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INTRODUCTION

Carotid intima media thickness (CIMT) may have clinical application as a marker of atherosclerosis development in the setting of various risk factors, a marker of response to therapy, a predictor of cardiovascular events and a marker of advanced vascular disease in the peripheral, carotid and coronary circulation. Moreover, Carotid artery intima media thickness (CA-IMT) represents a marker for sub-clinical atherosclerosis and an opportunity for early detection of pre-symptomatic individuals. **(Hodis et al., 1998)**

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A number of studies have demonstrated the strong relationship between IMT and cardiovascular risk factors. The strongest predictors of the 2-years increase in carotid IMT included age, low-density lipoprotein cholesterol, smoking and platelet aggregability. **(Salonen and Salonen, 1993; Chambless et al., 2002)**

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Progression of IMT is an age-related process which affects both sexes, but the increase in IMT with age is greater in men than in women. It has been suggested that the difference in IMT between men and women may be explained by sex differences in lumen diameter, and that sex differences in IMT merely reflect differences in physiology rather than differences in the extent of atherosclerosis. **(Bots et al., 1997a)**

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Obesity damages health, reduces quality of life and leads to premature death. A four-year controlled study by **Karason et al., (1999),** was carried out to investigate the extent of carotid artery atherosclerosis in obese subjects. They found that IMT progression rate was almost three times higher in the obese control group compared with lean controls.

Cigarette smoking is widely accepted as a major risk factor for the development of clinical cardiovascular disease, resulting from direct effects on atherosclerosis and hemostasis. Both active and passive smoking are associated with the progression of an index of atherosclerosis. Smoking is of particular concern for patients with diabetes and hypertension. The fact that pack-years of smoking but not current or past smoking was associated with progression of atherosclerosis suggests that some adverse effects of smoking may be cumulative and irreversible **(Howard et al., 1998)**.

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Intima media thickness of the carotid artery can be easily measured by non-invasive ultrasound techniques. B-mode ultrasound is commonly accepted as a non-invasive, safe, inexpensive and reliable method for measuring IMT of large arteries located close to the skin, such as the carotid and femoral arteries. **(Salonen and Salonen, 1990)**.

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AIM OF WORK

The present study is designed to explore the possible effects of age, sex and body mass index (BMI) on IMT of the carotid artery in normal Egyptian subjects. Another aim is to investigate the effect of smoking, as a risk for atherosclerosis on the carotid IMT in normal individuals.

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CAROTID INTIMA MEDIA THICKNESS

Structure of the arterial wall

A normal artery consists of 3 concentric layers that surround the arterial wall, each of which has distinctive composition of cells and extra-cellular matrix. The intima is the inner most layer of the arterial wall. It contains delicate connective tissue and occasional smooth muscle cells (SMCs) and macrophages. A monolayer of endothelial cells lines the luminal surface and forms physical and functional barrier between the flowing blood and the stroma of the arterial wall. A sheet of elastic fibers, the internal elastic lamina, separates the intima from the media layer. **(Stary et al., 1992)**

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The media is made up of synthesizing SMCs which produce collagen and contractile SMCs that are involved in the regulation of BP by vasoconstriction and vasodilatation. The extra-cellular matrix consists largely of elastic fibers and collagen, with a lesser content of proteoglycan holding the SMCs together. **(Ross and Glomset, 1976)**

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The adventitia, the outer most layer of the arterial wall, consists of loose connective tissue and variety of cells, including SMCs, fibroblasts, macrophages, mast cells and ganglionic cells. The outer part of this layer also contains vasa vasora, lymphatic vessels and nerves which provide the stimulus and blood supply to the media. The boundary between the media and the adventitia is

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demarcated by the external elastic lamina, the adventitia is often surrounded by a layer adipose tissue. **(Ross and Glomset, 1976)**

Morphological features of atherosclerosis

Atherosclerosis is an inflammatory disease caused by multi-genetic and environmental interactions and atherosclerotic lesions develop through a response-to injury mechanism. **(Ross, 1999)** Endothelial dysfunction is the earliest event of cardiovascular disease and a chain of events will lead to clinical and end stage cardiovascular diseases. Although the events leading to disease progression overlap and intervene, the modification at any point along this chain can influence the pathophysiological process, thus altering disease progression. **(Dzau et al., 2006)**

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محذوف: a multi-factorial disease,

محذوف: and the majority of cardiovascular diseases result from complications of atherosclerosis.

Atherosclerosis is characterized by patchy intramural thickening of the sub-intima that encroaches on the arterial lumen. Six major types of lesions reflect the early developing and mature stages of atherosclerosis, **(Stary et al., 1992)**:

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Type I lesion (the intimal lesion): contains atherogenic lipoproteins, which elicit an increase of macrophages in the arterial wall causing an adaptive intimal thickening. Macrophages accumulate lipids to form fatty streaks.

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Type II lesion: composed of layers of macrophages and SMCs, and has been found as early as the first decade of human life. Although fatty streaks are not clinically significant, they represent the precursor of more advanced lesion.

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Type III lesion (the intermediate lesion): consists of small scattered extracellular pools of lipids that disrupt the normal unity of the intimal smooth muscle layers. These lesions may be present after puberty.

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Type IV lesion (the atheroma): considered as the first advanced lesion. It is potentially symptomatic and frequent from the third decade on. It is characterized by accumulation of lipid rich necrotic debris and smooth muscle cells known as the lipid core. The nature of the intima above the lipid core can be changed by an increase in the fibrous connective tissue, forming a fibrous cap.

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Type V lesion (the fibroatheroma): When a lesion within the lipid core gets the fibrous cap it is classified as lesion type V.

Type VI lesion: generally formed from type IV and V lesions. It is complicated with a disruption of the lesion surface, hematoma or hemorrhage and thrombotic deposits.

A lesion of type V or VI composition usually begins to appear after the third decade of life. The most important clinical complication is an acute occlusion of the vessel due to formation of a thrombus or a blood clot, resulting in myocardial infarction or stroke. **(Stary et al., 1992), Figure (1)**

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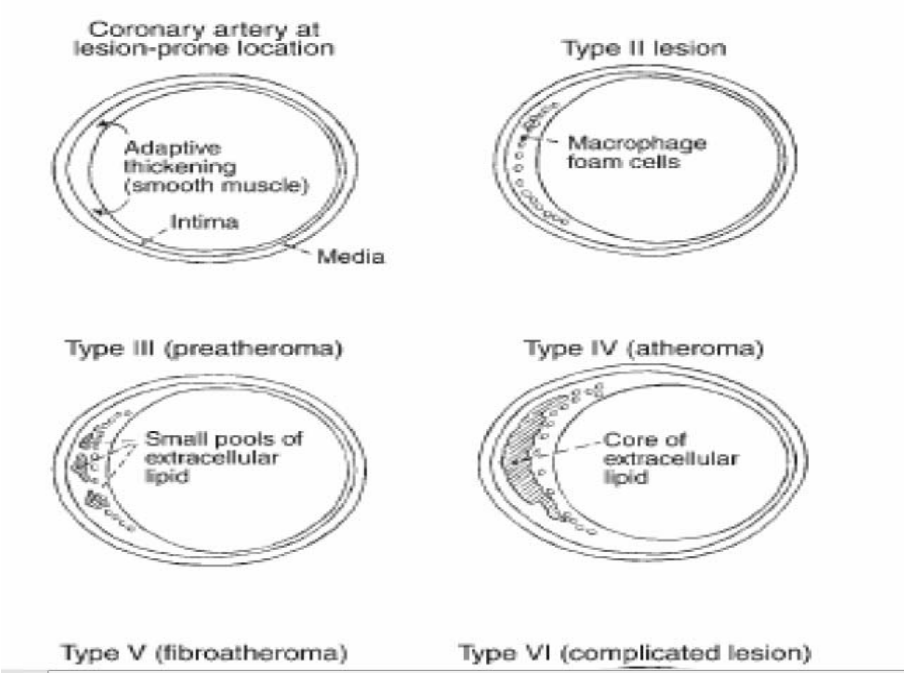

Figure (1): Cross section drawing of atherosclerotic lesions, **(Stray et al., 1992).**

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B-Mode Ultrasound: A Noninvasive Method for Assessing Atherosclerosis

Background

The first attempts to measure blood flow velocities by ultrasound occurred in the late 1950s, but the technique was invasive and not suitable for clinical use. The first clinical application of the transcutaneous non-invasive Doppler flow-meter was developed in 1958 in Japan by **Satomura et al.** who managed to measure arterial flow velocities. **Strandness et al.** in the late 1960s, diagnosed various arterial diseases by spectral analysis of Doppler signals. **(Quoated from Kaneko, 1986)**

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Introduction of pulsed Doppler instruments by Wells and Baker enabled for the first time, in the early 1970s, non-invasive regional measurements of blood velocity. In 1974, Baker combined pulsed Doppler with a real-time B-mode imager to form an instrument known as a duplex scanner. **(Barber et al., 1974, quoated from Beach et al., 2010)**

Duplex Doppler instruments allow the Doppler angle to be determined from the B-mode image and thus, with the addition of spectral analysis, enabled the accurate measurement of blood flow velocity. **(Rickey and Fenster, 1996)** Today, angiography is rarely done due to the risk of complications. In Sweden, about 80% of Carotid end-arterectomy (CEA) are performed exclusively on the basis of carotid duplex information regarding degree of stenosis. **(The National Board of Health and Welfare, 2007)**

Transcranial Doppler

At the end of the 1970s, it became possible to achieve a two-dimensional visualization of the intracranial structures in infants through the acoustic window of the anterior fontanel; the pulsations of the large cerebral arteries could be qualitatively evaluated. A major breakthrough occurred in 1982, when Rune Aaslid measured flow velocities in the vessels of the circle of Willis through the skull using the Transcranial Doppler (TCD) technique. In just a few years, this method was introduced for diagnostic purposes as well as therapeutic control of intracranial vascular disease in adults. **(Aaslid et al., 1982)**

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In the early 1990s, Spencer et al were able to demonstrate the occurrence of microembolic signals (MES) using TCD. Although individual MES are asymptomatic, it has been shown that presence of MES is associated with a high risk of future ischemic events. In recent years, the most important diagnostic development of TCD was the introduction of micro-embolic detection, the sensitivity of which was further increased by a new technique, Power M-mode Doppler. **(Moehring and Spencer, 2002)**

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Principles

Ultrasound B-mode imaging is based on the pulse-echo principle used in sonar, from which measurements of the arrival times of echoes from a source of pulsed ultrasound are used to create a two-dimensional real-time display of the echo producing structures. The positions of the structures relative to the source are computed using the arrival times and an assumed value for the speed of propagation of the ultrasound energy between the source and structures. The ultrasound instrumentation required for the noninvasive assessment of atherosclerosis in superficial vessels uses short (two to three cycles) pulses of approximately 10 MHz ultrasound. This provides an axial resolution of approximately 0.1 to 0.2 mm. The distance between structures (e.g., arterial adventitia and lumen) initially separated by more than this resolution distance can be reliably measured, and changes in this distance over time can be ascertained with considerably greater precision, as determined by the

changes in arrival times of the corresponding echoes. **(Bots et al., 2003)**

The extent of atherosclerosis can be quantified with individual wall thicknesses or composite measures based on measurements across multiple sites (e.g., the near and far walls of the internal carotid, bifurcation, and common carotid from the right and left sides). These composite measures may be raw sums or averages or may be estimates of these parameters from multivariate statistical methods. Individual measurements, such as those from the far wall of the common carotid, may be easiest to acquire. Composite measures may more broadly represent the total disease burden. Because they involve more information, if composite measures are estimated using appropriate multivariate methods, they are expected to provide the greatest statistical power and efficiency, and are recommended as primary outcome measures for most clinical research studies. **(Espeland et al., 2003)**

Reproducibility

Individual sonographer characteristics have potential to introduce significant variability into ultrasound readings. To reduce this, investigators have used a standard template to define angles of ultrasound interrogation. Sonographer variability can also be reduced in multi-center studies by utilizing centralized sonography suites that accommodate patients from several surrounding clinical sites. **(Bots et al., 2003)**

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Reader variability can also be substantial. For longitudinal studies this can be reduced by (1) reading all studies from a protocol by a single reader toward the end of the protocol to avoid "reader drift"; (2) automated image quantification; (3) training and retraining of readers as well as sonographers; (4) implementing an ongoing quality control program for both instrumentation and personnel and (5) central reading sites for multi-center trials. **(Bots et al., 2003)**

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The need for rapid recruitment of large samples for epidemiologic studies and clinical trials with ultrasound outcome has in some cases necessitated development of an international team effort and the protocols outlined above represent approaches implemented to overcome the substantial challenges encountered. With implementation of these quality control measures, the quantification of IMT in the carotid system is highly reproducible. **(Crouse et al., 2004)**

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Validity

The in vitro and in vivo experiments of **Pignoli et al., (1986),** focused on the aorta and common carotid arteries and indicated that IMT values obtained from B-mode imaging did not differ significantly from the IMT measured on pathologic examination. **Wong et al., (1993),** performed similar measurements on carotid and femoral arteries and concluded that B-mode imaging of IMT on the far (deeper) wall did not provide significantly different results from those obtained by histology.

Gamble et al., (1993) described in vitro and in situ experiments in the common carotid arteries of cadavers. These experiments indicated that B-mode imaging of the artery wall correlated best with the combined intimal-medial-adventitial thickness as measured from histologic sections and that increased wall thickness due to intimal atherosclerotic thickening still correlated well with the thickness obtained from B-mode images. Thickness measurements from the far (deeper) wall of a vessel are more clearly defined and valid than those from the near (shallower) wall, due to the basic physical principles used in constructing B-mode images.

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Carotid Intima-Media Thickness Measurement

In 2008, the American Society of Echocardiography **(ASE)** consensus statement defines CIMT as the combined thickness of the intimal and medial layers of the far arterial wall of the carotid artery. Carotid plaque is defined as focal arterial wall thickening 50% greater than the surrounding wall or a focal region of CIMT >1.5 mm. Although standard carotid duplex ultrasonography is primarily used to identify occlusive carotid plaque (advanced atherosclerosis), CIMT assessment measures arterial wall thickening (pre-atherosclerosis) and non-occlusive plaque formation (sub-clinical atherosclerosis). **(Stein et al., 2008)**

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The ASE consensus statement guidelines for carotid intima-media thickness measurement:

- The carotid arteries should be interrogated using a state-of-the-art ultrasound system with a linear-array transducer operating at

fundamental frequency of ≥7 MHz. The typical pixel size with imaging at 4 cm depth is approximately 0.11 mm.

- B-mode imaging is preferred over M-mode imaging (M-mode provides measurement of only a single point of thickness, rather than a segmental measurement).
- Digital images should be stored directly from the ultrasound system, rather than digitized video captures. CIMT imaging protocol
- Ultrasound images of the distal 1 cm of the far wall of each common carotid artery should be obtained and compared with values from a normative data set.
- These measurements should be supplemented by a thorough scan of the extra-cranial carotid arteries for presence of carotid plaques.
- Transverse B-mode scan (3- to 5-beat cine loop in each segment) from proximal CCA through middle of ICA.
- Internal and external carotid artery Doppler recordings (1 frame of each) at proximal 1 cm of each branch.
- Longitudinal plaque screen scan (3- to 5-beat cine loop from ≥ 3 different angles in each segment) at near and far walls of CCA, bulb, and ICA segments.
- CIMT imaging (3- to 5-beat cine loop and optimized R-wave-gated still frames at each angle) at distal 1 cm of each CCA.
- Mean CIMT values from the far walls of the right and left CCAs (mean to mean) should be reported.

Normal CIMT values have been defined on the basis of age and gender distribution curves within a general healthy population as reported in the ARIC study, **Table (I)** The ASE consensus statement concludes that CIMT values ≥ 75th percentile should be regarded as "high" values. Values that fall within the 25th to 75th percentile range are considered "average" and should not affect traditional risk estimates. Values that are ≤ 25th percentile are "low" and suggest lower cardiovascular risk. **(Chambless et al., 1997)**

Table (1): Carotid intima-media thickness values, adjusted for age, race and gender adapted from the Atherosclerosis Risk in Communities Study (ARIC), **(Chambless et al., 1997).**

Variable	CIMT (mm)	
	Women	Men
All-site mean*		
Mean	0.68 (0.65–0.71)	0.77 (0.73–0.81)
95th percentile	0.9800	1.1400
Third tertile	0.7057	0.8043
Second tertile	0.6070	0.6783
Carotid bifurcation		
Mean	0.78 (0.73–083)	0.90 (0.85–0.95)
Third tertile	0.8069	0.9358
Second tertile	0.6816	0.7729
Common carotid artery		
Mean	0.60 (0.62–0.70)	0.74 (0.69–0.79)
Third tertile	0.6296	0.6983
Second tertile	0.5425	0.5931
Internal carotid artery		
Mean	0.66 (0.62–0.70)	0.74 (0.69–0.79)
Third tertile	0.6794	0.7730
Second tertile	0.5733	0.6381

Data are expressed as mean (95% CI).
* Mean intima-media thickness of the far wall for 1-cm lengths of the carotid bifurcation, internal and common carotid arteries, right and left.

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Carotid IMT and Cardiovascular Disease Risk

CIMT has been associated with risk for stroke, myocardial infarction and death from coronary causes in several large observational studies. In the ARIC study, the investigators examined the association between CIMT and coronary artery disease over 4 to 7 years in 12,841 subjects (57% women) aged 45 to 64 years who were clinically free of disease at baseline. Hazard ratios for coronary artery disease comparing subjects with mean CIMT ≥1 mm with those with mean CIMT <1 mm, after adjustment for age, race, and study center, were 5.07 for women (95% confidence interval [CI] 3.08 to 8.36) and 1.85 for men (95% CI 1.28 to 2.69). **(Chambless et al., 1997)**

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A systematic review and meta-analysis of 8 large population-based observational studies (including >37,000 patients) of CIMT and cardiovascular disease risk concluded that for an absolute CIMT difference of 0.1 mm, the future risk for myocardial infarction increased by 10% to 15%, and the stroke risk increased by 13% to 18%. **(Lorenz et al., 2007)**

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Although the data supporting CIMT association with coronary artery disease are strongest for subjects aged 42 to 74 years, a few studies have demonstrated a strong relation between risk factor burden and CIMT in younger subjects (aged 18 to 42 years). **(Davis et al., 2001)**

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