The Relationship Between Carotid Intima-Media Thickness and Cardiac Syndrome X

Thesis submitted for partial fulfillment of Master degree in Cardiology

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ABSTRACT

Background: The aetiology of CSX is still a matter of controversy and its relation to early atherosclerosis has not been fully investigated. Previous studies, however, have demonstrated impairment in normal endothelial function of the coronary microvasculature, resulting in inadequate coronary flow reserve as the major pathogenic mechanism. Carotid intima-media thickness (CIMT) measured by ultrasonography is a non-invasive test used to assess the presence of atherosclerosis and has been shown to be an independent predictor of future cardiovascular events.

Aims: This study was performed to characterize the relation of carotid intima media thickness in patients with cardiac syndrome **X** compared to cardiac wise asymptomatic controls.

Methods and results: We studied 25 consecutive CSX patients (mean age 52±5 years, 13 women) and 25 healthy controls (mean age 51±6 years, 10 women). The two groups were comparable for baseline clinical variable and coronary artery disease risk factors except for an increased incidence of hypertension (68% vs. 16%, $P < 0.01$), and diabetes mellitus (52% vs. 8%, $P < 0.01$) in patients with CSX compared to control group respectively. Common carotid IMT values were significantly higher in patients with CSX compared to controls (0.9 [0.55–1.78] vs. 0.61[0.46–1.16] mm, $P<0.001$). This difference remained significant even after exclusion of patients with hypertension and diabetes mellitus. Three patients in CSX group had carotid atherosclerotic plaques with none in the control group.

Conclusions: This study showed that compared to control subjects, patients with CSX have increased mean common carotid artery IMT. The study demonstrated the usefulness of CIMT in predicting CSX patients. It raises the possibility that the pathogenesis of CSX may be an early form of atherosclerosis involving the coronary microvasculature.

Key Words: Cardiac syndrome X; Carotid intima-media thickness; Microvascular.

LIST of ABBREVIATIONS

ACC	American College of Cardiology
ACEI	Angiotensin Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
ADMA	Asymmetric Dimethylarginine
AHA	American Heart Association
ARIC	Atherosclerotic Risk In Communities
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CASS	Coronary Artery Surgery Study
CCA	Common Carotid Artery
CHD	Coronary Heart Disease
CIMT	Carotid Artery Intima-Media Thickness
CRP	C - reactive protein
CSX	Cardiac Syndrome X
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
ED	Endothelial Dysfunction
FH	Familial Hypercholesterolaemia
FRS	Framingham Risk Score
HbA1c	Glycated Hemoglobin
HERS	Heart and Estrogen-Progestin Replacement Study
IMT	Intima-Media Thickness
IMTa	Average Intima-Media Thickness
IMT (La)	Average Left Carotid Intima-Media Thickness
IMT (Ra)	Average Right Carotid Intima-Media Thickness
IRAS	Insulin Resistance Atherosclerosis Study
IVUS	Intravascular Ultrasound
KIHD	Kuopio Heart Disease Risk Factor Study
LDL	Low Density Lipoprotein
MARS	Monitored Atherosclerosis Regression Study
METEOR	Measuring Effect on Intima-Media Thickness and Evaluation of Rouvastatin
MI	Myocardial Infarction

MIBG	Metaiodobenzylguanidine
MRS	Magnetic Resonance Spectroscopy
MSCT	Multislice Computed Tomography
NCEP	National Cholesterol Education Program
NILS-LSA	National Institute for Longevity Sciences-Longitudinal Study of Aging
PHYLLIS	Plaque Hypertension Lipid Lowering Italian Study
PLAC	Pravastatin, Lipid and Atherosclerosis in Carotid Artery
SD	Standard Deviation
SHAPE	Screening For Heart Attack Prevention and Education
SOD	Superoxide Dismutase
SPECT	Single Photon Emission Computed Tomography
TIMI	Thrombolysis in Myocardial Infarction

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INTRODUCTION

The term «syndrome X» first used by Kemp [1] in 1973, is now frequently used as a diagnostic label for patients who have angina or angina-like discomfort, a positive stress test, and coronary arteries that appear normal or nonobstructed on angiography, with possible extracardiac causes of the chest pain, coronary spasm, and ventricular hypertrophy ruled out.[2]

Despite the extensive studies,[3,4] the pathophysiological mechanisms in **cardiac syndrome X** (CSX) remain unclear. Previous studies, however, have demonstrated impairment in normal endothelial function of the coronary microvasculature, resulting in inadequate coronary flow reserve as the major pathogenic mechanism,[5,6] Some researchers have found, in patients with CSX, endothelial dysfunction not only in the coronary circulation but also in the peripheral circulation, indicating that the syndrome may involve a generalized vascular disturbance.[7,8]

The mechanisms involved in the microvascular abnormalities in patients with CSX are likely to be multiple and heterogeneous, however the most accepted one is increased resistance to coronary flow,[9-11] attributed to endothelial dysfunction in coronary microcirculation as was first suggested by Motz *et al*.[5]

Endothelial dysfunction (ED) has been reported to be the initial step in atherosclerosis. In patients with microvascular angina, ED measurement may help in revealing the pathogenesis of the disease since it is still unclear whether the microvascular angina represents a separate entity or is just a first-step or a variant of coronary artery disease (CAD), in which angiographically recognizable atherosclerotic changes evolve due to a long-term exaggerated ED with a high prevalence of coronary artery spasm. Intima-media thickening (IMT) in the common carotid artery (CCA) is an initial marker of atherosclerosis that can be easily ultrasonographically evaluated.

Much attention has been currently focused on common carotid Intima Media Thickness (IMT) as a marker of atherosclerotic diseases and as a tool for gauging the effectiveness of atherosclerosis treatment.[12] Non-invasive techniques such as B-mode ultrasonography can directly evaluate carotid IMT.

Studies suggest that IMT is of high value as a marker of early atherosclerosis. There have also been studies on the relationship between CAD and ultrasonographic variables with mixed results on how carotid IMT relates to CAD.[13-16]

In a study of extracranial carotid arteries in 280 people, it was found that progression of atherosclerosis in the carotids is more marked in people with higher risk of CVD.[17]

In the Rotterdam study of 8000 individuals, patients with higher IMT stood a higher chance of stroke and MI.[18] The absolute ten-year risk of coronary disease rose from 13% to 23.4% with increase in IMT, while the risk of mortality increased from 15% to 46% in the same period.[18]

In another study, the relative risk of non-fatal MI and death increased 2.2 times, and the risk of acute coronary events increased 3.1 times with every 0.03 mm increase in carotid IMT, this prediction was regardless of the person's current lipid profile and other CAD risk factors.[19]

Another study examined the relation between IMT and the number of arterial beds with significant (> 50%) stenoses, including coronary, supra-aortic, renal and iliac/femoral arteries. It showed that IMT was significantly correlated to the number of coronary vessels with stenoses ($p<0.001$). So, IMT has been shown to be an independent predictor of significant multifocal atherosclerosis, showing high sensitivity and specificity for indicating more advanced atherosclerotic involvement.[20, 21]

Many studies such as the “Prospective Finnish Study”, “Atherosclerotic Risk in Communities (ARIC)”, the “Rotterdam Study” and the “Cardiovascular Health Study” showed a significant relation between IMT and cardiovascular risk and provided evidence that carotid IMT is related to future cerebrovascular and cardiovascular events. [22- 24]

Carotid intima-media thickness was recently found to be increased but folate levels decreased in patients with coronary slow flow. [25]

AIM of the WORK

This study was performed to characterize the relation of carotid intima media thickness in patients with cardiac syndrome **X** compared to cardiac wise asymptomatic controls.

REVIEW of LITERATURE

CHAPTER 1
CARDIAC SYNDROME X

Cardiac syndrome X is a clinical entity that needs to be distinguished from angina pectoris due to typical obstructive coronary heart disease. The occurrence of angina or angina-like discomfort with ST-segment changes suggestive of myocardial ischemia (Figure 1) in patients who otherwise have normal or nonobstructed coronary arteries on arteriography [27] is known as ‘‘syndrome X’’, as termed by Harvey Kemp in 1973,[1] or ‘‘cardiac syndrome X’’ (CSX), a name it acquired later in an attempt to differentiate this condition from the metabolic ‘‘syndrome X’’, currently known as ‘‘metabolic syndrome’’. CSX comprises a heterogeneous group of patients presenting with typical exertional chest pain, a positive exercise stress test, and angiographically normal epicardial coronary arteries, in whom non-cardiac causes of chest pain have been ruled out, along with coronary artery spasm (Prinzmetal’s variant angina), left ventricular hypertrophy, valvular heart disease, and cardiomyopathies.

Pathogenesis

The pathogenesis of cardiac syndrome X remains uncertain. Two mechanisms that are not mutually exclusive have been proposed: myocardial ischemia that might be caused by coronary microvascular dysfunction (ie, abnormal dilatory responses and/or increased vasoconstriction); and enhanced sensitivity to intracardiac pain or the so-called "sensitive heart" syndrome.[26-30] It is possible that the syndrome may result from a variable combination of coronary microvascular dysfunction and increased sensitivity to painful stimuli.[27]

Although several possible mechanisms have been proposed, data supporting the significance of myocardial ischemia remains inconclusive.

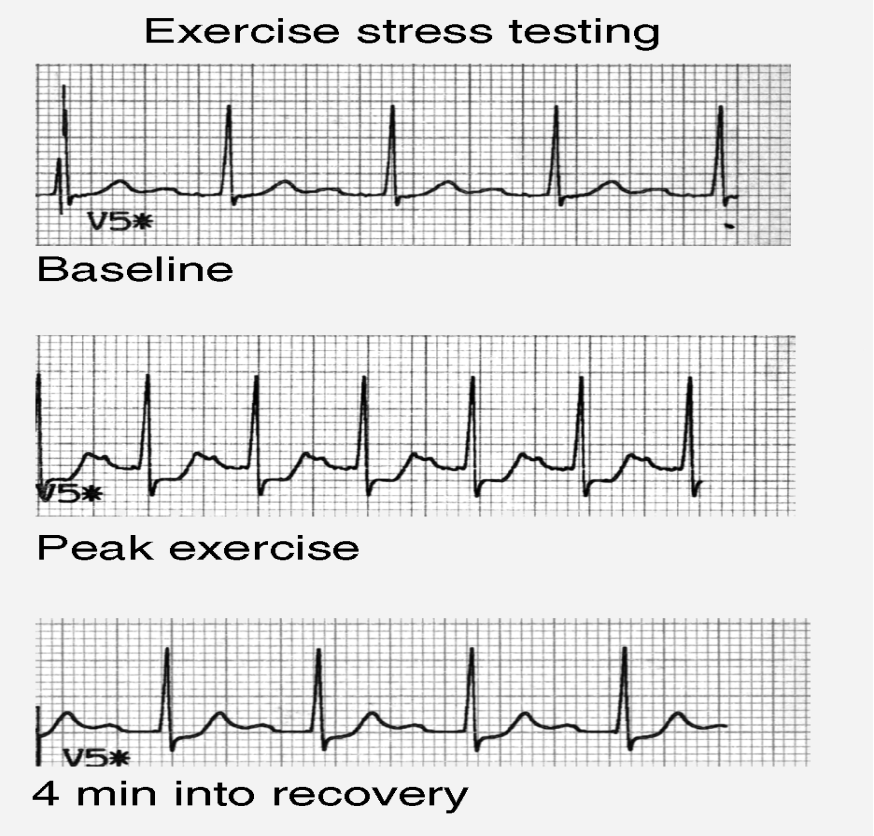

Figure 1: Typical electrocardiographic changes (ST-segment depression during exercise stress testing) suggestive of myocardial ischemia in a patient with cardiac syndrome X.

There are conflicting data concerning the possible role of myocardial ischemia in cardiac syndrome X. Exercise-induced perfusion defects have been noted in some studies.[30,31] However, in other series neither perfusion defects nor regional wall motion abnormalities were seen in response to stress with intravenous dobutamine or transesophageal atrial pacing, despite the provocation of chest pain.[32-34] Similarly, exercise-induced left ventricular (LV) dysfunction, suggestive of ischemia, was noted in one report,[35] but not in others.[32-34,36]

It is possible that ischemia in cardiac syndrome X is limited to the subendocardium, which might explain the inconsistent evidence of perfusion defects and LV dysfunction. Support for this hypothesis was provided in a study of 20 patients with well-defined cardiac syndrome X and 10 matched controls.[28] Perfusion of the subendocardium and subepicardium was assessed with cardiac magnetic resonance imaging (CMR) at baseline and during adenosine infusion. They found that: at baseline, regional perfusion was similar in the two groups. However, during adenosine infusion, control subjects had a homogeneous increase in perfusion of the

subendocardium and subepicardium, but patients with cardiac syndrome X had increased subepicardial, but not subendocardial perfusion, suggesting abnormalities in vasodilator response and subendocardial ischemia. All but one of the patients with cardiac syndrome X had intense chest pain during adenosine infusion.

These findings suggest that chest pain in patients with cardiac syndrome X may be due to subendocardial ischemia. However, an accompanying editorial suggested caution in interpreting these findings, especially that [26] earlier studies that reported evidence of ischemia with radionuclide myocardial perfusion imaging have not proven to be reproducible. The findings suggested heterogeneity in the increase of myocardial perfusion in response to adenosine. Because this occurs in response to a stimulus that does not significantly increase myocardial oxygen demand (adenosine), it is not clear that the impaired increase in perfusion should produce myocardial ischemia and ischemic chest pain.

Thus, further evidence is necessary to confirm the presence and significance of subendocardial ischemia in cardiac syndrome X.

More direct evidence of ischemia has been provided by measurement of myocardial high-energy phosphates after hand-grip exercise, using nuclear magnetic resonance spectroscopy.[37] In a study, however, only 7 of 35 women with chest pain and normal coronary angiograms had this abnormality, suggesting that the disease is heterogeneous. It is also possible that reduced perfusion limited to the subendocardium might not be detected with this technique.

The cardiac microvasculature in patients with cardiac syndrome X may have a reduced vasodilator, or even a paradoxical vasoconstrictor, response to several pharmacologic agents and exercise.[30,38-40] This coronary microvascular dysfunction may be part of a more generalized vascular disorder, since it is often associated with endothelial dysfunction of the peripheral conduit arteries and smooth muscle cell dysfunction in other organs such as the bronchi and the cerebral microcirculation.[8,41-44] Because of these abnormalities, cardiac syndrome X has also been called microvascular angina.