

Dossier de presse

Press book

French Core Laboratory IMT Commercializes Cardio Ultrasound Software

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by Kathy Mahdoubi, Editorial Coordinator

As a result of extensive involvement in clinical trials, Paris-based Intelligence in Medical Technologies, or IMT, has developed cardio ultrasound software that measures intima-media thickness and other risk factors for cardiovascular disease.

For more than 10 years, IMT has taken part in large, prospective and cross-sectional drug studies, many focused on the epidemiology and treatment of atherosclerosis in superficial blood vessels. These studies present compiled data from at least 25,000 participants and 600 medical centers in 50 different countries.

Founder Dr. Pierre-Jean Touboul applied the computing techniques developed during clinical trials to IMT's flagship cardio ultrasound software product, M'Ath, which stands for measurement of atherosclerosis. Touboul is well published in the medical community and has more than 25 years of experience with cardiovascular disease and imaging, says Aurelia Puech-Bournonville, study project manager at IMT.

"There are two faces to the company," Puech-Bournonville tells DOTmed News. "One is for the software and its development and the other is for central reading and clinical studies."

Touboul started working on a prototype for the software about sixteen years ago and the business side of IMT was created in 2002. M'Ath now has 1,200 users on five continents, and because the technology is just emerging, there is tremendous room for expansion across Europe, South America, the Middle East and Asia, she says.

The technology is a non-invasive means of examining the first two layers of the carotid arteries. More than 50,000 carotid arteries have been measured in clinical trials using the M'Ath software.

"This software offers the capability to measure intima media thickness, plaque thickness, and density stenosis degree and distensibility using automated detection algorithms," Puech-Bournonville explains. "Flow-mediated vasodilation of the brachial artery can also be measured in real time."

A Growing Sense of Urgency

Puech-Bournonville has watched the cardiovascular community shift from low interest in the measurement of intima-media thickness to a growing sense of urgency from facilities wanting to implement the technology.

"The measurement of IMT is really a new way of seeing things," says Puech-Bournonville. "The mentality has changed dramatically within the past three or four years. Now everybody wants our software."

M'Ath can run on any PC and plugs directly into the video output of any ultrasound device, including 3-D technologies, and it supports a variety of image formats and languages, says Puech-Bournonville. The software is independent and upgradeable, thereby preventing early obsolescence. IMT also sells the license in a turnkey workstation that comes with a high-performance laptop.

M'Ath is FDA approved and has received ISO 9001 certification and uses the CE mark. IMT organizes training for their software at their facilities in Paris, on site, or online. In addition, IMT has a development team currently working on IMT Live, which is designed for ultrasound image acquisition.

IMT is not the only producer of software that measures intima-media thickness in the field of ultrasonography.

"Other manufacturers have started to create similar technologies but they don't have the years of experience that we do," Puech-Bournonville says.

It appears to be a growing market for IMT. Slowing economies have not had too detrimental an effect on their bottom line. Puech-Bournonville attributes this to the affordability of the M'Ath software. Imaging centers spend several thousands of dollars for ultrasound equipment, whereas the software comes in packages for as low as 1,500 euros, she says.

Representatives of IMT are scheduled to attend the 2009 European Congress of Radiology (ECR) Conference in Vienna March 6 - 10.

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

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Key Words

Intima-media thickness • Consensus • Vascular ultrasound • Randomized clinical trials • Carotid diseases

Abstract

Intima-media thickness (IMT) is increasingly used as a surrogate end point of vascular outcomes in clinical trials aimed at determining the success of interventions that lower risk factors for atherosclerosis and associated diseases (stroke, myocardial infarction and peripheral artery diseases). The necessity to promote further criteria to distinguish early atherosclerotic plaque formation from thickening of IMT and to standardize IMT measurements is expressed through this updated consensus. Plaque is defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface. Standard use of IMT measurements is based on physics, technical and disease-related principles as well as agreements on how to perform, interpret and document study results. Harmonization of carotid image acquisition and analysis is needed for the comparison of the IMT results obtained from epidemiological and interventional studies around the world. The consensus con-

cludes that there is no need to 'treat IMT values' nor to monitor IMT values in individual patients apart from exceptions named, which emphasize that inside randomized clinical trials should be performed. Although IMT has been suggested to represent an important risk marker, according to the current evidence it does not fulfill the characteristics of an accepted risk factor. Standardized methods recommended in this consensus statement will foster homogenous data collection and analysis. This will help to improve the power of randomized clinical trials incorporating IMT measurements and to facilitate the merging of large databases for meta-analyses.

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Introduction

Decades of silent arterial wall alterations precede vascular clinical events, which then reflect advanced atherosclerotic disease. The first morphological abnormalities of arterial walls can be visualized by B-mode ultrasonography. This high-resolution, noninvasive technique is one of the best methods for the detection of early stages of atherosclerotic disease, because it is rapidly applicable, readily available and demonstrates the wall structure

Design, Baseline Characteristics and Carotid Intima-Media Thickness Reproducibility in the PARC Study

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Key Words

Intima-media thickness · Cardiovascular risk ·
Ultrasound, artery wall

Abstract

Background: Intima-media thickness (IMT) is associated with an increased risk of cardiovascular and cerebral ischemic events, but its correlation with the absolute cardiovascular risk is not known in large populations. The Paroi Artérielle et Risque Cardiovasculaire (PARC) Study is an epidemiological study designed to correlate conventional assessment of cardiovascular risk with the mean IMT of the common carotid. **Methods:** In the PARC study, 6,416 subjects were enrolled, including 80.7% subjects with cardiovascular risk factors and 19.3% without. A specific methodology was designed to harmonize the acquisition and processing of data at the 283 centers. Interreader agreement on image quality and IMT measurement of the common carotid artery (CCA-IMT) was assessed from a random sample of 10% of the PARC study population. **Results:** The intraclass correlation coefficient was 0.98 (95% CI 0.966–0.985), and the accuracy was high (standard deviation of the error measurement: 0.0185 mm). **Conclusions:** The reproducibility of

the measurements assessed by means of the intraclass correlation coefficient and the accuracy of the CCA-IMT measurement obtained in the PARC Study demonstrate the feasibility of large multicenter studies of IMT measurement.

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Background

Ultrasound measurement of the thickness of the two inner layers (i.e. the intima and media) of the arterial wall was first correlated with anatomy [1] 20 years ago, thus bringing a new dimension to cardiovascular risk evaluation. The association between intima and media thickness (IMT) and cardiovascular risk factors was then demonstrated by several epidemiological studies [2–7]. One of the major advances to result from its introduction is based on its ability to detect early arterial disease in asymptomatic individuals. However, many studies conducted in different countries have shown that IMT values differ from one country to another, which could partly account for the limitations of conventional cardiovascular risk evaluation [8].

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Carotid artery intima media thickness, plaque and framingham cardiovascular score in Asia, Africa/Middle East and Latin America: the PARC-AALA Study

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Abstract

Objective The PARC-AALA (Paroi artérielle et Risque Cardiovasculaire in Asia Africa/ Middle East and Latin America) study was designed to evaluate the correlation between intima-media thickness of the common carotid artery (CCA-IMT), carotid plaque and absolute cardiovascular risk in a multi-ethnic population.

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Methods An international, cross-sectional, study including 79 centres from 21 countries in Asia, Africa, the Middle East and Latin America. Two thousand three hundred and twenty-eight subjects, meeting all inclusion criteria, were stratified by risk factors groups (no modifiable factor or at least both uncontrolled hypertension and hypercholesterolemia). CCA-IMT, presence of plaque and cardiovascular risk factors were assessed for each individual.

Results Some intergeographical characteristics in demographics, and risk factors were found accompanying early atherosclerosis marker differences. In Asia where the subjects were at lower risk, the mean CCA-IMT was 4% lower than in Africa/ Middle East and Latin America. On multiple linear regression analysis CCA-IMT and carotid plaque were independently associated with increased Framingham cardiovascular score (FCS) without heterogeneity across geographic regions. CCA-IMT and carotid plaque explained roughly 20% of the FCS in both genders.

Conclusion The PARC-AALA study confirms the correlation between CCA-IMT and FCS in three different populations. Intima-media thickness (IMT) and plaque evaluation may represent a complementary predictive tool for detection of cardiovascular disease in individuals.

Keywords Carotid plaque · Framingham score · Hypercholesterolemia · Hypertension · Intima media thickness · Ultrasound

Plasma Homocysteine Levels and Parkinson Disease: Disease Progression, Carotid Intima-media Thickness and Neuropsychiatric Complications

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Abstract

Objective:

To determine whether plasma homocysteine (Hcy) levels are associated with clinical characteristics, neuropsychological and psychiatric manifestations and cardiovascular comorbidity in patients with Parkinson disease (PD).

Background:

Elevated Hcy levels are linked to atherosclerosis, vascular disease, depression, and dementia. Patients with PD treated with L-dopa have been shown to have elevated Hcy levels.

Design/Methods:

Idiopathic PD patients were evaluated using the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, Parkinson Psychosis Rating Scale, Beck Depression Inventory, Frontal Assessment Battery, Mini-Mental Status Examination, and several tests for frontal type cognitive functions. Fasting blood samples were collected for the measurement of Hcy, and carotid B-mode ultrasound was performed to measure intima-media thickness of the common carotid arteries.

Results:

Seventy-two consecutive PD patients (46 men; average age, 68.7 ± 11.6 years; average disease duration, 7.0 ± 4.7 years) were recruited. All but 10 patients were treated with L-dopa. The average level of Hcy was 16.4 ± 7.8 $\mu\text{mol/L}$, and 38.9% of the patients had Hcy level above the reference range (>15.0 $\mu\text{mol/L}$). The Hcy levels were associated with PD duration as they were with L-dopa treatment duration but were not associated with the parameters of disease severity or with L-dopa dose. The Hcy levels were associated neither with the common carotid intima-media thickness nor with cardiovascular morbidity. No association was found between Hcy and the neuropsychiatric features of PD such as depression, cognitive performance, or psychosis.

Conclusions:

Hyperhomocystinemia is common in L-dopa-treated PD patients but was not associated with neuropsychological complications (depression, dementia, and cognitive decline associated with frontal lobe functioning or psychosis), enhanced disease severity, or vascular comorbidity.

Key Words: Parkinson disease, neuropsychiatric complications, homocysteine

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Nonmotor complications in Parkinson disease (PD) become increasingly important as disease progresses. Among them are cognitive decline, dementia, depression, and psychosis.^{1,2} Their pathogenesis in PD is multifactorial. Elevated levels of homocysteine (Hcy), a sulfur-containing amino acid that occupies a central location in the metabolic pathways of thiol compounds, were shown in epidemiological and experimental studies to be linked with several conditions associated with vascular pathology including coronary artery disease, vascular dementia, and ischemic stroke.^{3–5} Neurodegenerative processes have also been linked to elevated Hcy, including cognitive decline and Alzheimer disease.^{6–9} Moreover, genetic and clinical data suggest roles for folate deficiency and Hcy in the pathogenesis of some psychiatric disorders such as depression and schizophrenia.^{10,11}

Plasma Hcy levels are elevated in patients with PD treated with L-dopa,^{12–16}

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Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings

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KEYWORDS

Angiography;
IVUS;
Ultrasound;
Carotid;
Coronary

Aims Although well supported by postmortem studies, the reliability of carotid atherosclerosis as surrogate marker of coronary atherosclerosis has been put in doubt by *in vivo* studies showing a poor correlation between carotid intima-media thickness (IMT) detected by external carotid ultrasound (ECU) and coronary stenosis assessed by quantitative coronary angiography (QCA). In the present study, we have investigated whether a stronger *in vivo* correlation between the two arteries can be obtained by using homogeneous variables such as carotid and coronary IMT, detected by ECU and intravascular ultrasound (IVUS), respectively.

Methods and results ECU, QCA, and IVUS measurements were made in 48 patients. Carotid IMT was correlated with both angiographic and IVUS findings. A significant but weak correlation was observed between ECU and QCA variables ($r \approx 0.35$, $P < 0.05$); the correlation between ECU and IVUS measurements of IMT was higher, with correlation coefficients ranging from 0.49 to 0.55. In patients with a QCA diagnosis of normal/intermediate coronary atherosclerosis, the presence of a carotid- $IMT_{mean} > 1$ mm was associated with an 18-fold increase in risk of having a positive IVUS test (OR = 17.99, 95% CI 1.83–177.14, $P = 0.013$) and with a seven-fold increased risk of having a significant IVUS coronary stenosis (OR = 7.4, 95% CI 1.27–44.0, $P = 0.028$).

Conclusion Carotid atherosclerosis correlates better with coronary atherosclerosis when both circulations are investigated by the same technique (ultrasound) using the same parameter (IMT). This supports the concept that carotid IMT is a good surrogate marker of coronary atherosclerosis.

Introduction

High resolution B-mode ultrasound is a non-invasive technique widely used to assess atherosclerosis in superficial arteries. It allows the accurate measurement of the distance between blood-intima and media-adventitia interfaces of the carotid wall, which is defined as carotid intima-media thickness (IMT).¹ Several authors have suggested that carotid IMT is a marker of atherosclerosis in other vascular beds.^{2–4} Indeed, an increased carotid IMT has been associated with a number of atherosclerosis risk factors,^{5–7} with the prevalence and extent of coronary artery disease (CAD)^{8,9} and with the incidence of new coronary and cerebral events.^{4,10} In view of these relationships, carotid IMT has been proposed as a surrogate endpoint to be

used in clinical trials as an alternative to coronary atherosclerosis.¹¹

In spite of the widespread use of carotid IMT as a surrogate for CAD, validation studies evaluating the correlation between carotid IMT measured by external carotid ultrasound (ECU) and CAD measured by quantitative coronary angiography (QCA) showed a relatively poor correlation ($r < 0.36$ on average).^{12–20} This finding has cast doubt on the reliability of carotid atherosclerosis as a surrogate marker of coronary atherosclerosis. Postmortem studies, however, have shown a far greater degree of correlation between the two arterial districts,^{21–24} which suggests that the poor correlation observed in ECU vs. QCA studies may be due more to technical issues than to differential effects of the traditional vascular risk factors on the carotid and coronary tissues.

Intravascular ultrasound (IVUS) is a unique imaging modality for the direct examination of vessel dimensions

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Intima-Media Thickness

A Marker of Accelerated Atherosclerosis in Women with Systemic Lupus Erythematosus

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ABSTRACT: Accelerated atherosclerosis is an emerging problem in patients with systemic lupus erythematosus (SLE). We planned an observational study to determine whether in patients with SLE carotid intima-media thickness (IMT) represents an early sign of accelerated atherosclerosis and to confirm that SLE adds to the traditional cardiovascular Framingham risk factors. Thirty females with SLE (age 18–65 years) underwent anamnestic, clinical, and laboratory evaluation and B-mode ultrasonography of carotid arteries, which provides a direct and noninvasive assessment of subclinical atherosclerosis. IMT measurements were performed on the right and left common carotid arteries 1.0 cm proximal to the carotid bulb and the mean IMT value was calculated with a dedicated software. The Framingham Point Score was also calculated for each subject. SLE patients showed a mean IMT value of 0.73 ± 0.12 (SD) mm. This value is significantly ($P < 0.05$) higher than that reported for an age-matched healthy female control population (0.66 ± 0.11 SD mm). A preliminary evaluation of the Framingham Point Score, estimating the 10-year risk for women to develop cardiovascular events, indicated an increased risk of early cardiovascular events in SLE patients. In our study we have shown that patients with SLE have an increased mean IMT value compared with a healthy females control. Moreover, the evaluation of the Framingham Point Score suggests that SLE is an additional risk factor for cardiovascular disease.

KEYWORDS: systemic lupus erythematosus; SLE; accelerated atherosclerosis; intima-media thickness; IMT; Framingham Point Score

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Variation in non-invasive measurements of vascular function in healthy volunteers during daytime

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A B S T R A C T

Although it is often recommended to standardize the time of day when performing non-invasive measurements of vascular function, the exact influence of the time of day on the outcome of IMT (intima-media thickness), PWV (pulse wave velocity), AIX (augmentation index) and FMD (flow-mediated dilatation) measurements has not been reported before. Nineteen healthy volunteers visited our department on two different occasions: the first visit was at 09:00 hours after an overnight fast, and the second visit was at 14:00 hours after a standardized breakfast. Non-invasive measurements of atherosclerosis were performed twice at 09:00 hours and once on the second visit at 14:00 hours. Measurement of IMT, PWV, AIX and FMD was reproducible according to the method of Bland and Altman. The absolute difference between repeated measurements at 09:00 hours showed no significant difference compared with the absolute difference between 09:00 and 14:00 hours for IMT (0.029 ± 0.014 compared with 0.021 ± 0.014 mm; $P = 0.27$), PWV (0.63 ± 0.50 compared with 0.75 ± 0.74 m/s; $P = 0.52$), AIX (4.0 ± 4.0 compared with 5.5 ± 5.2 %; $P = 0.35$) and FMD (3.8 ± 3.7 compared with 4.2 ± 2.9 %; $P = 0.70$). In conclusion, our results show that, in healthy volunteers during the daytime, IMT, PWV, AIX and FMD outcomes are not confounded by variation in the exact time of the examination as long as other (exogenous) conditions, including food intake, smoking and intake of alcohol, are carefully controlled for.

INTRODUCTION

Atherosclerosis is known to be a gradual process which can be measured with a variety of non-invasive techniques, each of which quantifies a different stage in the atherosclerotic process. Early functional changes can be quantified by FMD (flow-mediated dilatation), AIX (augmentation index) and PWV (pulse wave velocity), whereas IMT (intima-media thickness) and ABI (ankle-brachial blood pressure index) measurements can be used to quantify later and more structural changes in the arterial wall. As NIMA (non-invasive measurements of

atherosclerosis) become more and more important in clinical practice to evaluate the risk of CHD (coronary heart disease) and the effect of treatment, reliable and reproducible tests should be available, preferably during the course of the whole day for practical reasons.

It is recommended by International Task forces [1,2] to standardize patient conditions when performing NIMA, since there is abundant evidence that various exogenous variables, including smoking [3,4], vitamin intake [5,6], alcohol intake [7,8], use of oral contraceptives [9] and food intake [10–12], affect the outcome of PWV, AIX and FMD measurements. It is also often recommended

Key words: augmentation index, diurnal variation, flow-mediated dilatation, intima-media thickness, pulse wave velocity.

Abbreviations: ABI, ankle-brachial blood pressure index; AIX, augmentation index; CHD, coronary heart disease; FMD, flow-mediated dilatation; IMT, intima-media thickness; NIMA, non-invasive measurements of atherosclerosis; PWV, pulse wave velocity.

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Individual Measurement and Significance of Carotid Intima, Media, and Intima–Media Thickness by B-Mode Ultrasonographic Image Processing

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Objective—We assessed the clinical significance of intima (IT), media (MT), and intima–media (IMT) thickness of the common carotid artery using B-mode ultrasonographic image processing.

Methods and Results—One hundred seventy consecutive patients underwent common carotid artery scanning using high-resolution ultrasonography. A total of 150 patients could be analyzed off-line using ultrasonographic image processing, devised for individual measurement of IT, MT, and IMT. By univariate analysis, IT (range, 0.27 to 0.41 mm) was associated with age, whereas MT (range, 0.27 to 0.74 mm) and IMT (range, 0.49 to 1.12 mm) were associated with age, fibrinogen, and creatinine. Among atherosclerosis risk factors, hypertension was associated with thickness of all 3 layers, whereas smoking was associated with IT only. By multivariate analysis, IT was associated with age, hypertension, and smoking, whereas MT and IMT were associated with age, hypertension, and blood urea nitrogen level.

Conclusions—Carotid IT is associated with smoking, whereas age and hypertension are associated with thickness of all 3 arterial layers. Our results suggest a differential response of the vasculature to systemic risk factors. (*Arterioscler Thromb Vasc Biol.* 2006;26:2380-2385.)

Key Words: carotid arteries ■ atherosclerosis ■ risk factors ■ arterial intima ■ arterial media

Carotid artery intima–media thickness (IMT), which is the sum of the intima (IT) and media (MT) thickness, is independently associated with atherosclerotic risk factors and adverse cardiovascular events.^{1–4} Therefore, it has been used as an important atherosclerosis surrogate in clinical practice and in many clinical studies since Pignoli et al introduced the direct measurement of carotid IMT with ultrasound.⁵

Abnormal neointima formation is the main pathophysiological consequence of obliterative vascular disease, although atherosclerotic changes may also include smooth muscle proliferation and inflammatory processes in the media and adventitia.^{6,7} Therefore, we hypothesized that the intima and media have different clinical responses and roles to cardiovascular risk factor exposure and the development and pathophysiology of atherosclerosis.

We aimed to evaluate the response of the intimal and medial layers of the common carotid artery (CCA) to atherosclerosis risk factors, in terms of thickness of the layers, as assessed by high-resolution ultrasonography with an automated image-processing algorithm.

Methods

Study Population

One hundred seventy consecutive patients referred for ischemic heart disease screening were studied. Patients were included in this study if they provided informed consent and did not meet any of the following exclusion criteria: history of neck irradiation, carotid arterial surgery, previous dissection of the aorta or carotid artery, or cervical trauma. Twenty of the 170 patients (11.8%) enrolled were excluded from analysis because of poor delineation of the borders between the intima and media layers. This study was approved by the ethics committee of Konyang University Hospital and conducted in accordance with the Declaration of Helsinki. Patient laboratory data collected within 2 weeks of enrollment included a lipid profile and measurement of blood glucose, homocysteine, and fibrinogen levels.

Carotid Artery Scanning

The CCA was studied with high-resolution ultrasonography (Hewlett-Packard Sonos 5500) with a broadband (11 to 3 L) linear array transducer (Figure 1). Carotid arterial scanning was performed by a certified, blinded sonographer in a dark, air-conditioned room. The far wall of the right CCA was scanned longitudinally while the patient was in the supine position with head extended. To optimize the image quality, the depth control was fixed at 4 cm. The transducer frequency was set to 11 MHz during the entire analysis

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A study Influence of atherosclerosis risk factors on carotid artery wall thickness

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Abstract— The severity of carotid intima-media thickness (IMT), which is the sum of intima thickness (IT) and media thickness (MT), is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction. Evaluation of carotid IMT using ultrasonography is a validated quantitative method for assessing atherosclerosis, which is closely correlated with pathological findings observed in the carotid artery. However, the individual clinical significance of each layer of carotid artery has not been well studied. We intended to measure the IT, MT, and the IMT of carotid artery separately and tried to analyze the clinical significance. Two hundred and fifty consecutive patients (125 males, 125 females) underwent carotid artery scanning using high-resolution ultrasound. The images were off-line analyzed using B-mode ultrasound image processing, devised in our research. We measured the IT, MT, and IMT semi-automatically at the far wall of designated 1cm length of the right common carotid and calculated the average values over the 200 points. The IT ($p < 0.05$), MT ($p < 0.05$) as well as IMT ($p < 0.01$) of patients with atherosclerotic disease were significantly thicker than that of the patients without atherosclerotic disease. Patients with hypertension showed significantly thicker IT ($p < 0.05$), MT ($p < 0.01$), and IMT ($p < 0.01$) than that of the patients without hypertension. However, only IT was thicker in patients with smoking ($p < 0.05$) than that of the patients without smoking. Smoking was associated only with intima while hypertension was associated with the all three layer's thickness. This result suggests the atherosclerotic process can be different by cardiovascular risk factors. Therefore, clinical study with specific risk factors such as hypertension or smoking as in our study needs to focus on specific layer of vessel wall. **Key words:** Carotid artery, Intima thickness (IT), Media thickness (MT), Intima-media thickness (IMT), Ultrasound

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I. INTRODUCTION

Evaluation of carotid intima media wall thickness (IMT) using ultrasonography is a validated quantitative method for assessing atherosclerosis [1], that is closely correlated with pathological findings observed in the carotid artery [2]. Moreover, the appearance of atherosclerosis in the carotid

artery has been highly associated with atherosclerosis in the aorta and the incidence of coronary heart disease [3]. Therefore, the severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as myocardial infarction [4]. Carotid IMT consists of intima thickness (IT) and media thickness (MT). Arterial intima layer is the innermost coat of blood vessels, consisting of a thin lining of endothelial cells oriented longitudinally and arterial media layer is the middle coat of blood vessel walls, composed principally of thin cylindrical smooth muscle cells and elastic tissue, accounting for the bulk of the wall of most arteries. Abnormal neointima formation is the main pathophysiology of obliterative vascular disease, although atherosclerotic changes of vessel wall also includes smooth muscle proliferation and inflammatory process in media and adventitia. We hypothesized that IT and MT have a different clinical significance with regards to development and pathophysiology of atherosclerosis.

However, most studies used carotid IMT as a surrogate marker rather than separate measurement of IT and MT due to probably technical problems. It defines carotid IMT as the distance between the luminal border of the intima and the outer border of the media using high-resolution ultrasound. The border of intima layer can be identified as the first echogenic line from the lumen and the outer border of media layer as the second echolucent line in the high-resolution ultrasound. The measurement of carotid IMT is getting more precise by semiautomatic measurement rather than manual measurement [5]. And these semiautomatic measurements of carotid IMT give us more reliability in understanding many clinical studies as well as more important clinical significance about that. The neointima is developed by a migration, proliferation, and accumulation of vascular smooth muscle cells in the intima [6]. Medial thickness relates statistically to necrosis indirectly through associations with foam cells and fibroplasia.

We performed this study to evaluate the individual clinical significance of the intima layer and the media layer of the common carotid artery (CCA) by individual measurement using high-resolution ultrasound and newly devised image processing algorithm.

Lack of difference in the intimal medial thickness between the left and right carotid arteries in the young

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Background – Carotid intimal medial thickening (c-IMT) is an established surrogate marker for atherosclerosis. There have been sporadic reports about an increase of c-IMT on the left carotid artery among populations with a mean age of ± 50 years. **Objective** – The purpose of this study was to evaluate whether there is a difference in c-IMT between the two carotid arteries in a group of young healthy adults. **Methods** – Ninety-eight healthy adults with a mean age of 28 years underwent blood tests to evaluate various cardiovascular risk factors as well as automated ultrasonic measurements of their c-IMT on both carotid arteries. **Results** – No significant difference was noted between c-IMT on both sides. In fact, the c-IMT on left carotid artery in men ($n = 52$) was 0.625 ± 0.078 mm while on the right carotid it was 0.626 ± 0.075 mm ($P = 0.884$). The values for women ($n = 46$) were 0.615 ± 0.059 mm and for men 0.622 ± 0.0618 mm ($P = 0.582$), respectively. **Conclusion** – As opposed to a noted increase of c-IMT on the left carotid artery in older individuals, we did not find this difference in a group of young and relatively healthy adults. It is possible that if mechanical stress forces contribute to an enhanced left c-IMT, it takes a relatively long time to become evident.

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Key words: carotid intimal media thickness; atherosclerosis; young; ultrasound

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Introduction

It has been repeatedly shown that the measurement of the carotid intimal medial thickness (c-IMT) is a surrogate marker for an atherosclerotic disease (1–4). It is measured in both common carotid arteries (CCA) and expressed as the mean value obtained from these measurements (5). Yet it is not entirely clear whether the c-IMT is equal in both carotid arteries as several studies have shown a predilection for an increase of c-IMT in the left CCA. A putative explanation has been raised, namely that increased shear stress forces in the left carotid artery contribute to this inequality.

Acceptance of a different shear stress between the carotid arteries as a contributing factor would suggest that this difference be apparent from the beginning of the atherosclerotic process. However,

most studies in the past were performed in individuals at the age of 50 years or more, thus excluding the possibility to reveal the differences at an earlier stage of the disease.

We have presently embarked on a study that measured the c-IMT in a group of young adults. The findings are relevant for the understanding of potential mechanisms that underlie the development of increase of c-IMT at a relatively early stage of the disease.

Patients and methods

We have presently recruited apparently healthy volunteers, members of the medical staff of the Tel Aviv Sourasky Medical Center in Tel Aviv Israel. A written informed consent was obtained according to the instructions of the local ethics commit-

tee. An inclusion criterion was a healthy adult with no known illnesses and between 20 and 40 years of age. We excluded individuals who presented with any infectious/inflammatory condition during the two weeks before enrollment. In addition, pregnant women and women during menstruation were excluded. One patient was excluded because he had evident plaques on both carotids.

In order to evaluate how healthy our cohort was, we compared them to individuals who were evaluated at the Tel Aviv Medical Center Inflammation Survey (TAMCIS) (6, 7). TAMCIS is a survey of apparently healthy individuals that is currently taking place at our medical center and includes a relatively large cohort of individuals attending the Tel Aviv Sourasky Medical Center for a routine health examination. We included all eligible patients from the TAMCIS cohort between the ages of 20 and 40. We excluded patients by the same criteria used on the study cohort.

Carotid artery atherosclerosis was determined by ultrasonographic measurement of the c-IMT of the CCA 1.5–3 cm proximal to the carotid artery bifurcation of the left and right sides. c-IMT was measured at the far wall of the carotid artery, on a 10-mm segment and was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall (8). A computer software (M'ATH software) was used to calculate IMT by averaging 80–100 different samples of the examined carotid segment. The IMT value of each side represents an average of all the samples measured by the computer program.

Ultrasonographic scanning was performed by a single experienced sonography technician, blinded to the clinical data, who scanned the left and right CCAs using carotid duplex equipment (128XP/10, Acuson; Siemens, Erlangen, Germany) with a 7 MHz linear array transducer.

Venous blood was drawn from all the volunteers following a fasting period of 12 h and was analyzed for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose by using routine methods of the medical center biochemistry laboratory. The erythrocyte sedimentation rate (ESR) was measured by the method of Westergren (9), quantitative fibrinogen by the method of Clauss (10) and a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) autoanalyzer, while the high-sensitivity C-reactive protein (hs-CRP) was performed by using a Boering BN II Nephelometer (DADE Boering, Marburg, Germany) (11).

Statistical analysis

All data were summarized and displayed as the mean \pm SD for the continuous variables [age, body mass index (BMI), inflammation markers, etc.], and as the number of patients in each group for categorical variables (smokers). The hs-CRP has a non-normal distribution, and thus we used a logarithmic transformation that converts it to a normal distribution for all statistical procedures such as *t*-tests; all the results expressed as hs-CRP are a back-transformed geometrical mean and standard deviation. The one-sample Kolmogorov–Smirnov test was used to verify that the logarithmic transformation is normally distributed. For all continuous variables the paired sample *t*-test was used to evaluate the difference between the groups, while for all categorical variables the chi-square test was used for assessing the significant difference between the groups.

A *P* value < 0.05 was considered significant. The SPSS statistical package was used to perform all statistical evaluation (SPSS Inc., Chicago, IL, USA).

Results

We have evaluated 98 volunteers at a mean \pm SD age of 28.5 ± 4.4 years (52 men and 46 women), a BMI of 22.3 ± 3.2 kg/m² and with no known illnesses. Twelve (12.2%) of them were smokers. The mean \pm SD systolic blood pressure was 114.9 ± 14 and the diastolic was 73.5 ± 8 mmHg. Metabolic and inflammatory variables of male and female volunteers are presented in Tables 1 and 2. Each table also presents data regarding volunteers from the TAMCIS database. The lack of difference in mean and maximal c-IMT in both genders of the study population is represented in Table 3.

Discussion

The c-IMT has been extensively studied as a surrogate marker of the atherosclerotic disease (1–4). Increased c-IMT has been shown to be associated with increased incidence of myocardial infarction and stroke (12, 13). Thus, the accurate measurement of c-IMT could allow to single out individuals at risk for clinical events in advance.

However, c-IMT is usually presented as a mean of the two carotid arteries (5). If c-IMT is similar in both arteries, sampling one artery would be both time and cost-effective. In addition, risk factor models do not address any differences between the

Table 1 Demographic and laboratory variables of the male study population

	Study population (<i>n</i> = 52)	TAMCIS (<i>n</i> = 727)	<i>P</i> value
Age (years)	28.6 ± 3.2	28.8 ± 3.6	0.822
Number of smokers	7 (13.5%)	138 (19%)	0.148
BMI (kg/m ²)	23.8 ± 3.04	25.10 ± 3.2	0.004
Systolic blood pressure (mmHg)	121.4 ± 13.15	117.1 ± 9.8	0.042
Diastolic blood pressure (mmHg)	74.4 ± 7.4	73.15 ± 6.07	0.286
Glucose (mg/dl)	85.8 ± 8.6	87.8 ± 7.6	0.124
Total cholesterol (mg/dl)	169.1 ± 28.5	175.51 ± 30.2	0.131
LDL (mg/dl)	99.62 ± 25.19	106.70 ± 25.8	0.061
HDL (mg/dl)	50.1 ± 8.8	49.05 ± 9.7	0.410
Triglycerides (mg/dl)	101.24 ± 72.5	98.98 ± 52.6	0.830
Hemoglobin (g/dl)	14.9 ± 0.9	14.9 ± 0.9	0.781
WBCC (cells × 10 ³ /cm)	6.5 ± 1.4	6.6 ± 1.5	0.605
ESR (mm/h)	5.6 ± 3.7	7.6 ± 6.3	0.001
Fibrinogen (mg/dl)	233.9 ± 41.6	238.3 ± 48.5	0.482
hs-CRP (mg/l)	1.4 ± 1.4	1.9 ± 3.4	0.316

TAMCIS, Tel Aviv Medical Center Inflammation Survey; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBCC, white blood cell count; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

Table 2 Demographic and laboratory variables of the female population

	Study population (<i>n</i> = 46)	TAMCIS (<i>n</i> = 366)	<i>P</i> value
Age (years)	27.8 ± 4.9	28.2 ± 3.9	0.665
Number of smokers	5 (10.8%)	85 (23.2%)	0.07
BMI (kg/m ²)	20.8 ± 2.7	22.6 ± 3.6	0.000
Systolic blood pressure (mmHg)	108.7 ± 12.1	106.8 ± 9.5	0.364
Diastolic blood pressure (mmHg)	72.5 ± 8.9	68.9 ± 5.8	0.023
Glucose (mg/dl)	81.8 ± 6.2	83.6 ± 6.9	0.086
Total cholesterol (mg/dl)	181.2 ± 34.5	187.6 ± 28.7	0.240
LDL (mg/dl)	96.0 ± 26.8	102.0 ± 24.1	0.129
HDL (mg/dl)	70.4 ± 18.3	66.5 ± 14.40	0.178
Triglycerides (mg/dl)	79.9 ± 60.6	92.7 ± 43.6	0.180
Hemoglobin (g/dl)	12.8 ± 0.9	12.9 ± 1.0	0.291
WBCC (cells × 10 ³ /cm)	6.4 ± 1.3	7.0 ± 1.8	0.006
ESR (mm/h)	13.9 ± 9.3	14.9 ± 8.6	0.529
Fibrinogen (mg/dl)	270.8 ± 43.8	278.9 ± 54.3	0.270
hs-CRP (mg/l)	1.9 ± 1.7	3.4 ± 4.9	0.163

TAMCIS, Tel Aviv Medical Center Inflammation Survey; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBCC, white blood cell count; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

Table 3 Comparison of intimal medial thickness (IMT) between the left and right carotid arteries in males (*n* = 52) and females (*n* = 46)

	Left carotid artery	Right carotid artery	<i>P</i> value
Males			
Mean IMT	0.625 ± 0.078	0.626 ± 0.075	0.884
Max IMT	0.756 ± 0.108	0.756 ± 0.118	0.998
Females			
Mean IMT	0.615 ± 0.059	0.622 ± 0.0618	0.582
Max IMT	0.742 ± 0.090	0.748 ± 0.098	0.726

carotid arteries. However, several studies (14–16) have noted an increased c-IMT in the left carotid artery. In addition, endarterectomies have a higher prevalence on the left side (17). It has been suggested that increased shear forces in the left carotid artery contribute to this phenomenon. These studies were conducted on patients with a mean age of 50.1 (14–16). Furthermore, many of the patients had plaques evident on their c-IMT examinations. One study noted that 36.9% of the patients had atherosclerotic plaques on their examinations. Examining c-IMT in young patients could help prevent unwanted clinical sequelae and therefore, help in the management of patients at risk for cardiovascular events.

To our knowledge, only one study examined c-IMT in young individuals. In 1998, Frost and Beischer (18) did not find a difference between carotid sides in healthy and diabetic patients in a group of 40 patients. However, they measured maximal IMT and not mean c-IMT. In addition, their measurement was done manually and consisted of only two samples in contrast to our study in which we included 80–100 computer-derived samples per patient.

We aimed to evaluate the differences in c-IMT between the carotid arteries in individuals without clinically evident atherosclerotic disease. All patients did not have plaques evident by c-IMT examination. Furthermore, they were much younger than individuals in other reported studies (mean age of 28 vs 50).

We failed to find any differences between both carotid sides. This could indicate that the differences seen in older people occur due to a combined effect of various atherosclerotic risk factors as well as the potential differences between the shear forces between the two carotid arteries.

Our population was compared with a larger cohort of apparently healthy individuals in order to make sure that our cohort is relatively healthy. In fact, they had a lower BMI, lower (although not significant) percent of smokers, and lower concentration of several inflammatory biomarkers.

There have been reports that IMT progression accelerates in the elderly and therefore could account for the difference in IMT seen at older ages that are non-existent in younger patients (19). Thus, we raise the possibility that if mechanical shear stress forces do contribute to an accelerated development of the atherosclerotic process in the left carotid artery, they probably need a relatively prolonged period of time to become evident. Further studies are needed to elucidate this point of interest.

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Comparison of Carotid Intima-Media Thickness in Patients With Stable Angina Pectoris Versus Patients With Acute Coronary Syndrome

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In this study, we found that carotid intima-media thickness (IMT) was significantly increased and carotid artery atherosclerotic plaques were detected more frequently in patients who had early-onset coronary artery disease compared with control subjects (0.73 ± 0.10 vs 0.60 ± 0.10 mm, $p < 0.001$, and 40% vs 11%, $p < 0.001$, respectively). Further, patients who had coronary artery disease and presented with an acute coronary syndrome were found to have significantly increased carotid IMT compared with patients who had stable angina pectoris (0.76 ± 0.10 vs 0.70 ± 0.10 mm, $p < 0.05$). The IMT was greater in the patients who had acute coronary syndrome than in those who had stable angina pectoris. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96:643–644)

High-resolution B-mode ultrasound can measure the intima-media thickness (IMT) of the walls of the carotid arteries and the IMT correlates rather well to the presence of atherosclerotic narrowing of coronary arteries.¹ This report describes carotid IMT in patients who presented with acute coronary syndrome (ACS) and in those who presented with stable angina pectoris (SAP).

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We studied 146 patients who were <45 years old and categorized them into 3 groups. The first group consisted of 41 patients who had ACS and whose initial presentation was ST- or non-ST-segment elevation myocardial infarction or Braunwald's class IIIB unstable angina pectoris. The second group consisted of 32 patients who had chronic SAP. The remaining 73 subjects were included in the control group. Patients who had a history of myocardial infarction, unstable angina, percutaneous coronary intervention, carotid surgery, coronary bypass, chronic kidney disease, chronic inflammatory disease, or statin use were excluded from the study. Control subjects were chosen among those who had atypical chest pain, no history of coronary heart disease, and a negative result from stress testing.

A high-resolution ultrasound system equipped with a 13-MHz transducer (Vivid 7, General Electric Vingmed Ultrasound, Horten, Norway) was used for longitudinal scans of the far wall of the distal 2.0 cm of the 2 common carotid arteries, immediately proximal to the origin of the bifurcation, for assessing IMT. Three measurements of IMT were performed in the right and left carotid arteries and

were averaged to determine the mean IMT for each side and for the 2 sides combined. IMT was measured offline with computer software (M'ATH, Argenteuil, France), which can automatically define the IMT to within 0.001 mm. Carotid plaques were defined as a focal widening of the vessel wall relative to the adjacent wall that protruded into the lumen. For analysis, plaques were defined as simple or complex depending on their extension, echogenic composition, and surface characteristics as proposed by Lombardo et al.² The distance from the interface between the lumina and intima of the near wall to that of the far wall was defined as the lumen diameter. These procedures were performed within the first week of initial presentation to the hospital.

All patients who presented with ACS or SAP underwent coronary angiography. Significant coronary stenosis was defined by visual assessment as $\geq 70\%$ luminal narrowing in

Table 1
Baseline characteristics of study population

	ACS (n = 41)	SAP (n = 32)	Controls (n = 73)
Age (yrs)	41.2 \pm 3.7	41.7 \pm 2.8	41.8 \pm 3.7
Men	36 (88%)	30 (93%)	66 (90%)
Hypertension	11 (27%)*	3 (9%)	22 (30%)
Diabetes mellitus	14 (34%)*†	3 (9%)	3 (4%)
Smoker	24 (58%)	10 (31%)	18 (25%)
Dyslipidemia‡	15 (37%)	7 (22%)	26 (36%)
No. of coronary arteries narrowed			
1	21 (54%)	25 (78%)	—
2	9 (23%)*	3 (9%)	—
3	9 (23%)*	4 (12%)	—
Body mass index (kg/m ²)	27 \pm 3	28 \pm 4	28 \pm 4
C-reactive protein (mg/L)	9 \pm 7*†	4 \pm 2	3 \pm 1

* $p < 0.05$ compared with patients who had SAP.

† $p < 0.05$ compared with control group.

‡ Plasma total cholesterol level > 200 mg/dl or triglyceride level > 200 mg/dl.

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Table 2
Ultrasonic properties of carotid arteries of the study population

	ACS (n = 41)	SAP (n = 32)	Controls (n = 73)	p Value [‡]
Mean carotid IMT (mm)	0.76 ± 0.10* [†]	0.70 ± 0.10 [†]	0.60 ± 0.09	<0.001
Left carotid IMT (mm)	0.80 ± 0.13* [†]	0.70 ± 0.10 [†]	0.62 ± 0.10	<0.001
Right carotid IMT (mm)	0.72 ± 0.12 [†]	0.71 ± 0.14 [†]	0.58 ± 0.09	<0.001
Left lumen diameter (mm)	5.99 ± 0.80 [†]	5.89 ± 0.78 [†]	5.56 ± 0.86	<0.001
Right lumen diameter (mm)	6.11 ± 0.89 [†]	5.70 ± 0.72 [†]	5.54 ± 0.88	<0.001
Left carotid flow velocity (cm/s)	107 ± 23	102 ± 24	112 ± 14	NS
Right carotid flow velocity (cm/s)	105 ± 22	101 ± 30	107 ± 16	NS
Carotid plaque occurrence	23 (57%)* [†]	6 (19%)* [†]	8 (11%)	
Simple plaques	8 (20%)* [†]	5 (16%)	7 (10%)	
Complex plaques	15 (37%)* [†]	1 (3%)	1 (1%)	

* p < 0.05 compared with patients who had SAP.

[†] p < 0.05 compared with control group.

[‡] Analysis of variance.

any of the 3 major coronary branches or ≥50% luminal narrowing of the left main coronary artery.

Statistical analysis was performed with SPSS 9.0 for Windows (SPSS, Inc., Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables as percentage. Chi-square or Fischer's exact test was used for categorical variables. One-way analysis of variance with Dunnett's test or unpaired *t* test for pairwise comparisons was used for analysis of continuous variables. A multivariate logistic regression model in which age, gender, hypertension, diabetes, current smoking, dyslipidemia, and ischemic family history represented the independent variables was used to determine the increased carotid IMT. The IMT values within highest quartile were accepted as increased IMT. All p values < 0.05 were accepted as statistically significant.

Baseline characteristics of the study population are presented in Table 1. There were 27 patients who had ST-segment elevation myocardial infarction, 7 who had non-ST-segment elevation myocardial infarction, and 7 patients who had unstable angina pectoris. Patients who had ACS were more likely to have positive family history for coronary artery disease, diabetes mellitus, and multivessel disease than were patients who had SAP or controls. Ultrasonic properties of carotid arteries of the study population are presented in Table 2. Prevalence of complex carotid artery atherosclerotic plaques was higher in patients who had ACS than in those who had SAP. Carotid IMT was significantly increased in patients who had ACS and SAP compared with controls. The IMTs of patients who had ACS were significantly increased compared with those of patients who had SAP. Logistic regression analysis showed that diabetes mellitus is the independent predictor of increased carotid IMT

(odds ratio 6.04, 95% confidence interval 1.24 to 29.29, p = 0.025).

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This is the first study to show that patients who had an ACS were much more likely to have complex carotid plaques and greater IMT than were patients who had chronic SAP.

In the Atherosclerosis Risk In Communities (ARIC)³ study, mean carotid IMT was consistently greater in those who had prevalent clinical cardiovascular disease than in those who did not have disease. A previous observational study demonstrated a significantly increased carotid IMT in patients who were 30 to 50 years of age and had survived a myocardial infarction compared with control subjects.⁴ Our study extended this finding and demonstrated increased carotid IMT in patients who had ACS and those who had SAP. Our findings also showed significantly increased carotid IMT in patients who had ACS compared with those who had SAP.

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Arterioesclerosis subclínica, factores de riesgo cardiovascular clásicos y emergentes en niños obesos chilenos

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ABSTRACT

Arteriosclerosis can start in childhood and develops chronically depending on the load of cardiovascular risk factors (RF). **Objective:** To study classic RF, an emergent RF (high-sensitivity C-reactive protein: hsCRP) and two noninvasive early markers of atherosclerosis: brachial ultrasound endothelium-dependent dilation (EDD) and carotid intima-media thickness (IMT), in obese compared with normal children. **Method:** 26 obese children (BMI > Pc95) and 57 normal children (BMI: Pc 10 - 85) were evaluated with anthropometry, arterial pressure (AP), EDD, IMT, and determined plasmatic hsCRP, lipid profile and fast glucose. **Results:** 50% were girls and 41% prepubertal. Age: 9.9 ± 1.6 vs 9.8 ± 1.8 years (ns), zBMI: 2.0 ± 0.2 vs 0.17 ± 0.6 , waist circumference (%Media): 133.5 ± 16 vs $100.5 \pm 10\%$ in obese and normal respectively. The obese ones had higher Total Cholesterol, LDL-C, Triglyceride, hsCRP and lower HDL-C ($p < 0.005$). There was no difference in DMF: $9.03 \pm 5.2\%$ vs. $9.3 \pm 4.2\%$ and IMT: 0.49 ± 0.03 vs 0.50 ± 0.03 mm, fast glucose or AP. **Conclusion:** This group of obese chilean children present a higher load of classic RF, and hsCRP level than normal ones. Nevertheless, there was not difference in sub clinical arteriosclerosis subrogate markers.

(**Key words:** Obesity, children, atherosclerosis, cardiovascular risk-factors).

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Original Article

Cardiac troponin I and beta 2 microglobulin as risk factors for early-onset atherosclerosis in patients on haemodialysis

AYSEGUL ZUMRUTDAL,¹ SIREN SEZER,¹ SENOL DEMIRCAN,² GULSAH SEYDAOGLU,³ F NURHAN OZDEMIR¹ and MEHMET HABERAL⁴Departments of ¹Nephrology, ²Cardiology and ⁴General Surgery, Faculty of Medicine, Baskent University, Ankara and ³Department of Biostatistics, Faculty of Medicine, Cukurova University, Adana, Turkey**SUMMARY:****Aim:** To investigate the associations of different risk factors with carotid artery intima-media thickness (C-IMT) in non-diabetic haemodialysis (HD) patients who had no clinical evidence of atherosclerosis.**Methods:** Seventy-two HD patients (43 men, 29 women; mean age: 34.5 ± 10.6 years; mean time on HD: 47.9 ± 40.0 months) and 40 age- and sex-matched healthy controls (26 men, 14 women; mean age: 35.5 ± 7.1 years) participated in the study. The relationship between C-IMT and haematocrit-corrected erythrocyte sedimentation rate (Hct-corrected ESR), beta 2 microglobulin (beta2M) and serum cardiac troponin I (cTnI) levels beyond C-reactive protein (CRP), lipid profile and lipoprotein(a), fibrinogen, homocysteine and left ventricular hypertrophy (LVH) were examined.**Results:** Mean C-IMT of the HD patients was significantly greater than that of the control subjects (0.59 ± 0.06 vs 0.53 ± 0.07 mm, $P = 0.002$). C-IMT of patients was positively correlated with age ($r = 0.33$), body mass index ($r = 0.40$), Hct-corrected ESR ($r = 0.37$), CRP ($r = 0.34$), beta2M ($r = 0.34$), cTnI ($r = 0.26$), triglyceride ($r = 0.26$) and fibrinogen ($r = 0.28$) levels ($P < 0.05$ for all). The mean C-IMT was significantly greater in patients with LVH than it was in those without LVH ($P = 0.004$). In multivariate regression analysis, age ($P = 0.02$), beta2M ($P = 0.001$), log-transformed CRP ($P = 0.03$) and LVH ($P = 0.01$) were independently related with C-IMT.**Conclusion:** Besides well-known cardiovascular (CV) risk factors, cTnI and beta2M were related with C-IMT in that they may have important roles in early-onset atherosclerosis in this high-risk population.**KEY WORDS:** beta 2 microglobulin, cardiac troponin I, carotid intima-media thickness, early-onset atherosclerosis, haematocrit-corrected erythrocyte sedimentation rate, inflammation.

Atherosclerotic vascular disease is the most frequent complication in patients undergoing chronic haemodialysis (HD) treatment. Carotid intima-media thickness (C-IMT) measuring has been the only non-invasive imaging test recommended by the American Heart Association for evaluation of cardiovascular (CV) risk.¹ It is considered a valid surrogate end point that can be used in intervention studies that are aimed at modifying CV risk factors.² Several studies have reported the association of different CV risk factors (age, diabetes mellitus, systolic hypertension, left ventricular concentric hypertrophy, smoking, intact parathormone, lipid abnormalities, homocysteine and also inflammation (C-reactive protein)) with increased C-IMT in HD patients.^{3–8} Furthermore, prognostic value of ultrasonographic measurement of C-IMT in dialysis patients was

shown in a few studies. Nishizawa *et al.* found that increased C-IMT was an independent predictor of CV mortality in the HD population. Kato *et al.* showed that measurement of C-IMT was useful for predicting long-term mortality in patients on maintenance HD.^{4,9} In the current study, beyond well-known CV risk factors, we wanted to investigate the association of different parameters with C-IMT such as haematocrit-corrected erythrocyte sedimentation rate (Hct-corrected ESR), beta 2 microglobulin (beta2M) and serum cardiac troponin I (cTnI) in a selected group of HD patients without any clinical evidence of atherosclerosis. To avoid the masking effects of age and vasculopathic diseases, we evaluated correlates of C-IMT in patients less than 55 years old, and without diabetes mellitus.

Although ESR is widely used in the general population as an inflammation marker, it was judged to be of no clinical utility in chronic HD patients in the mid-1980s. However, it has recently been proposed that after correction of ESR values according to Hct levels in HD patients, Hct-corrected ESR could serve to select the inflammation-afflicted HD patients from those without this comorbid state.¹⁰ Patients

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Original Article

Microalbuminuria, but not cystatin C, is associated with carotid atherosclerosis in middle-aged adults

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Abstract

Background. Cystatin C, a marker of renal function, has been shown to be an independent predictor of cardiovascular disease (CVD) in older adults, but few data are available in middle-aged adults. Moreover, no study has compared cystatin C and microalbuminuria as risk factors for CVD outcomes in middle-aged adults, and it is not known whether cystatin C is related to an early stage of atherosclerosis.

Methods. We evaluated the relationships between serum creatinine, estimated glomerular filtration rate (GFR), serum cystatin C (all divided into tertiles), microalbuminuria and carotid atherosclerosis in a population-based random sample of 523 adults aged 35–64 years from the Seychelles (Indian Ocean). GFR was estimated using the modification of diet in renal disease (MDRD) equation. Intima-media thickness (IMT) was assessed by B-mode ultrasound.

Results. The mean age of the study sample was 52 years, and 55% were women. Carotid IMT was higher in participants with microalbuminuria (802 vs 732 µm, $P < 0.001$) and was inversely associated with GFR tertiles (from 728 to 809 µm, P for trend = 0.002). IMT was not associated with cystatin C or creatinine (P for trend = 0.10 and 0.16, respectively). In multivariate analyses adjusted for cardiovascular risk factors, the association between microalbuminuria and IMT remained ($P = 0.047$), while the association between GFR and IMT disappeared (P for trend = 0.33).

Conclusions. Microalbuminuria, but not cystatin C, is associated with carotid atherosclerosis beyond traditional cardiovascular risk factors among

middle-aged adults. Cystatin C does not have a stronger relationship with carotid atherosclerosis in middle-aged adults than creatinine.

Keywords: Africa; albuminuria; atherosclerosis; cystatin; Seychelles

Introduction

Cardiovascular diseases (CVD) are the leading causes of mortality and morbidity in western and developing countries [1,2]. Screening and treatment is one strategy for the primary prevention of CVD, but the highest-risk patients should be identified to maximize the benefit/cost ratio of treatments [3]. In recent years, several tests, ranging from serum to urinary markers, have been proposed as new cardiovascular risk factors or markers that may improve risk prediction and help to identify the highest-risk patients [4,5]. Among markers of renal function that have been associated with increased cardiovascular risk, cystatin C has recently been shown to be an independent predictor of cardiovascular events in a prospective cohort of adults aged ≥ 65 years [6]. Microalbuminuria has also been suggested as an independent predictor of cardiovascular events, including in subjects without diabetes [7]. The presence of chronic kidney disease, either manifested by albuminuria or reduced estimated glomerular filtration rate (GFR), appears to be an independent risk factor for CVD in prospective studies, particularly in high-risk populations [7].

It remains to be determined whether a mild decrease in GFR or other early markers of renal dysfunction are associated with increased cardiovascular risk in low-risk populations [7]. The association of microalbuminuria with cardiovascular events has, indeed, been less consistent in low-risk populations [7,8].

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Carotid intima-media thickness and carotid and/or iliofemoral plaques: comparison of two markers of cardiovascular risk in hypertensive patients

Jean-Michel Tartière, Olivier F. Henry, Hélène Safar, Jeanne-Marie Bureau, Xavier Girerd, Michel E. Safar and Jacques Blacher

Objective In order to optimize cardiovascular risk assessment, we compared the association of common carotid artery intima-media thickness (CCA-IMT) with carotid and/or iliofemoral (C/IF) plaques according to the presence or absence of cardiovascular disease (CVD) and belonging to a high cardiovascular risk group.

Design The study was conducted in 323 subjects presenting one or several cardiovascular risk factors in an internal medicine hospital department; 96 patients had one or more manifestations of cardiovascular disease.

Results Compared with patients with no C/IF plaques, patients with plaques at 1–4 sites presented an adjusted odds ratio (OR) [95% confidence interval] of presenting CVD of respectively [1: OR = 1.79 (0.64–5.04); 2: OR = 3.35 (1.27–8.85); 3: OR = 3.40 (1.09–10.62); 4: OR = 14.41 (3.75–55.40)]. On the other hand, the OR of CVD for 1 SD increment of CCA-IMT was: 0.95 (0.69–1.31). In the group of 199 patients, for which Framingham-based calculations of CV risks were methodologically accessible, both CCA-IMT and C/IF plaques were associated with all cardiovascular risks. Comparison of areas under receiver operating characteristic curves among association of C/IF

plaques and CCA-IMT with the presence of CVD showed a statistically significant difference (0.78 ± 0.09 versus 0.64 ± 0.09 , $P < 0.001$).

Conclusion Arterial plaques may constitute a better marker of the presence of CVD than CCA-IMT. Comparisons according to 10-year Framingham equations did not show statistical significance, but both measures seemed to be highly predictive and possibly complementary. Prospective studies are needed to confirm these findings. *J Hypertens* 21:739–746 © 2003 Lippincott Williams & Wilkins.

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Keywords: atherosclerosis, carotid, intima-media thickness, hypertension, essential, plaque, cardiovascular risk

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Introduction

Numerous studies have shown that carotid intima-media thickness (IMT) and presence of plaques are associated with cardiovascular risk factors [1–6]. Most recent prospective studies have shown an association between carotid IMT or aortic abdominal calcifications and occurrence of clinical manifestations of cardiovascular disease (CVD) [7–10]. Only two longitudinal studies have shown an association between carotid plaques and acute myocardial infarction or major cardiovascular events [10,11]. Most of these studies usually investigated carotid IMT and carotid plaques separately, and little information is available comparing the transverse association between these two determinants and the presence of CVD; even less information is available for other plaque locations such as iliofemoral arteries.

In the present study we examined the crude and adjusted associations between carotid IMT or carotid and/or iliofemoral (C/IF) plaques and the presence or absence of CVD or the level of cardiovascular risk group calculated from equations derived from the Framingham Heart Study and from the Framingham Offspring Study [12]. Finally, we compared the strengths of the associations of carotid IMT and, respectively, of carotid and/or iliofemoral plaques with the presence of CVD and with the 10-year Framingham cardiovascular risk.

Methods

Study cohort

From December 2000 to June 2001, around 400 patients entered the Department of Internal Medicine of Broussais Hospital for a cardiovascular check-up or-

Slow Coronary Flow is Associated with Carotid Artery Dilatation

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YIGIT, F., SEZGIN, A.T., DEMIRCAN, S., TEKIN, G., EROL, T. and MUDERRISOGLU, H. *Slow Coronary Flow is Associated with Carotid Artery Dilatation*. Tohoku J. Exp. Med., 2006, **209** (1), 41-48 — Slow coronary flow (SCF) in a normal coronary angiogram is a well-recognized clinical entity, but its etiopathogenesis remains unclear. Carotid intima-media thickness (CIMT) is a noninvasive marker of atherosclerosis. The aim of this study was to investigate the CIMT and diameter of carotid and coronary artery in relation to SCF. Twenty-four patients with angiographically diagnosed SCF (51 ± 7 years), and 26 age-matched subjects with normal coronary flow (NCF) (52 ± 8 years) in the coronary angiography were enrolled. Coronary flow rates were documented by thrombolysis in myocardial infarction (TIMI) frame count (TFC), a simple method for evaluating coronary blood flow. Carotid and coronary artery diameters and CIMT were measured. Mean TFC was significantly higher in patients with SCF than in patients with NCF ($p < 0.001$). There were no significant differences regarding maximum ($p = 0.84$) and mean CIMT ($p = 0.61$). On the other hand, carotid lumen ($p = 0.03$) and coronary artery diameters ($p = 0.001$) were significantly greater in patients with SCF than in subjects with NCF. There was a significant relation between mean coronary artery diameter and TFC ($p = 0.004$, 95% CI for OR: 1.61-11.87). In conclusion, these findings suggest that CIMT is not altered in patients with SCF as compared with those with NCF. However, carotid and coronary artery diameters are increased in patients with SCF as compared to those with NCF. Because the common carotid artery can be assessed in nearly every patient, carotid artery dilatation may be used as an early indicator for SCF. ——— slow coronary flow; carotid intima-media thickness; carotid artery diameter; coronary artery diameter

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Slow coronary flow (SCF) is identified by detection of slow dye progression in the coronary arteries during selective coronary angiography (Tambe et al. 1972). Histopathologic studies have revealed coronary microvascular disease in some patients who exhibit SCF (Mosseri et al. 1986; Mangieri et al. 1996), but this has not been extensively studied. It remains to be determined

whether or not diffuse atherosclerotic disease in the epicardial vessels and microvessels of the heart wall is associated with SCF.

New noninvasive tools have been developed to detect subclinical atherosclerosis. These methods, which measure parameters such as carotid intima-media thickness (CIMT), added a new dimension to cardiovascular research and clinical

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Intima-media Thickness and Arterial Stiffness of Carotid Artery in Korean Patients with Behçet's Disease

Behçet's disease (BD) is a systemic vasculitis involving diverse sizes of arteries and veins. We performed this study to evaluate the vascular changes by assessment of the arterial stiffness and intima-media thickness (IMT) of carotid artery in Korean patients with BD. Forty-one patients with BD and age-, and sex-matched 53 healthy subjects were recruited in this study. Carotid arterial stiffness and IMT were assessed by using high-resolution B-mode ultrasonography. Arterial stiffness parameters such as carotid arterial distensibility coefficient, stiffness index, and incremental elastic modulus (E_{inc}) were significantly increased in BD patients compared with those in healthy subjects, but not in IMT. Positive relationship was noted between age and IMT, whereas age of onset was significantly associated with arterial stiffness in BD. This finding suggests impaired endothelial function before visible structural changes of arterial wall in BD. Age and age of onset may be an independent risk factor for carotid IMT and arterial stiffness, respectively. Further studies in more large populations are required to confirm our results.

Key Words : Arterial Stiffness; Intima-media Thickness; Carotid Artery; Behçet's Disease

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INTRODUCTION

Behçet's disease (BD) is a chronic, relapsing, multisystemic inflammatory disorder of unknown cause, which is mainly characterized by recurrent aphthous oral ulcers, genital ulcers, uveitis, and skin lesions (1). A wide spectrum of clinical features is observed, including involvement of the ophthalmic, musculoskeletal, vascular, central nervous, and gastrointestinal systems. Diverse vascular complications, such as deep vein thrombosis, myocardial infarction, arterial aneurysm, and arterial thrombus formation have been noted in patients with BD in about 20% to 35% of cases, predominantly in male patients and those with venous lesions (2). In general, BD patients with major vessel involvements have a poor prognosis.

The histopathological features are mainly characterized by vasculitis, with prominent neutrophil and monocyte infiltration in perivascular lesions with or without fibrin deposition in the vessel wall (3). Although the pathogenic mechanism of vascular involvement in BD is under investigation, endothelial cell dysfunction is thought to play an important role in the development of these lesions (4-7). Endothelial

dysfunction leading to abnormal coagulation or fibrolytic activity and impaired brachial artery flow-mediated dilatation has been demonstrated in BD. Because flow-mediated dilatation is endothelium-dependent and is largely controlled by the release of endothelial nitric oxide (NO), an impairment in endothelium-dependent flow-mediated dilatation suggests a decreased endothelial NO activity (8). This lack of activity may contribute to the vascular lesions often seen in BD. In addition, endothelial NO has been found to directly regulate large artery stiffness in vivo (9, 10).

The development of atherosclerotic changes in the vessel wall is initiated by perturbations in endothelial function, reflecting a functional change before the presence of morphologic changes. Although a variety of methods have been developed to evaluate endothelial function, non-invasive high-resolution B-mode ultrasonography is typically used. Arterial intima-media thickness (IMT) is a relatively sensitive marker of early atherosclerotic vessel wall changes, especially in the common carotid artery (11, 12). Arterial stiffness is another parameter which predicts cardiovascular risk that has been found to reflect the functional properties of arteries (12).

Acute systemic inflammation and chronic systemic vasculi-

Original investigation

Open Access

Diabetes and pre-diabetes are associated with cardiovascular risk factors and carotid/femoral intima-media thickness independently of markers of insulin resistance and adiposity

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Abstract

Background: Impaired glucose regulation (IGR) is associated with detrimental cardiovascular outcomes such as cardiovascular disease risk factors (CVD risk factors) or intima-media thickness (IMT). Our aim was to examine whether these associations are mediated by body mass index (BMI), waist circumference (waist) or fasting serum insulin (insulin) in a population in the African region.

Methods: Major CVD risk factors (systolic blood pressure, smoking, LDL-cholesterol, HDL-cholesterol,) were measured in a random sample of adults aged 25–64 in the Seychelles (n = 1255, participation rate: 80.2%).

According to the criteria of the American Diabetes Association, IGR was divided in four ordered categories: 1) normal fasting glucose (NFG), 2) impaired fasting glucose (IFG) and normal glucose tolerance (IFG/NGT), 3) IFG and impaired glucose tolerance (IFG/IGT), and 4) diabetes mellitus (DM). Carotid and femoral IMT was assessed by ultrasound (n = 496).

Results: Age-adjusted levels of the major CVD risk factors worsened gradually across IGR categories (NFG < IFG/NGT < IFG/IGT < DM), particularly HDL-cholesterol and blood pressure (p for trend < 0.001). These relationships were marginally attenuated upon further adjustment for waist, BMI or insulin (whether considered alone or combined) and most of these relationships remained significant. With regards to IMT, the association was null with IFG/NGT, weak with IFG/IGT and stronger with DM (all more markedly at femoral than carotid levels). The associations between IMT and IFG/IGT or DM (adjusted by age and major CVD risk factors) decreased only marginally upon further adjustment for BMI, waist or insulin. Further adjustment for family history of diabetes did not alter the results.

Conclusion: We found graded relationships between IGR categories and both major CVD risk factors and carotid/femoral IMT. These relationships were only partly accounted for by BMI, waist and insulin. This suggests that increased CVD-risk associated with IGR is also mediated by factors other than the considered markers of adiposity and insulin resistance. The results also imply that IGR and associated major CVD risk factors should be systematically screened and appropriately managed.

Is There a Side Predilection for Cerebrovascular Disease?

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Abstract—In studies on carotid artery intima-media thickness and stroke, researchers implicitly assume that cerebrovascular abnormalities show a symmetrical distribution. To evaluate whether there is a difference in intima-media thickness between the 2 carotids, we compared left and right common carotid artery intima-media thickness as measured by B-mode ultrasonography in a group of 102 untreated hypertensive patients. This yielded a significant difference between both sides (left, 0.75 ± 0.11 mm; right, 0.71 ± 0.11 mm; $P < 0.001$). This was associated with a higher cross-sectional area of the intima-media complex and a higher flow velocity at the left side. Arterial diameters, however, were not different. We also assessed whether there is a side preference with respect to cerebrovascular accidents. To this end, we explored our population-based Stroke Registry of 1843 subjects and indeed found a significantly higher incidence of nonlacunar cerebrovascular stroke at the left side, whereas lacunar infarcts were symmetrically distributed. Our findings suggest a predilection for cerebrovascular disease at the left side, which may be related to greater hemodynamic stress and intimal damage in the left carotid artery. (*Hypertension*. 2003;42:56-60.)

Key Words: carotid arteries ■ atherosclerosis ■ cerebral arteries ■ stroke

An increase in carotid artery intima-media thickness (IMT) not only coincides with other risk factors such as hypercholesterolemia, hypertension, and diabetes mellitus but also correlates independently with clinical end points such as myocardial infarction and peripheral atherosclerosis.¹⁻⁷ Recent data have confirmed the relationship between IMT and stroke, especially of the nonlacunar subtype.⁸ Thus, an increase in IMT can be considered as a marker of cardiovascular risk. Usually, one averages measurements from the left and right common carotid artery for the determination of IMT.⁹ However, it is not known whether this is justified, as differences may exist in IMT between both arteries. Indeed, during routine assessment, we frequently noted a left-right difference in IMT. Other studies also suggest differences between left and right IMT,^{5,9} but it is not clear whether there is a systematic increase in favor of one side. This prompted us to systematically compare left and right IMT in a group of hypertensive patients who had been referred to our hospital for evaluation of their elevated blood pressure. Although an increased IMT of the internal carotid artery correlates well with the risk of both myocardial infarction and stroke, a higher IMT of the common carotid artery (CCA) is a good predictor of stroke incidence as well as prevalent stroke.^{10,11} Moreover, Cupini and coworkers⁸ demonstrated that CCA IMT values are higher in patients with nonlacunar stroke than in those with lacunar stroke, thereby lending further support

to the notion that an increased IMT is a marker of atherosclerotic (ie, nonlacunar) cerebrovascular complications rather than of microvascular (lacunar) lesions. For these reasons and because they are easier to perform and more reproducible, we restricted our measurements in the current study to the CCA.

Because an increased IMT may develop in response to high shear forces,¹² any difference between the left and right carotid artery IMT may reflect a differential effect of hemodynamic stress. Taking this a bit further, one could hypothesize that a left-right difference in the effects of hypertension on the cerebral vasculature may lead to an asymmetrical distribution of strokes as well. To examine this possibility, we also performed a retrospective analysis of the Maastricht Stroke Registry, which contains data on all stroke patients admitted to our hospital since 1988. This was done to assess whether there is a side preference in the occurrence of nonlacunar stroke in patients known to have been hypertensive before their stroke.

Methods

Study 1: IMT Measurements

Patients were selected from the hypertension outpatient clinic of the Department of Internal Medicine of the University Hospital of Maastricht. As part of the local protocol, IMT measurements were performed in all patients. For the current analysis, we selected 102

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Kardio News

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Atherosclerosis imaging is best suited for detecting the vulnerable patient: the bet is over

Atherosclerosis imaging has proven superior to conventional cardiovascular risk factor testing – the time has come to measure the biological expression of atherosclerosis non-invasively in order to increase the performance of risk prediction in Switzerland – and save money.

Introduction

People want to age healthy. What they fear most is an early stroke or a heart attack.

Heart attacks in asymptomatic people are fatal in 15% of cases with all its socioeconomic and disastrous consequences¹.

The U.S. Hastings Center has published a consensus paper including representatives of 14 countries. The main goal of medicine in the future was and naturally is the prevention of disease (SAMW August 2001).

Fifty percent of cerebral and myocardial ischemic events are not heralded by cardiovascular symptoms and remain unpredictable by conventional cardiovascular risk factors².

The tools to define an asymptomatic person's risk in primary care are all well known. They are primarily based on age and conventional risk factors. The ability of these risk charts to detect subjects at risk for heart attacks is however limited by low sensitivity of 34%, e.g. if PROCAM databases are used³.

Age and conventional risk factors are not satisfactory risk prediction tools. They are derived from higher risk populations than the Swiss (Framingham, Münster), are likely to overestimate risk in Switzerland and lead to costly and unnecessary drug treatment in some cases⁴. Importantly, none of these risk assessment tools are validated for Switzerland.

Opinion leaders are of course quite aware of this situation, but, because of "faute de mieux", everything is left as it is.

Others, however try to look beyond the horizon and aim at identifying the vulnerable patient through imaging (the vulnerable plaque⁵) or recommend the measurement of newer risk factors such as hsCRP, homocysteine, air pollution and depression, probably at the expense of lower specificity.

Yet another approach is to look at atherosclerosis directly and non-invasively.

Carotid Imaging

New tests have emerged, e.g. the total carotid plaque area as a risk prognosticator and tool for

atherosclerosis tracking and management in 1686 men and women followed over a period of 5 years⁶. This very important study will be discussed here. It was shown, that atherosclerosis has to be quantified and tracked, in order to treat it. As Dr. Spence states, you wouldn't treat blood pressure, without measuring it. I have measured total carotid plaque area in > 300 patients since April 2002. The data await to be analyzed and I call for a student.

Let us look a case to illustrate the importance of atherosclerosis imaging. For instance, you ask yourself about the risk of your patient to suffer a heart attack, or want to know his risk for stroke ?

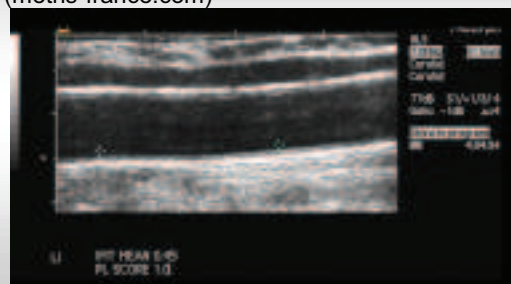
1. Carotid Intima: In order to answer this question, you will normally proceed as follows: the patient is found to be hypertensive and shows signs of ischemia on a surface electrocardiogram. You diagnose hypertensive heart disease, a condition with increased likelihood for stroke but not for myocardial infarction. Why ?

Hypertension is an independent risk factor for stroke, because it induces small vessel disease of the brain vasculature, a recognized cause of stroke in 25% of cases (lipohyalinosis and micro atheromata). Another 50% of strokes are caused by carotid atherosclerosis (arterio-arterial emboli). And finally, about 12% of your patients with hypertensive heart disease develop stroke due to atrial fibrillation. What is the role of atherosclerosis imaging in this case ?

Left ventricular hypertrophy is not readily depicted by surface ECG, you would need a screening echocardiogram. The cost is however quite superior than just measuring carotid IMT, which is an established risk factor for stroke⁷ and costs 35 Swiss francs at our institution measured by a semiautomatic software from France (M'ATH, Touboul).

Now, with this information, you end up to know, that your patient has a risk for stroke of around 12 cases per 1000 subjects per year, if mean maximum IMT is found to be 1.06-1.17.

Figure 1: IMT can be measured reliably with a caliper method, however I prefer the M'ATH software (metris-france.com)

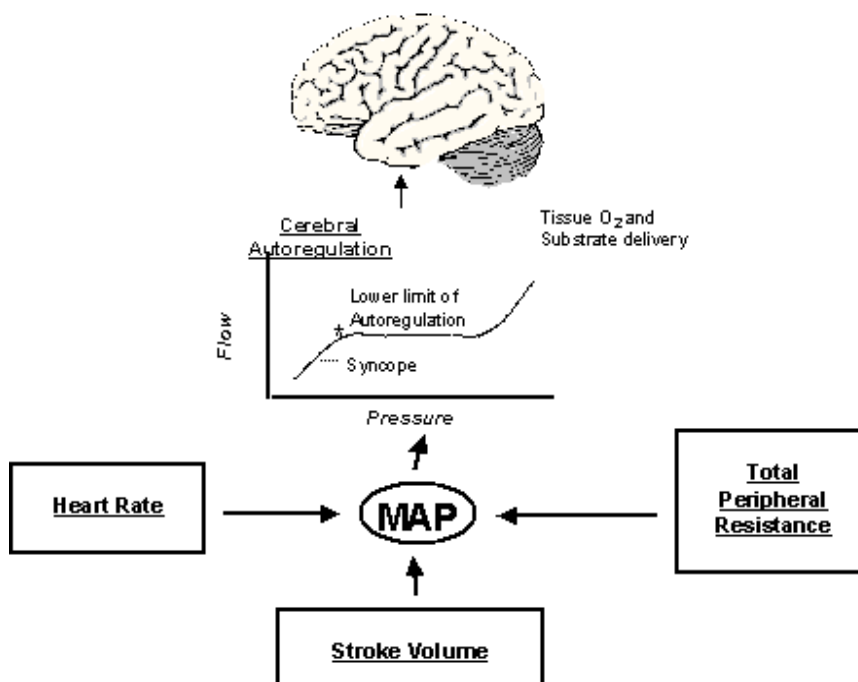


O01 SYNCOPES AND THE BRAIN: SLAVE TO THE BLOOD PRESSURE, OR PRIMARY REGULATOR?

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Syncopes ultimately occurs when cerebral perfusion is reduced below a critical level whereby there is inadequate delivery of oxygen and substrate to support neuronal metabolism. Under most circumstances, this occurs because of sudden hemodynamic collapse, and a resultant fall in perfusion pressure below the lower limit of autoregulation. However many patients describe symptoms in the upright position that could be attributed to cerebral hypoperfusion, despite a normal blood pressure. Moreover, some investigators report decreases in cerebral blood flow during orthostatic stress that may precede any hemodynamic deterioration, raising the possibility that a primary failure of autoregulation may precede and possibly even precipitate a secondary hemodynamic collapse. In this keynote address, the data for and against this hypotheses will be presented and a pathophysiological framework for the problem of syncopes will be developed.

Pathophysiology of Syncopes



O02 Clinical Aspects of Cerebral Autoregulation

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Cerebral autoregulation is a mechanism which protects the brain against the effects of extreme blood pressure changes. The dynamics and the function of this mechanism can be evaluated using transcranial Doppler and arterial blood pressure recordings. Methods to evaluate the autoregulation function have included dynamic and static testing, and also evaluation of spontaneous fluctuations in blood pressure and blood flow velocity.

Investigations using transcranial Doppler have revealed new knowledge regarding behavior of the system under normal conditions and also under the effects of anesthetic agents, changes in CO_2 , and other environmental influences. Alteration in autoregulatory function has also been studied in a variety of disease states including head injury, cerebrovascular occlusive disease, stroke, subarachnoid hemorrhage.

The response under normal conditions, environmental influences, and in the setting of disease states will be discussed.

O03 INFLUENCE OF END-TIDAL CARBON DIOXIDE PRESSURE ON THE POSTURAL REDUCTION IN CEREBRAL BLOOD VELOCITY

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Background: In the upright body position the cerebral blood flow is challenged by a reduction in mean arterial pressure at brain level ($\text{MAP}_{\text{brain}}$) and a reduction in end-tidal CO_2 concentration ($\text{P}_{\text{et}}\text{CO}_2$). This study addressed the hypothesis that restriction of the postural fall in $\text{P}_{\text{et}}\text{CO}_2$ increases the transcranial Doppler-determined middle cerebral artery (MCA) mean blood velocity (V_{mean}) in the upright position.

Methods: In 10 healthy young adults, the contribution of $\text{P}_{\text{et}}\text{CO}_2$ and posture on the MCA V_{mean} and systemic hemodynamic variables was evaluated by 5 min head-up tilting (HUT) at two levels of $\text{P}_{\text{et}}\text{CO}_2$. During free breathing (HUT_{FB}), the postural fall in $\text{P}_{\text{et}}\text{CO}_2$ was unrestricted and during rebreathing (HUT_{RB}) the postural fall in $\text{P}_{\text{et}}\text{CO}_2$ was restricted by the use of an expiratory CO_2 rebreathing device.

Results: Systemic hemodynamic responses to both tilts did not differ. As expected, after 1 min HUT_{FB} , the reduction in $\text{P}_{\text{et}}\text{CO}_2$ was larger than during HUT_{RB} (6.8 ± 4.3 vs. 1.7 ± 1.6 mmHg). This was also at 3 and 5 min, respectively, 6.6 ± 5.1 vs. 3.1 ± 1.4 mmHg and 6.3 ± 4.8 vs. 2.3 ± 0.8 mmHg ($p < 0.05$). The reduction in MCA V_{mean} during HUT_{FB} was larger (10 ± 4 vs. 3 ± 4 $\text{cm} \cdot \text{s}^{-1}$; $p < 0.05$) at 1 min, but not at 3 min (8 ± 5 vs. 6 ± 3 $\text{cm} \cdot \text{s}^{-1}$) or at 5 min (7 ± 5 vs. 6 ± 4 $\text{cm} \cdot \text{s}^{-1}$).

The postural decline in MCA V_{mean} during the first 60 s of HUT_{FB} was followed by a steady increase of 1.13 $\text{cm} \cdot \text{s}^{-1} \cdot \text{min}^{-1}$ ($p < 0.05$).

Conclusions: The postural fall in MCA V_{mean} is related to the $\text{P}_{\text{et}}\text{CO}_2$ in the first minute only. From then on, the 4 mm Hg difference in $\text{P}_{\text{et}}\text{CO}_2$ does not affect the MCA V_{mean} . This questions the contribution of the fall in $\text{P}_{\text{et}}\text{CO}_2$ to the reduction in MCA V_{mean} during prolonged orthostatic stress.

O04 The relationships between flow in the internal Carotid artery and collateral function in the circle of Willis.

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Background: Large multicenter studies have shown that carotid surgery reduces the risks for stroke in patients with symptomatic severe carotid artery stenosis. The grading of the stenosis in these studies depended on selective carotid angiography, a method that is seldom used nowadays. Carotid ultrasound has shown a good correlation to angiography and is often used in these cases. A good collateral function increases the intracerebral blood pressure and can affect the blood flow through the carotid artery stenosis and therefore the estimation of the degree of stenosis.

The aim of the present study was to try to find relations between degree of the stenosis and the collateral function in the circle of Willis.

Methods: The maximal systolic and diastolic velocities were determined in the internal carotid artery (ICA) with Duplex ultrasound. The function of the anterior communicating artery and the blood flow velocity in the middle cerebral artery were estimated with transcranial Doppler (TCD) with and without proximal compression of the common carotid artery.

Material: The results of the carotid Doppler and TCD were examined retrospectively. 658 studies of 357 patients (age 67 range 39-89 years) were evaluated.

Results: Spontaneous collateral flow compensation in the circle of Willis as a marker of hemodynamic significant stenosis was seen (with few exceptions) only in stenosis of 70% or more. Low ICA flow velocity despite high-grade carotid artery stenosis was seen in 10 % of the patients.

Conclusion: Spontaneous collateral flow in the circle of Willis indicates a carotid artery stenosis of >70%. Data about collateral function can influence the estimation of the degree of carotid artery stenosis. TCD-examination should therefore be included in investigation of patients with suspicion of symptomatic carotid artery stenosis.

O05 carotid intima media thickness asymmetry in an untreated uncomplicated hypertensive population

SA Rodríguez Hernández², MP van Boxtel¹, AA Kroon², WH Mess², J Lodder², J Jolles¹, PW de Leeuw². EURON¹, CARIM² and University Hospital Maastricht, The Netherlands

Background: For the determination of intima media thickness (IMT) usually the average of several measurements in the left and right common carotid artery is calculated. However, it is not known whether differences exist between both carotid arteries. The present study assesses the concordance between the IMT of the left and right carotid artery.

Methods: We studied the IMT of both carotid arteries in 102 untreated uncomplicated hypertensives. We measured the IMT of the posterior wall of the left and right common carotid artery at 1 cm proximal to the bulb from an anterolateral and posterolateral view (SONOS 5500; Agilent-Philips; linear array transducer, 3-11 MHz). The enddiastolic B-mode images were analyzed offline with an automated edge-tracking method (M'ath, version 2.0.1; Metris, France). The average IMT was measured over a length of 10 mm, and the mean of both the anterolateral and posterolateral view were calculated and used for further analysis. Also, the lumen diameter was measured. Additionally, flow velocity indices were derived (syst, diast, pulsatility index[PI], resistance index [RI]) from the Doppler spectrum.

Results:

Age (yrs) 56 ± 11

Sex (m/f) 61/41

BMI, kg/m² 29 ± 6

Clinic SBP (mmHg) 165 ± 7

Clinic DBP(mmHg) 94 ± 8

Left IMT (mm) $0,752 \pm 0,11$

Right IMT (mm) $0,717 \pm 0,11^*$

*t-test paired samples $p < 0,001$

There was no left right difference of the lumen diameter or velocity parameters.

Conclusions: Our data demonstrate that in the investigated population the carotid IMT is significantly lower on the right side. It is proposed that this is related to the anatomical differences between the left and right arteries branching off the aortic arch. Whether these findings have consequences for the formation of atherosclerosis and/or cerebral complications remains to be determined.

O06 Dynamic cerebral autoregulation disturbances correlate with severity of brain trauma

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Background: Head injured patients run a high risk of secondary brain ischemia associated with or due to cerebral autoregulation (CA) failure. To prevent such events a non-invasive continuous monitoring system is lacking. We investigated whether assessment of phase shift as an index of CA might be a useful candidate for such purposes. **Method:** Cerebral blood flow velocity (V) in the MCA and arterial blood pressure (BP) were recorded simultaneously over 6 minutes, and the phase shift between V and BP at 0.1 Hz was calculated by means of transfer function analysis. Recordings were performed in 33 normal subjects under normo- and hypocapnic conditions to generate normative data. 27 patients with severe head trauma (GCS ≤ 8) underwent serial follow up investigations of phase shift and CT scanning during the first 8 days after trauma allowing a comparison between phase shift and CT scanning in a total of 115 instances. Traumatic lesions (in the MCA territory) on CT scan were classified in to: 0, no lesion; 1, small lesion (diameter < 3 cm); 2, large lesion (diameter >3 cm). At each instance, the patients were classified into being normocapnic or hypocapnic. **Results:** Normative phase shift was 78 ± 28 in normocapnia, and 101 ± 25 in hypocapnia. In the trauma patients, CA was classified disturbed when phase shift was below the 2SD-limit (22° in normocapnia, 51° in hypocapnia). A disturbed CA was significantly ($p < 0.01$) more frequent in the CT group 2 (19 out of 42) compared to group 0 (7/44) and 1 (5/29). **Conclusion:** Phase shift changes correlate with the severity of injured brain tissue. As an index of CA it seems a promising tool for continuous long term monitoring of CA dynamically. Grants: BMBF 01 K0 9707, DFG Mü 1433/4-1

O07 Improvement in the Transcranial Doppler Parameters of Hypertensive Patientes after treatment with an Angiotensinl-Converting Enzyme inhibitor

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BACKGROUND: This study was designed to demonstrate the cerebral hemodynamic changes related to hypertension using transcranial doppler sonography.

METHOD: To investigate the effects of antihypertensive drug and to demonstrate the hemodynamic changes related to hypertension 75 stroke free hypertensive patients assigned to be treated with an angiotensin I converting enzyme inhibitor cilazapril and 20 with beta blocker atenolol for 6 months. Because of correlation in hemodynamic changes occurring in long standing patients we measured the flow velocities/FV/ and Gosling resistance index / PI / of MCA with EME TC 2000 before and 6 months of administration drugs in two different groups: the patients with shorter duration of hypertension and longer duration / less than 5 years and more than 5 years /.

RESULTS: There occurred significantly changes in hemodynamic parameters / $p=0,039$ in first group treated with cilazapril/hypertension less than 5 years/ in FV and $p=0,001$ in PI. Second group of patients treated with cilazapril/hypertension longer than 5 years/ FV $p=0,014$ and PI $p=0,013$. These differences were not observed in patients who took atenolol. In the first group /duration of hypertension less than 5 years/ FV $p=0,73$, PI $p=0,22$ and in the second group /hypertension more than 5 years/ FV $p=0,46$ PI $p=0,85$.

CONCLUSION: Transcranial doppler sonography can be a sensitive tool in the investigation of vascular impairment caused by hypertension and follow up hypertensive patients.

Considering all these facts the ACE inhibitors with their characteristics can contribute not only in hypertension treatment but also in prevention of cerebrovascular diseases.



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Association of a Corrected QT Interval with the Carotid Intima-Media Thickness and the Severity of Coronary Artery Disease in Patients with Coronary Artery Disease.

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BACKGROUND AND OBJECTIVES: A prolonged heart rate-corrected QT interval (QTc) is known to be related to an increased risk of coronary artery disease (CAD) and sudden cardiac death, while the carotid intima-media thickness (IMT) is related to CAD. We sought to evaluate the relationship among the QTc, the carotid IMT and the severity of CAD. **SUBJECTS AND METHODS:** The QTc and the carotid IMT were measured in 165 consecutive patients who underwent coronary angiography. The measurement of the QTc was done automatically by a digital QT Guard™ system (GE Marquette Medical System, Milwaukee, USA) and the carotid IMT was measured by M'ATH software (METRIS Co., Argenteuil, France). The severity of CAD was divided into minimal disease (90, 54.5%), one-vessel disease (32, 19.4%), and multi-vessel disease (43, 26.1%), according to the number of vessels that were narrowed by more than 50%. **RESULTS:** The mean values of the QTc were 415.1±20.5 msec in the minimal disease group, 411.7±17.0 msec in the one-vessel disease group and 434.2±46.1 msec in the multi-vessel disease group. The QTc was correlated with age ($r=0.236$, $p=0.002$), HDL cholesterol ($r=-0.160$, $p=.043$), the right carotid IMT ($r=0.17$, $p=0.026$), the left carotid IMT ($r=0.178$, $p=0.022$) and the severity of CAD ($r=0.243$, $p=0.002$). On the multiple linear regression analysis after adjustment for age and HDL cholesterol, the QTc was an independent factor for the severity of CAD. **CONCLUSION:** These results suggest that repolarization abnormalities are associated with the severity of CAD and they may reflect the severity of the morphologic atherosclerotic surrogates.



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Correlation between the Carotid Intima-Media Thickness and the Plaque Burden of the Left Main Coronary Artery Using Ultrasonography.

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BACKGROUND AND OBJECTIVES: It has been reported that the common carotid artery (CCA) intima-media thickness (IMT) correlates to angiographically determined coronary artery stenosis. The aim of this study was to evaluate the correlation between the carotid IMT and left main (LM) plaque using ultrasonography. **SUBJECTS AND METHODS:** In fifty patients (mean age 59.6+/-9.9, males 35 (70%)) with coronary artery disease (CAD), the risk factors of atherosclerosis were evaluated and coronary angiographs obtained. The carotid IMT was measured in the far wall of both CCAs, with a 10 MHz linear probe, and the value of the IMT was automatically calculated using programmed software (M'ATH, METRIS Co., Argenteuil, France). The LM plaque was measured by intravascular ultrasound. The maximal thickness, ratio of the maximal thickness, cross-sectional area (CSA) and burden of the plaque were measured at 2 mm intervals, and the average values calculated. **RESULTS:** In the right common carotid artery, the maximal IMT significantly correlated with the mean plaque CSA and plaque burden of the LM ($r=0.375$, $p=0.007$, $r=0.408$, $p=0.003$, respectively). The mean IMT significantly correlated with the plaque burden of the LM, but not with the mean plaque CSA of the LM ($r=0.357$, $p=0.011$, $r=0.264$, $p=0.063$, respectively). In the left common carotid artery, the maximal IMT was not significantly correlated with the mean plaque CSA and plaque burden of the LM ($p=0.251$, $p=0.218$, respectively). The mean IMT was not correlated with the mean plaque CSA and plaque burden of the LM ($p=0.249$, $p=0.078$, respectively). **CONCLUSION:** There was a significant correlation between the right CCA IMT and plaque burden of the LM in patients with CAD.

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Placebo-Controlled Trial of High-Dose Atorvastatin in Patients With Severe Cerebral Small Vessel Disease

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From INSERM U-698 and Department of Neurology and Stroke Centre (P.C.L., J.L., F.G.-R., A.J., D.B., P.J.T. P.A.), Bichat University Hospital, Denis Diderot University and Medical School, Paris, France; Neuroradiology Unit (I.F.K.), Department of Radiology, Bichat University Hospital, Denis Diderot University and Medical School, Paris, France; Department of Biostatistics and Clinical Research (E.V.), Fernand Widat University Hospital, Denis Diderot University and Medical School, Paris, France.

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Background and Purpose—Uncontrolled studies have shown that statins can improve cerebral vasoreactivity (CVR) in patients with mild small vessel disease. We sought to determine whether high-dose atorvastatin increases CVR compared with placebo in patients with severe small vessel disease.

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Methods—Ninety-four adults with recent lacunar stroke were randomly allocated in a double-blind manner to 80 mg of atorvastatin daily or matching placebo after stratification for hypertensive and diabetic status. The primary end point was change in CVR after 3 months of treatment. Secondary outcomes were changes in brachial and carotid artery endothelial-dependent vasodilations.

Results—At baseline, all patients had a severely impaired CVR (mean, 12.1%; 95% CI, 9.5–14.7) and carotid (mean, -0.25%; 95% CI, -1.17–0.67) and brachial artery (mean, 2.72%; 95% CI, 1.39–4.05) endothelial function. Despite reductions of 55% in low-density lipoprotein cholesterol and of 30% in high-sensitivity C-reactive protein in the active arm compared to placebo, atorvastatin 80 mg per day did not improve CVR or endothelial dysfunction of carotid and brachial arteries.

Conclusion—We found no positive effect of 3-month treatment with atorvastatin on severe cerebral microvasculature endothelial dysfunction in patients with lacunar stroke.

Key words: atorvastatin • cerebral vasoreactivity • endothelial dysfunction • lacunar stroke

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Association between fibrinogen levels and fibrinogen G-455 A polymorphism and preclinical atherosclerosis in the general population

Abstract number: OC241

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Several prospective studies have demonstrated that plasma fibrinogen is a risk factor for incident arterial thrombosis, but its association with the development of atherosclerosis is however, uncertain. We evaluated plasma fibrinogen, C-reactive protein (CRP) and a polymorphism in the beta fibrinogen region (G-455 A) to verify their association with increased intima-media thickness (IMT), a marker of preclinical atherosclerosis, in the general population. 2373 subjects (1304 females, 1069 males) previously enrolled in the VITA Project, with a median age of 54 years were studied. In all subjects, IMT was measured in common carotid arteries using a B-mode ultrasonography and a digital acquisition/measurement software (M'ath, Metris, France). Fibrinogen was measured against a plasma calibrated by the clot-weight method; CRP by a sensitive nephelometric method (Behring). G-455 A polymorphism was determined by PCR analysis. Logistic regression was used to model for the individual probability of having a IMT above the age-adjusted reference limit or a atherosclerotic plaque. In a multivariate analysis that accounted for the effect of gender, cholesterol and smoke, subjects with a fibrinogen level above the third tertile had a 1.7-fold increased probability of having an IMT above the upper limit ($P = 0.03$) and a 1.6-fold increased probability of having an atherosclerotic plaque. The effect was independent from CRP level, that was a risk factor for increased IMT ($OR = 1.7$, $P = 0.02$) but not for plaques ($OR = 0.9$, $P = 0.45$). The G-455 A polymorphism had a clear effect on fibrinogen levels, but the effect on IMT was only marginal and observed only in H_2/H_2 carriers (mean IMT 0.68 vs. 0.66, $P = 0.60$). In conclusion increased fibrinogen levels are associated with preclinical atherosclerosis; the effect seems largely independent from the G-455 A polymorphism and CRP levels.

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[Bae JH](#), [Bassenge E](#), [Lim DM](#), [Synn YC](#), [Kim KY](#), [Schwemmer M](#).

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BACKGROUND: To evaluate the effects of the calcium channel blocker lacidipine on vascular responses, such as endothelial function and carotid intima-media thickness (IMT), and on levels of high-sensitivity C-reactive protein (hs-CRP) in patients with coronary artery disease (CAD). **METHODS:** Endothelial function was assessed by measuring the flow-mediated vasodilation (FMD) of the brachial artery and IMT was measured in the common, bifurcating, and in the internal carotid artery by using high-resolution ultrasound. The study population consisted of 96 consecutive patients [mean age 60 years, male (n) = 70] who showed at least one coronary artery narrowed by more than 50% (coronary angiography). These patients were randomly assigned to lacidipine treatment (4 mg/day, n = 48) or to a placebo (n = 48). We measured FMD, IMT, and hs-CRP prior to and after 6 months of treatment and following coronary angiography in all patients. **RESULTS:** Clinical and medical history revealed no significant differences between the groups. IMT of the common carotid artery was significantly diminished from 0.92 +/- 0.15 to 0.87 +/- 0.15 mm 6 months after treatment with lacidipine (p < 0.005). However, IMT of any region in the carotid artery did not show any significant changes in the placebo group. Endothelial function and hs-CRP levels were slightly improved (insignificant) in the lacidipine group. In the placebo group, there were no significant changes. **CONCLUSION:** Lacidipine leads to a significant reduction of the common carotid artery IMT as well as to a decrease in markers of inflammation in patients with CAD during a relatively short period (6 months).

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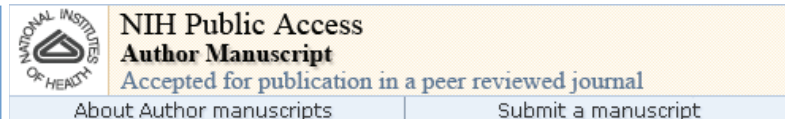
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Genetic and Environmental Contributions to Carotid Intima-Media Thickness and Obesity Phenotypes in the Northern Manhattan Family Study

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Abstract

Background and Purpose

Both carotid intima-media thickness (IMT) and obesity are independent determinants of stroke and cardiovascular disease. The prevalence of obesity is higher in Hispanics. The genetic basis of IMT and obesity has not been well-characterized in Caribbean Hispanics. The purpose of this study was to examine the genetic and environmental contributions to IMT and obesity in this population.

Methods

The data included 440 subjects from 77 Caribbean Hispanic families. Mean IMT and maximum IMT were measured in the internal carotid artery, common carotid artery, and carotid bifurcation. The total IMT was calculated as the mean value of IMT at all segments. Obesity phenotypes included body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), and skin-fold thickness. Variance component methods were used to estimate age-adjusted and sex-adjusted heritability. Bivariate analyses were conducted to test for genetic and environmental correlations between IMT and obesity.

Results

Heritabilities for IMT ranged from 9% to 40%, with the highest for total maximum IMT and lowest for internal carotid artery maximum IMT. Heritabilities for BMI, waist circumference, WHR, and skin-fold thickness were 44%, 47%, 5%, and 36%, respectively. There were significant genetic, but not environmental, correlations between IMT and BMI, waist circumference, and skin-fold thickness. There were no genetic or environmental correlations between IMT and WHR.

Conclusions

We found a substantial genetic contribution to IMT, BMI, waist circumference, and skin-fold thickness. Obesity and IMT may share common genetic factors. Future gene mapping studies are

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Inflammatory Bowel Disease Is Not Associated With Increased Intimal Media Thickening

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ABSTRACT

OBJECTIVES: Several studies have suggested that chronic inflammatory diseases might be associated with an acceleration of the atherosclerotic process. There is little information on the effect of chronic inflammation in patients with inflammatory bowel disease (IBD) on the presence of increased intimal media thickening (IMT), a surrogate marker for atherosclerotic diseases. In this work our aim was to determine whether IBD is a risk factor for increased IMT.

METHODS: IMT was measured by ultrasound of the carotid arteries; a computer software program was used to analyze 80–100 independent IMT samples from each carotid artery segment in 61 patients with IBD (45 with Crohn's disease and 16 with ulcerative colitis) and in 61 controls matched for age (± 2 yr), sex, body mass index (BMI, ± 2 kg/m²), and smoking status.

RESULTS: Inflammatory markers (erythrocyte sedimentation rate, fibrinogen, high-sensitive C-reactive protein) were significantly ($P < 0.001$) elevated in IBD patients compared with controls. Even though there was a disease duration of 8.7 ± 8.5 yr, the mean IMT of IBD patients was similar to that of the control group (0.66 ± 0.09 vs 0.64 ± 0.07 mm; $P > 0.05$).

CONCLUSIONS: Despite chronic inflammation, IBD patients had IMT values similar to those of the controls. Thus, unlike other inflammatory diseases, IBD appears not to be a risk factor for accelerated atherosclerosis.

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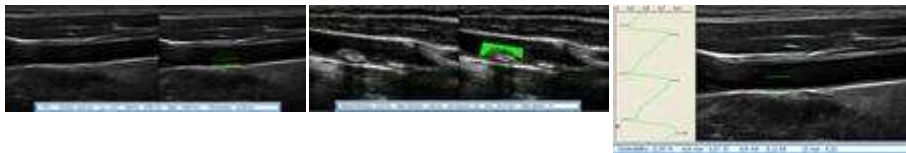


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