Can single cIMT measurement during echocardiography affect further investigation decision for coronary artery disease?

Ekokardiyografi esnasında tek cIMT ölçümü koroner arter hastalığı yönünden daha ileri araştırma kararını etkiler mi?

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Abstract

Objective: This study was aimed to evaluate whether there is any potential role of the measurement of the carotid intima-media thickness (cIMT) in patients with suspected coronary artery disease (CAD) during the echocardiography session on decision-making to refer patients for further diagnostic evaluation such as gated myocardial perfusion imaging (gMPI).

Methods: cIMT of 199 consecutive patients was measured during the echocardiography session and all patients underwent gMPI. According to gMPI results, patients were divided into two groups as CAD and normal groups and according to cIMT measurements patients were divided into four subgroups.

Results: Although, there was a good correlation between the age and cIMT values of the patients (r=0.546, p<0.001), the correlation between the summed stress scores and the age of the patients was very weak (r=0.142, p=0.045) and the correlation between the summed stress scores and the cIMT values was very weak (r=0.107, p=0.131). The cIMT measurements of the CAD group (0.74±0.17 mm) were significantly higher than those of the normal group (0.67±0.16 mm) (p=0.012), but after the age correction, the significance between the cIMT measurements of the CAD and the normal groups was not found (p=0.131). Besides, the relationship between the categorical cIMT values of both the CAD and the normal groups was insignificant (p=0.059) and the correlation between the increasing cIMT values and the presence of detectable CAD was also very weak (r=0.187, p=0.08).

Conclusion: cIMT can predict occurrence of cardiovascular events in subjects, but single cIMT measurement during echocardiographic examination does not seem to have potential role on decision making for further investigation in patients with suspected CAD.
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Key words: Carotid intima-media thickness, gated myocardial perfusion imaging, atherosclerosis, ultrasonography

Özet

Amaç: Çalışmanın amacı, şüpheli koroner arter hastalığı (KAH) olan olguların ekokardiyografi oturumu esnasında ölçülen karotis intima-mediya kalınlığının (kIMK), gated miyokardiyal perfüzyon görüntüleme (gMPG) gibi daha ileri tanısal yöntemlere yönlendirilmesinde olası bir rolünün olup olmadığının araştırılmasıdır.

Yöntemler: Ekokardiyografi esnasında kIMK ölçülen 199 ardışık hastaya gMPG yapılmıştır. gMPG sonuçlarına göre hastalar normal ve KAH olmak üzere iki gruba, kIMK ölçümlerine göre ise hastalar dört alt kategorik gruba ayrılmıştır.

Bulgular: Hastaların yaşı ve kIMK ölçümleri arasında iyi bir korelasyon (r=0,546, p<0,001) saptanırken, "summed stress" skorları ile hastaların yaşları arasındaki korelasyon zayıf (r=0,142, p=0,045) ve "summed stress" skorları ile kIMK ölçümleri arasındaki korelasyon ise çok zayıf (r=0,107, p=0,131) olarak bulunmuştur. KAH olan grubun kIMK ölçümleri (0,74±0,17 mm) normal gruba (0,67±0,16 mm) oranla istatistiksel olarak anlamlı yüksek (p=0,012) iken, yaş düzeltmesi yapıldıktan sonra bu istatistiksel olarak anlamlı farkın kaybolduğu gözlenmiştir (p=0,131). Ayrıca, KAH grubu ile normal grubun kategorik kIMK ölçümleri arasındaki ilişki istatistiksel olarak önemsiz olarak bulunmuş olup (p=0,059), artan kIMK ölçümleri ile KAH varlığı arasındaki korelasyonun da istatiksel olarak çok zayıf olduğu gözlenmiştir (r=0,187, p=0,08).

Sonuç: kIMK ölçümü, kardiyovasküler olayların gelişme riskini öngörebilse de ekokardiyografi esnasındaki tek kIMK ölçümünün koroner arter hastalığı yönünden şüpheli olguların daha ileri değerlendirilmesi hakkında karar verme konusunda potansiyel bir rolü yok gibi görünmektedir.
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Anahtar kelimeler: Karotis intima-mediya kalınlığı, gated miyokardiyal perfüzyon görüntüleme, ateroskleroz, ultrasonografi

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Introduction

The carotid intima-media thickness (cIMT) was measured non-invasively by Pignoli et al. (1) in 1986, for the first time and they have shown highly significant association between histological findings of the common carotid artery (CCA) and respective ultrasound examinations. Since then, B-mode ultrasonography has been used to measure cIMT for the detection and monitoring of arterial wall changes allowing better understanding of the development and progression of atherosclerosis. cIMT results from a complex interaction between risk factor levels for CAD and the vessel wall layers, and it reflects the cumulative exposure to risk factors over time. It remains a structural measurement and therefore it is an anatomic marker of generalized arterial disease such as atherosclerosis. Because of the presence of strong correlations between atherosclerosis in various vascular beds, the measurement of cIMT is becoming increasingly accepted as a surrogate marker of generalized atherosclerotic involvement of arteries (2). Especially, cIMT correlates with coronary IMT much better and this supports the concept that cIMT is a good surrogate marker of coronary atherosclerosis (3).

Atherosclerotic vascular disease begins in childhood and symptomatic coronary artery disease generally occurs when atherosclerosis progresses to flow-limiting disease that causes ischemia, or when a thrombus forms on an existing plaque as a result of rupture or erosion. The risk factors for atherosclerotic cardiovascular disease are well established, but their usefulness as accurate predictors for developing the disease is limited (1). Since, most heart attacks and strokes occur in people at average risk factor level who are classified by traditional risk factor scoring as low or intermediate risk (2). Whereas, tests for subclinical atherosclerosis detected and quantified noninvasively may provide prognostic information beyond that provided by traditional risk factor scoring alone (4) and they can show the cumulative effect of all risk and susceptibility factors combined-known and unknown (5). Currently, over 20 cohort studies performed among subjects with or without previous vascular disease, and with and without CAD risk factors, showed consistently that increased cIMT relates to increased cardiovascular risk, independently of established vascular risk factors (4-7). Hence, it is recommended use of cIMT by ultrasound in asymptomatic adults at intermediate risk according to traditional risk factor scoring (4).

Since, the cIMT measured by high-resolution B-mode carotid ultrasound is a well validated tool for detecting subclinical atherosclerosis (3), and cIMT values add additional information beyond traditional risk factors for classifying patients in regard to the likelihood of presence of significant angiographic coronary artery disease (8), cIMT measurement may predict the functional consequences of atherosclerosis in coronary artery tree and it may play a role in diagnostic management of patients with suspected CAD.

In this context, the aim of this study was to detect whether there is any effect of the measurement of cIMT during the echocardiographic examination on decision making to refer patients for further diagnostic evaluation such as gated myocardial perfusion imaging (gMPI).

Methods

Study population

A total of 199 consecutive patients [119 men (60%), 80 women (40%); age range: 20-85 years; mean±SD: 54±14 years] referred to gMPI for known or suspected coronary artery disease were included into this study. Patients were divided into two subgroups according to their gMPI findings. Patients in the normal group had no perfusion defects on their scans. The other one was the CAD group that patients had reversible or fixed perfusion defects on their scans and their history and ECG findings were also consistent with their scintigraphic findings. All the measurements of the cIMT of the patients were performed during the echocardiographic examination before gMPI test. In the literature, the cutoff for normal cIMT value was defined as below 75^{th} percentile adjusted for age and sex or cIMT cutoff values of 1 mm in different studies (9). Our cIMT measurements were less than those reported threshold values and for the ease of the the statistical analysis, the patient population were categorized into four subgroups as A (cIMT: ≤0.60 mm), B (cIMT: 0.61-0.70 mm), C (cIMT: 0.71-0.80 mm), D (cIMT: ≥0.81 mm) to evaluate the correlation between the increasing cIMT values and the presence of CAD. A structured interview and clinical history had been already acquired, and cardiac risk factors had been assessed at the beginning of the study. Exclusion criteria were the visualization of substantial changes in carotid arteries such as atherosclerotic plaques causing trouble in measurement of cIMT. All vasoactive medications were withheld for at least 24 hours before gMPI. The hospital ethics committee approved the study protocol.

gMPI data acquisition protocol and data analysis

149 patients of the study group underwent gMPI according to two-day (stress-rest Tc-99m MIBI) protocol. Following symptom-limited treadmill exercise using the standard Bruce Protocol, 740-925 MBq (20-25 mCi) of Tc-99m MIBI (Cardio-SPECT, Medi-Radiopharma, Budapest, Hungary) was injected intravenously at peak stress and thereafter all acquisitions were initiated 30±15 min while the patients were in supine position. On following day, 30±15 min after the injection of Tc-99m MIBI rest single-photon emission computed tomography (SPECT) imaging was performed. Remaining 49 patients underwent gMPI according to stress-redistribution Thallium-201 (Tl-201) protocol. According to this protocol, 5-10 minutes after the injection of 74-111 MBq (2-3 mCi) of Tl-201, stress gated SPECT imaging and 4 hours after redistribution SPECT imaging were performed. In addition to symptom-limited treadmill exercise test, pharmacological stress testing with adenosine (Apoteket Produktion&Laboratorier AB, Formvagen, Sweden) was also performed in 14 patients who were not able

to exercise according to standard 6-minute adenosine protocol (10).

Daily quality control of the gamma camera was performed routinely before the first study of the day in a routine fashion. SPECT images were acquired with a dual-head dedicated cardiac gamma camera (Optima; GE, Milwaukee, WI) fitted with LEHR collimators with 64 projections at 28 s per projection over 180° (from 45° RAO to 45° LPO). A 15% window was centered over the 140-keV photo peak. Data were stored in a 64 x 64 matrix, and 1.33 zoom was applied. No attenuation or scatter correction was used. Filtered back projection reconstruction used a ramp filter followed by 2-dimensional Butterworth filtering (order, 5; cutoff frequency, 0.52 cycle/pixel).

Scintigraphic images were analyzed qualitatively and semi-quantitatively by 2 experienced observers in consensus by using commercially available software (Quantitative gated SPECT and quantitative perfusion SPECT of Cedars Sinai Medical Center). Semi-quantitative visual interpretation to detect both extent and severity of perfusion defects was performed using 20 segments for each reoriented image set (11). Segments were scored by consensus of observers using a five-point scoring system (0=normal, 1=equivocal, 2=moderate, 3=severe reduction of radioisotope uptake, and 4=absence of detectable tracer uptake). Summed stress scores were obtained by adding the scores of the 20 segments of the stress images. Normal studies were defined as those studies having <5% myocardium abnormal (equivalent to a summed stress score <4).

cIMT measurement technique and instrumentation

A GE Health Care Logic 9 (Milwaukee, WI, USA), high- resolution ultrasound scanner with a high frequency (9 or 14 MHz) linear array transducer was used to measure cIMT of the patients. For the examination of the carotid arteries, the necks of the subjects were turned slightly to the left or right side. The carotid artery is imaged in a longitudinal plane, the transducer approximately 45 degrees to the vertical, with the internal jugular vein used as a window. Manual measurement was performed 2 cm or more proximal to the flow divider in far wall of the common carotid artery. The selected image was maximized and the gain settings optimized to visualize the far wall of the carotids. After freezing the image, the operator sets the starting and ending point of the 1-cm measurement area manually and 5 measurements in 1 cm length were manually obtained by placing electronic calipers at the edge of the far wall of each segment (Fig. 1). The average of five data point acquisitions was then calculated.

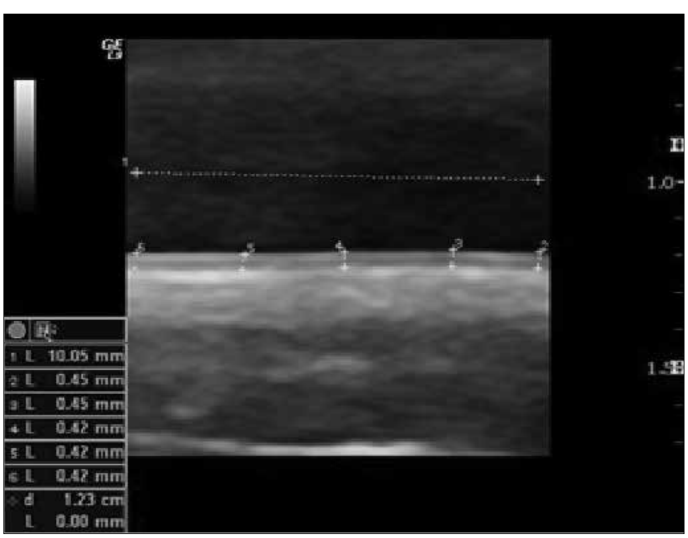

Figure 1. The measurement of cIMT by ultrasonography
cIMT - carotid intima - media thickness

Statistical analysis

Statistical analyses were performed with SPSS (version 16.0 for Windows; SPSS, Chicago, IL). Continuous variables are expressed as mean±SD. The independent samples t test was used to compare the age and cIMT measurements of both the CAD and the normal groups, and Mann-Whitney U test was used to compare the summed stress scores and the ejection fractions of both the CAD and the normal groups. The independent samples t test was also used to compare the left and the right cIMT measurements. We compared the categorical variables of cIMT values of the patients with the normal and the CAD groups by using the Chi-square test and correlations among the groups were analyzed by Kendall's tau-c test. The age of the patients was thought as a confounding factor and its effect was eliminated by ANCOVA analysis. Statistical significance was examined by 2-sided tests. Values of $p<0.05$ were considered statistically significant.

Results

After the evaluation of history, ECG and scintigraphic images of the patients, 52 (26%) of 199 patients [36 men (18%), 16 women (8%)] had perfusion defects on their gMPI scans indicating the presence of CAD. The history of CAD was positive in 50 (96%) of 52 patients and 26 (50%) of these patients had already coronary artery by-pass grafting before the gMPI test. Besides, the SSS values of the CAD group (10.23±9.06) were significantly higher than those of the normal group (2.35±2.95) ($p<0.001$) and, the ejection fraction measurements of the CAD group (52.21%±14.56) were also significantly lower than those of the normal group (63.04%±8.88) ($p<0.001$). These findings supported the thought that the discrimination between the normal and the CAD group was effectively done.

The values of the left cIMT measurements (0.69±0.17 mm) were higher than those of the right cIMT (0.66±0.16 mm) and this difference was statistically significant ($p<0.001$). The correlation between the left and the right cIMT measurements were also good ($r=0.635$, $p<0.001$). For this reason, only the left cIMT values were used for all other comparisons.

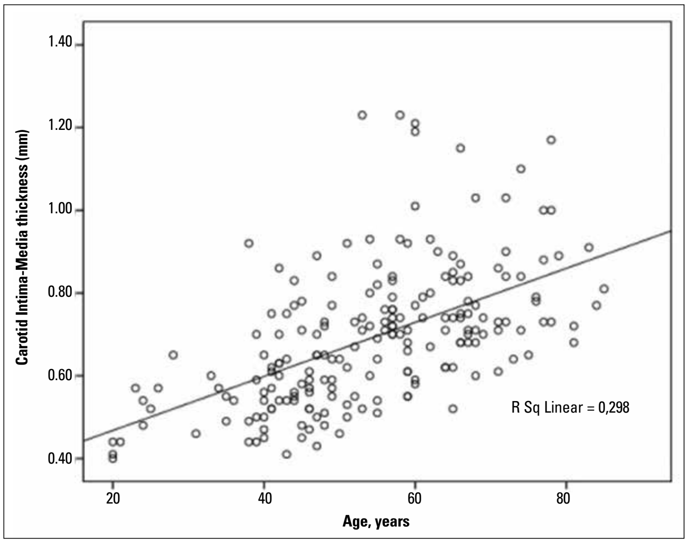

Figure 2. Scatter plot of age and cIMT measurements
cIMT - carotid intima-media thickness

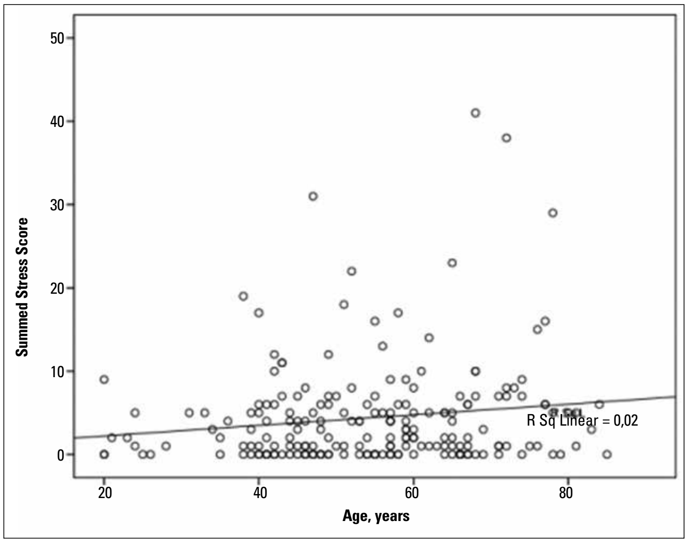

Figure 3. Scatter plot of age and SSS
SSS - summed stress scores

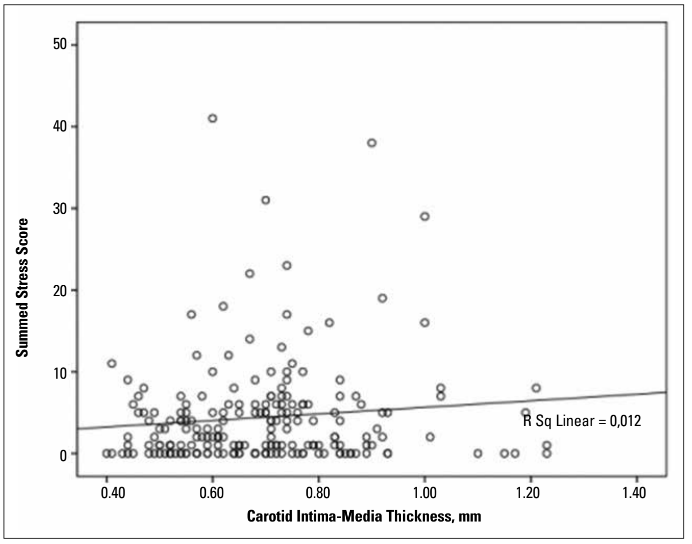

Figure 4. Scatter plot of SSS and cIMT measurements
cIMT - carotid intima - media thickness, SSS - summed stress scores

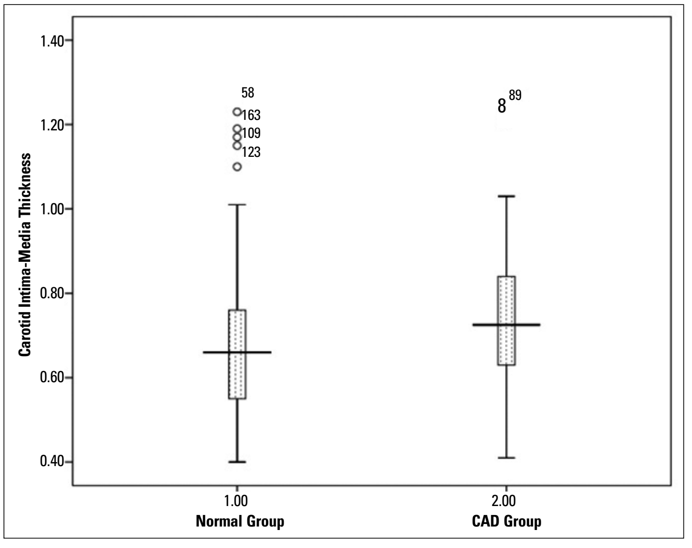

Figure 5. Boxplot of cIMT measurements in normal and CAD groups
CAD - coronary artery disease, cIMT - carotid intima-media thickness

Although, there was a good correlation between the age and cIMT values of the patients (r=0.546, p<0.001) (Fig. 2), the correlation between the summed stress scores and the age of the patients was very weak (r= 0.142, p=0.045) (Fig. 3). The correlation between the summed stress scores and the cIMT values was also very weak and statistically not significant (r= 0.107, p=0.131) (Fig. 4).

The cIMT measurements of the CAD group (0.74±0.17 mm) were higher than those of the normal group (0.67±0.16 mm), and this difference was statistically significant (p=0.012) (Fig. 5). On the other hand, the mean age of the CAD group (58.56±12.41 years) was also significantly higher than that of the normal group (52.90±14.35 years) (p=0.012). Since, the probability of both developing CAD and an increase in thickness of the carotid intima-media distance tend to increase with time, the age of the patients was thought as a confounding factor. Hence, the cIMT measurements of the CAD group were not significantly higher than those of the normal group (p=0.131) after the age correction.

Quantitative variables of the cIMT were categorized to evaluate the relation between the increasing cIMT values and the presence of CAD (Table 1). There was not statistically significant relationship between the categorical cIMT values of both the CAD and the normal groups (p=0.059). Besides, the correlation between the increasing cIMT values and the presence of detectable CAD was not also statistically significant (r= 0.185, p=0.06).

Discussion

In our study, cIMT measurements were significantly higher in detectable CAD group, but the age of the patients seems to be

Table 1. Cross-table of cIMT measurements and gMPI results

cIMT	gMPI		Total
	CAD	Normal	
A	10	57	67
B	11	30	41
C	16	33	49
D	15	27	42
Total	52	147	199

CAD - coronary artery disease, cIMT - carotid intima-media thickness, gMPI - gated myocardial perfusion imaging

responsible for this difference due to significantly increased mean age in the CAD group. Besides, the good correlation between the age and cIMT measurements was not detected between summed stress scores and the age of the study population.

Actually, regarding cardiovascular risk factors, an increased age has the most impact on an increased CIMT: depending on different studies, age may explain 50%–80% of the variability for an increased CIMT (12). Atherosclerosis is a chronic progressive disease that generally begins as a fatty streak in the aorta shortly after birth and it is a lifelong process, the measurement of the cIMT demonstrates momentary section of its slow pathophysiological progression in the carotid arteries. Hence both the thickness of the carotid intima and media distance and incidence of the coronary artery disease increase in time, and it is a common finding to detect the thickened carotid intima-media complex and together with detectable CAD in the elderly patients. As supporting to this opinion, in rodent and nonhuman primate models of aging, age-associated arterial changes are observed with advancing age, even though these animals tend not to develop atherosclerosis (13, 14).

According to our results, there is not significant relationship between the increasing cIMT values and the presence of CAD, and the correlation between the summed stress scores and cIMT measurements of the study population was very weak. These data lead us to think that cIMT measurement is a weak indicator of predicting flow-limiting consequences of the atherosclerosis in the coronary arteries. Although, cIMT measurements can be used as a surrogate marker of atherosclerosis, increased cIMT may be related to intimal or medial hypertrophy or both, and may be an adaptive response to changes in flow, wall tension, or lumen diameter (15). Because, it is well-established that cIMT increases with advancing age, even in the absence of overt or occult atherosclerosis, as a result of thickening of both the intimal and medial layers (2). These alterations encompass many factors that have been implicated in the pathogenesis and progression of atherosclerotic plaques, such as endothelial dysfunction; increased endothelial cell adhesiveness and permeability; increases in procoagulant, vasoconstrictive, and inflammatory molecules; increases in cytokines and chemokines; increased oxidative stress; and proliferation and migration of smooth muscle cells (2). Thus, intimal-medial thickening is a feature of arterial wall aging that is not synonymous with subclinical atherosclerosis, but is related to it because the cellular and molecular alterations that underlie intimal-medial thickening have been implicated in the development, progression, or both of atherosclerosis. Carotid wall thickening represents subclinical vascular disease, the pathophysiologic substrate that explains why CIMT is a risk factor and a marker of CVD risk (16). Therefore, it appears that the burden of atherosclerosis in the carotid arteries measured by cIMT can't give a clue about the presence of its developing complications in the coronary arteries detected by gMPI.

The summed stress scores demonstrating the extent and severity of perfusion defects were significantly higher in the CAD group and systolic functions of patients in this group were significantly depressed. Stress gMPI is widely available and the best validated noninvasive means to evaluate patients with symptoms for detecting CAD at an earlier stage. gMPI provides data about the extent and the severity of perfusion defects and functional parameters of the left ventricle during the systole and the diastole. On the other hand, it should be emphasized that negative stress gMPI test only implies a lack of flow limiting disease and favorable short-term prognosis; it does not indicate lack of atherosclerotic disease. In contrast, scanning protocols of cIMT can provide data regarding to the atherosclerotic disease from in early and asymptomatic stages to advanced forms of disease. It provides structural information regarding to vessel wall and therefore it is an anatomic marker of generalized arterial disease such as atherosclerosis.

It has been reported that increased cIMT was a strong predictor of the extent of abnormal perfusion and improved identification of patients with severely abnormal perfusion in asymptomatic diabetic patients (17). According to our results, this finding does not seem to be true for general population. Authors have already mentioned that patients were referred from a diabetes clinic and may thus represent a more high-risk group than the general asymptomatic population. Actually, occult CAD has been reported to be present on MPI in 1/3 patients with diabetes mellitus without abnormal electrocardiographic findings or evidence of peripheral arterial disease (18). In the imaging cohort of another multicenter study, 22% of the type 2 diabetic patients showed abnormal MPI results (19).

According to the Mannheim Consensus recommendations, cIMT measurements were obtained from the distal 2 cm of the common carotid artery over a distance of approximately 1.0 cm in a region free of focal plaque (20). Besides, cIMT was measured from the far wall of the common carotid artery, since it has been reported to be the most appropriate site for IMT measurement, compared with other vascular sites (21). Although, improvements in ultrasound systems and software refinements have largely eliminated the limitations of cIMT measurement related to ultrasound resolution and reproducibility of single measurement, repeated cIMT measurements remains difficult because identification of the identical carotid segment on return visits is challenging (22). For this reason, we intended to evaluate the potential value of single cIMT measurement on decision-making for further diagnostic work-up.

cIMT as measured by B-mode ultrasound of carotid arteries, is a simple and non-invasive imaging test assessing structural changes in the arterial wall and has been widely used as a surrogate marker of atherosclerotic disease. Technically, it has been usually measured in CCA, rather than the carotid bulb or internal carotid artery, because CCA is easily visualized perpendicular to the ultrasound beam and provides more accurate, reproducible, and quantitative measurement (20). On the other hand, carotid plaque predominantly occurs at sites of nonlaminar turbulent flow such as in the carotid bulb and the proximal internal carotid artery, but rarely in the CCA except in advanced atherosclerotic disease (6). It has been reported that carotid plaque has been shown to be more closely related to CAD and to predict coronary events than cIMT (9). Similarly, carotid plaque burden in the carotid arteries by 3D quantification by ultrasound was found to correlate more closely with coronary atherosclerosis than cIMT (23). Since quantification of CIMT and carotid plaque formation provide different information of the atherosclerotic status and burden in the carotid artery, a thorough scan of all carotid arteries, including plaque assessment, may increase sensitivity for identifying subclinical vascular disease. Taken together these two parameters have been shown to result in a superior risk prediction for coronary heart disease than with one of the parameters alone (24). In our study we only measured the cIMT and not evaluating other parts of the carotid by ultrasound can be thought as a limitation of the study.

Study limitations

Although, the main potential disadvantage of manual cIMT measurement is user dependent variability in cIMT readings, automatic edge detection software was not used for cIMT measurements in our study due to absence of the program. Most studies, even providing reference values for cIMT used manual reading techniques, but the manual measurement of cIMT may be biased by the lack of expertise or by some subjective judgment of the observer that causes variability in measurements even in the same images (25). Manual and automated methods are reliable for cIMT measurements, but semi-automated border detection programs tend to improve reproducibility and shorten reading time, especially among newer readers. On the other hand, these programs tend to produce somewhat thicker cIMT values than manual tracing, especially if the generated borders are left unedited. Moreover, when ultrasound images show clear interfaces automated edge detection programs work well, whereas when the interfaces on the ultrasound images are less clear, the automated edge detection program needs to be manually overridden, thereby eliminating the advantages of the use of automated edge detection (7, 26, 27). Although we believe that results of manual measurements of cIMT by a well-trained expert are similar to ones detected by automatically, it was recommended use of a semiautomated border detection program with validated accuracy (2).

Conclusion

As a conclusion, atherosclerosis is a chronic progressive disorder of the vessel walls and coronary artery disease is just one of its complications. Although, cIMT may predict occurrence of cardiovascular events in subjects with or without clinical manifestations of ischemic heart disease, single cIMT measurement during echocardiography session does not seem to have potential role on decision making for further investigation in patients with suspected CAD.

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