Intima-Media Thickness, a New Tool for Diagnosis and Treatment of Cardiovascular Risk

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Introduction

Various non-invasive markers of early arterial wall alteration are currently available such as arterial wall thickening and stiffening, endothelial dysfunction and coronary artery calcification. Of them, intima media thickness (IMT) of large artery walls, especially carotid, can be assessed by B-Mode ultrasound in a relatively simple way and represents a safe, inexpensive, precise and reproducible measure. This explains why IMT is more and more widely used in clinical research: (i) for testing the value of new or emerging risk factors by means of observational or epidemiological studies in groups of patients or in general populations and (ii) for evaluating effects of risk factor modifications by various drugs on the progression of early arterial wall alteration in therapeutic trials. In clinical practice the measurement of IMT is not yet done as a routine investigation but the predictive value of IMT with regards to cardiovascular complications has been established in several prospective studies and suggests that IMT measurement might participate in the future in the stratification of cardiovascular risk of asymptomatic patients in primary prevention. The present review describes the methods of measurement and "normal" values of IMT, the relations of IMT with atherosclerotic risk factors, cardiovascular damages and clinical events, and the effects of treatments, - namely antihypertensive and lipid lowering drugs - on IMT progression over time.

Methods Of Measurement

There are important differences in B-Mode measurement of carotid IMT between laboratories. They can concern the IMT image acquisition (in relation with the segment and/or the wall of measure) as well as the IMT image analysis with regards to the type of measure (mean maximum, mean random, mean over 1 cm). They also concern the determination of the echo boundary defining the IMT interfaces which may be a manual cursor placement or an automated computerized edge detection (Table 1). Roughly two main approaches are used for measuring IMT according to the above criteria (i) the measurement at multiple extracranial carotid sites in both near and far walls and (ii) the automated computerized measurement restricted to the far wall of the distal common carotid artery.

<table>
<thead>
<tr>
<th>Image Acquisition</th>
<th>Segment: CCA, bulb, ICA, right/left</th>
</tr>
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<tbody>
<tr>
<td>Wall: Far, Near</td>
<td></td>
</tr>
<tr>
<td>Type of Measure</td>
<td>Mean of several maximum measures (2 to 12)</td>
</tr>
<tr>
<td></td>
<td>Mean of randomly selected measures (3 to 5)</td>
</tr>
<tr>
<td>Methods of analysis</td>
<td>Mean of measures over 1 cm (≥ 100)</td>
</tr>
<tr>
<td></td>
<td>Manual cursor placement</td>
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<tr>
<td></td>
<td>Automated computerized edge-detection</td>
</tr>
</tbody>
</table>

Table 1. Methodological criteria taken into account for measuring carotid IMT.

CCA= Common carotid artery; ICA: Internal Carotid Artery

Multiple carotid sites measurement

This approach usually consists in measuring IMT in the near and far walls of the three main segments of extracranial carotid arteries (common carotid, bifurcation, internal carotid) on both sides. For each segment, ultrasound scan is performed in more than one direction, the maximal value of IMT is selected, and the final IMT considered is the average of IMT values at the 12 sites examined. Alternatively the IMT considered may be the average of maximum IMT values at only 6, 4 or even 2 carotid segments, or the average of randomly selected IMT measures in 3 to 5 carotid segments (Table 1). Measurements are usually done on the basis on a video image by visual assessment of the leading edges (i.e. the upper demarcation line of the echogenic zone) of the blood-intima and media-adventitia interfaces defining IMT. The analysis
of IMT interfaces is performed off-line, manually or semi-automatically with the assistance of a computerized program, by placing a cursor on the interfaces in the digitized video image of the initial scan. As measurement of IMT at multiple carotid sites frequently incorporates plaque thickness because plaques are common in the carotid bifurcation and internal carotid artery of subjects with increased risk for cardiovascular disease. This explains why the so-measured IMT can be considered as a marker of early carotid atherosclerosis.

Far wall common carotid computerized measurement
Another methodology is to restrict IMT measurement to the far wall of the distal segment of the common carotid artery [9-10]. This superficial and strength segment offers the best geometric conditions for obtaining a high precision and reproducibility rate of ultrasound IMT measurement [10]. Firstly, IMT is not measured at a single point but averaged on about a hundred points of measure along at least 1 cm of longitudinal length of the vessel. Secondly, the distal carotid provides an optimal ultrasound image defining clearly IMT, i.e. the double line pattern: this image consists of two parallel echogenic interfaces: the first one between the blood and the intima, and the other between the media and the adventitia [7]. Lastly, IMT image is frozen in telediastole by means of ECG triggering to avoid a confounding effect of pulsatile deformation of wall thickness, and transferred to a computer [9]. Then a program of analysis based on the determination of gray level density and special recognition tissular algorithms allows to perform an automated measurement of IMT without reader-dependence. Furthermore, when a second measurement of IMT is performed subsequently within a longitudinal investigation, the computerized analysis program allows to generate the “anatomic profile” of the vessel obtained at the first examination and stored in the computer memory [9]. The anatomic profile helps the sonographer to adjust the probe in the same position as for the first examination [9]. These computerized procedures improve the precision and reproducibility rate of the IMT measurement, providing about 3% of relative difference between two successive measures [11]. However the measurement of IMT in the distal common carotid artery suffers from the inability to assess whether IMT does represent atherosclerosis (intimal thickening) or vascular hypertrophy (medial thickening) or both phenomena. The reason is that ultrasonography cannot distinguish between intimal thickness and medial thickness in the IMT measurement because of insufficient axial resolution. Therefore IMT, when measured in the distal common carotid artery free from intrusive atherosclerotic plaque, should be considered as a marker of early arterial wall change rather than as a surrogate for atherosclerosis.

Precision and reproducibility of measurement
Phantom studies have shown that distances similar to the intima-media thickness of the carotid arterial wall can be measured with B-mode ultrasound system with an axial resolution of 0.2 to 0.4 mm at a precision of about 0.03 to 0.05 mm [12]. Indeed, the incorporation of subpixel interpolation to evaluate echo boundaries allows to detect changes in the echo separation that are 5 to 10 times smaller than the axial resolution of the ultrasound transducer [10]. Furthermore, the intraobserver variability of IMT measurement was lower in studies limited to the common carotid arterial far wall (mean±SD difference of 0.02±0.02 mm) than in studies including multiple measurements at different carotid sites (difference of 0.06±0.06 mm) [5]. In most studies the intraobserver and interobserver variability were similar. Lastly, the studies using an automated computerized IMT measurement rather than a manual cursor placement reported the best reproducibility [5].

Normal Values
Since increased IMT has increasingly become a target for detecting early alteration of the arterial walls, it is of major clinical relevance to define the threshold values beyond which IMT may be considered as abnormally high [5]. So the ultrasonography diagnosis of “increased” IMT in one individual at risk for atherosclerosis might help to better stratify the risk of the patient [5]. The normal values of carotid IMT are highly dependent on the methodology used for its measurement. They have generally been established on the basis of the distribution of IMT values within a general healthy population [8,13]. The normal IMT values being strongly influenced by age and sex should be considered by gender (men or women) or by range of age (for example decades) [8,9]. The definition of the upper normal limit used for defining normal range of IMT is arbitrary, and frequently set at the 75 th upper percentile of the IMT distribution (Figure 1). However since IMT is considered as a candidate marker of cardiovascular risk [2], its normal value should be interpreted in terms of increased risk rather than in terms of statistic distribution within a population. Epidemiological studies should contribute to define the threshold of IMT above which the cardiovascular risk begins to increase sharply. The epidemiological data currently available indicate that a value of IMT at or above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease (see below).

Relation With Cardiovascular Risk
Close relations of IMT have been found with a number of cardiovascular risk factors [3,14-20]. Traditional risk factors such as male sex [9], aging [17], overweight [17], elevated blood pressure [21-26], high blood cholesterol [27-29], diabetes [30-32] and cigarette smoking [33-34] are positively associated with carotid IMT in observational and epidemiological studies in patients at cardiovascular risk and in general populations. Of all traditional risk factors, hypertension seems to have the greatest effect on IMT, probably via medial hypertrophy which is a process specifically related to this disease [27-29]. Cumulative effects of classical risk factors exist also on IMT,
as shown by the positive relationship found between the multifactorial risk score of Framingham and carotid IMT [34]. New or emerging risk factors have been also tested with regards to their relation with carotid IMT (Table 2) [36-71]. Some of them have shown consistent association with increased IMT such as various lipoproteins [35, 36, 37, 38], psychosocial status [39,40], plasma viscosity [41-42] and hyperhomocysteinemia [59, 60, 62, 63] (Table 2). Carotid IMT has also been found to be associated with some cardiovascular alterations or organ damages [72-93]: (i) in the brain with white matter lesions assessed by magnetic resonance imaging [87] (ii) in the heart with angiographically-assessed coronary artery disease [93], electron beam computed tomographically-assessed coronary artery calcification [92], and echocardiographic left ventricular hypertrophy [60, 82] (iii) in the kidneys with microalbuminuria in diabetic patients [91] (iii) in the lower limb arteries with decreased ankle to arm systolic pressure index [76] and (iii) in the brachial artery with endothelial dysfunction attested by decreased vasodilatory response after reactive hyperemia post arterial occlusion [75]. All the relations of IMT with cardiovascular risk factors and organ damages indicate that increased IMT may be considered as a comprehensive picture of the alterations caused by multiple risk factors over time on the arterial walls.

### Table 2. Association between emerging or new cardiovascular risk markers and carotid IMT

<table>
<thead>
<tr>
<th>Risk Marker</th>
<th>Population (study)</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>Healthy adults (ARIC) type II diabetics</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>LDL particle size</td>
<td>Healthy adults (ARIC)</td>
<td>Yes</td>
</tr>
<tr>
<td>Apo E polymorphism</td>
<td>Subjects with and without CAD</td>
<td>Yes</td>
</tr>
<tr>
<td>Post prandial triglyceride</td>
<td>Mild hypercholesterolemic</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxidized LDL antibodies</td>
<td>Healthy adults</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Vascular stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Healthy subjects (IRAS)</td>
<td>Yes</td>
</tr>
<tr>
<td>Plasma Insulin</td>
<td>Healthy subjects (IRAS)</td>
<td>Yes</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>Healthy subjects (IRAS)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Gene polymorphism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipidoma lipase</td>
<td>Dyslipidemic (ARIC) Healthy adults (STANISLAS)</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Apo E4</td>
<td>Healthy adults (STANISLAS)</td>
<td>No</td>
</tr>
<tr>
<td>Angiotensin converting enzyme</td>
<td>Healthy adults/low risk subjects/diabetics</td>
<td>Yes/No/Yes</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Healthy adults (UDAS)</td>
<td>No</td>
</tr>
<tr>
<td>Methocobalamin</td>
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<tr>
<td>Methylfolate</td>
<td>Healthy subjects (UDAS/ARIC/Rotterdam)</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe homocysteinemia</td>
<td>Homocystanemia</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>Chlamydiae pneumoniae</td>
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<tr>
<td>Cystic acidemia virus</td>
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<td>Herpes virus</td>
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<tr>
<td>Other factors</td>
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<td></td>
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<tr>
<td>Healthy</td>
<td>Healthy post menopause women</td>
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</tr>
<tr>
<td>Social inequality</td>
<td>Healthy adults (ARIC)</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Healthy adults (ARIC)</td>
<td>No</td>
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<tr>
<td>Birth weight</td>
<td>Healthy adults</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Healthy men</td>
<td>No</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>Blood and plasma viscosity</td>
<td>Healthy adults</td>
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<td></td>
<td>Blood and plasma viscosity</td>
<td>Healthy adults</td>
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</tbody>
</table>

### Relation With Clinical Events

Several prospective studies in asymptomatic subjects in primary prevention have tested the predictive value of IMT with regards to clinical cardiovascular complications [94-99] such as myocardial infarction or stroke (Table 3). The KIHD Study, in middle-aged healthy Finnish men, has shown that the increase of carotid IMT (at 1 mm or above) was associated with twice greater risk for acute myocardial infarction over 3 years [94]. The ARIC study in several US communities, has shown that the increase of carotid IMT (at 1 mm or above) was associated with an increased risk ratio of coronary event over a period of 4 to 7 years (risk ratio of about 2 and 5 in 45-64 years men and women, respectively) [95-96]. The CHS Study in US elderly subjects has shown that the increase of carotid IMT (at 1.18 mm or above) was associated with a four times greater risk for combined acute myocardial infarction and stroke over 6 years [97]. The Rotterdam Study in elderly Dutch subjects has shown that the increase of carotid IMT (at 1.16 mm or above) was associated with a four times greater risk for combined acute myocardial infarction and stroke over 3 years [98]. Also studies in secondary prevention, in particular the CLAS study [99] in patients with established coronary artery disease, has shown that for each 0.03 mm increase per year in common carotid IMT, the relative risk for any coronary event was 3.1. All these studies are concordant for demonstrating that increased IMT is a powerful predictor of coronary and cerebrovascular complications whatever the method and the site of measurement, including the distal common carotid far wall IMT. However the predictive power seems less strong for IMT measured only in the distal common carotid than for IMT measured at multiple extracranial carotid sites.
Therapeutic Trials On Imt

Because of its quantitative value and high precision and reproducibility rate, carotid IMT measurement is more and more frequently used in therapeutic trials to test the effects of drugs [4], especially lipid lowering and antihypertensive drugs. A number of trials have compared effects of lipid lowering drugs (resins or statins) and placebo on the progression of carotid IMT over several years. Most of them (CLAS with Colestipol/Niacin [100]; REGRESS [101] KAPS, [102], LIPID and CAIUS [104] with Pravastatin; ACAPS [105] and MARS [106] with Lovastatin) have shown that active drug decreased significantly the progression of IMT as compared with placebo in high-risk asymptomatic patients and in those with established coronary artery disease. Some of these trials have also shown that the reduction in IMT progression was associated with a lower incidence of cardiovascular complications so leading to consider IMT as a surrogate marker for cardiovascular complications [99].

Other trials have compared effects of calcium antagonists with another drug (diuretic or beta-blockant) or with placebo on the progression of carotid IMT in hypertensive or coronary patients [107-111]. Two trials, MIDAS [107] and VHAS [108], have not demonstrated a clear beneficial effect of calcium antagonist as compared with diuretics. The MIDAS Study concluded for no difference in IMT effects of Isradipine and hydrochlorothiazide because there was no divergence in the slope of IMT progression between both treatments but when the data were analyzed as IMT change from baseline after 3 years on treatment difference existed favoring Isradipine [107]. The VHAS study also concluded for a significant greater effect of verapamil than chlorthalidone on IMT progression but only when the slope of IMT was corrected by the initial value of IMT [108]. A substudy of the INSIGHT Trial [109], has found a clear cut difference in the progression of carotid IMT over 4 years between Nifedipine GITS and a diuretic combination of hydrochlorothiazide and amiloride in hypertensive patients at high risk for cardiovascular disease. Lastly the PREVENT Study in coronary patients has shown that Amlodipine retarded significantly the progression of carotid IMT over 3 years as compared to placebo [111].

Clinical Perspective Of Imt Measurement

Since Carotid IMT is a marker of early arterial wall change including atherosclerosis and/or vascular hypertrophy, its detection by B-Mode ultrasonography might participate in the diagnosis of high cardiovascular risk in primary prevention and to the decision to treat aggressively patients at risk with drug treatments of modifiable risk factors [5]. Before proposing the routine measurement of IMT in clinical practice several limitations have to be overcome, such as the standardization of methods of measurements (including the site and the analysis of the measure) and a precise definition of the threshold of IMT above which the risk of cardiovascular event can be considered to substantially increase in one individual [112].

Conclusion

IMT assessed by B-Mode ultrasound in superficial large arteries, especially the carotid, is of major relevance with regards to the following points: (i) reflection of multiple risk factors; (ii) mirror of atherosclerotic burden and/or index of cardiovascular growth in particular in hypertension; (iii) predictor of subsequent events, (iii) end-point for therapeutic trials. However the role of IMT measurement as a screening tool in asymptomatic patients with conventional cardiovascular risk factors is not yet clearly defined, mainly because of methodological obstacles. It can be anticipated however that identifying the presence of increased IMT in the carotid arteries of one individual with intermediate cardiovascular risk would lead to classify him into the high risk category and therefore would influence the aggressiveness with which risk factor modification is done [5].

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References


