



## Opium addiction as an independent risk factor for coronary microvascular dysfunction: A case–control study of 250 consecutive patients with slow–flow angina



Ali Esmaili Nadimi <sup>a,b,\*</sup>, Farah Pour Amiri <sup>a</sup>, Mahmood Sheikh Fathollahi <sup>c</sup>, Gholamhossien Hassanshahi <sup>d</sup>, Zahra Ahmadi <sup>b</sup>, Ahmad Reza Sayadi <sup>e</sup>

<sup>a</sup> Dept. of Cardiology, Medical School, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>b</sup> Occupational Environment Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>c</sup> Dept. of Social Medicine and Occupational Environment Research Center, Medical School, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>d</sup> Molecular Medicine Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>e</sup> Social Determinants of Health Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

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### ABSTRACT

**Background:** Approximately 20% to 30% of patients who undergo coronary angiography for assessment of typical cardiac chest pain display microvascular coronary dysfunction (MCD). This study aimed to determine potential relationships between baseline clinical characteristics and likelihood of MCD diagnosis in a large group of patients with stable angina symptoms, positive exercise test and angiographic ally normal epicardial coronary arteries.

**Material and methods:** This cross-sectional study included 250 Iranian with documented evidence of cardiac ischemia on exercise testing, class I or II indication for coronary angiography, and either: (1) angiographically normal coronary arteries and diagnosis of MCD with slow-flow phenomenon, or (2) normal angiogram and no evidence of MCD. All patients completed a questionnaire designed to capture key data including clinical demographics, past medical history, and social factors. Data was evaluated using single and multivariable logistic regression models to identify potential individual patient factors that might help to predict a diagnosis of MCD.

**Results:** 125 (11.2% of total) patients were subsequently diagnosed with MCD. 125 consecutive control subjects were selected for comparison. The mean age was similar among the two groups (52.38 vs. 53.26%,  $p = ns$ ), but there was a higher proportion of men in the study group compared to control (42.4 vs. 27.2%,  $p = 0.012$ ). No significant relationships were observed between traditional cardiovascular risk factors (diabetes, hypertension, and dyslipidemia) or body mass index (BMI), and likelihood of MCD diagnosis. However, opium addiction was found to be an independent predictor of MCD on single and multivariable logistic regression model (OR = 3.575, 95%CI: 1.418–9.016;  $p = 0.0069$ ).

**Conclusions:** We observed a significant relationship between opium addiction and microvascular angina. This novel finding provides a potential mechanistic insight into the pathogenesis of MCD with slow-flow phenomenon.

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### 1. Introduction

While atherosclerotic epicardial coronary artery disease (CAD) is the most common cause of myocardial ischemia resulting in symptoms of stable angina, approximately 50% of patients who undergo coronary angiography for assessment of typical cardiac chest pain lack flow-limiting CAD [1], and up to 20% to 30% have evidence of microvascular dysfunction (MCD) [2]. The coronary circulation, as the main source oxygen and nutrients supply to the myocardium, is a coordinated system of capacitance (epicardial coronary artery 500  $\mu\text{m}$  to 5 mm) and resistance

vessels (pre-arterioles 100–500  $\mu\text{m}$ , intramural arterioles <100  $\mu\text{m}$  and capillaries <7  $\mu\text{m}$ ) [3]. MCD involves a phenomenon in which maximal hyperemic extrinsic stimuli (e.g., adenosine) enhance coronary volumetric blood flow less than 2.5-folds, which is the lower limit of normal flow reserve in coronary arteries free of significant obstructive CAD [4]. The etiology of microvascular angina is likely multi-factorial, however several contributory pathogenic mechanisms have been proposed, including endothelial dysfunction, insulin resistance [5], abnormal autonomic control [6], altered cardiac sensitivity [7] and estrogen deficiency [8]. Women (usually during per menopausal period) develop signs and symptoms of myocardial ischaemia more than men, but also exhibit obstructive CAD to a lesser extent than men when investigated with coronary angiography [9,10]. MCD can occur with or without co-existent obstructive CAD and/or myocardial disorders [11].

\* Corresponding author at: Dept. of Cardiology, Medical School, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

E-mail address: [dr\\_esmaeili\\_n@yahoo.com](mailto:dr_esmaeili_n@yahoo.com) (A. Esmaili Nadimi).

MCD is an important differential diagnosis to consider in patients with chest pain and objective evidence of myocardial ischaemia, who lack obstructive CAD [12]. The role of traditional cardiac risk factors (e.g. hypertension, hyperlipidemia, diabetes, smoking and familial history of premature CAD) is well established in atherosclerotic CAD, however the relationship between these risk factors and MCD has been less extensively investigated [13,14]. In this study, we investigated potential relationships between patient demographics and traditional cardiovascular risk factors, social factors, and risk of MCD in patients with typical ischemia-induced angina and no evidence of obstructive CAD.

## 2. Materials and methods

### 2.1. Study subjects

This cross-sectional study was undertaken on 250 Iranian men and women with documented evidence of cardiac ischemia in addition class I and II indication for coronary angiography (patients with the following criteria during treadmill exercise test; ST-segment changes, ejection fraction less than 45%, chest pain, electrocardiographic abnormalities in favor of ischemia, tachycardia and recurrent ventricular fibrillation despite adequate anti-arrhythmic treatment) were visually investigated in at least four left coronary and two right coronary views using angiography technique (shimadzu ceiling suspend image op111, Japan). Patients were recruited to the study if they did not show a visible atherosclerotic, lesion on conventional coronary angiography performed by an expert cardiologist. Patients were divided in two different groups including patients with visible microvascular disorder based on the angiographic findings, i.e. the time of contrast media removal from coronary system was longer than three heart beats ( $n = 125$ ) and those with normal coronary status ( $n = 125$ ). Patients showing signs of cardiomyopathy or a decreased left ventricular ejection fraction

(LVEF), using digitalis, left ventricular hypertrophy, mitral valve prolapse, pre excitation syndrome, significant valvular heart disease, severe hypertension, using anti-depressant medication, history of cardiac surgery, and CAD were excluded from the study due to their confounding effects on exercise test results (non-coronary causes of ST-segment depression and false positive exercise test results) [15] (Fig. 1). All patients were then assessed for risk factors by filling out a questionnaire. All of contributors (with chest pain and also positive ETT) either patient or control (patients with angiographically normal coronary arteries) were referred to the angiography department of Alie-bne-Abitaleb University Hospital, Rafsanjan, Southeastern Iran during June 2012 to June 2013. A separate questionnaire was filled out regarding medical history (age, sex, smoking behavior, opium addiction, history of diabetes, hyperlipidemia, hypertension, body mass index (BMI) measure, familial history of CAD and their symptoms) for each attendee. Presence of MCD was determined in accordance to previously published standardized methods of angiographic assessment in the literature [16] and when three or more beats are required to pacify the distal vasculature. This approach is frequently used in diagnosing the no-reflow phenomenon and has also been used to diagnosed the CSFP (Coronary Slow Flow Phenomenon) [17].

### 2.2. Study size

By considering significance level of 0.05 ( $\alpha = 0.05$ ) and study power of 90% ( $\beta = 0.10$ ) and equality of sample size in both case and control groups, sample size was determine 125 in per groups.

### 2.3. Stress testing and angiography

A standard Bruce protocol was employed using ACT (arshia crown teb tertrainer class 11 ce 0124) for exercise stress test. During the exercise

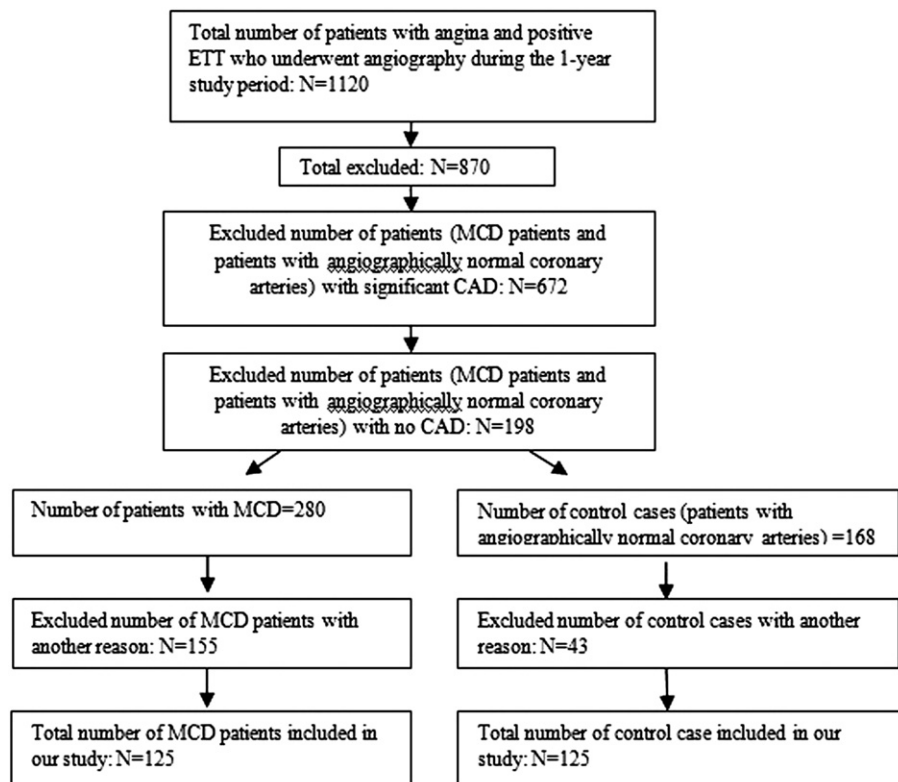


Fig. 1. Shows flow chart to explain how patients were selected.

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