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Research

# Relationship between using raw opium and opioids with coronary artery stenosis based on coronary angiography findings

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## ABSTRACT

Coronary artery disease (CAD) is one of the major reasons of morbidity and mortality in the world. The present study aimed to investigate the relationship between using opium and coronary artery stenosis among patients who underwent coronary artery angiography. A total of 242 patients, attending Imam Ali Hospital in Kermanshah, Iran, who were referred for coronary angiography were studied. Patients were interviewed about using opium before angiography. They were divided to two groups of users and non-users of opium. Coronary vessels were evaluated after angiography based on stenosis severity. Using descriptive statistics and frequency tables, data was analyzed with *t-test* and Chi-squared statistical tests and multi variable analysis were used to determine the relation among variables and comparing the differences. The most common abused drug was opium and the most common route was via inhalation. Coronary vessel lesions were more prevalent among opium users (60%) in comparison with non-users (26%). LAD (left anterior descending) artery lesion was the most common case among the patients. Of 82 opium users, 65 cases had coronary artery lesions and 17 did not have such lesions. Opium usage, omitting the effects of other confounding factors such as BMI and smoking, was considered as an independent risk factor resulting in coronary lesions.

**Key words:** Coronary artery disease, opioid, opium, coronary artery, angiography.

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## 1. INTRODUCTION

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide (1). It is estimated that in 2025, cardiovascular diseases mortality will be the leading cause of death (2). CAD is one of the most common and important causes of death and disability in Iranian population (3). It seems that 50% of deaths in Iran are attributed to CAD (4). Etiology of CAD is often atherosclerosis of epicardial coronary arteries. Important risk factors for

CAD include diabetes mellitus (DM), hypertension, dyslipidemia, obesity, and smoking. Other risk factors are older age, male gender, and positive family history of CAD (5). Drug addiction is one of the most challenging problems in societies. It not only causes behavioral and social disturbances, but also affects physical health of addict persons and put huge amounts of monetary losses on families as well as the society (6). Using opium is one of the most important problems in social health of societies including Iran. There is a false belief

among people of some Asian and Middle Eastern countries that using opium prevents occurrence of DM, hypertension, and CAD. This false belief has resulted in such state that considerable number of people uses opium in these communities (7). Opioids exert their effect through three receptors including mu, kappa, and delta. It seems that kappa and delta receptors are involved in opioids' cardiovascular system effects as well as opioid-related preconditioning effects (8, 9). Morphine which is a medical derivative of opioids has an important role in treatment of cardiovascular conditions such as acute pulmonary edema, cardiac ischemia, and acute myocardial infarction (MI). On the other hand, we observe morphine abuse (9). According to 20 cohort studies, the main cause of mortality in opium abusers was traffic accidents followed by CAD. The risk of mortality due to CAD is higher in opium abusers compared to general population (10). Opium abuse is in a critical situation in many countries, especially in southern Asian countries. Opium abuse frequency in Iran is diverse in different age and socio-economic groups and has been reported from 2.1 to 20% in general population (11). The usual route of opium use is via inhalation (12). Some studies in Iran have noted opium abuse as a risk factor for CAD (13). In contrast, Marmor et al. in an autopsy study of opium addicts reported that the prevalence of CAD in opium users was less than non-users (14). If it can be demonstrated that opioids are risk factor for CAD or even they affect the severity of CAD, education in society can be implemented to reduce opium use and this can lead to improvement in community health and create a general belief about the adverse effects of opium on CAD. In addition, via demonstration of this effect, this can be used as a clinical point. Based on reports made by the Iranian Ministry of Health and Medical Education, in Iran and Kermanshah CAD is the leading cause of mortality in terms of reported death cases and is the second most common cause in terms of years of life lost. Considering that Imam Ali medical center is the sole specific center for cardiovascular diseases in Kermanshah and the study population is reflective of presenting patients as well as high prevalence of opium use in this province, Imam Ali medical center is a suitable place to study this topic. In this study, the relationship between use of raw opium and opioids with stenosis of coronary arteries in patients who underwent coronary arteries angiography was studied.

## 2. MATERIALS AND METHODS

In this cross-sectional study, 242 patients who were candidate for coronary arteries angiography were included. The decision to perform diagnostic angiography was made according to clinical complaint, physical examination; echocardiography, stress exercise test and thallium scan results. Exclusion criteria consisted of congenital cardiac diseases, valvular heart diseases, taking opium as medication, and those who were using opium as a recreational drug and less than 3 months duration. The recruited patients were divided into two groups of opium-users and opium non-users. In opium-users group, detailed interview was carried out to find out the type of opioid used, its amount and duration of opium use. To define opium users, we recruited criteria of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th edition) (9). DSM-IV criteria to diagnose substance addiction are (at least two criteria out of three criteria are needed to make the diagnosis):

1. Tolerance: gradual increase in substance abused to achieve the signs of taking that substance (intoxication)
2. Withdrawal symptoms occur upon not taking or decreasing in taking that substance
3. Constant desire or unsuccessful try to decrease or cut in taking that substance
4. Disturbed social, occupational, or recreational activities
5. Continuing to use the substance despite awareness about its adverse effects

Based on these criteria, the patients are divided into three groups as follows:

1. Non-user
2. Occasional user (they do not have addiction to opium, but use it irregularly)
3. Current user (they have used opium regularly during the past three years)

Other CAD risk factors including hypertension, diabetes, dyslipidemia, positive family history for CAD, smoking, age, and gender were recorded based on interview, physical examination, and routine laboratory tests. After performing angiography, the patients were divided into two groups as control

(normal angiography result) or experimental (having lesion in coronary arteries). To improve the study and better generalization of the results, matching was not done and effects of confounding variables such as smoking and body mass index as well as other CAD risk factors were controlled in data analysis. To quantify the percentage of coronary artery stenosis, QCA (quantitative coronary angiography) was applied:

1. Mild CAD (stenosis < 50%)
2. Moderate CAD (stenosis between 50 and 70%)
3. Severe CAD (stenosis > 70%)

Stenosis of more than 50% was considered significant CAD. Then, based on the number of coronary arteries involved the patients were divided into three groups:

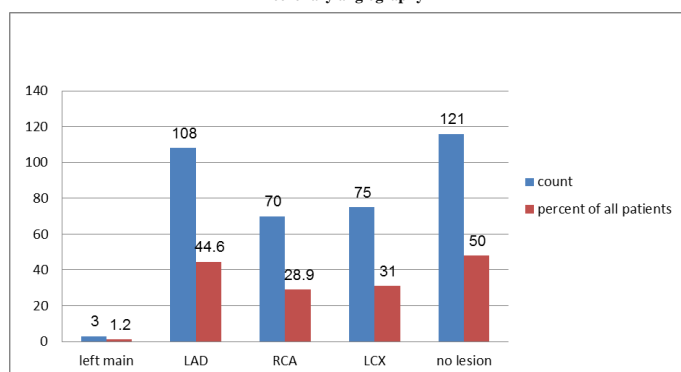
1. Single vessel disease
2. Two-vessel disease
3. Three-vessel disease

The gathered data were entered into the SPSS software for Windows. Descriptive indices such as frequency, percentage, and mean (standard deviation, SD) were used to express data. To compare desired variables between opium users and non-users, the chi-squared test and t-tests were applied. The significance level was set at 0.05.

### 3. RESULTS AND DISCUSSION

According to coronary angiography results, 121 patients had CAD (115 males and 11 females) and 121 patients did not have CAD (91 males and 20 females). Fig. 1 shows frequency (percentage) distribution of patients according to coronary angiography results.

Figure 1. Frequency (percentage) distribution of the studied patients according to the report of coronary angiography



Abbreviations: LAD= left anterior descending; RCA= right coronary artery; LCX= left circumflex

In CAD group, the most and least common involved arteries were LAD (left anterior descending artery) in 108 subjects and left main artery (3 cases), respectively. Eight-two patients were opium users (18 past users, 54 current users, and 10 occasional users). Raw opium (73 cases) was the most common form of opioid abused followed by methadone (8 cases) and heroin (1 case). The most common route of drug abuse was via inhalation (70 cases) followed by eating (10 cases), injection (1 case), and inhalation-eating (1 person). Of 82 patients who were opium users, 65 patients had CAD and 17 did not have CAD. The route of drug abuse did not have relationship with presence of CAD (P= 0.08) (Table 1).

Table 1. Mean (±standard deviation) age, BMI, systolic blood pressure, diastolic blood pressure, and blood glucose concentration in patients with coronary lesion (CAD) vs. normal coronary angiography report.

Category	Coronary artery disease	Normal coronary angiography	P value
Age, year	60.09 (±10.15)	50.82 (±10.05)	0.03
BMI (body mass index), kg/m <sup>2</sup>	26.1 (±6.05)	25.7 (±5.55)	0.5
Systolic blood pressure, mmHg	126.52 (±26.1)	119.87 (±17.33)	0.02
Diastolic blood pressure, mmHg	77.61 (±10.38)	76.36 (±8.68)	0.07
Blood glucose level, mg/dL	114.65 (±106.93)	96.83 (±13.12)	0.07
Diabetes frequency	15%	8.6%	0.07

Table 2 shows comparison of opium use and CAD in smokers vs. non-smokers.

Table 2. Comparison of opioid abuse in smokers vs. non-smokers based on presence of CAD

Group	Type	CAD	Normal coronary angiography
Smoker	Opium user	21	13
	Opium non-user	32	44
Non-smoker	Opium user	38	13
	Opium non-user	24	21

The relative frequency of opium abuse in CAD group, either in smokers or in non-smokers, was higher compared to relative frequency of opium use in control group (non-CAD cases). The Mantel-Haenszel model demonstrated this relationship with controlling the effect of smoking (P< 0.03). However, regarding the low sample size of the study, we cannot consider this relationship significant at each category (smoker and non-smoker). Frequency of opium users in different groups of coronary arteries involved is presented in Table 3.

Table 3. Frequency distribution of opium abuse based on number of coronary arteries involved in CAD patients

Group	Number of coronary arteries involved (i.e., stenosis $\geq$ 50%)					Total
	No lesion	Single vessel	Two vessels	Three vessels	Four vessels	
Opium user	27	18	12	25	0	82
Opium non-user	94	24	24	16	2	160
Total	121	42	36	41	2	242

The most common form in opium users was three-vessel involvement. The relative frequency of opium use in patients with significant CAD (i.e., stenosis  $\geq$  50%) was higher than this frequency in those without significant CAD ( $P = 0.001$ ). With increased number of vessels involved, the likelihood of opium use was higher. Using multivariable analysis in binary logistic model, the association of related factors with outcome factor (presence of CAD) was studied (with excluding unrelated factors). In the last stage, only those factors remained which had effective relationship with outcome in multivariable analysis. Age, gender, and opium use had relationship with outcome. In this study, it was revealed that opium use has relationship, as an independent factor, with CAD. With controlling the confounding effect of other CAD risk factors such as smoking and BMI, opium use still had relationship with coronary angiography results and CAD was more common in opium users compared to non-users (60% vs. 26%). Currently opium abuse is a general health concern in our country. On the other hand, CAD is one of the major causes of morbidity and mortality in Iran. Studies have been done previously in the country to evaluate the effect of opium use on CAD. In a study by Roohafza in Isfahan, it was reported that opium use does not increase cardiovascular disease risk and does not increase mortality and morbidity following acute MI (15). In Marmor et al. study, it was shown that CAD was less frequent in methadone and other opioids users compared to non-users (14). But other studies indicate adverse effects of opium use and the role of opium as a cardiovascular disease risk factor. In a study by Masoumi in 2010 at Shafa Hospital in Kerman, opium abuse was reported as an independent risk factor for CAD. In this study, the effect of other risk factors such as smoking was controlled (16). In Ebrahimi et al. study titled "CAD and risk fac-

tors in Iran", the prevalence of CAD and related risk factors including dyslipidemia, diabetes, smoking, metabolic syndrome, hypertension, obesity, and addiction. They noted that CAD prevalence and related risk factors are more common in Iran compared to southern and middle Asian countries and addiction is a suggested risk factor for CAD (17). Shirani in a study in 2010 on 1,339 patients who were candidate for angiography showed that opium has neither cardiovascular nor carotid arteries atherosclerosis protective effect (19). Sadeghian in a study in 2007 on 299 patients (age range of  $57.5 \pm 10.3$  years) who were candidate for angiography showed that prevalence of opium use in patients was 13.4% and in males it was 19.7%. He also reported that there was a direct relationship between opium abuse and angiography findings in CAD patients and opium use had a significant relationship with severity of CAD (3). Sadeghina in a study performed in 2010 on 299 patients who were candidate for angiography reported that there was a relationship between opium use and severe CAD and with increased age and smoking, this relationship was more significant (18). Azod et al. study in 2008 showed that opium use has no beneficial effect in improvement of blood glucose in diabetics (19). Also, Kouros et al. in 2009 showed that opium aggravated hypercholesterolemia and atherosclerosis in rabbits and is suggested as a risk factor (20). Hosseini in a study in 2012 on patients who were candidate for angiography evaluated the cardiovascular diseases risk factors in CAD patients including BMI, age, waist circumference, waist-to-hip ratio, hypertension, diabetes, smoking, and addiction. He showed that older age, higher blood glucose level, male gender, higher waist-to-hip ratio and opium use were significantly more common in CAD patients in comparison to non-CAD patients (21). All these studies, comparable to the current obtained results, have demonstrated the relationship between opium abuse and CAD. Adverse effects of opium include stimulation of inflammatory factors and disturbance in coagulation. The role of inflammatory factors in atherosclerosis is documented. Asgari et al. in a study in 2008 showed that C-reactive protein (CRP) level is significantly higher in opium users. Also, they noted that many cardiovascular diseases risk factors in opium addicts are significantly increased such as glycosylated hemoglobin, lipoprotein A, CRP, aPOB, and liver enzymes (22). Also in some recent studies, increased level of plasma fibrinogen has been reported in opium users compared to normal individuals. Increased fibrinogen level results in

initiation or aggravation of atherosclerosis (23). Chronic use of opium increase substance P, calcitonin, adenosine, and adenylyl cyclase. These substances have protective effect on heart function (8). But in case of kappa receptor stimulation by opium, the effects will be different. Atchison et al. showed that kappa-opioid receptor stimulation causes worsening of myocardial perfusion and increase in infarct size (24). Also, Coles et al. demonstrated that kappa-opioid receptor blockade results in alleviation of arrhythmia reperfusion (25). We know that morphine has significant effects during cardiovascular events including acute pulmonary edema and causes pain alleviation, decreased preload and afterload, however chronic use of opioids is a risk factor for CAD.

#### 4. CONCLUSION

Recent studies contradict beneficial effects of opium chronic use in patients with cardiovascular diseases, diabetes, and hypertension. In fact, chronic use of opium is an independent risk factor and therefore it is prudent to change the attitude of the community towards this issue via implementing educational programs to raise their knowledge. The practical conclusion of this study is that symptomatic patients with positive history of opium use who present to hospitals are more likely to have CAD. The symptoms of such patient may be less severe in early stages. On the other hand, due to palliative effects of opium, the angina pain in CAD patients who use opium may be subtle and therefore the patient seek medical attention later and upon presentation, the disease has progressed to more severe stages. On the other hand, opium use prevents acute complications of acute coronary syndromes (ACS). Therefore, the probability of survival in ACS patients who use opium and becoming chronic CAD is higher. The higher number of involved coronary arteries in such patients indicates this hypothesis. Therefore, presentation of opium users to medical centers is an alarm to consider the likelihood of CAD. This study evaluated the relationship of opium use with patients who were candidate for angiography. The studied sample was not selected from general population. Therefore, generalization of the obtained findings to general population needs population-based studies. Therefore, limitation of demonstrating a causal relationship remains.

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#### AUTHORS CONTRIBUTION

This work was carried out in collaboration between all authors.

#### CONFLICT OF INTEREST

Authors have declared that no conflict interests exist.

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