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Intima-Media Thickness Measurements in the Carotid and Femoral Artery as an Indicator of Symptomatic Coronary Atherosclerosis

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For editorial comment see p. 242.

Key Words

Intima-media thickness · Atherosclerosis · Carotid artery · Femoral artery · Ultrasound

Abstract

Background: Ultrasonographically determined intima-media thickness of peripheral arteries is frequently used as an indicator of generalized and coronary atherosclerosis. Generally, the carotid artery is used. Measurements in the femoral artery have received little attention. ***Objective:*** In this study we investigated which of the ultrasonographically determined intima-media thickness measurements in either the common carotid artery, the carotid bulb, the common femoral artery or the superficial femoral artery is the best indicator for clinical coronary atherosclerosis. ***Methods:*** We determined the intima-media thickness in the common carotid artery, the carotid bulb, the common femoral artery and in the superficial femoral artery by B-mode ultrasonography in 78 patients with clinically proven severe coronary atherosclerosis and in 47 age-matched population controls. The odds ratio for the presence of coronary atherosclerosis was determined for every quintile of the intima-media thickness measurements in the arteries. Furthermore receiver operating characteristic (ROC) curves were constructed for the arteries to visualize the discriminating power of the measurements in these arteries. ***Results:*** For every quintile, the odds ratios (for the presence of clinical coronary atherosclerosis) of the measurements were the highest in the carotid bulb (range 3.7–7.1) and in particular in the common femoral artery (9.8–27.9). Inspection of the ROC curves showed that the test performance (i.e. sensitivity and specificity) to discriminate between individuals with clinical coronary atherosclerosis and the population controls was best for the femoral artery. The curves of the other three arteries were similar. ***Conclusion:*** The results of our study indicate that intima-media thickness measurements in the common femoral artery are a better indicator of coronary atherosclerosis than in the other three arteries.

Introduction

Intima-media thickness of peripheral arteries determined by B-mode ultrasonography is often used as an indicator of generalized and coronary atherosclerosis. It is mainly used in cross-sectional studies but recently also in clinical trials [1, 2]. Ultrasonographically determined intima-media thickness of superficial arteries has proven to be accurate [3, 4] and reproducible [5]. Numerous studies found a clear relation between ultrasonographically determined intima-media thickness and established risk factors of cardiovascular disease, such as serum cholesterol

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levels and blood pressure [6–8]. Furthermore intima-media thickness in the carotid artery proved to be a good indicator of the extent of atherosclerosis in the coronary and other peripheral arteries [9, 10]. Recent studies showed that intima-media thickness in the carotid arteries can even be used as a predictor for future cardiovascular events [11, 12].

In most of the studies in which intima-media thickness measurements were used as an indicator, the measurements were performed in one or more segments of the carotid artery (i.e. common carotid artery, carotid bifurcation and internal carotid artery). Even though the femoral artery is as well accessible by ultrasonography as the carotid artery, measurements in the femoral artery have received little attention. Only a few studies compared intima-media thickness in the carotid and femoral artery to the extent and severity of coronary atherosclerosis [13, 14]. The results of these studies suggest that intima-media thickness in the femoral artery compared to the carotid artery is a superior indicator for the extent and severity of coronary atherosclerosis.

In this study we measured intima-media thickness in the common carotid artery, the carotid bulb, the common femoral artery and in the superficial femoral artery and examined the association of the measurements in these arteries with the presence of symptomatic coronary atherosclerosis. Furthermore we investigated the power of wall thickness measurements in the four arterial segments to discriminate between individuals with clinically proven coronary atherosclerosis and population controls with no symptomatic coronary heart disease.

Methods

Subjects

In this study we included 78 male patients who had undergone coronary bypass graft surgery and 47 age-matched male population controls without clinical signs of coronary heart disease. The coronary bypass patients were treated with oral anticoagulants after surgery and were selected from the archives of the Leiden Anticoagulant Clinic. The group of population controls consisted of 34 healthy age-matched friends or neighbours of the coronary bypass patients and 13 age-matched individuals who received temporary oral anticoagulant treatment because of an orthopaedic condition, such as orthopaedic surgery or a fracture (selected from the archives of the Leiden Anticoagulant Clinic). All population controls were asked to fill out a translated version of the questionnaire of Rose et al. [15] to exclude individuals with clinical signs of coronary atherosclerosis. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center and all individuals gave their informed consent.

Measurement of the Intima-Media Thickness

Intima-media thickness measurements were determined in the far walls of the common carotid artery, the carotid bulb, the common femoral and superficial artery A detailed description of the technique is given elsewhere [5]. In brief, we used an Aloka SSD 1200 ultrasound machine with a 7.5-MHz linear transducer to visualize the intima-media complex in the far wall of the arteries The images were frozen during the R-phase of the cardiac cycle using an ECG-triggering device that was attached to the ultrasound machine. Subsequently, two images of the arteries on each side were recorded on a S-VHS video tape and later digitalized and saved on a CD recordable. At a later stage, the images were loaded into a personal computer with a cardiovascular measurement system [16]. Six measurements of the intima-media complex as defined by Pignoli et al. [3] were performed for every image. All measurements were made in the far wall. The measurements in the common carotid artery were performed in the area 2 cm proximal from the carotid bulb. The measurement area in the carotid bulb was defined as the area 1 cm proximal from the flow divider of the carotid bifurcation. In the femoral artery, the measurements were made 2 cm proximal from the site where the common femoral artery splits into the deep and superficial femoral branch The measurement area of the superficial femoral artery was defined as the area 2 cm distal from its origin The measurements in all four images of every arterial segment (left and right side combined) were averaged, resulting in a single mean intima-media thickness of the common carotid artery, the carotid bulb, the common femoral artery and the superficial femoral artery. All image acquisitions and measurements were performed by one investigator (A.Š.). During the actual measurements, the investigator was blinded to the identity of the subjects

Analysis

The distribution of the intima-media thickness of all arterial segments proved to be positively skewed and the data were therefore transformed logarithmically prior to the analysis. To determine which artery is the best indicator for coronary atherosclerosis and whether increased intima-media thickness is related to the presence of clinical signs of coronary atherosclerosis, we divided the distribution of the thickness of each arterial segment into quintiles Subsequently, we used the boundaries of each quintile as a cut-off point to determine the odds ratio of such a cut-off point for the presence of clinical coronary atherosclerosis. For these analyses the first quintile was used as the reference value. To determine the discriminating power of the intima-media thickness of each artery on a continuous scale, we visualized the test characteristics by using a receiver operating characteristics (ROC) curve [17, 18], a plot of the true positive (i.e. sensitivity) fraction against the false-positive fraction (i e. 1 – specificity) for varying cut-off points The area under the line in such a graph can be regarded as a measure of the discriminating power of the test.

Results

The group of population controls (mean age: 63, range: 33–76) was slightly younger than the coronary bypass graft patients (mean age: 66, range: 42–84 years). Figure 1 shows the comparison of intima-media thickness in the

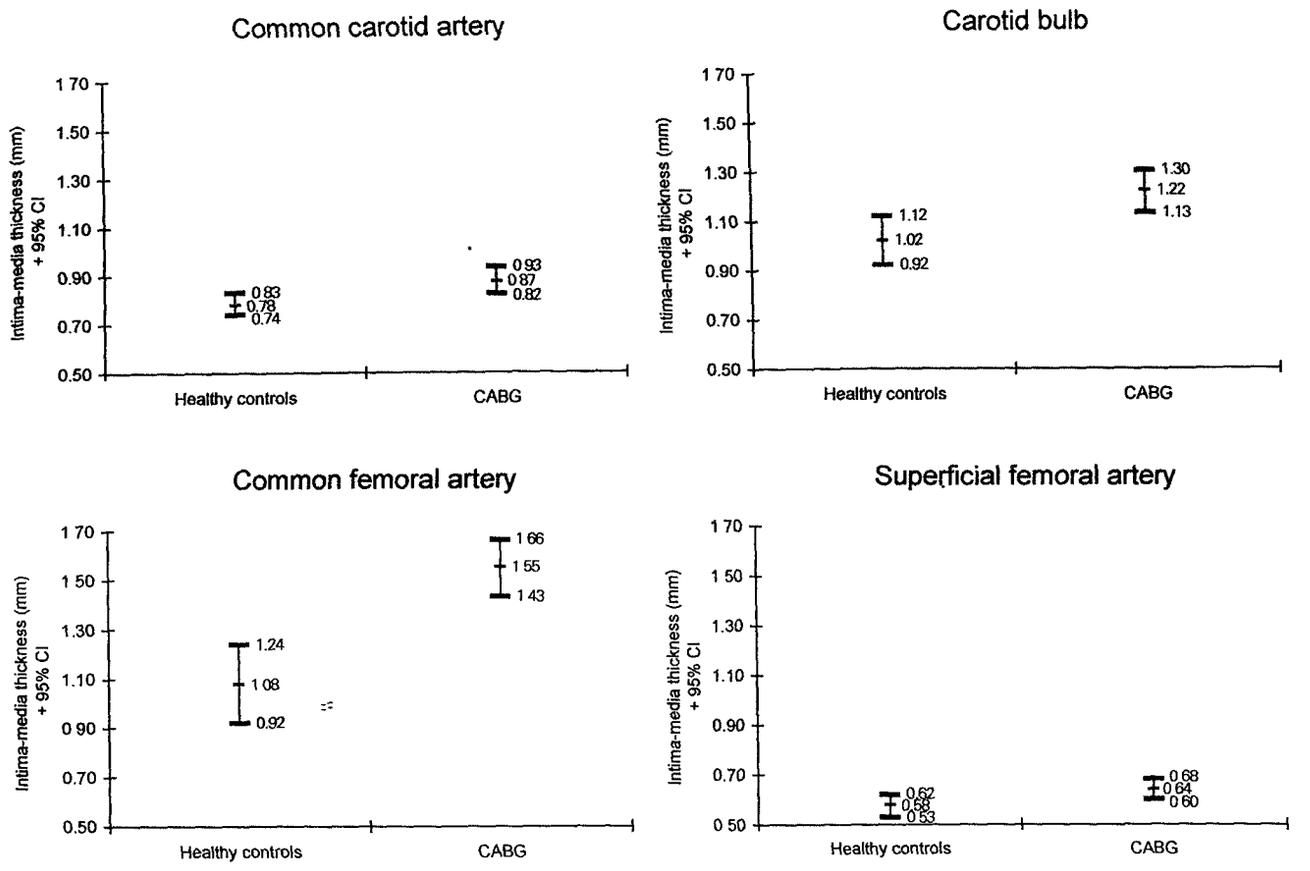

Fig. 1. Visual comparison of the intima-media thickness in the common carotid artery, the carotid bulb, the common femoral artery and the superficial femoral artery between patients with clinically proven coronary atherosclerosis and population controls without symptomatic coronary heart disease. The mean and 95% CI of the intima-media thickness is indicated by horizontal dashes.

four arterial segments between the patients with clinical atherosclerosis and the population controls. The largest difference in intima-media thickness was found for the common femoral artery (geometric mean difference: 0.40 mm, 95% CI: 0.26–0.53). Within the carotid artery, a higher difference in the carotid bulb was found (geometric mean difference: 0.17 mm, 95 CI: 0.070–0.28) than in the common carotid artery (geometric mean difference: 0.095 mm, 95% CI: 0.016–0.17) between the patients and population controls. The difference of arterial wall thickness in the superficial femoral artery (geometric mean difference: 0.10 mm, 95% CI: 0.020–0.19) turned out to be similar to the one in the common carotid artery.

To study whether an increasing intima-media thickness in the arterial segments is related to the presence of clinical coronary atherosclerosis we divided the measurements into quintiles of the intima-media thickness in the four arterial segments. Subsequently, we used each quintile as a cut-off point to determine the odds ratio of that cut-off point for the presence of clinical atherosclerosis. The first quintile was used as reference. Table 1 shows the cut-off points based on the quintiles and the accompanying odds ratios. For all arteries, we found increasing odds ratios with increasing values of the cut-off points. The odds ratios determined for the carotid bulb (range: 4.0–7.1) and in particular for the common femoral artery (range: 9.8–27.9) were the highest for every cut-off point. For lower cut-off points the odds ratios for the common carotid artery (range: 2.1–3.4) and the superficial femoral artery (range: 1.5–5.9) were similar. But for the higher

Table 1. Odds ratios for symptomatic coronary atherosclerosis for increasing cut-off points of the intima-media thickness in the common carotid artery, the carotid bulb, the common femoral artery and the superficial femoral artery

Artery	Cut-off point, mm	Odds ratio	95% CI
Common carotid artery	0.69	2.1	0.8–5.5
	0.76	3.0	1.1–8.5
	0.85	2.5	0.8–7.7
	0.96	3.4	0.9–13.8
Carotid bulb	0.84	4.0	1.5–11.0
	1.00	4.6	1.6–13.4
	1.16	7.1	2.2–24.2
	1.42	7.1	1.7–31.7
Common femoral artery	0.84	9.8	3.0–33.4
	1.15	15.2	4.4–56.3
	1.47	17.3	4.5–72.4
	1.77	27.9	4.9–190.7
Superficial femoral artery	0.49	1.5	0.6–4.1
	0.56	2.0	0.7–5.8
	0.60	3.0	0.9–9.8
	0.69	5.9	1.2–33.4

cut-off points the superficial femoral artery proved to be superior in comparison to the common carotid artery as an indicator of coronary atherosclerosis.

To determine the discriminating power of the intima-media thickness measurements in the four arterial segments for the presence of clinical coronary atherosclerosis, ROC curves were constructed for every arterial segment (fig. 2). In general, better test performance is indicated by a ROC curve that is higher and more to the left in the ROC space, or in other words with a higher area under the curve (maximum = 1) [17, 18]. Inspection of the curves shows that the test performance (i.e. sensitivity and specificity) of intima-media thickness measurements to differentiate between individuals with clinical coronary atherosclerosis and population controls was best for the common femoral artery (calculated area under the curve: 0.79). The curves and the calculated areas under the curves of the other three arteries were similar.

Discussion

In this study we investigated which of the intima-media thickness measurements in either the common carotid artery, the carotid bulb, the common femoral artery or the superficial femoral artery best predict the presence of clinical coronary atherosclerosis. We studied the discriminating power of early atherosclerotic measurements in these arterial segments to differentiate between subjects with and without clinical signs of coronary atherosclerosis. The intima-media thickness in the common femoral artery best reflects the atherosclerotic state in the coronaries, followed by the measurements in the carotid bulb. Intima-media thickness measurements in the common carotid artery turned out to have the lowest discriminating power.

Intima-media thickness measurements in peripheral arteries determined by B-mode ultrasonography are frequently used in studies as an indicator of coronary and generalized atherosclerosis [1, 2, 6–8, 19, 20]. Using ultrasonographically determined intima-media thickness measurements as an indicator has some important advantages: the examination is cheap, easy and fast to perform, it is non-invasive and the technique has proven to be very reproducible [5, 21]. One might, however, wonder whether intima-media thickening truly represents an early stage in atherogenesis or just a reaction to haemodynamic factors. Numerous studies showed a clear relation of intima-media thickness in peripheral arteries with the established risk factors of atherosclerosis [6–8]. Furthermore it was shown that intima-media thickness measurements in peripheral arteries reflect the extent of atherosclerosis well in other peripheral arteries and the coronary arteries [9, 10]. In two recent studies, it was proven that intima-media thickness measurements in the carotid artery may be used as a predictor of future coronary events [11, 12]. The results of our study confirm that intima-media thickness measurements in peripheral arteries can be used as a marker for the presence of symptomatic coronary atherosclerosis. Since the carotid artery is well accessible by high-frequency ultrasonography, the carotid artery is usually used as the site to quantify the intima-media thickness in most studies. Although the femoral artery is as well accessible for ultrasonography, it is generally not used to measure vessel wall thickness.

The results of this study are in accordance with the results of a recent study performed by Lekakis et al. [13]. In their study the atherosclerotic vessel wall measurements in the femoral artery proved to be a better indicator of coronary atherosclerosis determined by coronary angiography than measurements in the common carotid artery, the carotid bulb or the internal carotid artery. Similar results were found in a study by Megnien et al. [14] in which the femoral artery proved to be superior to the common carotid artery as a marker of coronary atherosclerosis determined by ultrafast computer tomography.

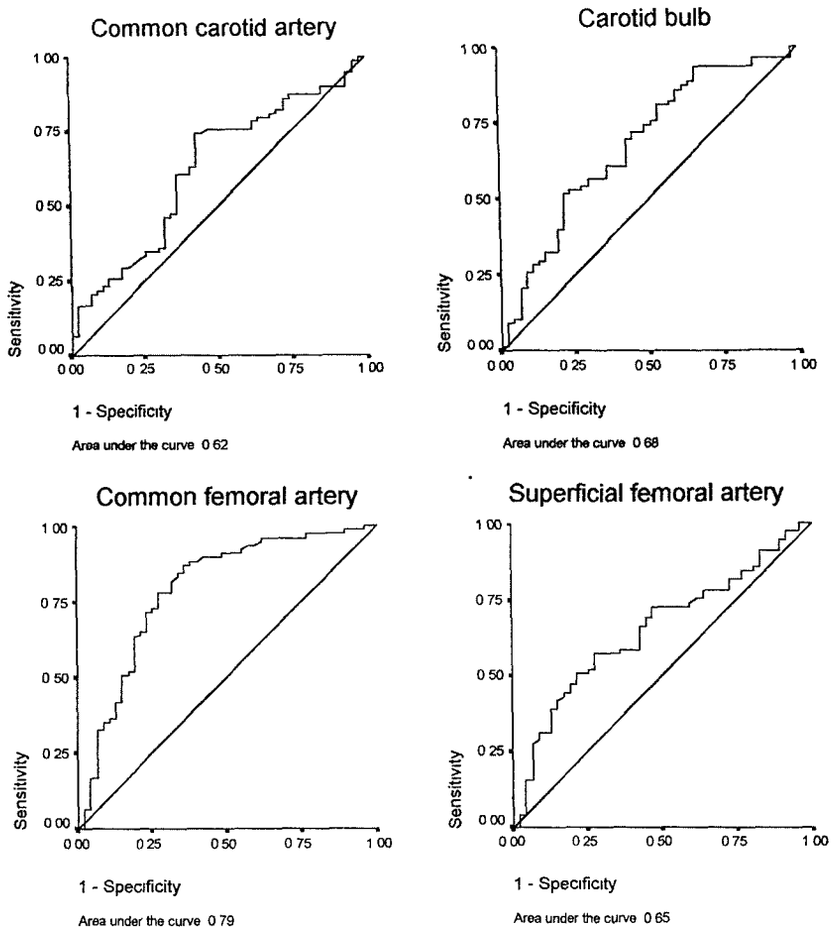

Fig. 2. Plot of the true-positive fraction (sensitivity) against the false-positive fraction (1 – specificity) for the intima-media thickness measurements in the common carotid artery, the carotid bulb, the common femoral artery and the superficial femoral artery based on the 78 patients with coronary atherosclerosis and 47 population controls without symptomatic coronary heart disease. The area under the curve (maximum = 1) is an indication of the discriminating power of the intima-media thickness measurements as a test to differentiate between individuals with clinical coronary atherosclerosis and individuals without symptomatic coronary heart disease.

In another study [22] in which the measurements in the common carotid artery, the carotid bulb and the common femoral artery were compared, the thickness in the carotid bulb turned out to be the best indicator for the extent of coronary atherosclerosis. In that study, however, only a small number of subjects were included.

We compared early atherosclerotic vessel wall changes in individuals with coronary atherosclerosis to population controls without obvious coronary atherosclerosis. The presence of symptomatic coronary atherosclerosis in the population controls was excluded by a translated version of the questionnaire of Rose et al. [15]. This questionnaire discriminates between individuals with and without symptomatic coronary atherosclerosis; however, it does not discriminate between the presence and absence of actual atherosclerotic plaques, but only those that are symptomatic. Regarding the age of the subjects, it is very probable that a number of the population controls had non-symptomatic atherosclerotic changes in the coronaries and therefore were not completely free from atherosclerosis. On the other hand, it is expected that on average the extent of coronary atherosclerosis in coronary bypass graft patients is much larger than in population controls without symptomatic coronary heart disease.

Our study indicates that intima-media thickness measurements in the carotid bulb and in particular in the femoral artery are a better indicator of coronary atherosclerosis than measurements in the common carotid artery and superficial femoral artery. A plausible explanation might be that the haemodynamic conditions in the common femoral artery and carotid bulb are more closely related to those in the coronary arteries than the conditions in the common carotid artery and the superficial femoral artery which are more straight arterial segments.

Although atherogenesis usually is a generalized process involving most arteries, as confirmed by a recent study [P. Bucciarelli: Arterial intima-media thickness and its relationship with cardiovascular disease and atherosclerosis: A possible contribution of medium-sized arteries; unpubl. data], it is generally acknowledged that some arterial segments, in particular those with curves and near bifurcations, are more prone to develop earlier and more extensive atherosclerotic plaques.

The choice which site should be used as a marker of coronary atherosclerosis should not only be based on the strength of its relation to the extent of coronary atherosclerosis. Other test characteristics, such as reproducibility of the measurements, should also be taken into account. In a recent study we found that in comparison to the other three arterial sites the measurements in the common carotid artery were best reproducible and least affected by progressed atherosclerotic changes in the arterial segment [5]. These results and the results of the present study suggest that when intima-media thickness measurements are performed to detect the presence of coronary atherosclerosis, the femoral artery is the recommended site to perform the measurements. On the other hand, if progression of atherosclerotic changes has to be evaluated, as in clinical trials, measurements in the common carotid artery are most recommended. Since the ultrasound examination is easy and fast, the best choice is probably to perform the measurements in more than one arterial segment (e.g. common carotid artery, carotid bulb and common femoral artery).

Acknowledgments

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