NONINVASIVE MEASUREMENT OF EARLY ATHEROSCLEROSIS BY HIGH-RESOLUTION B-MODE ULTRASONOGRAPHY

Milan Halenka

3rd Department of Internal Medicine, University Hospital, 775 20 Olomouc,Czech Republic

Received August 31, 1999

Key words: Early atherosclerosis / Intima-media thickness / B-mode ultrasound imaging / Cardiovascular risk factors

Development of sophisticated noninvasive methods permits the identification of asymptomatic subjets with early atherosclerosis. High-resolution B-mode ultrasound measurement of the intima-media thickness (IMT) is a safe and reproducible way of quntifying early changes in the arterial wall, mainly in the carotid arteries. Increased carotid IMT is associated with major cardiovascular risk factors and seems to be a powerful predictor of cardiovascular events, especially coronary artery disease.

Atherosclerosis is the leading cause of death and disability in most industrialized nations. It leads to an epidemic of myocardial infarction, ischemic stroke, occlusion of peripheral vessels and sudden death. Better understanding of the nature of the atherosclerosis and its consequences is being reflected in lower mortality and increased quality of life. Death from stroke and heart disease have declined during the last 20 years in western countries. At this time many interventions are aimed at the sequelae of atherosclerosis rather than the arterial disease itself. Most current clinical care and research are focused on persons who are symptomatic. Such endeavors are important but treatments are prescribed very late in the course of atherosclerosis. In this stage the arterial disease has progressed to advanced lesions – a complex plaque that may involve fibrosis, ulceration, hemorrhage or thrombosis. Often therapies are expensive and can be complicated by adverse reactions.

Atherosclerosis is an evolving, progressive arterial disease that in earliest forms is present in young persons. 100% of subjects aged 25–34 years showed fatty streaks and fibrous plaques in the distal portion of the common carotid artery and 20% had calcified plaques (an autopsy study). In older populations, there is a large number of subjects who have asymptomatic atherosclerosis. In the Cardiovascular Health Study (CHS) 31% of adults at least 65 years of age had evidence of clinical cardiovascular disease and using noninvasive testing, a further 37% of adults had subclinical cardiovascular disease. Interventions before the development of clinical disease may be indicated in these patients[1–4].

Past research has focused on the prevention of clinical endpoints such as stroke or myocardial infarction. Identification of risk factors that accelerate the evolution of atherosclerosis has promted clinical trials of treatments that might slow the course of the arterial disease. Development of sophisticated noninvasive tests, including the measurement of carotid intima-media thickness (IMT) by high-resolution B-mode ultrasound, permits the detection of early arterial lesions in asymptomatic populations. In addition, serial measurements can easily be made so that progression of IMT can be used as a primary outcome measure for clinical trials. Development of noninvasive techniques for examining the walls of arteries greatly expedites clinical research on therapies that might halt progression or foster regression of atherosclerotic lesions. Lumen stenosis tends to occur later in the atherosclerotic process, initially there is a compensatory dilatation in response to accumulation of atheromatous material until approximately 40% of the lumen is occupied by plaque. Development of B-mode ultrasound allows visualization of the artery wall, permitting detection and quantification of very early changes. Measurement of IMT is highly reproducible, and the intrasonographer and intrareader error is small. IMT in the carotid artery can be examined at regular intervals and progression or regresssion of the lesion can be assessed. Rates of progression in control groups have ranged from 0,006 mm/year in asymptomatic subjects to 0.06 mm/year in subjects with the coronary artery disease (CAD)[5,6].

Ultrasonographic images of the arterial wall are based on the difference in the acoustic impedance between tissues separated by an interface. The ultrasonic image formed by the arterial wall is characterized by two parallel echogenic lines separated by a hypoechogenic space – the "double line" pattern. On the basis of the physical principles of ultrasound, the thickness of an echogenic line does not correspond to any anatomic structure but is mainly dependent on the signal processing of the ultrasound scan. Compared with corresponding histologic tunica, ultrasound overestimated the thickness of the intima and adventitia and underestimated the thick-

ness of the media. Thus, the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line is the combined thickness of the intimal and medial layers – the intima-media thickness (IMT). Among studies are methodologic differences concerning probe frequency (5–10 Mz), site and number of measurements, type of IMT parameter (maximum or mean IMT), manual or computer-assisted analysis. Practical experience shows that higher frequency transducer produce higher-quality images. The „gold standard" of off-line analysis is the video-image analysis. Early attempts to quantify extracranial carotid arterial wall thickness (AWT) using B-mode ultrasound focused on measurements at a single site and demonstrated the feasibility of obtaining such measurements but had considerable interobserver variability. Latelly it vas demonstrated that reliability could be markedly improved if attentiones focused on an aggregate sum or mean of AWT measurements from several sites of extracranial carotid artery. Subsequently has been evaluated the associations of AWT with cardiovascular disease risk factors and with clinical coronary heart disease. It is necessary to use precisely defined measurement protocol and training and certification of ultrasound sonographers and readers. Irrespective of method certain technical questions have not yet been answerd, including the validity of measurements from the near as opposed to the far wall and the use of measurements from the internal carotid artery (ICA) and the bulb as well as the common carotid artery (CCA). Several informative protocols have been developed that combine informations from B-mode and Doppler ultrasound, which have the potential advantage of quantifying lumen stenosis, but the potential disadvantage of categorization of information according to the method of collection. Yearly progression rates for AWT in the CCA, bulb and ICA should be about 0.01–0.015 mm/year. This progression rate is observed in healthy populations, whereas populations with cerebrovascular or cardiovascular disease may progress rapidly. The sources of variability in AWT measurements are numerous and, in general, use of an aggregate of several measurements results in more reliable data than use of measurements made at a single site. Precision is of extreme importance in quantifying progression of atherosclerosis. Studies that incorporate the ICA are potentially hampered by the less complete visualizability of this segment as compared with the CCA. It was observed that whereas more than 95% of the walls of the CCA, as well as more than 85% of the walls of the bifurcation, could be adequately visualized in replicate, 15% of the walls of the ICA could not be visualized at all and only 62% could be imaged in replicate. For this reason, aggregate measures of the IMT have generally been chosen as the primary index of analysis for several studies of atherosclerosis progression[7–11].

For a long time, epidemiologic studies of cardiovascular diseases have focused on clinical endpoints such as myocardial infarction, sudden cardiac death or stroke. The recent availability of noninvasive methods capable of quantifying atherosclerosis is of great importance for epidemiologic and clinical research on the pathophysiology of the atherosclerotic process, as well as for prevention trials. Presently, several ongoing epidemiologic studies are based on high-resolution B-mode ultrasound measurement of IMT, considered as a safe and reproducible way of quantifying early changes is the arterial wall, mainly in the carotid arteries. However, the interpretation of their findings is limited by a lack of measurement standardization. Moreover, there is no agreement between studies about the threshold beyond which IMT could be considered pathologic. Together with differences in populations, this situation explains the large variability of the prevalence rates of IMT observed in various studies. On the other hand, most conventional cardiovascular risk factors – age, hypertension, diabetes mellitus, smoking-have been consistently related to an increase in IMT[12,13]. Moreover, associations with newer or less established risk factors have also been described, including fasting insulin[14], lipoprotein(a)[15], hemostatic and fibrinolytic parameters[16], hyperhomocysteinemia[17] and factors involved in oxydative modification of low-density lipoprotein cholesterol[18–20] or regulation of the renin-angiotensin system[21]. In conclusion, IMT is clearly associated with an atherogenic profile, suggesting it may be a marker of early atherosclerosis. IMT measurements represent a very promising method for a better understanding of the mechanisms involved in the initiation and development of the atherosclerotic process. In particular, B-mode ultrasonography offers the great advantages of being applicable to healthy populations and relatively low in cost, while providing reliable estimates of early disease of arterial wall. This technique is simple and generally considered reproducible, it has an important limitation in that it cannot distinguish the intima from the medial layer. Although the general principles of IMT measurements are comon to all B-mode ultrasound studies, the methodology used shows important variations both in scanning and in reading procedures. There is general agreement that the near wall is less easy to image reliably than the far wall. The ultrasoud studies have focused on IMT measurements at the common carotid artery (CCA), where the double-line pattern is easier to visualize, whereas other studies have included IMT measurements at the bifurcatin and the internal carotid artery (CCA) because these arterial locations are more prone to atherosclerosis. These differences between arterial segments reflect the physiologic increase in wall thickness due to hemodynamic stresses in bifurcation and branching zones, as well as the comparatively greater frequency of atherosclerotic lesions in these locations than in straight segments such as the CCA, which is generally affected only in endstage disease. A cutoff point of 0.75 mm or 1 mm was chosen to identify subjects as having an arterial wall thickening. Plaques have been defined as a mineralization or a protrusion into the lumen, a definition is sometimes combined with wall thickness measurements (more than

1 mm, 1.5 mm or 2 mm). The limits of normality may vary according to the characteristics of the population (age, sex, race)[22].

In the Atherosclerosis Risk in Communities (ARIC) study[23], the Cardiovascular Health Study (CHS)[1] and the Rotterdam Study[24], subjects with myocardial infarction, angina pectoris or peripheral vascular or cerebrovasculr disease had significantly higher mean carotid IMT. In the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD)[13,25] the maximal IMT of the common carotid artery was a significant predictor of subsequent myocardial infartion. Finally increased carotid IMT is associated with traditional cardiovascular risk factors including age, male sex, hypertension, smoking, diabetes mellitus, insulin resistance, lipoprotein(a) and LDL cholesterol. An inverse relationship has been shown for high-density lipoprotein cholesterol (HDL) and use of postmenopausal hormonal replacement[26].

Increased AWT is also associated with high consumption of saturated fat. Some trials have been completed that tested effects of lipid-lowering therapies using measurements of carotid IMT to monitor responses. In these studies, Pravastatin, Lipids and Atherosclerosis in the Carotid arteries (PLAC-II)[27] and the Kuopio Atherosclerosis Progression Study (KAPS)[28] with pravastatin, the Asymptomatic Carotid Artery Progression Study (ACAPS)[29,30] with lovastatin, both a hydroxymethyl-glutaryl-CoA reductase inhibitors, are reassuring that lipid-lowering therapies can promote reduction in carotid AWT as a preventive measure. Progression of carotid bifurcation stenosis with increased risk of stroke correlate primarily with elevated low-density lipoprotein (LDL) cholesterol, fibrinogen and a history of coronary artery disease (CAD), insignificantly with high-density lipoprotein (HDL) cholesterol. Because of atheromatous lesions can enlarge abluminally to balloon the vessel outward without decreasing luminal diameter, AWT or IMT might offer a more accurate index of atheromatous burden, and migth provide a more accurate measure of carotid bifurcation progression, particularly as they may relate to risk factors. It is noteworthy that progressing subjects had statistically higher levels of LDL cholesterol and fibrinogen. Progression of IMT coralate with this factors – LDL cholesterol, age, smoking, rapid progression occured in those subjects with preexisting carotid atheroslcerosis (presence of a plaque by ultrasound or IMT 1.1 mm and more).[1,3,13]

Whereas the prognostic significance of left ventricular hypertrophy (LVH) is well established, the potencial clinical relevance of vascular hypertrophy has only recently begun to emerge. Furthermore, these alterations in vascular structure appear to parallel those that occur in the left ventricule in hypertension. The strongest determinants of vascular size and LVH are age and systolic blood pressure. In the longitudinal KIHD study isolated carotid IMT is associated with a 2.17-fold increase in subsequent risk of myocardial infarction and for each 0,1 mm increase in CCA-IMT the risk of myocardial infarction increased by 11%. The risk of subsequent myocardial infarction was further increased by the presence of small or large atherosclerotic plaques. This findings confirms the well established association of carotid and coronary atherosclerosis and suggest that IMT may in some instances indicate early or diffuse atherosclerosis. Consistent with this hypothesis is the finding in the Rotterdam Study of an association between CAA-IMT and lower extremity atherosclerosis[24]. Given the association of increasing LVH with increased risk of stroke in the Framingham population and the association of LVH with an increased likehood of both carotid hypertrophy and atherosclerosis, independent of other risk factors,vascular hypertrophy may directly predispose to cerebral ischemia and thromboembolic disease[31,32].

Hypertensive subjects has significantly higher IMT values than normotensive subjects. The mean difference in the CCA-IMT was in the range of 0.06–0.25 mm. There was found a significant association with systolic blood pressure, which seems to be one of the most powerful risk factors for AWT, especially in elderly populations[33,34]. Currrent smokers have significantly higher IMT values than never smokers. The mean difference in the IMT ranged from 0.05 mm to 0.10 mm. A small but significant increase in IMT among passive smokers has also been reported in the ARIC study[35]. The relations of IMT to blood lipids and lipoproteins are of prime importance. Case-control studies have found that the CCA of hypercholesterolemic patients showed IM thickening in comparison with normocholesterolemic subjects. The mean difference between case and control subjects was about 0.13 mm. An interesting study performed in children suggest that AWT might be rapidly affected by lipid disorders, since an increased CAA-IMT was detectable from age 6 year in hypercholesterolemic children[18,19,27,28,29,30,36,37]. Among hemostatic parameters fibrinogen is now considered a powerful cardiovascular risk factor. In the ARIC study has been inconsistently related to IM thickening[16]. Concerning the other factors, there are too few data to draw any conclusions.

Atherosclerosis is the leading cause of death and disability in the developed world. It affects the majority of populations, starting from adolescence. Because of the adaptive abilities of arteries to compensate the reduced blood flow, its clinical manifestations usually appear in the middle or old age. Atherosclerotic disease may remain symptomless for decades too, and its first manifestation can be severe, even deadly. For these reasons, prevention of atherosclerotic disease or of its progression has become an important goal in medicine. Therefore it is necessary to be able to assess not only the presence and the severity of the disease in symptomatic subjects but also in asymptomatic subject, in the best case in the stage of early atherosclerosis.This requires an athically acceptable method that carries no risk and can be repeated. High-resolution B-mode imaging of atherosclerosis is a safe and relatively inexpensive way to asses large superficial arteries. It provides structural

information and enables quantitative measurements such as the intima-media thickness of arterial wall.

REFERENCES

1. O'Leary, D. H., Polak, J. F., Kronmal, R. A., Kittner, S. J., Bond, M. G. (1992) Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. Stroke *23*, 1752–60.
2. Kuller, L., Borhani, N., Furberg, C., Gardin, J., Manolio, T., O'Leary, D., Psaty, B., Robbins, J. (1994) Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. Am. J. Epidemiol. *139*, 1164–79.
3. Howard, G., Sharret, A. R., Heiss, G., Evans, G. W., Chambless, L. E. and the ARIC investigators (1993) Carotid artery intimal-medial thickness: distribution in general populations as evaluated by B-mode ultrasound. Stroke *24*, 1297–304.
4. Bonithon-Kopp C., Jouven, X., Taquet, A., Touboul, P. J., Guize, L., Scarabin, P. Y. (1993) Early carotid atherosclerosis in healthy middle-aged women: a follow-up study. Stroke *24*, 1837–43.
5. Salonen, R., and Salonen, J. T. (1991) Determinants of carotid intima-media thickness: a population-based ultrasonographic study in eastern Finnish men. J. Intern. Med. *229*, 225–31.
6. Crouse, III, J.R., Goldbourt, U., Evans, G., Pinsky, J., Sharret, A. R., Sorlie, W., Heiss, G. for the ARIC investigators (1994) Arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke *25*, 1354–59.
7. Crouse, J. R. and Thompson, C. J. (1993) An evaluation of methods for imaging and quantifying coronary and carotid lumen stenosis a atherosclerosis. Circulation *87,* (Suppl. II), 17–33.
8. Salonen, J. T. and Salonem, R. (1993) Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation *87,* (Suppl. II), 56–65.
9. Salonen, R., Haapanen, A., Salonen, J. T. (1991) Measurement of intima-media thickness of common carotid arteries with high-resolution B-mode ultrasonography: inter- and intraobserver variability. Ultrasound Med. Biol. *17*, 225–30.
10. Wendelhag. I., Gustavsson, T., Suurkula, M., Berglund, G., Wikstrand, J. (1991) Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. Clin. Physiol. *11*, 565–77.
11. Bots, M. L., Mulder, P. G. H., Hofman, A., van Es, G. A., Grobbee, D. E. (1994) Reproducibility of carotid wall thickness measurements. The Rotterdam Study. J. Clin. Epidemiol. *47*, 921–30.
12. Heiss, G., Sharret, A. R., Barnes, R., Chambless, L. E., Szklo, M. (1991) Carotid atherosclerosis measured by B-mode ultrasound in poulations: associations with cardiovascular risk factors in the ARIC study. Am. J. Epidemiol. *134*, 250–56.
13. Salonen, R. and Salonen, J. T. (1990) Progression of carotidf atherosclerosis and its determinants: a population-based ultrasonography study in eastern Finnish men. Atherosclerosis *81*, 33–40.
14. Folsom, A. R., Eckfeldt, J. H., Weitzman, S., Ma, J., Chambless, L. E., Barnes, R. W., Cram, K. B., Hutchinson, R. G. for the Atherosclerosis Risk in Communities (ARIC) study investigators (1994) Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size and physical activity. Stroke *25*, 66–73.
15. Schreiner, P. J., Morrisett, J. D., Sharrett, R., Patsch, W., Tyroler, H. A., Wu, K., Heiss, G. (1993) Lipoprotein(a) as a risk factor for preclinical atherosclerosis. Arterioscler. Thromb. *13*, 826–33.
16. Folsom, A. R., Wu, K. K., Shahar, E., Davis, C. E. for the Atherosclerosis Risk in Communities (ARIC) study investigators (1993) Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. Arterioscler.Thromb. *13*, 1829–36.
17. Malinow, M. R., Nieto, F. J., Szklo, M., Chambless, L. E., Bond, G. (1993) Carotid artery intima-media thickening and plasma homocysteine in asymptomatic adults. The ARIC study. Circulation *87*, 1107–13.
18. Sharret, A. R., Patsch, W., Sorlie, P. D., Heiss, G., Bond, M. G., Davis, C. E. (1994) Associations of lipoprotein cholesterols, apolipoproteins A–I and B and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) study. Arterioscler.Thromb. *14*, 1098–104.
19. Salonen, J. T., Salonen, R., Seppanen, K., Kantola, M., Suntioinen, S., Korpela, H. (1991) Interaction of serum copper, selenium and low-density lipoprotein cholesterol in atherogenesis. Br. Med. J. *302*, 756–60.
20. Salonen, J. T., Yla-Herttuala, S., Yamamoto, R., Butler, S., Korpela, H., Salonen, R. (1992) Autoantibody against oxidised LDL and progression of carotid atherosclerosis. Lancet *339*, 883–87.
21. Bonithon-Kopp, C., Ducimetiere, P., Touboul, P. J., Feve, J. M., Billaud, E., Courbon, D., Heraud, V. (1994) Plasma angiotensin-converting enzyme activity and carotid wall thickening. Circulation *89*, 952–54.
22. Wikstrand, J., Wendelhag, I. (1994) Methodological considerations of ultrasound investigation of intima-media thickness and lumen diameter. J. Intern. Med. *236*, 555–9.
23. Burke, G. L., Evans, G. W., Riley, W. A., Sharret, A. R., Howard, G., Heiss, G. (1995) Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) study. Stroke *26*, 386–91.
24. Bots, M. L., Hofman, A., Grobbee, D. E. (1994) Common carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. Arterioscler. Thromb. *14*, 1885–91.
25. Salonen, J. T. and Salonen, R. (1991) Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler. Thromb. *11*, 1245–49.
26. Manolio, T. A., Furberg, C. D., Shemanski, L., Psaty, B. M., O'Leary, D. H., Tracy, R. P., Bush, T. L. and the CHS collaborative group (1993) Association of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. Circulation *88*, 2163–71.
27. Crouse, III, J. R., Byington, R. P., Bond, M. G., Espeland, M. A., Furberg, C. D. (1995) Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries (PLAC-II). Am. J. Cardiol. *75*, 455–59.
28. Salonen, R., Nyssonen, K., Porkkala, J., Salonen, J. T. (1994) Kuopio Atherosclerosis Progression Study (KAPS): the effect of pravastatin on atherosclerotic progression in carotid and femoral arteries. Circulation *94*, 1–127.
29. Furberg, C. D., Adams, H. P., Jr., Applegate, W. B., Byington, R.P., Espeland, M. A., Hartwell, T. (1994) Effect of lovastatin on early atherosclerosis and cardiovascular events. Circulation *90*, 1679–87.
30. Adams, H. P., Jr., Byington, R. P., Hoen, H., Dempsey, R., Furberg, C. D. for the Asymptomatic Carotid Artery Plaque Study (ACAPS) research group (1995) Effect of cholesterol-lowering medications on mild atherosclerotic lesions of the carotid arteries and on the risk of stroke. Cerebrovasc. Dis. *5*, 171–77.
31. Cuspidi, C., Boselli, L., Bragato, R., Lonati, L., Sampieri, L., Bocciolone, M., Leonetti, G., Zanchetti, A. (1992) Echocardiographic and ultrasonographic evaluation of cardiac and vascular hypertrophy in patients with essential hypertension. Cardiology *80*, 305–11.
32. Roman, M. J., Pickering, T. G., Pini, R., Schwartz, J. E., Devereux, R. B. (1995) Prevalence and determinants of cardiac and vascular hypertrophy in hypertension. Hypertension *26*, 369–73.
33. Bots, M. L., Hofman, A., de Bruyn, A. M., de Jong, P. T. V. M., Grobbee, D. E. (1993) Isolated systolic hypertension and vessel wall thickness of the carotid artery. The Rotterdam Elderly Study. Arterioscler. Thromb. *13*,64–69.
34. Suurkula, M., Agewall, S., Fagerberg, B., Wendelhag, I., Widgren, B., Wikstrand, J. on behalf of the Risk Intervention Study (RIS) group (1994)Ultrasound evaluation of atherosclerotic manifestations in the carotid artery in high-risk hypertensive patients. Arterioscler. Thromb. *14*, 1297–304.
35. Howard, G., Burke, G. L., Szklo, M., Tell, G. S., Eckfeldt, J., Evans, G., Heiss, G. (1994) Active and passive smoking are associated with increased carotid wall thickness. The ARIC study. Arch. Intern. Med. *154*, 1277–82.

36. Fisicaro, M., Da Col, P. G., Tonizzo, M., Fonda, M., Bollini, M., Cattin, L. (1994) Early carotid atherosclerosis in asymptomatic adults with primary moderate hypercholesterolemia: a case-control study. Atherosclerosis *106*, 255–61.

37. Pauciullo, P., Iannuzzi, A., Sartorio, R., Irace, C., Covetti, G., Di Costanzo, A., Rubba, P. (1994) Increased intima-media thickness of the common carotid artery in hypercholesterolemic children. Arterioscler. Thromb. *14*, 1075–79.