European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management
2007; 8: No. 11
revised version

ASSESSMENT OF PRECLINICAL TARGET ORGAN DAMAGE IN HYPERTENSION: CAROTID INTIMA-MEDIA THICKNESS AND PLAQUE

Enrico Agabiti Rosei, M. Lorenza Muiesan, Clinica Medica, University Hospital, Brescia, Italy

Carotid intima-media thickness and plaque

High-resolution ultrasound of the carotid arteries may allow the measurement of the intima-media complex in the arterial wall. Population studies, such as the Vobarno [1], the Rotterdam [2] and the Cardiovascular Health Study [3], have clearly demonstrated that systolic blood pressure is a major determinant of an increase in intima-media thickness (IMT) in the carotid arteries, particularly in hypertensive patients.

Methods of measurement

There are different methods for measuring IMT. The three most frequently used measurements in clinical trials are as follows [3–6]: 1) Mean of the maximum IMT of the 4 far walls of the carotid bifurcations and distal common carotid arteries (CBM_{max}), 2) Mean maximum thickness (M_{max}) of up to 12 different sites (right and left, near and far walls, distal common, bifurcation and proximal internal carotid), and 3) Overall single maximum IMT (T_{max}). Analysis may be performed by manual cursor placement or by automated computerised edge detection. In order to optimise reproducibility with the last method, IMT measurement is restricted to the far wall of the distal segment of the common carotid artery, thus providing about 3% of relative difference between two successive measurements [7, 8].

Clinical and epidemiological studies have given useful information on the reproducibility of repeated IMT measurements. Salonen and Salonen have indicated that inter-observer and intra-observer variation coefficients of 10.5% and 8.3% respectively resulted [9]. In the ACAPS study [5] the mean replicate difference was 0.11 mm and in the MIDAS [10] 0.12 mm. In the MIDAS the arithmetic difference of the mean max IMT in replicate scans was calculated as 0.003 ± 0.156 mm. More recently the ELSA (European Lacidipine Study of Atherosclerosis) included more than 2000 patients, in whom the cross-sectional reproducibility of ultrasound measurements at baseline was calculated as follows: the overall coefficient of reliability (R) was 0.859 for CBM_{max}, 0.872 for M_{max} and 0.794 for T_{max}; intra-reader and inter-reader reliability was 0.915 and 0.872 respectively [5].

Data collected in the VHAS (Verapamil in Hypertension and Atherosclerosis Study) [6] and the ELSA studies have shown a high prevalence of carotid wall structural changes in hypertensive patients. In the VHAS study 40% of the patients had a plaque (IMT > 1.5 mm) in at least one site along the carotid arteries and only 33% of patients had normal carotid arterial walls. In the ELSA study 82% of 2259 essential hypertensives had a plaque (IMT > 1.3 mm). Moreover, in the RIS study (Risk Intervention Study) patients with severe essential hypertension and high cardiovascular risk had a significantly higher prevalence of atherosclerotic lesions compared to control subjects [11].

The normal IMT values are influenced by age and sex. Normal IMT values may be defined in terms of statistical distribution within a healthy population; however, they may be better defined in terms of increased risk and available data indicate that IMT > 0.9 mm represents a risk of myocardial infarction and/or cerebrovascular disease [2, 3, 11–15].

Ultrasonic plaque morphology may add useful information about plaque stability and may correlate with symptoms. In addition to the visual judgment of plaque echolucency and homogeneity, the use of non-invasive methods that may quantify the tissue composition of the vascular wall (such as videodensitometry or the analysis of the integrated backscatter signal) has been proposed for the assessment of the cellular composition of atherosclerotic plaque, particularly of earlier lesions [16, 17]. Furthermore, plaque volume assessment by three-dimensional reconstruction of ultrasound or NMR images has been proposed to better evaluate atherosclerotic lesion changes.

Relationship to cardiovascular risk and to clinical events

Traditional risk factors, which include being of male sex, ageing, being overweight, elevated blood pressure, diabetes and smoking, are all positively associated with carotid IMT in observational and epidemiological studies. Hypertension, and particularly, high systolic blood pressure values, seems to have the greatest effect on IMT [19]. About 30% of hypertensive subjects may be mistakenly classified as at low or moderate added risk without an ultrasound for carotid arterial thickening or plaque, whereas vascular damage places them in the high-added risk group [18].

In addition, new risk factors, including various lipoproteins, plasma viscosity and hyperhomocysteinaemia, have demonstrated an association with increased IMT. Patients with metabolic syndrome have higher IMT than patients with individual metabolic risk factors. Carotid IMT has also been found to be associated with preclinical cardiovascular alterations in the heart, brain, kidney and lower-limb arteries.

Several studies have demonstrated and confirmed the important prognostic significance of IMT, as measured by ultrasound. In their prospective study Salonen et al. [12] observed in 1288 Finnish male subjects that the risk for coronary events was exponentially related to the increase in IMT in the common carotid and in the carotid bifurcation. In a larger sample of middle aged subjects (13,780) enrolled into the ARIC (Atherosclerotic Risk In The Communities) study [13] IMT, measured by ultrasound, was associated with an increased prevalence of cardiovascular and cerebrovascular diseases. In the Rotterdam study [2] IMT was shown to predict the risk of myocardial infarction and cerebrovascular events during a mean follow-up period of 2.7 years. The Cardiovascular Health Study [3] has prospectively evaluated 4,400 subjects aged over 65 years for a follow-up period of 6 years; the annual incidence of myocardial infarction or stroke increased in the highest quintiles of IMT measured in the common and the internal carotid arteries.

A recent metanalysis of data collected in 8 studies in general populations, including 37,197 subjects who were followed up for a mean of 5.5 years, has demonstrated that for an absolute carotid IMT difference of 0.1 mm, the future risk of myocardial infarction increases by 10% to 15%, and the stroke risk increases by 13% to 18% [15] (Table 1).

Effect of treatment

Therapeutic double-blind trials have shown that antihypertensive drugs may have a more or less marked effect on carotid IMT progression. A recent metaregression analysis [20], including 22 randomised controlled trials, has evaluated the effects of an antihyper-

Table 1. Hazard ratio (HR) for 0.1 mm difference in common carotid IMT (modified from ref. 15)

Event	HR	(95% confidence intervals)	N° patients
Adjusted for age and sex			
Myocardial infarction	1.15	1.05–1.17	30,162
Stroke	1.18	1.16–1.21	34,335
Adjusted for age, sex and other cardiovascular risk factors			
Myocardial infarction	1.1	1.08–1.13	30,162
Stroke	1.13	1.10–1.16	34,335

tensive drug versus placebo or another antihypertensive agent of a different class on carotid IMT. The results have shown that compared with non-treatment, diuretics ± beta-blockers or ACE inhibitors, or calcium channel blockers attenuate the rate of progression of carotid intima-media thickening. In the prevention of carotid intima-media thickening, calcium-antagonists are more effective than ACE inhibitors, which in turn are more effective than placebo or non-treatment, but not more active than diuretics ± beta-blockers (Table 2). The odds ratio for all fatal and non-fatal cardiovascular events in trials comparing active treatment with placebo reached statistical significance ($P = 0.007$).

Table 2. Effect of antihypertensive treatment on changes in IMT in trials with antihypertensive drugs (Modified from ref. 20)

Antihypertensive treatment	Comparison	Change IMT μm/year (95% confidence intervals)
All trials (n = 1780)	Placebo (n = 1549)	–7 μm (–12 to –2) $p = 0.01$
ACE inhibitors (n = 1161)	Placebo (n = 929)	–6 μm (–12 to 0.4) $p = 0.41$
Beta-blockers (n = 428)	Placebo (n = 434)	–10 μm (–33 to 13) $p = 0.02$
All trials (n = 2285)	Diuretics/beta-blockers (n = 2279)	–3 μm (–5 to –0.3) $p = 0.03$
Calcium-antagonists (n = 1811)	Diuretics/beta-blockers (n = 1808)	–5 μm (–9 to –1) $p = 0.007$
ACE inhibitors (n = 319)	Diuretics/beta-blockers (n = 321)	–1 μm (–5 to 2) $p = 0.52$
ACE inhibitors (n = 142)	Calcium-antagonists (n = 145)	–23 μm (–42 to –4) $p = 0.02$

The results of the PHYLLIS study have reported that in hypertensive and hypercholesterolaemic patients the administration of pravastatin prevents the progression of carotid intima-media thickening, seen in patients treated with hydrochlorothiazide, but the combination of pravastatin and the ACE-inhibitor fosinopril had no additive effect [21].

Few studies including a relatively small number of patients have shown lower IMT during treatment with angiotensin II antagonists than in patients treated with beta-blockers [22].

An ongoing study (Multicenter Olmesartan Atherosclerosis Regression Evaluation MORE) will give a more precise assessment of the effect of long-term treatment with an AT_1 receptor antagonist (olmesartan) and with a beta-blocker (atenolol) on carotid atherosclerosis, even with the use of the non invasive 3-D plaque measurement.

No significant changes in plaque composition were observed after 4 years of treatment with either lacidipine or atenolol in patients participating into the ELSA study, suggesting that treatment with a calcium antagonist may slow IMT progression without influencing the characteristics of plaque tissue [23].

Conclusions

An ultrasound examination of the common, bifurcation and internal carotid arteries should be performed in hypertensive patients with concomitant risk factors, such as smoking, dyslipidaemia, diabetes or a family history of cardiovascular diseases. However, before routine measurement of IMT may be proposed in wide clinical practice for stratifying cardiovascular risk, methodological standardisation for IMT measurement needs to be further implemented.

Quantitative B-mode ultrasound of the carotid arteries requires appropriate training. In the presence of increased IMT or plaque in the carotid arteries an aggressive approach to risk-factor modification should be considered.

References

1. Muiesan ML, Pasini GF, Salvetti M, et al. Cardiac and vascular structural changes: prevalence and relation to ambulatory blood pressure in a middle aged general population in northern Italy: the Vobarno Study. Hypertension 1996; 27: 1046–1053.
2. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997; 6 (5): 1432–1437.
3. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, for the Cardiovascular Health Study Collaborative research Group. Carotid intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999; 340: 14–22.
4. Furberg CD, Adams HP jr, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation 1994; 90: 1679–1687.
5. Tang R, Henning M, Thomasson B, et al. Baseline reproducibility of B mode ultrasonic measurement of carotid artery intima-media thickness: the European Lacidipine Study on Atherosclerosis (ELSA). J Hypertens 2000; 18: 197–201.
6. Zanchetti A, Agabiti-Rosei E, Dal Palu' C, Leonetti G, Magnani B, Pessina A, for the Verapamil in Hypertension and Atherosclerosis Study (VHAS) Investigators. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long--term randomized treatment with either verapamil or chlortalidone on carotid intima-media thickness. J Hypertens 1998; 16: 1667–1676.
7. Bots M, Evans G, Riley W, Grobbee DE. Carotid intima-media thickness measurements in intervention studies design options, progression rates, and sample size considerations: a point of view. Stroke 2003; 34: 2985–2994.
8. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim Carotid Intima-Media Thickness Consensus (2004 –2006). An Update on Behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2006; 23: 75–80.
9. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter and intra-observer variability. Ultrasound Med Biol 1991; 17: 225–230.
10. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). JAMA 1996; 276: 785–791.
11. Suurkula M, Agewall M, Fagerberg B, Wendelhalg I, Widgren B, Wikstrand J. Ultrasuond evaluation of atherosclerotic manifestations in the carotid artery in high risk hypertensive patients. Risk intervention Study (RIS) Group. Arteriosclerosis & Thrombosis 1994; 14 (8): 1297–1304.
12. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991; 11: 1245.
13. Chambeless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharret AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study 1987–1993. Am J Epidemiol 1997; 146: 483–494.
14. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of arterial intima-media thickness in predicting clinical coronary events. Ann Int Med 1998; 128 (4): 262–269.
15. Lorenz M, Markus H, Bots M, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta--analysis. Circulation 2007; 115: 459–467.
16. Puato M, Faggin E, Rattazzi M, et al. on behalf of the Study Group on Arterial Wall Structure. In vivo non invasive identification of cell composition of intimal lesions: a combined approach with ultrasonography and immunocytochemestry. J Vasc Surg 2003; 38: 1390–1395.
17. Ciulla M, Paliotti R, Ferrero S, et al. Assessment of carotid plaque composition in hypertensive patients by ultrasonic tissue characterization : a validation study. J Hypertens 2002; 20: 1589–1596.
18. Cuspidi C, Ambrosioni E, Mancia G, Pessina AC, Trimarco B, Zanchetti A. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the assessment of prognostic risk observational survey. J Hypertens 2002; 20: 1307–1314.
19. Zanchetti A, Bond MG, Hennig M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: Principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002; 106: 2422–2427.
20. Wang JG, Staessen JA, Li Y, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke 2006; 37: 1933–1940.
21. Zanchetti A, Crepaldi G, Bond G, et al., on behalf of PHYLLIS Investigators. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis. Principal results of PHYLLIS — a randomized double--blind trial Stroke. 2004; 35: 2807–2812.
22. Agabiti-Rosei E, Muiesan ML, Rizzoni D. Angiotensin II antagonists and protection against subclinical cardiac and vascular damage. In: Angiotensin II Receptors Antagonists. Mancia G (ed). 2nd edition. 2006: 111–126.
23. Paliotti R, Ciulla M, Hennig M, et al. Carotid wall composition in hypertensive patients after 4-year treatment with lacidipine or atenolol: an echoreflectivity study J Hypertens 2005; 23: 1203–1209.