	57.03±13.6	p=0.01
Body mass index	23.58±5.37	23.96±5.51	23.21±5.31	p=0.62
Systolic blood pressure (mmHg)	127.14±11.49	129.84±10.08	124.44±12.35	p=0.09
Diastolic blood pressure (mmHg)	80.96±9.65	79.24±10.48	82.68±8.61	p=0.21
Heart rate (ppm)	84.7±19.07	76.28±21.56	93.12±11.40	p=0.001

Table 2 cIMT measurement

cIMT	Descriptive statistics (mean±SD)		
	All (n = 50)	Male (n =25)	Female (n = 25)
RT cIMT in Systole	0.43±0.064	0.47±0.057	0.39±0.041
RT cIMT in Diastole	0.45±0.067	0.48±0.061	0.41±0.050
LT cIMT in Systole	0.43±0.060	0.46±0.054	0.39±0.040
LT cIMT in Diastole	0.44±0.064	0.48±0.056	0.41±0.051

3.1 Inter-operator reproducibility

Inter-operator agreement in measuring cIMT (total number (n)=400, n=200 per operator) was moderate with ICC values of 0.68 (95% confidence interval (CI) 0.50 – 0.79, p<0.001, Figure 2A). Additionally, a linear regression was created to show the variability and distribution of cIMT measured by the operators. Bias in measurements was -0.02±0.05 mm (limit of agreement (LoA) -0.14 – 0.08, Figure 2B). The ultrasound measurement results for each operator with columns for bias and limits of agreement (upper and lower) is provided in (Table 3).

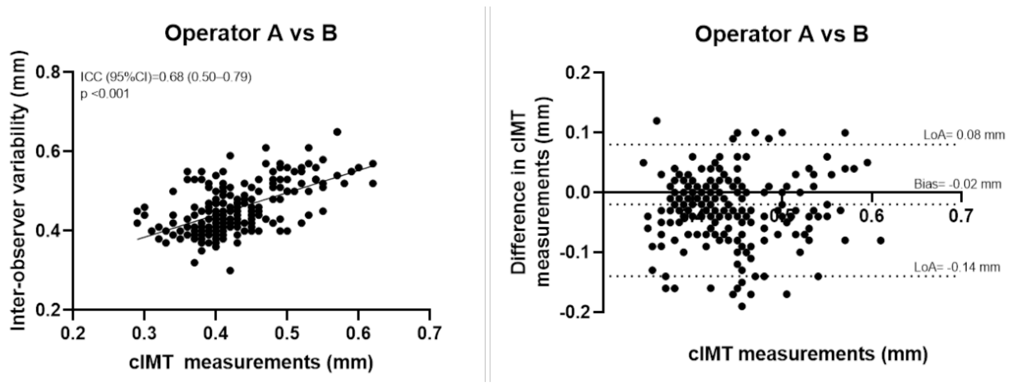

Figure 2 **Inter-operatorand Bland-Altman agreement for cIMT measurements.** Intraclasscorrelation and linear regression of cIMT measurements (A).Bland-Altman assessment of cIMT measurements between operators (B)(total number of cIMT measurements (n)= 400). ICC: Intraclasscorrelation; CI: confidence interval; LOA = limit of agreement.

3.2 Gender, cardiac cycle, and contralateral variations in cIMT

Males had significantly higher cIMT compared to females, with a mean difference of +0.08 mm (95% confident interval (CI) 0.07–0.10, p<0.001, n=200, Figure 3A). There was no significant difference in cIMT measured at different cardiac cycles (mean difference (MD) -0.005 mm, 95% CI -0.02-0.01, p=0.51, n=200, Figure 3B) nor between right and left (MD 0.003 mm, 95% CI -0.01 - 0.02, p=0.70, n=200, Figure 3C).

Table 3 Table of bias and limit of agreement (upper and lower) for measurements between operators

Measurement	Bias	Limit of agreement	
		Upper	Lower
RT B-mode cIMT in Systole	-0.0232	0.092344706	-0.138744706
RT B-mode cIMT in Diastole	-0.0324	0.083152849	-0.147952849
LT B-mode cIMT in Systole	-0.0174	0.090667668	-0.125467668
LT B-mode cIMT in Diastole	-0.0384	0.077815854	-0.154615854

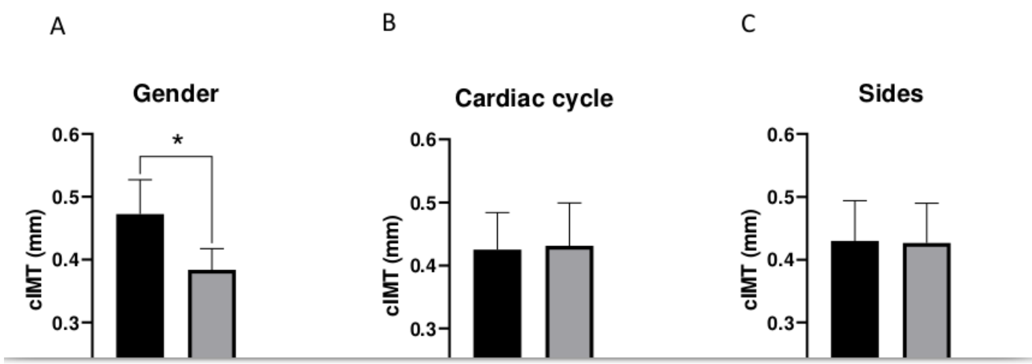

Figure 3 **Differencein cIMT between gender (A), cardiac cycle (B), and contralateralsides (C) (mean±SD).** *p≤ 0.05 using independent t-test.

4. DISCUSSION

This study provides insights into the measurement variability of carotid intima-media thickness (cIMT) and the factors gender, cardiac cycle phases, contralateral sides, and inter-observer differences.

Inter-observer variability is a critical factor when using ultrasound-based measurements in clinical practice. The moderate ICC value of 0.68 suggests that while there is reasonable agreement between observers, some variability persists [12]. The Bland-Altman analysis indicated a small bias of -0.02 mm, demonstrating that inter-observer differences are minimal but should still be addressed to improve reproducibility [13]. This finding is consistent with previous studies that have identified operator experience, transducer positioning, and manual measurement techniques as sources of variability [14]. Automated measurement tools may help reduce this variability by eliminating subjective interpretation [15]. Thus, implementing automated measurement systems and providing thorough operator training can minimize variability and enhance the reliability of cIMT as a diagnostic tool. Salonen et al. performed a study on the measurement of cIMT using inter- and intra- observer variability testing [16]. The study shows that the variations between observers account for most of the measurement variability in ultrasonographic B-mode

IMT measurements, while within-observer variability over time seems to be proportionately small. Consistently, our study focused in the assessment of the inter-observer variability and showed similar finding.

Males in the study exhibited significantly thicker cIMT than females. Research consistently shows that males reveal significantly thicker carotid intima-media thickness (cIMT) compared to females.

The mean difference of 0.08 mm aligns with existing literatures, which attributes these gender differences to variations in hormonal profiles and cardiovascular risk factors [17, 18]. Wu et al. [18] found a mean difference of 0.036 mm, while Tan et al. [19] and Mazurek et al. [20] are also reported thicker cIMT in males. Age, BMI, and LDL/HDL ratio were identified as common factors affecting cIMT in both sexes, with stronger effects in males.

The observed gender differences underscore the need for sex-specific normative values when interpreting cIMT measurements in clinical settings, highlighting that clinicians should consider sex-based reference ranges when interpreting cIMT results. This is particularly important in preventive cardiology, where early detection of subclinical atherosclerosis can guide lifestyle modifications and therapeutic interventions.

This study found no statistically significant differences in cIMT between systole and diastole, despite theoretical expectations that arterial wall tension might fluctuate throughout the cardiac cycle with the greatest variation observed in children [21, 22]. This finding is consistent with earlier research, which suggests that cIMT remains relatively stable across cardiac cycles in healthy individuals [23]. However, in populations with cardiovascular disease, where arterial stiffness and compliance are reduced, the impact of the cardiac cycle on cIMT may be more pronounced [24].

Similarly, no significant differences were found in cIMT between the right and left carotid arteries. This aligns with previous research suggesting that cIMT measurements from the left and right sides are generally comparable in healthy populations [25]. While some studies have suggested that the left carotid artery may show slightly thicker cIMT due to anatomical and hemodynamic factors [26]. Interestingly, a study found that The reproducibility of CIMT measurements in young adults in good health is highest when values from the maximal and minimal arterial diameters and/or both carotid arteries are combined [3]. Our results did not reveal any notable discrepancy between the two sides in this healthy cohort. This finding supports the practice of measuring cIMT on either side of the carotid artery for clinical and research purposes, although in patients with cardiovascular disease or increased risk, differences between the sides may become more pronounced due to localized atherosclerotic development or vascular changes.

These findings suggest that cIMT is a complex measure influenced by various factors and should be interpreted cautiously in clinical settings. As well as individual experience or technique can impact the measurement of cIMT . Thus, clinicians should be aware of this variability, as it might affect the reproducibility and accuracy of cIMT as a diagnostic tool.

Therefore, to make the measurement of cIMT more reliable, it is recommended to conduct further research in higher-risk populations to clarify the clinical relevance of both cardiac cycle-related variability and potential side-specific differences in cIMT. Additionally, a standardized approach could enhance measurement consistency, which is important when utilizing cIMT as a cardiovascular risk indicator. Also, using a gender-specific reference ranges for cIMT to improve diagnostic accuracy, are all crucial in such study. Lastly, the analysis method (i.e. manual vs automated)that is used when measuring the cIMT should be taking into consideration.

5. CONCLUSION

CIMT measurements using B-mode ultrasound showed moderate inter-observer variability was observed, with not show significant effects of cardiac cycle or contralateral carotid arteries on cIMT measurements. cIMT is significantly influenced by gender highlighting the need for gender-specific reference ranges to ensure accurate use of cIMT as a diagnostic tool in clinical practice. Future studies should explore these factors in populations with cardiovascular risk to further understand the cIMT's role in early atherosclerosis detection.

6. CONFLICTS OF INTEREST

All authors declare no conflict of interest.

7. ETHICAL APPROVAL

This study was approved by the Biomedical Ethics Research Committee of the Faculty of Medicine at King Abdulaziz University (reference no: 490-21)

8. FUNDING

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