

INTRODUCTION

Coronary artery disease (CAD) is a narrowing of the small blood vessels that supply blood and oxygen to the heart. CAD is also called heart artery disease. Cardiovascular diseases (CVDs) are the number one cause of death globally. More people die annually from CVDs than from any other cause. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. Over three quarters of CVD deaths take place in low- and middle-income countries. Out of the 16 million deaths under the age of 70 due to non-communicable diseases, 82% are in low and middle income countries and 37% are caused by CVDs.

Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies. People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidemia or already established disease) need early detection and management using counseling and medicines, as appropriate (*WHO, 2015*).

Despite the development of preventive medicine, CAD is still a major cause of death throughout the world (*Lloyd-Jones*

et al., 2010). With respect to the primary prevention of CAD, detecting the presence of coronary arteriosclerosis is important because early and strict management of coronary risk factors may prevent the progression of coronary plaque instability in those patients. However, detecting the early stage of coronary plaque is challenging because mild plaque burden normally presents no symptoms, even during exercise.

Recent studies revealed that epicardial adipose tissue (EAT) mediates coronary plaque formation (*Iacobellis et al., 2003*) and is associated with fatal and nonfatal coronary events (*Mahabadi et al., 2013*). Importantly, because EAT locates within the pericardial sac, the coronary artery could be directly influenced by inflammatory cytokines, which are released from peri-coronary EAT (*Shimabukuro et al., 2013*). Abdominal visceral adipose tissue (VAT) is also associated with plaque morphology (*Ohashi et al., 2010*) and inflammatory cytokine secretion as well as increased reactive oxygen species generation that may contribute to its progression (*Yudkin et al., 2005*). Different types of adipose tissue depot may play differential roles in the progression of CAD; however, this issue is not yet fully understood.

Various methods to quantify visceral adipose tissue directly by expensive magnetic resonance imaging and radiation-exposing computed tomography, as well as indirectly by anthropometric measures (e.g. waist circumference & body-mass index) exist (*Wheeler et al., 2005*).

Magnetic resonance imaging is the gold standard technique to accurately measure visceral adiposity, although there is some concern about the accuracy of actual visceral adiposity content based on single slice sampling (i.e. whole body magnetic resonance imaging scan is the true gold standard) (*Thomas et al., 1998*).

Waist circumference as a measure of visceral obesity may be less reliable in older persons. Also, waist circumference may be a better measure of subcutaneous rather than visceral obesity (*Bonora et al., 1995*). Anthropometric techniques requiring measurement of the waist (e.g. waist circumference & waist-to-hip ratio) may not account for possibly confounding subcutaneous adipose tissue especially in more obese individuals though waist circumference is considered an accepted measure of intra-abdominal adiposity (*Kamel et al., 2000*). Body-mass index, an anthropometric measure of visceral adiposity is suggested to be a poorer indicator of cardiovascular risk than waist circumference across ethnicities, suggesting that body-mass index may not be a very good measure of visceral obesity (*Yusuf et al., 2005*).

Echocardiography is non-invasive and safe measure of EAT. It is also relatively cost and time efficient since it may be part of the routine assessment that patients suspected to be at risk for cardiovascular or metabolic illness undergo. Only very few limitations exist (*Iacobellis et al., 2003*).

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EAT measurement could be used as a quantitative indicator of metabolic disorders and systemic atherosclerosis and also as a key for CAD risk stratification. Therefore, administration of EAT thickness measurement in the clinical practice could be of tremendous assistance in identifying patients at risk and guiding them in controlling the risk factors appropriately and, if required, undergoing supplementary evaluations with invasive approaches (*Toufan et al., 2012*).

AIM OF THE WORK

The aim of this study is to validate the association between echocardiographic epicardial adipose tissue thickness and the severity of coronary artery disease.

CORONARY ARTERY DISEASE

1. Overview

Ischemic Heart Disease is one of the groups of conditions which are known as cardiovascular disease - the others being cerebrovascular disease, hypertension, heart failure and rheumatic disease (*World Health Organization, 2009*). Ischemic Heart Disease is defined by a joint International Society and Federation of Cardiology and World Health Organization task force as myocardial impairment due to an imbalance between coronary blood flow and myocardial requirements caused by changes in the coronary circulation (*Warrell et al., 2004*).

2. Definition of Ischemic Heart Disease

Ischemic heart disease (IHD) is a condition which results from reduced blood supply to the heart muscle. This usually involves impairment of blood flow through the coronary arteries, most commonly caused by atherosclerotic narrowing, but occasionally due to arterial spasm (*Warrell et al., 2004*).

The reduction in blood supply to the heart muscle can result in a number of clinical presentations:

1. Chronic stable angina (angina pectoris)
2. Acute coronary syndromes such as myocardial infarction and unstable angina
3. Chronic ischemic heart disease such as silent myocardial ischemia.
4. Sudden cardiac death

2.1. Definition of Chronic Stable Angina

Chronic stable angina was first identified by Heberden in 1768 who described the condition as resulting in a pain that had a “sense of strangling and anxiety”, further stating that individuals suffering from angina “are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it were to extinguish life, if it were to increase or continue; but the moment they stand still, this uneasiness vanishes. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm” (*Warrell et al., 2004*).

Many individuals describe angina pain as a ‘tight, crushing ache’ rather than a pain specifically. The pain may be central or sometimes left sided, and may radiate to the left arm, the front of the neck, lower jaw or teeth. The pain is most commonly caused by coronary artery insufficiency due to atherosclerotic disease, but can also be more rarely caused by conditions unrelated to atherosclerosis including valvular heart disease and uncontrolled hypertension.

Stable angina can be distinguished from other ischemic heart diseases by factors which provoke or relieve the symptoms. Symptoms often occur on exercise, especially in cold or windy weather, or after a meal, or when an affected

individual experiences emotional distress. It should be noted that atypical symptoms can occur, particularly in women, the elderly and diabetics. Chronic stable angina is relieved by rest. If angina symptoms do not subside on rest, an alternative diagnosis should be sought.

2.2. Definition of Acute Coronary Syndromes

At any point during the development of atherosclerotic conditions, plaque may detach or tear from the vessel wall prompting platelet aggregation and thrombus formation. If the artery is occluded, the blood flow to the myocardium is compromised and necrosis occurs. This results in changes which can be detected on electrocardiogram and is known as an acute-ST elevation myocardial infarction (STEMI). If the artery is only partially occluded, or only for a short period of time then the blood flow is either not severely or intermittently compromised. This results in some damage to the myocardium, but no significant changes on electrocardiogram and is known as a non-ST elevation myocardial infarction (NSTEMI). The presence of necrosis in the myocardial tissue can be detected by a rise in a cardiac specific serum biomarker such as troponin. When myocardial ischemia is present, but necrosis is absent (evidenced by a normal troponin level), this is known as unstable angina (*National Clinical Guideline Centre for Acute and Chronic Conditions, 2009*).

2.2.1. Definition of Myocardial Infarction (MI)

Despite the introduction of new universal definitions as to what constitutes a myocardial infarction, and the factors which differentiate unstable angina from a MI, there is still a degree of ambiguity as to the specific diagnostic criteria which are applied to each acute cardiac syndrome (*SIGN, 2007*).

The new European Society of Cardiology and American College of Cardiology definition of myocardial infarction (*Thygesen et al, 2007*) states that the term can be applied when there is evidence of myocardial necrosis consistent with myocardial ischemia, listing a number of criteria which if met, means the formal diagnosis of myocardial infarction can be used. These criteria include:

- I. Detection of a rise and/or fall of cardiac biomarkers (usually troponin) to assess the degree of necrotic damage to the myocardium, together with evidence of one or more of the following symptoms:
 1. Symptoms of ischemia
 2. ECG changes indicating new ischemia (e.g. left bundle branch block)
 3. Development of pathological Q waves on an ECG
 4. Imaging results indicating loss of myocardial tissue or abnormal wall motion.
- II. Sudden cardiac death involving cardiac arrest often with preceding symptoms of myocardial ischemia and

possibly accompanied with fresh evidence of ST elevation and evidence of fresh thrombus at coronary angiography or at autopsy.

- III. Specific criteria for diagnosis of myocardial infarction in percutaneous cardiac infusion or coronary artery bypass grafting patients would be indicated where patients with a normal baseline troponin levels elevation of cardiac biomarkers above the 99th percentile Upper Reference Limit are indicative of periprocedural myocardial necrosis.
- IV. The above criteria also apply to patients undergoing Coronary Artery Bypass Graft.
- V. Pathological findings of acute myocardial infarction.

Other diagnostic classifications also use serum troponin levels to indicate a threshold for diagnosis of myocardial infarction, but the levels used for each syndrome may *differ* (*SIGN, 2007*).

2.2.1.1. Clinical Classification of Myocardial Infarction

There is a recent universal classification of the different types of myocardial infarction (*Thygesen et al., 2007*) which can occur. These are:

- ❖ **Type 1:** Spontaneous myocardial infarction related to ischemia caused by a primary coronary event, such as plaque fissuring or rupture

- ❖ **Type 2:** Myocardial infarction secondary to ischemia resulting from an imbalance between oxygen demand and supply, such as coronary spasm
- ❖ **Type 3:** Sudden death from cardiac disease with symptoms of myocardial ischemia, accompanied by new ST elevation or left bundle branch block, or verified coronary thrombus by angiography. In this type of myocardial infarction death occurs before blood samples can be obtained
- ❖ **Type 4:** Myocardial infarction associated with primary percutaneous coronary intervention
- ❖ **Type 5:** Myocardial infarction associated with coronary artery bypass graft

3. Etiology of IHD

The risk of developing ischemic heart disease is influenced by a number of factors. These include: increasing Age, male gender, diet, physical inactivity, obesity, alcohol consumption, psychosocial wellbeing, hypertension, elevated serum cholesterol levels, diabetes, ethnic origin, and smoking.

3.1. Etiology of stable angina

Chronic Stable angina results from the development of focal atherosclerotic plaques in the intimal layer of the epicardial coronary artery. The plaques impair the coronary lumen and may limit blood flow to the myocardium, especially during periods of increased myocardial oxygen demand. Although at rest a

reduction of 75% in the capacity of the lumen is required to precipitate symptoms, during exertion symptoms may occur when the lumen is impaired by as little as 30%.

Plaque-fissure in a minor atherosclerotic lesion may breach the artery's internal elastic lamina, leading to platelet deposition, thrombus formation, reduction in blood flow and possibly coronary dissection and acute occlusion. This process may change the pattern of angina from stable to unstable, and/or lead to an acute myocardial infarction.

3.1.2. Etiology of Acute Myocardial Infarction (AMI)

Acute myocardial Infarctions are caused by irreversible necrosis of cardiac muscle:

- ❖ Nearly always (in 90%) due to occlusion of a coronary artery by atherosclerosis, with or without superadded thrombus.
- ❖ Rarely due to coronary embolus (e.g. in atrial fibrillation or infective endocarditis).

The extent of necrosis which occurs may be limited by the degree of collateral blood supply. Coping mechanisms supplied by collateral vessels are better developed in an individual who has an existing history of chronic stable angina. In this case the infarct is often then smaller than would occur in an individual who has developed a sudden occlusion.

4. Diagnosis of Coronary Artery Disease

4.1 Diagnosis of Chronic Stable Angina

The diagnosis of chronic stable angina involves clinical assessment, laboratory investigations and a number of specific cardiac investigations which may be invasive or non-invasive. Initial diagnosis and assessment is usually undertaken in an outpatient setting. An important aspect of the diagnosis is confirming the extent of ischemic heart disease, and therefore an indication of the prognosis for the individual in order to identify those who are progressing to more acute coronary symptoms.

In many cases a working diagnosis of angina can be formed on clinical history alone, with subsequent investigations confirming the extent of the condition. However, it should be noted that a significant proportion of individuals who present with chest pain may not have angina, and early identification of alternative diagnoses should be sought (*SIGN, 2007*).

4.1.1. Clinical Features

There are four areas which indicate features characteristic of angina:

- 1) Location is often retrosternal or left side of chest and can radiate to left arm, neck, jaw or back
- 2) Character: Type of discomfort is often described as a pressure, tightness, or a dull or heavy pain. The pain may be strangling or constricting.

- 3) Duration: Typically the symptoms last up to several minutes after exertion or emotional stress has stopped. Symptoms rarely last longer than 10 minutes. If an individual reports longer attacks, an alternative diagnosis should be sought.
- 4) Relation to exertion: Angina is typically exacerbated by exertion or emotional stress and eased with rest. The symptoms may be precipitated by cold weather or following a meal.

Atypical symptoms (more common in older individuals, women and diabetics) include epigastric pain, breathlessness, or nausea (*Fox et al., 2006; SIGN, 2007*). Angina is characteristically relieved by glyceryl trinitrate. Individuals who report chest pain at rest or on minimal exertion may have unstable angina and should be considered for hospital admission. Angina can be graded by severity using the Canadian Cardiovascular Society (CCS) class scale (*Campeau, 1976*). The classes of severity are shown in the table below.

Table (1): The classes of severity of angina:

Class	Description
I	Ordinary activity such as walking or climbing stairs does not always precipitate angina.
II	Angina precipitated by emotion, cold weather or meals and by walking upstairs.
III	Marked limitation of ordinary physical activity.
IV	Inability to carry out any physical activity without discomfort. Anginal symptoms may be present at rest.

4.1.2. Other History

An individual presenting with symptoms indicative of angina should have a full cardiovascular risk assessment. This should additionally include evaluation of:

- Body mass index (BMI) or waist circumference (WC)
- Heart murmurs
- Psychosocial factors such as depression or social isolation
- Physical activity levels.

4.1.3. Physical Examination

Physical examination is often normal, unless the patient is seen during an episode of pain, when tachycardia or transient arrhythmia may be present. Features which may indicate predisposing factors include:

- 1) Signs of hyperlipidemia.
- 2) Evidence of vascular disease.
- 3) Elevated BP.
- 4) Pallor of anemia.
- 5) Evidence of a previous MI.
- 6) Conditions other than coronary heart disease which can occur with angina including aortic stenosis, uncontrolled atrial fibrillation, cardiomyopathy.

This may include signs of severe ischemic myocardial dysfunction and/or cardiac failure such as a raised jugular venous pressure, ankle edema, basal lung crackles, displaced apex beat, resting tachycardia or pulsus alternans.