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# Chest Pain and Exercise Induced Ischemia with Angiographically Insignificant Coronary Arterial Disease: Clinical Presentation and Follow-Up

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**Abstract**

Angiography of patients with typical chest pain reveals normal epicardial coronary arteries in about 15-20%. ECG changes suggestive of myocardial ischemia during exercise also can be demonstrated in this subset of the patients. Total 58 patients (42 females) with mean age 42±7 years who were undergoing coronary angiogram in the Department of Cardiology, University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2005 to December 2009 were evaluated. The patients were recruited on the basis of presence of history of chest pain, with normal resting ECG and ischemia like ECG changes during exercise stress test. 32.8% patients had hypertension and 15.5% were diabetics, 19.0% had dyslipidemia and 6.9% had family history of ischemic heart disease. All the patients were having positive exercise stress test. Angiographic findings showed luminal irregularities in 29.3% patients, 15.5% patients had luminal stenosis less than 30% and rest had normal coronary angiogram. Follow up of the patients after one and six months of angiogram was done. After one month 63.8% patients remained symptomatic and after six months 63.3% patients remained symptomatic despite maximum medical management. The pathophysiology and appropriate management of this subset of the patients still remained a challenge for physicians. Optimum management of cardiovascular risk factors is very important issue in this group of patients.

**Key words:** Angiography, Epicardial coronary arteries, Exercise stress test, Cardiovascular risk factors.

## Introduction

The typical angina pectoris and a positive stress test in the presence of angiographically normal coronary arteries is found in about 15-20% of patients undergoing cardiac catheterization.[1–4] In about 50% of these patients anginal pain is attributed to changes in coronary microvasculature.[5–7] We usually classify them as Syndrome X and Microvascular Angina. Syndrome X is defined by a typical angina pectoris with normal or near normal (<40% stenosis) coronary angiogram with or without ECG change or atypical angina pectoris with normal or near normal coronary angiogram plus a positive non-invasive test (exercise tolerance test or myocardial perfusion scan) with or without ECG changes.[8,9] Patients with coronary artery spasm (Prinzmetal's or variant angina), left ventricular hypertrophy, systemic hypertension, and valvular heart disease are not included in this syndrome.[10] The term "Microvascular Angina" (MVA) includes all such patients with coronary microcirculatory derangements but with normal coronary angiograms irrespective of the presence or absence of exercise- induced ST segment depression.[11]

The exact pathophysiological mechanisms underlying these conditions are not well understood, and many mechanisms for the chest pain have been suggested. In some studies, microvascular dysfunction has been proposed as the cause [12-14] whereas in others, metabolic abnormalities, such as net myocardial lactate production have been demonstrated.[15-19] Noninvasive imaging has been used to determine whether ischemia is present or not. Controversial findings have been reported regarding left ventricular function in MVA. Though regional wall motion abnormalities have been reported using stress nuclear techniques, two dimensional echocardiography has not disclosed any segmental contractile dysfunction.[20]

The remaining 50% of these patients have non cardiac causes of chest pain, such as gastro-esophageal reflux, hernia, or degeneration of the skeletal system. Differential diagnosis between cardiac and non cardiac origin often is difficult but necessary for initiation of the appropriate therapy. In fact, a substantial number of these patients continue having chest pain after angiography and will undergo repeated coronary catheterizations thereafter.[21]

In this study we analyzed and followed up consecutively this subset of the patients in our center.

## Materials and methods

This prospective observational study was conducted in the Department of Cardiology, University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2005 to December 2009. Total 58 patients (42 females) with mean age, 42±7 years; range, 35-56 years, who were undergoing coronary angiogram recruited on the basis of the following criteria: a history of chest pain, with normal resting ECG or nonspecific disturbances of ventricular repolarization (flat and low-voltage negative T waves) and ischemia like ECG changes during exercise stress test (horizontal or down sloping ST segment depression ≥ 0.1 mV of the baseline value 0.08 seconds after the J-point). All patients had a normal resting echocardiogram. Hypertension was defined as a blood pressure >140/90 mm Hg. Diabetes mellitus was defined as fasting blood glucose level ≥ 7.0 mmol/l or patient is receiving oral hypoglycemic drugs or insulin. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dl, low density lipoprotein (LDL) ≥ 130 mg/dl and high density lipoprotein (HDL) ≥ 40 mg/dl in male ≥ 50 mg/dl in female. Mitral valve prolapse, primary myocardial disease, or any other valvular or congenital heart disease patients were excluded from the study. A period of pharmacological washout of at least 72 hours was allowed before the stress test in the patients who were taking β blockers, non-dihydropyridine $Ca^{++}$ channel blockers, or nitrate. The stress test was always performed within the 3 weeks preceeding of the coronary angiogram. Each subject was informed of the investigative nature of the study, and written consent was obtained before entry. After the angiogram all the patients were prescribed low dose aspirin, nitrate, β blocker and statin and followed up after one month and six months of angiogram. In follow up patients were interviewed about any change in their symptoms and a 12 lead ECG was done.

## Statistical analysis

Statistical analysis was done by SPSS (Statistical Package for Social Science) software for windows version 12.0. Data were expressed in number, percent or mean±SD.

## Results

### Demographic and clinical characteristics

The demographic and clinical characteristics of 58 cases are listed in Table 1. Total 58 consecutive patients [42 (72.4%) women and 16 (27.6%) men] were included in the study. Mean age was 42±07 years and range, 35 to 56 years. BMI was 25.7±3.9 All were having angina pectoris (Canadian Cardiovascular Society, CCS class III or IV). 19 (32.8%) patients had hypertension and 9 (15.5%) were diabetics. 11 (19.0%) had dyslipidemia. 4 (6.9%) had family history of ischemic heart disease. All the patients were having positive exercise stress test.

**Table 1. Demographic and clinical characteristics of the patients (N=58).**

| Variables | Numbers or Mean±SD | Percent (%) |
|---|---|---|
| Age | 42±07 | - |
| Female | 42 | (72.4%) |
| Male | 16 | (27.6%) |
| BMI | 25.7±3.9 | - |
| Hypertension | 18 | (32.8%) |
| Diabetes mellitus | 09 | (15.5%) |
| Dyslipidemia | 11 | (19.0%) |
| Family history of ischemic heart disease | 4 | (6.9%) |

All the data are in total number, percent or mean±standard deviation.

Figure 1 shows the ECG findings of the subjects. Nonspecific ST-T changes were found among the 64% subjects whereas it was normal among 36% of subjects.

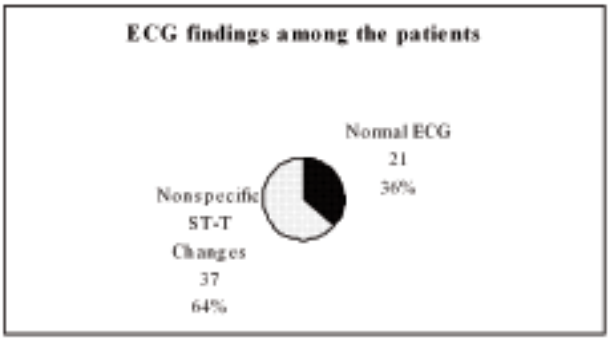


**Figure 1**. Frequency distribution of the ECG findings among the patients

Angiographic findings showed luminal irregularities in 17 (29.3%) patients, 9 (15.5%) patients were having luminal stenosis less than 30% and remaining patients have normal coronary angiogram. (Table 2 & Figure 2)

**Table 2. Angiographic findings of the patients (N=58)**

| Angiographic findings | Numbers | Percent (%) |
|---|---|---|
| Luminal stenosis ≤ 30% | 9 | 15.5 |
| Luminal irregularities | 17 | 29.3 |
| Normal | 32 | 55.2 |

All the data are in total number and percent.

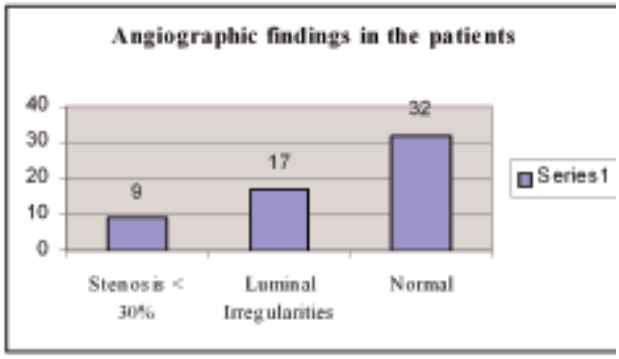


**Figure 2.** Angiographic findings of the patients (N=58)

Table 3 shows the follow up data of the patients after one and six months of angiogram. After one month 63.8% patients remain symptomatic and after six months 63.3% patients remain symptomatic though 15.5% cases were dropped out during six months follow up.

**Table 3. Follow up data of the patients.**

| Number of the patients | Symptoms persisted | Symptoms ameliorated |
|---|---|---|
| **After 1 month** | | |
| 58 | 37(63.8%) | 21(36.2%) |
| **After 6 months** | | |
| 49 | 31(63.3%) | 18(36.7%) |

All the data are in total number and percent.

**Discussion**

Cannon and Epstein[11,22] have proposed that dysfunction of small intramural pre-arteriolar coronary arteries might be the cause of the reduced flow reserve in patients with chest pain and normal coronary arteries. It is worth noting that in the absence of atherosclerotic disease of large epicardial arteries, almost all coronary resistance is located in the microcirculation. According to Chilian et al,[23] a significant proportion (40-50%) of total coronary resistance resides in arterioles greater than 100μm. Furthermore, there is evidence for adrenergically mediated vasoregulation in coronary arterioles with a resting diameter greater than 100μm in which the presence of both α-l and α-2 adrenergic receptors have been demonstrated.[26]

In this study the majority of the study population was comprised of women. All of the subjects were having typical anginal pectoris but most of them having normal coronary angiogram. Data from the WISE study[25] indicate that typical vs. atypical angina does not discriminate between obstructive and non-obstructive coronary disease in a population of women undergoing coronary angiography. Women with angina and normal angiograms may present with symptoms of both stable and unstable angina. The majority of patients seem to be between these two extremes, with a variable prevalence of the two types of symptoms.

Opherk et. al.[26] first reported the finding of reduced coronary flow reserve in patients with angina and "normal" angiograms using the argon washout method. Several investigators using different techniques, such as coronary sinus thermodilution, positron emission tomography, and intracoronary Doppler velocity, have subsequently confirmed this finding.[27-29] More recent studies addressed this issue calculating myocardial perfusion by magnetic resonance imaging.[30,31] Approximately 25% of the population of patients with angina and "normal" or near-normal angiograms had an abnormally reduced flow reserve using this technique.[31] Gated single-photon emission computed tomography,[31] and positron emission tomography[29] can also detect abnormal flow reserve patterns. The prevalence of vascular dysfunction by coronary flow assessment,[29] single photon emission computed tomography,[31] or positron emission tomography[28] consistently demonstrate abnormalities in 50% to 60% of women with "normal" or near-normal angiograms, suggesting that vascular dysfunction is common in this population. However we did not apply these methods to find out abnormal flow reserve in our study population.

All of the subjects in this study were prescribed beta blockers and nitrate together with aspirin and atorvastatin. Around 36% subjects were benefited with regimen where as 63% subjects remained symptomatic. During the six months follow up around 16% cases were dropped out and never returned for follow up. We are not considering them symptom free; they may be searching some holistic approach or alternate medicine. Observational evidence does not support the widespread use of calcium antagonists in patients with "normal" angiograms because they seem to do little to prevent chest pain during daily life in these patients.[32-34] Nitrates are referred to be of help in some patients but not in others. The placebo effect of nitrates cannot be ruled out. β Blockers have been shown to be highly effective for reduction of chest pain episodes during daily life.[33] There are several potential mechanisms by which β blockers may act in reducing chest pain recurrences. They may counteract the pro-ischemic effects of increased adrenergic tone or may

simply reduce myocardial oxygen demand. β Blockers are endothelium-dependent vasodilators as well.[35] The proven benefit of exercise training in this population suggests that mechanism of adrenergic modulation plays a role.[36]

In conclusion patients with angina but normal or non-obstructive coronary angiograms have traditionally been reassured that they do not have heart disease, but many of these patients have persistence of symptoms, are repeatedly hospitalized. Uncertainty about the mechanism of the symptoms and treatment efficacy can potentially lead to continuation of symptoms, difficulties in management, and neglect of atherosclerotic cardiac risk factor treatment.

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