INTRODUCTION

The most common cause of death due to cardiovascular diseases is coronary artery disease (CAD) which is a progressive inflammatory condition with underlying atherosclerosis in its etiology. It is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium with oxygen and nutrients ***(Libby et al., 2002).***

The symptoms and signs of CAD are noted in the advanced state, after decades of progression, some of these atheromatous plaques may rupture and start limiting blood flow to the heart muscle. Most individuals with CAD show no evidence of disease for decades as the disease progresses before the first onset of symptoms finally arises, often as a sudden heart attack. CAD is the most common cause of sudden death and also the most common reason for death of men and women over 20 years of age ***(Libby et al., 2002).***

Peripheral artery disease (PAD) is a common circulatory problem in which narrowed arteries reduce blood flow in limbs.

When PAD develops, extremities-usually legs-don't receive enough blood flow to keep up with demand. This causes symptoms, most notably leg pain when walking called intermittent claudication (IC) ***(Leng & Fowkes 1992).***

PAD is also likely to be a sign of a more widespread accumulation of fatty deposits in arteries (atherosclerosis). This condition may be reducing blood flow to heart and brain, as well as legs.

As atherosclerosis is progressive and diffuse pathological disorder which can simultaneously affect multiple vascular beds, PAD often coexist with other manifestations of systemic atherosclerotic process including CAD ***(Vink et al 2002, Weber et al 1988).***

Diagnosing PAD in patients with CAD can help to tailor exercise regimen in cardiac rehabilitation program to fit these patients, in addition early treatment and/or intervention may help to control progression of the disease.

AIM OF THE WORK

The aim of this study is to investigate for prevalence of undiagnosed lower extremities peripheral arterial disease (LEPAD) using ABI among Egyptian patients with documented CAD undergoing cardiac rehabilitation program.

Chapter 1

VASCULAR BIOLOGY AND PATHOBIOLOGY OF VASCULAR DISEASE

Introduction:

The arterial system was thought to be inactive tubes for blood passage, but now recognized as a living, dynamic tissue that plays a pivotal role in atherosclerosis and other disease processes ***(Ross & Glomset 1976)***. An appreciation of normal vascular anatomy, biology, and physiology is essential in understanding the varied pathophysiologic manifestations of atherosclerosis, which can occur as early as adolescence ***(Ross & Glomset 1976, Libby 1995, Tuzku et al., 2001).***

Anatomy of the vessel wall:

The normal vessel wall is best described as a trilaminar structure ***(Ross & Glomset 1976, Libby 1995, Gravanis 2000)*** *(Figure 1)*

Tunica intima:

The inner most layer is the tunica intima or interna, which itself consists of three layers:

1) The endothelium.

2) Subendothelial layer.

3) Elastic or fenestrated layer.

Tunica media:

The next layer is the media, which is essentially the muscular wall of the artery.

Tunica adventitia:

The outer most layer is the adventitia or externa, which contains collagen fibrils, vasa vasorum, and nerve endings.

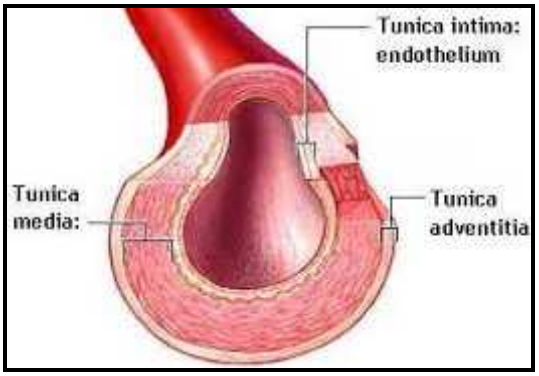

Figure (1): Anatomy of arterial wall ***(Libby 1995)***

Differences within the vascular tree:

Large elastic arteries like the aorta, have a thin arterial wall relative to their lumen. These arteries have several unique structural features allowing absorption of the kinetic energy of left ventricular systole and avoiding structural compromise. These features include the following:

1) Endothelial cells are polygonal.

2) Endothelium may not include distinct internal elastic membrane; instead, the longitudinal intimal elastic fibers merge with the elastic fibers of the media.
3) Adventitia of these arteries is relatively thin, poorly Organized, and merges with the surrounding connective tissue.
4) No distinct external elastic membrane.
5) Dense lamellar media with multiple layers of elastic laminae arranged in a spiral manner.

These properties enable the large elastic arteries to have maximum tensile strength and also afford distensibility and elasticity ***(Ross & Glomset 1976, Gravanis 2000).***

On the other hand, smaller muscular arteries, such as the coronary arteries, have a thick arterial wall relative to the lumen, elongated endothelial cells, and a true basal lamina. These arteries have smooth muscle cells entrenched within the matrix and interspersed with elastic plates in a less organized fashion. In this circuit, the blood flow is a function of myocardial capacitance ***(Ross & Glomset 1976, Gravanis 2000).***

Lastly, significant differences in the vasa vasorum exist between the large elastic arteries and small muscular arteries. These differences may play a role in the distinct forms of arteriopathy seen in these vascular beds ***(Gossl et al., 2003, Hayden & Tyagi 2004).***

Role of Endothelial Shear Stress (ESS) in the Natural History of Coronary Atherosclerosis:

Endothelial shear stress is the tangential stress derived from the friction of the flowing blood on the endothelial surface of the arterial wall ***(Slager et al., 2005).***

Role of Low ESS in Atherosclerosis includes:

- Low ESS attenuates nitric oxide (NO)-dependent atheroprotection ***(Lam et al., 2006).***
- Low ESS promotes low-density lipoprotein cholesterol uptake, synthesis, and permeability ***(Liu et al., 2002).***
- Low ESS promotes oxidative stress ***(Harrison et al., 2006, Hwang et al., 2003, Mcnally et al., 2003).***
- Low ESS promotes inflammation ***(Orr et al., 2005, Collins et al., 2001, Mohan et al., 2003, Nagel et al., 1999).***
- Low ESS promotes vascular smooth muscle cell migration, differentiation, and proliferation ***(Malek et al., 1999, Palumbo et al., 2002)***
- Low ESS increases plaque thrombogenecity by downregulating the expression of endothelial nitric oxide synthase (eNOS) and prostacyclin, well known for their anti-thrombotic properties ***(Ziegler et al., 1998, Qiu and Tarbell, 2000)***

Differences within coronary arteries:

Coronary lesions commonly occur at the proximal portion of the coronary arteries and at bend points or bifurcational points of the coronary vascular tree ***(Gotsman et al., 1992)*** Biomechanical studies correlated secondary flow patterns and areas of low shear stress in these areas prone to atherosclerosis. These physiologic and morphologic characteristics also cause endothelial cells in proximal segments of the coronary tree to be polygonal ***(Ross & Glomset 1976, Libby 1995, Gravanis et al., 2000).*** These cells may become retracted, thus compromising the intimal permeability. ***(Cines et al., 1998, Fuster et al., 1992).*** Additionally, blood pressure-derived tensile stress and thicker media may contribute to the proximal portion of the epicardial coronary arteries being more susceptible to atherosclerosis development and progression ***(Gravanis 2000, Cines et al., 1998, Fuster 1992).***

On the other hand, the straighter portions of distal segments are less commonly diseased. Biomechanical factors such as decreased shear stress, tensile stress, and the thinner media make the distal coronary arteries less prone to advanced atherosclerosis. The phenotype of endothelial cells in more distal segments is more elongated, keeping in the direction of blood flow ***(Ross & Glomset 1976, Libby 1995, Gravanis et al., 2000).***

Lastly, intercoronary and intracoronary differences in vasa vasorum have also been described to be related to the nonrandom atherosclerotic sites within the coronary tree ***(Gossl et al., 2003, Hayden & Tyagi 2004)*** However, the focal discontinuous anatomic distribution of atherosclerosis and its predilection is incompletely understood ***(Ross & Glomset 1976, Fuster et al., 1992).***

Heterogeneity of atherosclerosis between arterial beds:

As atherosclerosis is a systemic condition, it is clear that there is variability in the degree to which the arterial beds develop atherosclerotic disease. Postmortem studies revealed that the coronary arteries have the highest prevalence of atherosclerosis compared to other arterial beds ***(Vink et al., 2002, Weber et al., 1988)*** (Table 1)

Renal arteries and branches of the lower extremity vasculature, including the iliac and femoral vessels, have a moderate atherosclerotic burden.

The common carotid also has a moderate degree of atherosclerosis, whereas the internal carotid and the intracerebral arteries have a mild degree of atherosclerotic burden.

It is also notable that the brachial and radial arteries have moderate atherosclerosis, whereas the internal mammary artery

generally has minimal atherosclerotic disease ***(Galili et al., 2004, Tector et al., 1981)***

The following table illustrates the percentage of incidence of atherosclerosis in different body arteries.

Table (1): Area stenosis of different artery types.

Artery type	*Area stenosis*
Coronary	*44.3 (31.7-58.4)*
Common carotid	*16 (12.2-23.4)*
Internal carotid	*2.7 (1.1-8.3)*
Renal	*15 (4.7-36.9)*
Common iliac	*18.8 (13.2-29)*
External iliac	*10.6 (6.6-19.6)*
Internal iliac	*29.7 (19.5-47.9)*
Femoral	*24.9 (5.5-44.1)*
Brachial	*12.1 (5.2-18.1)*
Radial	*15.1 (9.3-24.6)*
Middle cerebral	*9.1 (2.1-19.2)*
Internal mammary	*12.5*

(Vink et al., 2002)

Clinical significance of vascular bed atherosclerotic heterogenicity:

The heterogeneous distribution of atherosclerotic disease between vascular beds is of clinical importance. In general, the coronary arteries are more likely to have atherosclerosis than other vascular beds, so presence of atherosclerosis in other vascular beds is indicative of coronary artery disease ***(Grundy et al., 2004).***

American College of Cardiology/American Heart Association guidelines for management of patients with PAD suggest evaluation for coronary artery disease in patients with significant non-coronary bed atherosclerosis ***(Hirsch et al., 2006).***

Risk factors for atherosclerosis:

Atherosclerosis is defined as chronic inflammatory disease caused by sustained injury to the vessel wall often initiated in childhood and usually presenting clinically in middle to old age. Nikolaj Nikolajewitch Anitschkow, a Russian scientist, is credited as the first person to recognize the atherogenic potential of dietary cholesterol ***(Finking & Hanke 1997).*** His initial experiments, published in 1913, demonstrated that atherosclerotic lesions in rabbits are proportional to the amount of cholesterol consumed.

Since Anitschkow did his observations in rabbits, a causal role for cholesterol has been confirmed in humans, and constituent components of cholesterol transport have been isolated. These include low-density lipoprotein (LDL) and lipoprotein (a), which correlate with risk for atherosclerosis, and high-density lipoprotein (HDL), which is inversely related to risk. Other metabolic conditions also identified as causal factors for atherosclerosis such as diabetes mellitus (DM), hyperhomocysteinemia and hypertryglyceridemia.

Plaque evolution and classification:

The classic classification scheme of atherosclerosis was proposed by Stary and colleagues, and consists of six types of lesions extending from type I lesions consisting of isolated foam cells to type VI lesions, which are mature complex atherosclerotic plaques ***(Stary et al., 1995)*** *(Table 2) and (figure 2)*

Table (2): Stages of atherosclerosis progression Stary classification scheme.

Nomenclature and histology	*Main growth mechanism*	*Earliest onset*	*Clinical correlation*
Type I (initial) lesion *Isolated macrophage foam cells*	*growth mainly by lipid accumulation*	*From first decade*	*Clinically silent*
Type II (fatty streak) lesion *Mainly intracellular lipid accumulation*			
Type III (intermediate) lesion *Type II changes & small extracellular lipid pools*		*From third decade*	
Type IV (atheroma) lesion *Type II changes & core of extracellular lipid*			*Clinically silent or overt*
Type V (fibroatheroma) lesion *Lipid core and fibrotic layer, or multiple lipid cores & fibrotic layers, or mainly calcific, or mainly fibrotic*	*Accelerated smooth muscle and collagen increase*	*From forth decade*	
Type VI (complicated) lesion *Surface defect, hematoma-hemorrhage, thrombus*	*Thrombosis, hematoma*		

(Stary et al., 1995)

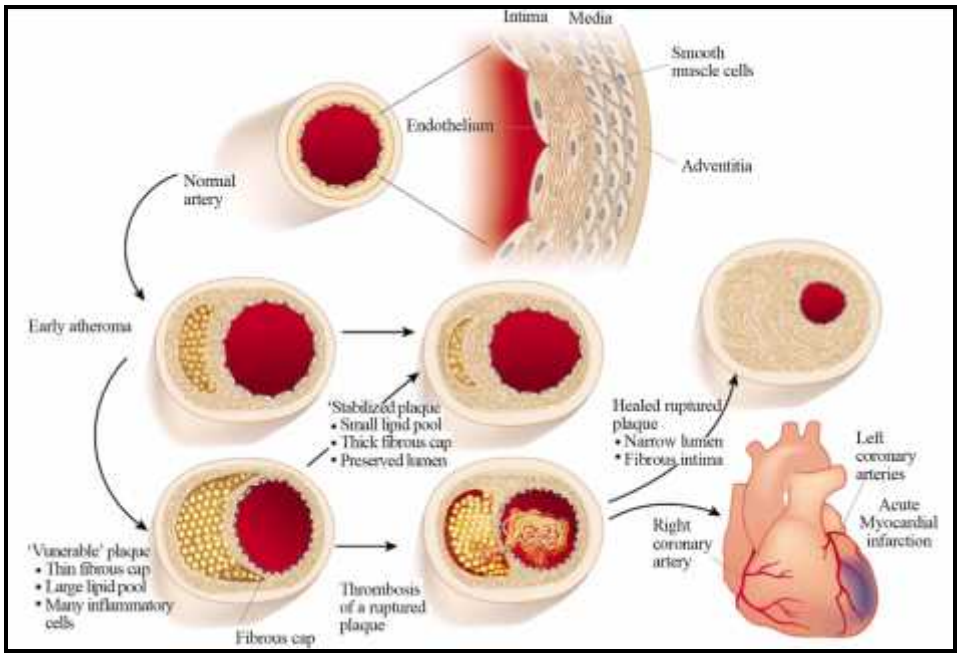

Figure (2): Atherosclerosis progression ***(Libby 2002)***

Plaque vulnerability:

The natural history of a stable plaque may take one of several courses.

In the coronary arteries, as an example, the plaque may remain quiescent with no symptoms or may progress to limit coronary flow reserve and cause symptoms of stable angina. However a minority of plaques will cause an acute coronary syndrome (ACS), ranging from unstable angina (UA) to an acute ST-segment elevation myocardial infarction (STEMI).

The conversion of stable to unstable plaque has little to do with the severity of the underlying lesion. Histologic studies

of autopsy specimens identified several features that appear to be associated with plaques more vulnerable to rupture. These include a thin fibrous cap, a large lipid core, and an abundance of inflammatory cells largely concentrated at the shoulder regions of the plaque ***(Libby 1995)*** *(figure 3)*

The key regulator of plaque vulnerability is inflammation. From a cellular and molecular standpoint, the structural integrity of the plaque depends on a balance between two components of the fibrous cap; smooth muscle cell mass and extracellular matrix content. Smooth muscle cell accumulation is a product of migration of cells from media to populate the neointima and their subsequent proliferation. Attrition of smooth muscle cells comes primarily from apoptosis. There is evidence that cytokines released from inflammatory cells control apoptosis of smooth muscle cells within the fibrous cap ***(Seshiah et al., 2002).***

The other contributor to fibrous cap integrity is extracellular matrix content, which is a balance between production from smooth muscle cells and degradation.