Pattern of Aortic Stiffness in Young Egyptian Adults with Coronary Artery Disease

Thesis
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List of Abbreviations

Abb.	Full Term
2D	Two dimensional
ACAPS	Asymptomatic Carotid Artery Progression Study
ACE i	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndrome
AD	Aortic distensibility
ADMA	Plasma asymmetric dimethylarginine
AGEs	Advanced glycation end products
AoIMT	Aortic intima media thickness.
APWV	Aortic pulse wave velocity
AS	Aortic stiffness
ASI	Aortic stiffness index
BMI	Body mass index
BMI	Body mass index
CA	Coronary Angiography.
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAIUS	Carotid Atherosclerosis Italian Ultrasound Study
CCA	Common carotid artery.
CELIMENE	Celiprolol Intima-Media Enalapril Efficacy Study
CFA	Common femoral artery.
CFPWV	Carotid-femoral pulse wave velocity
cIMT	Carotid intima-media thickness
CT	Computed tomography.
CVA	Cerebrovascular accidents.
CVD	Cardiovascular disease
CW	Continuous wave Doppler
DALY s	Disability-adjusted life years
DBP	Diastolic blood pressure
DD	Diastolic diameter
DM	Diabetes Mellitus.
ECM	The extracellular matrix
ECs	Endothelial Cells
eNOS	Endothelial nitric oxide synthase
EPCs	Endothelial progenitor cells
ESC	European Society of Cardiology
FBN	Fibrillin
FH	Familial Hyperlipidemia
FMD	Flow Mediated Dilation
FMD	Flow-Mediated Dilation method
FRS	Framingham risk score.
GWASs	Genome-wide association studies
HbA1c	Glycated haemoglobin
HDL	High-Density Lipoprotein
HRT	Hormone replacement therapy
hsCRP	High-Sensitivity C-Reactive Protein
HTN	Hypertension.
ICAM-1	Intercellular adhesion molecule 1.
IL-1	Interleukin -1

List of Abbreviations (Cont…)

Abb.	Full Term
IMC	: Intima-media complex
IMT	: Intima-media thickness
IRAS	: Insulin Resistance Atherosclerosis Study
KAPS	: Kuopio Atherosclerosis Prevention Study
KIHD	: Kuopio Ischaemic Heart Disease Risk Factor Study
LAD	: Left anterior descending artery
LCA	: Left coronary artery
LCX	: Left circumflex artery
LDL	: Low-density lipoprotein.
Lp a	: Lipoprotein a
LV	: Left ventricular
LVSD	: Left ventricular systolic diameter.
MARS	: Monitored Atherosclerosis Regression Study
MESA	: Multi-Ethnic Study of Atherosclerosis
MI	: Myocardial Infarction
M-mode	: Motion mode.
MMP	: Matrix metalloprotease
MRI	: Magnetic resonance imaging
NAC	: N-acetylcysteine
NO	: Nitric Oxide
NOS	: Nitric oxide synthase
NSTE-ACS	: Non ST elevation acute coronary syndrome.
PAD	: Peripheral arterial disease.
PAT	: Peripheral artery tonometry
PCVMETRA	: Prevention Cardio-Vasculaire en Medecine du Travail
PHYLLIS	: The Plaque Hypertension Lipid Lowering Italian Study
PLAC-II	: Pravastatin, Lipids, and Atherosclerosis in the Carotid arteries
PlGF	: Placental growth factor
PWV	: Pulse wave velocity
RCA	: Right Coronary artery
REGRESS	: Regression Growth Evaluation Statin Study
SBP	: Systolic blood pressure
SD	: Systolic diameter
SFA	: Superficial femoral artery :
SIS	: Segment involvement score
SMC	: Smooth muscle cells
SNPs	: Single-nucleotide polymorphisms
STEMI	: ST Elevation Myocardial infarction
VCAM-1	: Vascular cell adhesion molecule 1
VEGF	: Vascular endothelial growth factor
VHAS	: Verapamil in Hypertension and Atherosclerosis Study
VLA-4	: Very late antigen 4
VSMC	: Vascular smooth muscle cell
YLDs	: Years lived with disability
YLLs	: Years lost due to premature death

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in the world and is predicted to remain so for the next 20 years [1].

Endothelial dysfunction develops from the first decade of life as a response to genetic and environmental risk factors and seems to be the causal pathway for the initiation and progression of atherosclerosis [2].

A number of large epidemiologic studies have identified numerous risk factors for the development and progression of atherosclerosis. Age is one of the most important risk factors of the disease [3]. Although coronary heart disease primarily occurs in patients over 40 years of age, younger men and women may be affected [4, 5]. Epidemiological studies showed that cardiovascular deaths occur at younger age in low and middle-income countries in comparison to high income countries [6]. The prevalence of CAD in young adults is difficult to establish accurately since it is frequently a silent process [7]. Although CAD is an uncommon entity in young patients, it constitutes an important problem for the physician and the patient because of the devastating effect of this disease on the more active lifestyle of young patients[8].

Current guidelines for the primary prevention of CAD recommend initial assessment and risk stratification with global risk score, in which age is the most potent factor determining risk. Recognizing that risk assessment strategies may inadequately assess cardiovascular disease risk in young patients, noninvasive measures of atherosclerosis have emerged as adjuncts to traditional cardiovascular disease risk factors in an attempt to refine risk stratification and the need for more aggressive preventive strategies [9].

Non-invasive measurement techniques of atherosclerosis, like carotid artery B-mode ultrasound, aortic pulse wave velocity (PWV), carotid artery duplex scanning and ultrasound-based endothelial function studies have emerged as valuable tools to characterize the physiologic and anatomic structural modifications in the arterial wall[10].

Aortic stiffness occurs as a result of atherosclerosis, hypertension, ageing or other pathologic conditions. Accordingly; the forward pulse wave travels faster and the arterial waves reflected from the periphery reach the heart earlier [11]. The aortic pulse wave velocity (APWV) reflects the central arterial stiffness. It's a marker of atherosclerosis inversely related to distension capacity. It has attracted much interest in recent years as a measure of conduit artery stiffness. Different studies showed that higher APWV is a predictive marker for cardiovascular events, ischemic stroke and coronary artery disease [12].

Ultrasound is used to monitor the carotid intima-media thickness (IMT) owing to its high-resolution, non-invasiveness and ability to detect the early stages of atherosclerotic disease [13]. Due to the fact that carotid IMT provides information on the atherosclerosis extent, it can be very useful in the cardiovascular risk assessment. Until now, carotid IMT has been associated with the risk of coronary artery disease, stroke, and myocardial infarction. An increased IMT has been shown to be associated with the presence and extent of coronary artery disease (CAD [14-17].

AIM OF THE WORK

1. To investigate the correlation between aortic stiffness and coronary artery disease presence and severity in young Egyptian adults.

2. To correlate between aortic stiffness, carotid intima media thickness and endothelial function in Egyptian adults with CAD.

ATHEROSCLEROSIS

Atherosclerosis is the major cause of morbidities and mortalities worldwide [(18)].

More people die annually from cardiovascular deaths than from any other cause. Low- and middle-income countries are disproportionally affected: over 80% of CVD (cardiovascular disease) deaths take place in low- and middle-income countries and occur almost equally in men and women[(19)].

The term atherosclerosis is of Greek origin, meaning thickening of the intimal layer of arteries and accumulation of fat. Fatty material is located in the central core of the plaque, covered by fibrous cap. The term, atherosclerosis consists of two parts; atherosis (accumulation of fat accompanied by several macrophages) and sclerosis (fibrosis layer comprising smooth muscle cells (SMC), leukocytes, and connective tissue)[(20,21)].

Normal Artery structure:

An understanding of the pathogenesis of atherosclerosis first requires knowledge of the structure and biology of the normal artery and its indigenous cell types [(22)].

The Cell Types that Comprise the Normal Artery

1- Endothelial Cell

The endothelial cell of the arterial intima constitutes the crucial contact surface with blood. Arterial endothelial cells possess many highly regulated mechanisms of capital importance in vascular homeostasis that often go awry during the pathogenesis of arterial diseases [(23)]. For example, the endothelial cell provides one of the only surfaces, either natural or synthetic, that can maintain blood in a liquid state during protracted contact (Fig1). This remarkable blood compatibility derives in part from the expression of heparin sulfate proteoglycan molecules on the surface of the endothelial cell. These molecules, like heparin, serve as a co-factor for antithrombin III, causing a conformational change that allows this inhibitor to bind to and inactivate thrombin[(22)].

The surface of the endothelial cell also contains thrombomodulin, which binds thrombin molecules and can exert antithrombotic properties by activating proteins S and C. Should a thrombus begin to form; the normal endothelial cell possesses potent fibrinolytic mechanisms associated with its surface [(22)].

ECs (Endothelial Cells) have a common origin but acquire "bed-specific" characteristics during development. The ECs that form the inner lining of all blood vessels arise during embryogenesis from regions known as the blood islands, located on the embryo's periphery [(24-26)].

Peripheral blood appears to contain endothelial precursor cells that may help repair areas of endothelial desquamation[(27)].

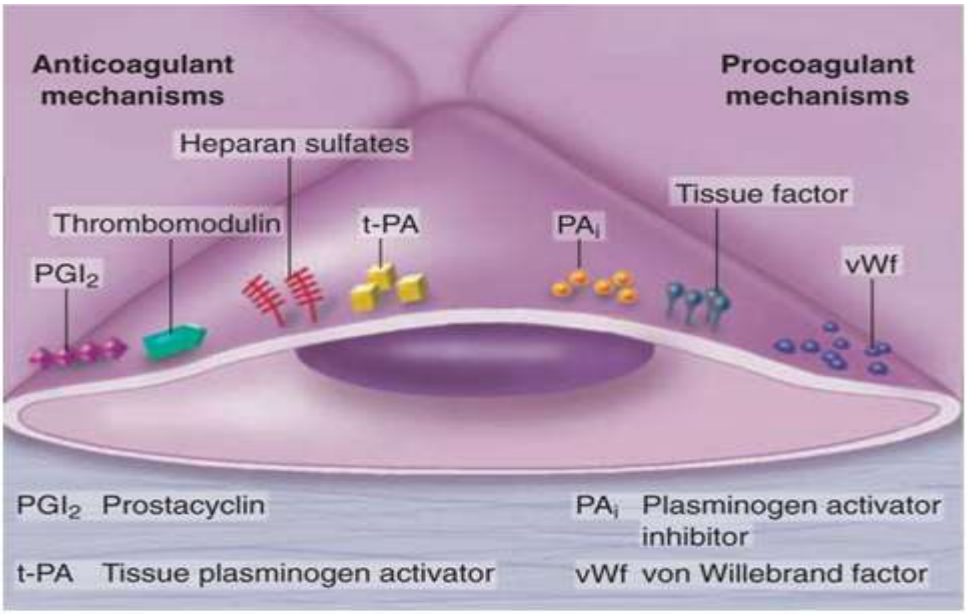

Figure (1): Vascular Endothelial cell [(22)].

2- Arterial Smooth Muscle Cells

The second major cell type of the normal artery wall, the smooth muscle cell (SMC) has many important functions in normal vascular homeostasis, as a target of therapies in cardiovascular medicine, and in the pathogenesis of arterial diseases. These cells contract and relax and thus control blood flow through the various arterial beds, generally at the level of the muscular arterioles. In the larger types of arteries involved in atherosclerosis, however, abnormal smooth muscle contraction may cause

vasospasm, a complication of atherosclerosis that may aggravate the embarrassment of blood flow [(22)].

In contrast with ECs, thought to derive from a common precursor, SMCs can arise from many sources [(28)]. The heterogeneity of SMCs may have direct clinical implications for explicating several common observations, such as the propensity of certain arteries or regions of arteries to develop atherosclerosis or heightened responses to injury (e.g., the proximal left anterior descending coronary artery), and medial degeneration (e.g., the proximal aorta in Marfan syndrome) [(29)]. The plasticity of SMCs may even extend to giving rise to cells with characteristic and functions of mononuclear phagocytes in atherosclerotic plaques [(30)].

The layers of the arterial wall:

1- The Intima

Normal arteries have a well-developed tri-laminar structure. The innermost layer, the tunica intima, is thin at birth in humans and many nonhuman species. Although often described as a monolayer of endothelial cells abutting directly on a basal lamina, the structure of the adult human intima is actually much more complex and heterogeneous [(22)].The endothelial monolayer resides on a basement membrane containing nonfibrillar collagen types, such as type IV collagen, laminin, fibronectin, and other extracellular matrix molecules. With aging, human arteries develop a more complex intima containing arterial SMCs and fibrillar forms of interstitial collagen (types I and III). The SMC produces these extracellular matrix constituents of the arterial intima. The presence of a more complex intima, known by pathologists as diffuse intimal thickening, characterizes most adult human arteries. Some regions in the arterial tree tend to develop thicker intima than other regions, even in the absence of atherosclerosis. For example, the proximal left anterior descending coronary artery often contains an intimal cushion of SMCs more fully developed than that in typical arteries. The diffuse intimal thickening process does not necessarily go hand in hand with lipid accumulation, and may occur in individuals without substantial burden of

atheroma. The internal elastic membrane bounds the tunica intima abluminally, and serves as the border between the intimal layer and the underlying tunica media [(22)].

2- The Tunica Media

The tunica media lies under the intima and internal elastic lamina. The media of elastic arteries such as the aorta have well-developed concentric layers of SMCs, interleaved with layers of elastin-rich extracellular matrix. This structure appears well adapted to the storage of the kinetic energy of left ventricular systole by the walls of great arteries. The media of smaller muscular arteries usually have a less stereotyped organization. SMCs in these smaller arteries generally embed in the surrounding matrix in a more continuous than lamellar array. The external elastic lamina bounds the tunica media abluminally, forming the border with the adventitial layer [(22)].

3- The Adventitia

The adventitia of arteries has typically received little attention, although appreciation of its potential roles in arterial homeostasis and pathology has recently increased. The adventitia contains collagen fibrils in a looser array than is usually encountered in the intima. Vasa vasorum and nerve endings localize in this outermost layer of the arterial wall. The cellular population in the adventitia is more sparse than in other arterial layers. Cells encountered in this layer include fibroblasts and mast cells. Emerging evidence suggests a role for mast cells in atheroma and aneurysm formation in animal models, but their importance in humans remains speculative[(31)].