Intima-Media thickness at the Origin of the Right Subclavian Artery as an Early Marker of Cardiovascular Risk

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Objective: Common carotid artery intima-media thickness (IMT) is considered a factor of cardiovascular risk and an early marker of coronary artery disease. This study aimed to investigate the existence of a correlation between IMT in the carotid arteries and at the origin of the right subclavian artery, as well as to evaluate IMT in the subclavian artery as an earlier marker of cardiovascular risk.

Methods: One hundred and six consecutive patients, 52 males and 54 females, average age 51 years, underwent color Doppler ultrasonography to evaluate carotid and right subclavian arteries. The relationship between carotid IMT and right subclavian IMT was assessed using the Pearson's correlation coefficient analysis and a 95% confidence interval. Reliability of right subclavian artery IMT measurement for the diagnosis of early thickening (considering a > 0.8 mm carotid thickness as reference) was described as to sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Cut-off values for the right subclavian IMT were indicated by the ROC curve, and p values ≤ 0.05 were considered statistically significant.

Results: Out of the 41 patients whose carotid arteries were IMT-free, 30 (73%) had right subclavian artery IMT values > 0.8 mm. The mean IMT value for the carotid artery was 0.87 mm (SD = 0.23) and for the subclavian artery, 1.17 mm (SD = 0.46), with a 0.31 correlation coefficient (95% CI: 0.12; 0.47). The ROC curve analysis indicated a cut-off value of 0.7 mm for the right subclavian artery IMT, using as reference a 0.8 mm cut-off value for the carotid artery (91% sensitivity, 27% specificity, 66% PPV, 65% NPV, and 66% accuracy).

Conclusion: Our study showed that carotid artery IMT correlates well with right subclavian artery IMT. With a 0.7 mm cut-off value, it is possible to detect IMT in the right subclavian artery earlier than in the carotid arteries. The IMT at the origin of the right subclavian artery can be considered an earlier marker for the assessment of cardiovascular risk.

Key words: Media-intima thickening, coronary arteriosclerosis, myocardial infarction, early diagnosis.

Atherosclerosis is a generalized disease of the artery wall that may progress, recede, or stabilize depending on several factors[1]. This dynamic process is characterized by artery wall remodeling, which may go unnoticed for a long time or may be clinically observable as an acute vascular event. The detection of cardiovascular disease markers enables early intervention on modifiable factors for atherosclerosis, such as lifestyle changes, strict management of arterial hypertension, hyperlipidemia and diabetes mellitus[2].

Carotid artery intima-media thickness (IMT), as measured by high-resolution vascular ultrasonography, is currently considered a marker of generalized atherosclerotic disease, mainly of early coronary artery disease[2-8]. Enlargement of the carotid intima-media complex is associated with most cardiovascular risk factors: male gender, familial history of cerebrovascular accident or acute myocardial infarction, smoking, diabetes mellitus, hyperlipidemia, left ventricular hypertrophy, hyperhomocysteinemia, and age[9-17]. Carotid artery IMT helps to determine more accurately the cardiovascular risks of hypertensive patients with no injury to the target organ as evidenced by routine tests, such as the electrocardiogram[18-20].

As a marker of cardiovascular risk, IMT can be detected in the distal common carotid artery, at carotid bifurcation, in the internal carotid and, more recently, in the common femoral artery[21,22]. Nevertheless, studies have shown that the measurement of the IMT in the internal carotid shows a better correlation with risk factors for coronary artery disease[23].

In routine studies of the brachiocephalic branch and the origin of the right subclavian artery in patients referred to our laboratory for cardiovascular risk assessment [by measurement of the carotid artery IMT, we observed that some patients with no carotid intima-media thickness showed IMT at the origin of the right subclavian artery. For this reason, the objective of this study was to investigate the existence of an association between carotid artery IMT and at the origin of the right subclavian artery, and also evaluate if IMT measured in the right subclavian artery could be considered an earlier marker for cardiovascular disease.

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Methods

One hundred and six consecutive patients underwent high-resolution vascular ultrasonography to have their carotid and subclavian arteries evaluated.

Inclusion criteria for the study were asymptomatic subjects with risk factors for coronary artery disease, such as: male patients over 55 years of age and female patients over 65 years of age; systemic arterial hypertension; diabetes mellitus; smoking; hyperlipidemia; obesity; sedentarism and familial history of early coronary artery disease.

Criteria for exclusion were subjects with no risk factors for cardiovascular disease, and the presence of atherosclerotic plaque in the carotid arteries, as shown by color Doppler vascular ultrasonography.

Measurement of IMT was taken at the common distal carotid (1-2 cm proximal to carotid bifurcation), and bilaterally in the internal carotid, as well as at the origin of the right subclavian artery. During the analysis, the greatest right and left carotid IMT values were considered, as well as the value measured at the origin of the right subclavian artery. The right subclavian artery was easily evaluated since it is more superficial than the contra-lateral subclavian artery; however, this does not denote advantages or technical limitations relative to the carotid arteries. The left subclavian artery was not included in the study due to its deeper location that limits assessment of the origin of this vessel.

The measurement of the intima-media complex was performed with the help of Siemens Sonoline Elegra® vascular ultrasonography equipment. A 7.5 mHz linear transducer was used, with a frequency range of 7-9 mHz, longitudinal section and B-mode images. Thickness measurement was performed at the anterior or posterior artery wall, as the distance between two echogenic lines corresponding to the lumen-intima and media-adventitia interfaces of the artery wall[17,24-26].

The relationship between carotid artery IMT and right subclavian artery was assessed using Pearson´s correlation coefficient and a 95% confidence interval. Taking into consideration the carotid classification as a reference standard for the diagnosis of early thickening (values ≥ 0.8 indicated early thickening), a ROC curve was adjusted for subclavian ITM values and the cut-off value was determined for this same classification. To evaluate the result obtained, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for the subclavian IMT in identifying early thickening. In order to evaluate the reproducibility of the method, two independent observers measured the carotid IMT of thirteen patients. Variance components and a 95% confidence interval were used throughout the analysis.

Results

Fifty-two men (49%) and 54 women (51%), between 23 and 83 years of age (average age 51 ± 13.19 years) were evaluated.

Table 1 shows the prevalence of the risk factors studied for coronary artery disease.

Correlation between carotid artery IMT and right subclavian artery IMT - Taking into consideration a > 0.8 mm value for the right subclavian artery IMT, 41 carotid arteries were IMT-free, whereas 30 (73%) right subclavian arteries showed IMT > 0.8 mm. Out of the 65 carotid arteries with early thickening, 59 (91%) subclavian arteries showed IMT > 0.8 mm.

The average IMT value obtained in the carotid artery (Chart 1) was 0.87 mm (0.5 mm minimum, 1.3 mm maximum, 0.9 mm median, and standard deviation 0.23). The mean IMT value obtained in the right subclavian artery (Chart 2) was 1.7 mm (0.4 mm minimum, 2.8 mm maximum, 1.1 mm median, and 0.46 standard deviation). The analysis of reproducibility of the method indicated a 10.2% error between the [two] investigators.

The correlation coefficient between the carotid artery IMT and the right subclavian artery IMT was 0.31%, with a 95% confidence interval ranging from 0.12 to 0.47.

Subclavian artery IMT as an indicator of early thickening - A 0.8 mm carotid thickening was established as the standard cut-off value for the diagnosis of early IMT. Therefore, carotid IMT values under 0.8 mm were considered normal, whereas values over 0.8 mm were considered as early thickening. According to the ROC curve (Chart 3), 0.7 mm was the cut-off value for the IMT at the origin of the right subclavian artery that best characterizes the thickening.

The 0.7 mm cut-off value at the origin of the right subclavian artery, when compared to the 0.8 mm IMT reference value in the carotid arteries, showed sensitivity, specificity, PPV, NPV, and accuracy values of 91%, 27%, 66%, 65%, and 66%, respectively. Table 2 displays sensitivity levels for other IMT cut-off values in the right subclavian artery.

Discussion

The identification of artery wall changes in asymptomatic subjects indicates the need for a more strict control of cardiovascular risk factors, seeking to prevent future coronary events.

Population and hospital-based studies used non-invasive techniques to evaluate early changes in the structure and function of the artery wall, such as the measurement of the intima-media complex, investigation of endothelial dysfunction, and coronary artery calcification[25,27,28].

Carotid artery IMT measurement is a safe, low-cost, and easily reproducible method suitable for identifying those patients with subclinical atherosclerotic disease and higher risks for coronary artery disease[7,25,29,30].

Studies determined 0.8 mm as the reference value for early thickening of the intima-media complex associated with an increase in cardiovascular risks[4,18,31-33]. Groot et al conducted a study with 315 patients with familial hypercholesterolemia compared to 118 controls, and showed that an intima-media thickening of up to 0.8 mm would be considered normal. The familial hypercholesterolemia patients reached a 0.8 mm IMT value at the age of 40 years, whereas control group patients reached such a value only at 76 years of age, when their cardiovascular risk would be greater due to age[4].

Asymptomatic individuals with a low to intermediate pre-test probability of coronary artery disease, and a carotid IMT value over 1 mm, are at a higher risk of developing coronary

Risk factors for CAD	Number of patients
Systemic arterial hypertension	36 34%
Diabetes mellitus	4 4%
Smoking	28 26%
Hyperlipidemia	39 37%
Obesity	19 18%
Sedentarism	30 28%
Family history of CAD	42 40%

Table 1 - Prevalence of risk factors for coronary artery disease (CAD)

events in the future[8,25,29,30,34]. Multicentric studies showed that patients with an IMT greater than 1 mm have a higher risk of acute myocardial infarction within four years[7,29,30]. Since the objective of our study was to determine an earlier marker of cardiovascular risk, we used a 0.8 mm cut-off value.

In this study, the correlation coefficient between the carotid artery IMT and the right subclavian artery IMT was 0.31, with a 95% confidence interval ranging from 0.12 to 0.47. The fact that zero is not included in this interval indicates the significance of this correlation. However, considering the limits of the 95% confidence interval, it is clear that despite the low value of the lower limit, the upper limit indicates a good correlation between the carotid artery IMT and the right subclavian artery IMT.

In this study, considering a 91% sensitivity value, a 0.7 mm IMT was determined for the right subclavian artery (lower than the 0.8 mm reference value used for the carotid artery). This suggests that the measurement of the thickening at the origin of the subclavian artery can be an earlier marker of cardiovascular risk.

The IMT, measured by B-mode ultrasound image, consists of the distance between two echogenic lines corresponding to the lumen-intima and media-adventitia interfaces of the artery wall. Since even high-resolution vascular ultrasonography is incapable of distinguishing the intima layer from the media layer of the artery wall, the intima-media complex measurement is routinely used. An increase in the thickness of the intima-media complex may be due to thickening of the media layer or the intima layer. It is known that the atherosclerotic disease affects primarily the intima layer of the artery wall. Carotid and subclavian arteries are elastic arteries, consisting mainly of the intima layer and a very small muscle component. By contrast, in peripheral arteries such as the femoral artery, medial muscle layer prevails. Therefore, carotid and subclavian IMT represents mainly thickening of the intima layer, which is associated with the presence of atherosclerotic disease[3,26,35,36]. A carotid artery IMT value over 1.3 mm is considered an atherosclerotic plaque[37].

One possible explanation for the earlier intima-media thickening in the right subclavian artery would be the presence of greater vessel angulation at its origin as compared to the carotid artery bifurcation. Higher speeds in the inner curvature border, as observed at the origin of the right subclavian artery, are responsible for the increase in endothelial surface stress and shear forces at the site[38]. The artery wall stress

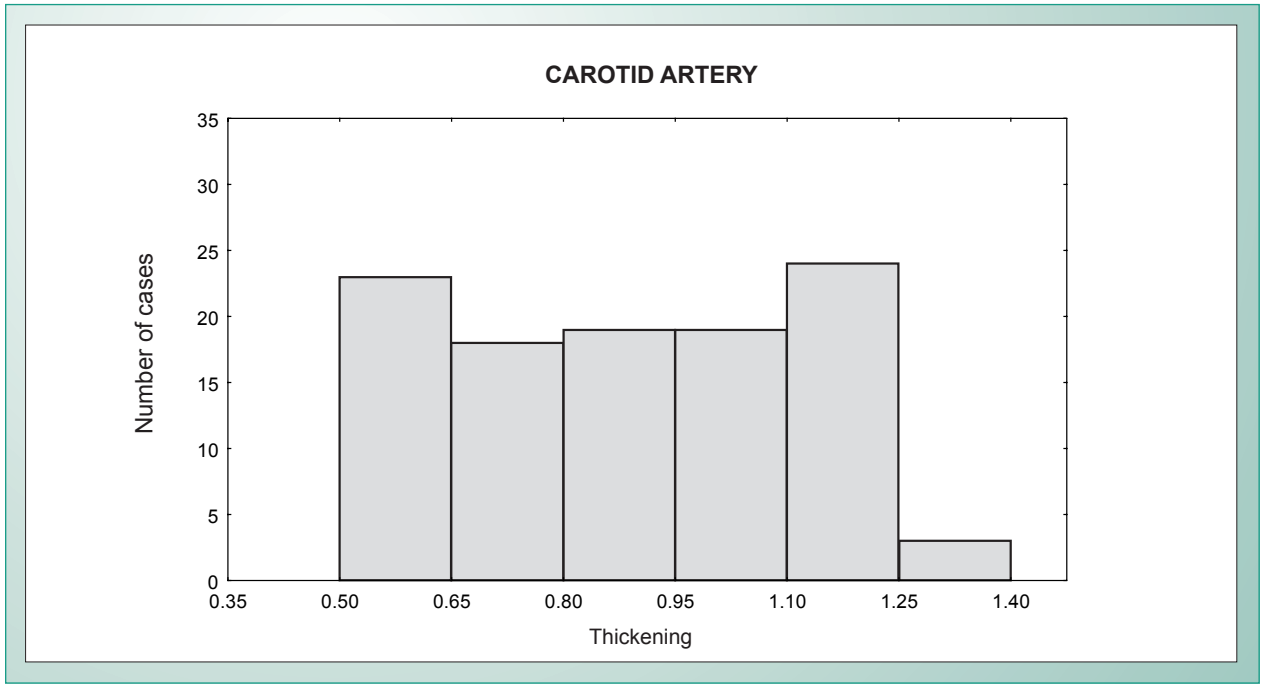

Chart 1 - *Distribution of the highest IMT values observed in the carotid arteries*

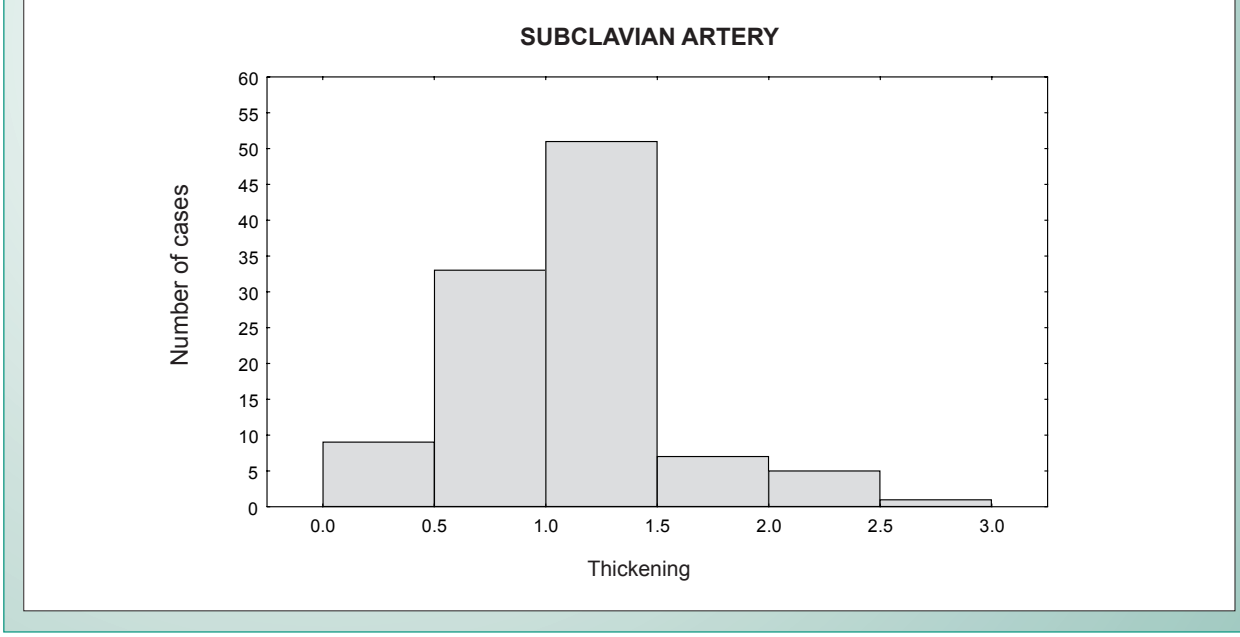

Chart 2 *- Distribution of the highest IMT values observed in the right subclavian artery.*

Indexes	< 0.8; ≥ 0.8	< 0.9; ≥ 0.9	< 1; ≥ 1	< 1.1; ≥ 1.1	< 1.2; ≥ 1.2
Sensitivity	90.8%	81.5%	81.5%	67.7%	56.9%
Specificity	26.8%	31.7%	36.6%	51.2%	75.6%
PV+	66.%	65.4%	67.1%	68.8%	78.7%
PV-	64.7%	52.0%	55.6%	50.0%	52.5%
Efficiency	66.0%	62.3%	64.2%	61.3%	64.2%

** The reference standard was the 0.8 mm cut-off value for the carotid artery IMT (<0.8 mm normal; ≥ 0.8 early IMT).*

Table 2 - Indexes of right subclavian artery thickening according to different cut-off values

and the resulting greater shear force would contribute to the development of the intima-media thickening and a posterior atherosclerotic plaque at the site. Back in 1963, Texon proposed that lower inner wall pressures would favor atheroma deposition in the curvatures[39]. However, there are no studies in medical literature associating right subclavian artery IMT and cardiovascular risk factors.

This study observed that out of the 41 patients whose carotid arteries were IMT-free, thirty (73%) had right subclavian artery IMT values > 0.8mm. This finding shows that, even when the carotid artery is normal, the subclavian artery may show thickening of the intima-media complex. Consequently, the presence of IMT may be detected earlier in the subclavian artery rather than in the carotid artery, enabling an earlier prescription of aggressive management of cardiovascular risk factors in order to prevent future coronary events.

The authors conclude that there is an association between carotid artery IMT and the IMT at the origin of the right subclavian artery. With a 0.7 mm cut-off value, it is possible to detect IMT earlier in the subclavian artery than in the carotid arteries. The IMT at the origin of the right subclavian artery may be considered an earlier marker for the evaluation of cardiovascular risks.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

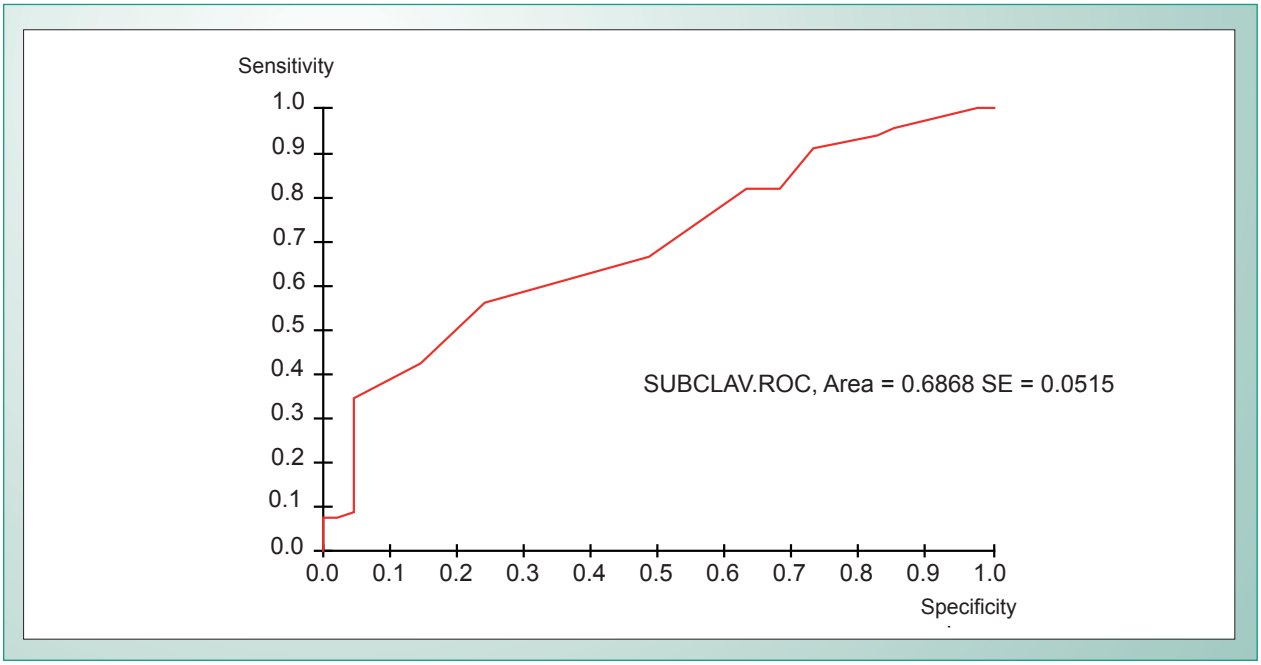

Chart 3 - *ROC curve data used for the definition of the cut-off value that best characterizes thickening for the right subclavian artery.*

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