Non-obstructive acute CoronarySyndrome and Khat chewing

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DOI: https://doi.org/10.47372/uajnas.2016.n2.a16

Abstract

Nonobstructive coronary artery disease (NCAD)occurs in 10% to 25% of patients undergoing elective coronary angiography, while nonobstructive acute coronary syndrome (NACS) accounts up to 6% of patients with troponin-positive ACS. In Yemen, prior studies have assessed outcomes among myocardial infarction (MI)khat chewers, who had nonobstructive lesions on angiography. However; correlation between NACS and Khat use is yet not discussed. Our study aimed to defining the clinical outcomes of patients, presenting with unstable angina (UA) or non ST segment elevation myocardial infarction (NSTEMI), but had stenosis ≤ 50% on angiography. Our main goal is to show the association between outcomes and khat chewing among patients with NASC. Data for this retrospective study were obtained from the sector of health care and related clinics at the Yemeni Petroleum Company in Aden- from January 2005 through September 2010. The study group consisting of 114 to ACS patients was divided into two subgroups: patients with stenosis < 20% and patients with stenosis more than 20 but less than50%. They were compared with patients in a control group (n=213), who had critical coronary stenosis, sufficient enough to warrantenough (≥70%) percutaneous coronary intervention (PCI). Our results showed that patients with NACS were more likely to be female, younger, with fewer risk factors, compared to the control. MI or PCI occurred was in 1.75 % or 3.5% of patients with NACS and in 5.16% or 17.37% (respectively) of patients with critical obstructive ACS. Cardiac death was observed less frequently in patients with NACS, compared to those with critical obstructive disease (1.75 % vs 4.23%). Sub analysis of the study group showed that, the 2nd subgroup patients (stenosis 20%-50%) were older male with an increasing frequency of nondiabetic patients and heavy khat chewing, compared to the 1st subgroup (stenosis<20%). Follow-up data showed that no deaths in the 1st subgroup and two cardiac deaths (3.7%) in the 2nd (P=0.001). Rehospitalization, PCI or cardiac decompensation were found significant in the 2nd subgroup. We concluded that the prognosis of patients with nonobstructive ACS was better than that of patients with critical obstructive ACS; although patients with stenosis 20-50% had a worse prognosis than did those with less stenosis or normal coronary arteries.

Key words: Acute coronary syndrome, khat chewing, nonobstructive stenosis, critical stenosis.

Introduction

Over recent years, interest in nonobstructive coronary events has intensified, bringing new questions to the fore, particularly in terms of epidemiology, prognosis and treatment. This refers to patients, clinically presenting with unstable angina (UA) or non ST segment elevation myocardial infarction (NSTEMI), but angiographically have nonobstructive lesions. (NOL)Nonobstructive coronary artery disease (NCAD)occurs in 10% to 25% of patients undergoing planned coronary angiography, while nonobstructive acute coronary syndrome (NACS) accounts to approximately 6% of patients with troponin-positive ACS, **(18, 21)**. Although this problem is associated with adverse outcomes, its clinical importance remains underestimated,**(18, 21)** NOL can be defined as atherosclerotic plaques that would not be expected to obstruct blood flow.Although such lesions have been characterized incorrectly as "insignificant" in the medical literature **(16, 22, 24, 31)**, yet different studies have noted that the majority of plaque ruptures and resultant MIs arise from nonobstructive plaques, **(21,28)**.

In Yemen, Khat chewing has been established as an independent risk factor for ACS. Different authors have reported a higher incidence of nonobstructive ACS among khat chewing,**(2, 30)**. The First and Second Gulf Registries of Acute Coronary Events (Gulf RACE-1 & 2) from 6 Middle Eastern countries including Yemen have recently shown that Khat chewing is associated with worse outcome in patients with acute coronary syndrome (ACS), compared with non-Khat users who are mainly from different Gulf populations.**(1, 2)**

Fresh leaves and young stems from the plant khat (Catha Edulis Forskal) are chewed daily by over 20 million people corresponding author has functioned as medical and cardiac consultant million people on the Arabian Peninsula and East Africa, for their euphoric properties, **(4)**. Cathin one, cathine and norephedrine, alkaloids contained in the plant are structurally and pharmacologically related to amphetamine, **(15) (17).**Fresh khat is reported to contain an average of 36 mg cathinone, 120 mg cathine and 8 mg norephedrine per 100 g leaves, **(12).** Khat has direct effects on the cardiovascular system due to indirect sympathomimetic activity of cathinone **(4)**, causing clear increases in heart rate and blood pressure in humans, **(13).**

During the last decade, studies focused on clinical, pharmacological and experimental themes, relatedto ACSand khat chewing. These included clinical and therapeutic outcomes of ACS inkhat chewers, dose-response relationship between the quantity of khat chewed and risk of MI and the effect of drugs used for management of ACS in these patients,**(3,4,**7**).** However, few studies recently attempt to concentrate on relationship between khat chewing and angiographic findings. In a recent study, Al-Motarreb and others have assessed outcomes among MI khat chewers, who had nonobstructive lesion on angiography. **(3,5,7).**Nevertheless; correlation between chronic Khat use and NSTEMI/UA patients with angiographically nonobstructive lesions yet is not studied. Subsequently, our study aimed at defining the demographic and clinical characteristics of NSTEMI/ UA patients, who had NOL on angiography and to evaluate their long-term prognosis, compared with patients who had critical obstructive lesions on angiography. Furthermore, we tried to examine whether a subdivision of the non obstructive ACS study group could provide more information about this clinical entity, concerning the role of khat chewing in inducing non obstructive "malignant" lesions.

Objectives of study

- To compare clinical and prognostic characteristics in NSTEMI/ UA patients who have non obstructive lesions on angiography and patients with critical obstructive disease.
- To determine the differences in clinical and prognostic aspects between patients within the study group: patients with normal angiograms and those within stenosis ≤ 50%
- To define the association between non obstructive ACS and Khat chewing.

Patients and methods

Data for this retrospective study were obtained from the sector of health care and related clinics at Yemeni Petroleum Company in Aden-Yemen, where the. This clinic's database included the records of all consecutive patients who had been seen and followed up from January 2005 through September 2010 with diagnosis of ACS, including unstable angina/NSEMI. All patients had undergone cardiac catheterization in Cardiac Surgery Center at Althawra Hospital, Sana'a. Of the 773ACS patients who were screened, 114 (14.75%), had stenosis ≤ 50% (study group), and 213 (27.55%) had sufficient stenosis (> 50%) requiring percutaneous coronary intervention/PCI (control group). Four hundred and forty-six (446) patients were excluded from both groups: 351 (45.41%) with STEMI and 95 (12.29%) with single vessel disease.

Study population

The study group consisted of 114 patients whose coronary angiogram showed coronary stenosis 20-50% (Figure 1) Within this group, we defined two subgroups: patients with normal angiogramsor stenosis less than 20% (undetectable atherosclerosis or no apparent ACS) and patients with stenosis 20% - 50% (patients with nonobstructive ACS). For methodological purpose, we classified this whole group, conditionally as group of patients with nonobstructive ACS. Such patients were compared with patients in a control group (n=213), who had coronary

stenosis substantial enough (>50%) to warrant percutaneous coronary intervention. This control was defined group as patients with obstructive ACS.
Excluded patients from both groups involved the following: patients with ST-segment-elevation myocardial infarction (STEMI); false diagnosis of STEMI as indicated by pacemaker rhythm or bundle-branch block upon electrocardiography (ECG); single vessel coronary disease; Takotsubo-like left ventricular cardiomyopathy; renal failure defined here as elevation of creatinine (> 2.5 mg/dl or >220 μmol); infectious disease (clinical signs, C reactive protein >100 mg/L).
We excluded myocarditis by cardiac magnetic resonance imaging (MRI)and microbiological studies.

History of Khat chewing among included patients

Khat chewing was considered only in patients with history of daily Khat chewing, with a duration ≥ 2 years, and for an interval ≥ 3 hours. Heavy Khat chewing was included in patients with history of daily prolonged chewing of expensive or moderately expensive khat according to WHO definitions. For this purpose, a list of khat types containing more than 40 types was used , with corresponding concentrations. (12)

Electrocardiographic evaluation

All ECGs were evaluated for ST-segment depression(≥ 0.05 mV), Q waves, and T-wave inversion (≥0.1 mV).

Coronary angiography

Angiographic definitions were considered with standard angiographic descriptions, non obstructive ACS was defined as a coronary artery stenosis 20% or greater but less than 50% in any epicardial coronary artery. Obstructive ACS was defined as any stenosis greater than 50% in any coronary artery. No apparent ACS was defined as all coronary stenoses less than 20% or luminal irregularities or normal arteries. **(8, 20)**. Two subgroups within the study population were isolated and defined (patients with ≤50% diameter stenosis):

- patients with no apparent ACS or without detectable atherosclerosis: in this subgroup, we included patients, who had normal angiograms or stenosis less than 20%.
- and patients with detectable atherosclerotic nonobstructive ACS: in this subgroup, we included patients who had 20%-50% diameter stenosis were included.

Outcomes

Follow up data were obtained by reviewing the patient's clinic records, or by periodic outpatient visits. Anginal class by Canadian Cardiovascular Society (CCS) was noted, and events were identified as myocardial infarction or cardiac decomposition or as those requiring re intervention or rehospitalization, while primary outcome was the 1-year hospitalization for MI, secondary outcomes included 1-year all-cause death and 1-year cardiac mortality. Mortality was measured, using VA vital status data.

Statistical analysis

Demographics characteristics (age, sex, parameters of Khat chewing) and CAD risk factors (hypertension, hyperlipidemia, diabetes, persistent smoking) were estimated. Continuous variables were expressed as mean ± SD and comparisons for continuous variables were performed using Student's t test. All P values were 2-tailed, and a P value < 0.05 was considered to be statistically significant.

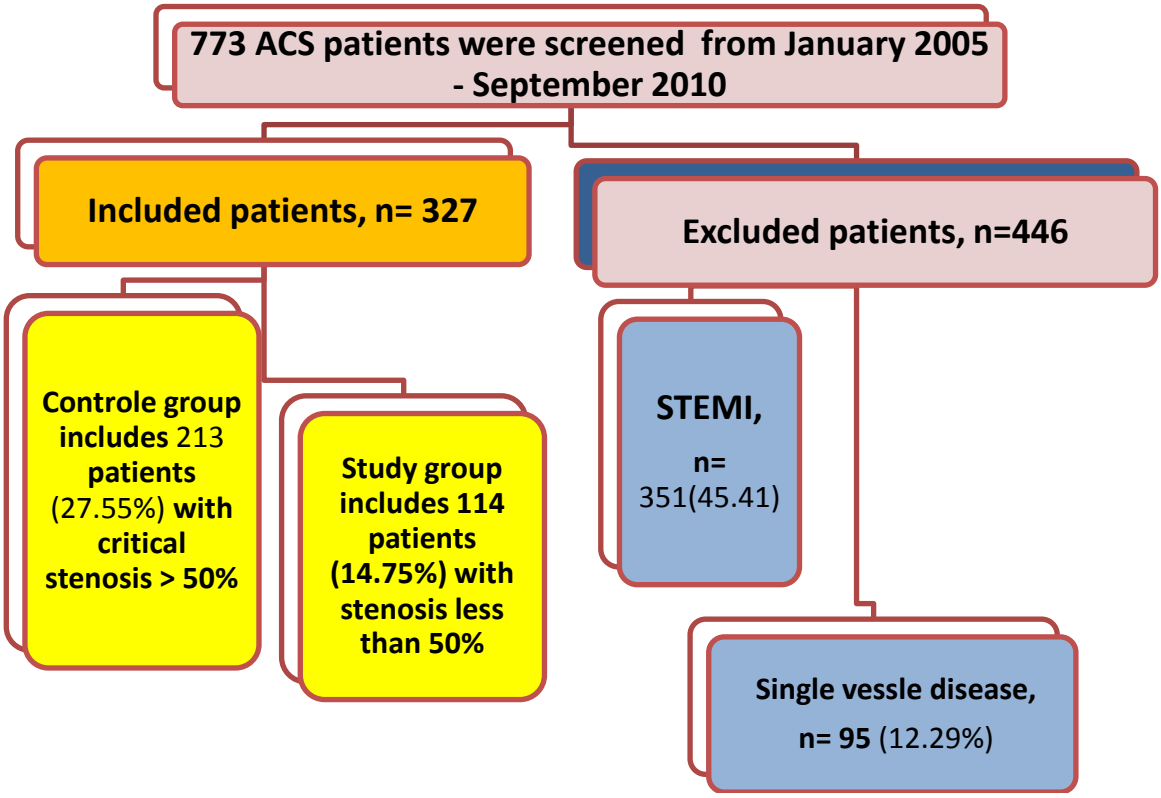

Figure 1: Study design: Of the 773ACS patients who were screened, 114 (14.75%), had stenosis ≤ 50% (study group), and 213 (27.55%) had sufficient stenosis (> 50%) to require PCI (control group). Four hundred and forty-six (446) patients were excluded from both groups: 351 (45.41%) with STEMI and 95 (12.29%) with single vessel disease.

Definitions

Although, this study was retrospective, all described events and terms were consisted with standard definitions:

Unstable Angina (UA) is diagnosed by Braunwald's criteria 1989 and revisited classification (2000).

Non -ST elevation myocardial infarction(NSTEMI) is diagnosed also by Braunwald's criteria 1989, including, elevation of troponin I or T, according to the standard measurements.

Diabetes mellitus (DM): It was defined as chronic use of antihyperglycemic drugs or previously documented diagnosis from medical record or established during hospital stay by repeated fasting blood glucose estimation to be ≥126 mg/dl.

Hypertension: is defined as chronic use of antihypertensive drugs or a previously documented blood pressure 140/90 mmHg for non-diabetics and 130/80 for diabetics from medical record. Positive family history for CAD is defined as ischemic heart disease in the father or a brother diagnosed before age 55 years and in the mother or a sister diagnosed before the age of 65 years.

Smoking: Any present or previous use of cigarettes is considered smoking.

Dyslipidemia: Fasting LDL level ≥130mg/dl is considered as dyslipidemia.

No apparent or undetectable ACS: ACS, including UA/STEMI**,** according to Braunwald's criteria, with angiographic findings of luminal stenosis less than 20%, including normal angiography or luminal irregularity.

Non obstructive ACS:ACS, including UA/STEMI**,** accordingtoBraunwald's criteria, with angiographic findings of luminal stenosis more than 20% and ≤ 50% in single, double or three epicardial coronary arteriesor left main stem artery**.**

Obstructive ACS:ACS, including UA/STEMI**,** accordingtoBraunwald's criteria, with angiographic findings of luminal stenosis more than 50% in single, double or three epicardial coronary arteriesor left main stem artery**.**

Critical obstructive ACS: Obstructive ACS requiring invasive procedure(PCI) or surgery(CABG).

Intraluminal thrombus is defined as an intraluminal filling defect separate from the adjacent vascular wall.

An**ulcer** is defined as a breakdown of the plaque surface,

Vasospasm is defined as a stenosis that could be reversed by the application of nitrates.

Takotsubo-like left ventricular cardiomyopathy is defined as hypokinesis or akinesis from the mid-portion to the apex of the left ventricle together with hyperkinesis in the base.

Results

Demographic and clinical characteristics of the study groupcompared tothe control

During the study period, 773 patients with ACS were screened and followed up in our clinic. Of them, 114 patients (14.75%) had coronary luminal stenosis ≤ 50% (study group, patients with nonobstructive ACS), and 213 (27.55%) had stenosis > 50%, requiring PCI (control group, patients with critical obstructive ACS). According to our above criteria, 446 patients were excluded from both groups: 351 (45.41%) with STEMI and 95 (12.29%%) with single vessel disease, not requiring PCI.

So, our study included 327 ACS patients (unstable angina / NSTMI), as 114 of them were with angiographically with stenosis≤ 50% (study group, nonobstructiveACS) and 213 patients with criticalobstructive stenosis requiring PCI (control group, criticalobstructive ACS).

As shown in table 1, study population patients with nonobstructive disease were compared to patients with critical obstructive disease (control) in terms of demographic and clinical features, characteristic for ACS with unstable angina/NSTEMI.

As compared to control, mean of age in the study group was 53.43years versus66.54 years, males were ~35% v/s 78.9 %, age > 65 years-14.04% v/s 29.11%, two or more cardiovascular risk factors – 18.3% v/s 65.7%. (Table 1)

Significant differences between these 2 groups of patients were found in relation to history of CAD or PCI and history of previous myocardial infarction, and with regard to diabetes mellitus. No significant differences were found between the study group and control concerning hyperlipidemia, hypertension nor regarding persistent smoking.

Although Khatchewing is found more frequently in patients with critical obstructive disease, further subanalysis within the study group will reveal a significant increasing of khat chewing within patients with stenosis 20%-50%, compared to patients without detectable atherosclerosis. (Table 4)

Para clinical characteristics of patients with no obstructive ACS, compared to those with obstructive ACS

Laboratorial variable analysis showed insignificant differences between the study group patients, compared with the control in term of troponin I and CRP. Hyperlipidemia was found to be more frequent in the study group but with no significant difference (Table 2).

According to the ACS register of our clinic during the study period,538patients were with positive troponin, 37 patients (6.88%) were with non obstructive lesions.

ECG study revealed a significant frequency of ST-segment depression, T wave inversion and arrhythmias in the study group, compared to the control. Less significantly, ST-segment elevation was found to be more frequent in the controlin compared to control study group.(Table 2)

Investigation of the echocardiographic results showed that global left ventricular (LV) wall hypokinesis was found only in the control. Mean LV ejection fraction was 50.36% in patients with nonobstructive disease, v/s 45.09% in patients with nonobstructive disease.(Table 2)

Angiographic findings

As we mentioned above, angiographically, the study group involved 114 ACS patients with coronary stenosis ≤ 50%. Within this group, we defined 2 subgroups:

- patients with no apparent or undetectable atherosclerosis: those with normal angiograms or stenosis less than 20% and patients with non obstructive atherosclerosis: those with stenosis 20%-50%.

We found no apparent disease in 60 patients (52.63%) and stenosis 20- 50% (non obstructive atherosclerosis) in 54 patients (47.37%).

Coronary artery angiographic analysis in the second subgroup showed that 58% of lesions were located mainly in the left anterior descending coronary artery, 29% in the right coronary artery and 13% in the right circumflex artery. These non obstructive lesions were distributed as single vessel disease (53%), double vessel disease (33%) and three vessel disease (14%).

Patients with critical obstructive lesions (the control, n=213) were distributed as double vessel disease (48.83%), three vessel disease (38.02%) and left main disease (13.15 %). Patients with single vessel disease > 50% were excluded from the control.

Prognosis of non obstructive ACS patients, compared to **critical obstructive ACS**

As shown in Table 3, follow-up data revealed significant differences between the two groups, concerning therapy with aspirin, clopidogrel and warfarin, incidence of anginal episodes during follow-up and anginal status by Canadian Cardiovascular Society (CCS). MI or revascularization occurred in 1.75 % or 3.5% of patients with nonobstructive ACS patients and in 5.16% or 17.37% (respectively) of patients with critical obstructive ACS. Rehospitalization and cardiac decomposition were observed in both groups, but more frequently in the control group. Cardiac death was observed less frequently in patients with nonobstructive ACS, compared to those with critical obstructive disease (1.75 % vs 4.23%). Analysis of all mortality causes in the study group showed that 2 patients died due to cardiogenic shock following MI and the other 2 patients died at hospital of noncardiac causes (malignancy) Table 3.

Table 1: Demographic and clinical characteristics of the study group (patients withnonobstructive CAD), compared to the control (patients with obstructive CAD)

Characteristics	NonobstructiveACS	Obstructive ACS (control)	P Value
No of patients	114	213	
History of CAD , n (%)	49 (42.98)	155 (77.7%)	**< 0.5**
History of MI , n (%)	8 (7.0)	32 (15.02%)	**< 0.5**
History of CABG , n (%)	-	14 (6.57%)	**< 0.5**
History of PCI , n (%)	12 (10.53)	86 (40.38%)	**< 0.5**
Mean of age (years)	53.43	66.54	**< 0.5**
Age ≥ 65 years , n (%)	16 (14.04)	62 (29.11%)	**< 0.5**
Male gender	40 (35.09)	168 (78.87 %)	**< 0.5**
Risk factors ≥ 2	22 (19.29)	140 (65.73)	**< 0.5**
DM	20 (17.54)	104 (48.83%)	**< 0.5**
AHT	45 (39.47)	130 (61.03%)	**> 0.5**
Hyperlipidemia	61(53.51)	86 (40.38%)	**> 0.5**
Persistent smoking	42 (36.84)	104 (48.83%)	**> 0.5**
Khat chewing	51 (44.74)	168 (78.78%)	**> 0.5**
Heavy Khat chewing during last week	21 (18.42)	106 (49.77%)	**< 0.5**
Heavy Khat chewing prior to attacks	18 (15.79)	86 (40.38%)	**< 0.5**

Table 2: Paraclinical characteristics of patients with nonobstructive CAD, compared to obstructive CAD

Characteristics	Patients with nonobstructive CAD	Patients with obstructive CAD	P Value
Number of patients	114	213	
Elevated Troponin I (n, %)	37 (32.46)	97 (45.54)	**> 0.5**
Elevated CRP (n, %)	38 (33.3)	121 (56.81)	**> 0.5**
Dyslipidemia (n, %)	61(53.51)	86 (40.38%)	**> 0.5**
ST depression > 0.05 mV (n, %)	34 (29.82)	127 (59.62%)	**< 0.5**
ST elevation > 0.05 mV (n, %)	35 (30.70)	67 (31.46)	**> 0.5**
T wave inversion ≥ 0.1 mV (n, %)	31(27.19)	116 (54.46%)	**< 0.5**
Arrhythmias (n, %)	30 (26.32)	115 (53.99%)	**< 0.5**
Segmental hypokinesia (n, %)	37 (32.46)	78 (36.62%)	**> 0.5**
Global hypokinesia with EF< 35% (n, %)	0	75 (35.21%)	**0.001**
Mean ejection fraction (EF) %	50.63	45.09	**< 0.5**

Table 3:Prognosis of patients with nonobstructive ACS, compared to patients withcritical obstructive ACS

Characteristics	Patients with nonobstructive ACS	Patients withcritical obstructive ACS	P Value
Number of patients	114	213	**-**
Therapy with aspirin, clopidogrel or warfarin, n (%)	52 (45.61)	197 (92.49)	**< 0.05**
Absence of angina during follow-up, n (%)	85 (74.56)	110 (51.64)	**< 0.05**
Angina pectoris CCS class III- IV, n (%)	6 (5.26)	18 (8.45)	**> 0.05**
MI during follow-up, n (%)	2 (1.75)	11 (5.16)	**< 0.05**
All deaths n (%)	4 (3.50)	12 (5.63)	**> 0.05**
Cardiac deaths n (%)	2 (1.75)	9 (4.23)	**< 0.05**
Rehospitalization, n (%)	17 (14.91)	133 (62.44)	**< 0.05**
Cardiac decompensation, n (%)	2 (1.75)	10 (4.69)	**< 0.05**
PCI or CABG during follow-up, n (%)	4 (3.50)	37 (17.37)	**< 0.05**

Clinical and prognostic characteristics of the study subgroups patients

Further analysis of the study group revealed significant differences between the two subgroups: 60patients (52.63%) were within undetectable atherosclerosis and 54 patients(47.37%) werewithin stenosis 20%-50%. Patients who had undetectable atherosclerosis on angiography were younger (mean age, 47.23 years ± 16.2) than the patients within coronary stenosis less than 50% (mean age,59.62 years± 11).

In comparison with to patients with coronary stenosis 20%-50%,patients with undetectable atherosclerosis were mostly females (83.34% vs 42.59, p value < 0.5) and presented with fewer cardiovascular risk factors (for AHT 38.33% vs 40.741%, for hyperlipidemia 42.9% vs 66.67%). Exception was observed in DM, as it occurred more frequently in patients with undetectable atherosclerosis 23.33% vs 11.12%. Age ≥ 65 years was found more frequently in patients with detectable atherosclerosis (stenosis 20%-50%).

Significant differences between the two subgroups of patients were found regarding Khat chewing, heavy Khat chewing prior to anginal attacks, or during last week before attacks. Khat chewing was more frequently found in patients with stenosis less than 50% (~ 74% vs 18.34%). History of heavy Khat chewing prior to anginal attacks or during the last week was found to be higher inpatients with stenosis less than 50% rather than in patients with undetectable atherosclerosis (27.78 % vs 5%, and 31.48% vs 6.7%, respectively).

Troponin and CRP studies revealed insignificant differences between these two subgroups. (Table 4), ST depression and T wave inversion were observed in both subgroups without significant difference.Mean ejection fraction was insignificantly higher among patients who had undetectable atherosclerosis than among patients who had stenosis 20%-50% (52.10% vs 49.16%).

Follow -up data revealed significant differences between the two subgroups of patients within non obstructive ACS. Therapy with aspirin, clopidogrel and warfarin, incidence of anginal episodes during follow-up and advanced anginal class by Canadian Cardiovascular Society CCS were significantly more frequent among the second subgroup than among the first subgroup. (Table 5).Cardiac decompensation was observed only in the 2nd subgroup (P=0.001).Rehospitalization or revascularization were found significantly in the 2nd subgroup, compared to the1st.As shown in Table 5, myocardial infarction and cardiac death were only observed among patients within the second subgroup in3.7% for each outcome(P=0.001).

Table 4: Demographic, clinical and paraclinical characteristics of patients with nonobstructive ACS

Characteristics	**Undetectable atherosclerosis**	**Stenosis < 50%**	**P Value**
No of patients	60	54	
History of CAD	19 (31.67)	30 (55.55%)	**> 0.05**
History of MI	2 (3.3)	6 (11.12)	**< 0.05**
Mean age/years	47.23	59.62	**< 0.05**
Age ≥ 65 years	4 (6.66)	12 (22.22%)	**< 0.05**
Male gender	9 (16.67)	31 (57.41%)	**< 0.05**
≥ 2 risk factors	7 (11.67)	15 (27.78 %)	**< 0.05**
DM	14 (23.33)	6 (11.12)	**> 0.05**
AHT	23 (38.33)	22 (40.74%)	**> 0.05**
Hyperlipidemia	25 (41.67)	36 (66.66%)	**> 0.05**
Persistent smoking	21 (34.94)	21 (38.89%)	**> 0.05**
Khat chewing	11 (18.34)	40 (74.07)	**< 0.05**
Heavy Khat chewing during last week	4 (6.66)	17 (31.48)	**< 0.05**
Heavy Khat chewing prior to attacks	3 (5.0)	15 (27.78 %)	**< 0.05**
Elevated Troponin I	16 (26.67)	21 (38.89)	**> 0.05**
Elevated CRP	16 (26.67)	22 (40.74%)	**> 0.05**
ST depression > 0.05 Mv	13 (21.67)	21 (38.89)	**> 0.05**
T wave inversion ≥ 0.1 Mv	16 (26.67)	15 (27.78)	**> 0.05**
Arrhythmias	14 (23.3)	21 (38.89)	**> 0.05**
Mean ejection fraction %	52.10	49.16	**< 0.05**

Table 5: Prognosis of patients with nonobstructive ACS

Characteristics	Undetectable atherosclerosis	Stenosis < 50%	P Value
No of patients	60	54	-
Therapy with aspirin, clopidogrel or warfarin, n (%)	13 (21.67)	39 (72.22)	**< 0.05**
No angina during follow-up	56 (93.33)	30 (55.56)	**< 0.05**
Angina pectoris CCS class III-IV	1 (1.67)	5 (9.26)	**< 0.05**
MI during follow-up	0 (0.0)	2 (3.70)	**< 0.05**
All deaths	0 (0.0)	4 (7.41)	**< 0.05**
Cardiac deaths	0 (0.0)	2 (3.70)	**0.001**
Readmission to hospital	2 (3.34)	15 (27.78)	**< 0.05**
Cardiac decompensation	0 (0.0)	2 (3.70)	**0.001**
PCI or CABG during follow-up	1 (1.67)	3 (5.56)	**< 0.05**

Discussion

The characterization and outcomes of unstable angina(UA)/NSTEMI patients who present with ACS, but angiographically with non obstructive lesions remain debatable. Lack of longitudinal outcomes data on non obstructive ischemic syndromes is a principal cause behind the limitation and controversy of data, needed for understanding their risks for adverse cardiac implications,**(22)**Previous studies had proved that dynamic changes in epicardial coronary artery tone and abnormalities of coronary microcirculation were responsible for IHD in a large proportion of patients, even in the absence of significant coronary atherosclerosis,**(19)**Previously, a concept of an insubstantial but "malignant" stenosis was developed by Scheffold and others to describe non obstructive coronary lesions, that has a pathogenesis and prognosis resembling that of ACS with coronary stenosis substantial enough to warrant PCI **(27)**.

The aim of this study is to define the demographic and clinical features of patients with nonobstructive ACS and to evaluate their long-term prognosis, compared with patients with critical obstructive ACS. A main goal was to analyze the association between khat chewing and the clinical and prognostic tendencies of non obstructive ACS patients.

Our results supported the concept that nonobstructive CAD is not *insignificant* but somewhat is associated with a significant risk for cardiovascular morbidity and mortality, especially in association with Khatchewing. After we carefully excluded other causes of ACS, based on Braunwald's guides for diagnosis and evaluation of UN/NESTMI, we observed this phenomenon at a rate of 15%. This finding agrees well with other the findings of other studies. **(24, 9)**

Compared with the control (obstructive critical ACS), patients with nonobstructive ACSwere more likely to be female, younger, with fewer risk factors. They had less frequent prior history of MI, and coronary revascularization. Females in the nonobstructive groupwere three times more than those with obstructiveACS. These patients with nonobstructive lesions showed markedly an increasing frequency of nondiabetic patients, although the dyslipidemia was found to be more, compared with the control. While Khatchewing was found more frequently in patients with critical obstructive disease, further subanalysis within the study group revealed a significant increasing of khat chewing within patients with stenosis, between20 -50% compared to patients without detectable atherosclerosis.

Demographic, clinical and prognosis of nonobstructive ACS among khat chewers

Our analysis of the study group patients revealed two subgroups with different characteristics and outcomes. This subdivision of the study group patientsmight help in understanding the

pathogenesis of this syndrome, especially in patients who use regularly khat. More than half of our study group had normal coronary arteries or stenosis less than 20% without any suspected atherosclerosis, while the rest showed signs of atherosclerosis (20–50% diameter stenosis).

Use of comparative analysis between these two subgroups was an effective approach to evaluate the clinical, angiographic and prognostic tendencies, observed in the nonobstructive ACS group. Patients in the first subgroup (with normal angiograms or stenosis less than 20%) were younger female with fewer cardiovascular risk factors (mean of age-47.23years). In contrast, the second subgroup patients were older male with an increasing frequency of non diabetic patients and khat chewers (mean of age-59.62 years). However, DM and khat chewing were to be found more determining factors, that define the angiographic trends and differences in these two subgroup.

DM occurred less frequent in the second subgroup patients, who had stenosis < 50%, (11.12% against 23.33% for patients with undetectable atherosclerosis and 49% for patients with criticalstenosis),while history of khat chewing, heavy chewing prior to anginal attacks, heavy chewing during anginal presentation, and related hypertension were frequent in the male patients with nonobstructive lesions, all of these findings were not characteristic for the females in both subgroups of the study group population.

The prognosis of patients with non obstructive ACS seems to be better than that of patients with critical obstructive ACS; although patients with stenosis 20%-50% had a worse prognosis than did those with normal coronary arteries or stenosis less 20%. In our study cardiac death and cardiac decompensation occurred in both study and control groups; however, cardiac death and myocardial infarction were found only in patients with detectable non obstructive ACS (stenosis 20%-50%), compared to patients with undetectable atherosclerosis (stenosis less 20%). These findings are consistent with new large multicenter studies. In an American national cohort of patients undergoing elective coronary angiography, non obstructive CAD, compared with no apparent CAD, was associated with a significantly greater 1-year risk of MI and all-cause mortality.(22) Similar results were found in studies, **(18)** including patients with acute coronary presentations (UA/NSTEMI). Concerning, association with khat chewing, our results are also consistent with previous studies of the GULF RACE 2 study **(1).** In this study, 18.3% of khat chewers with ACS who had coronary angiography had normal coronary arteries or *non significant* lesions, and the remaining patients had evidence of significant coronary artery stenosis. Another Yemeni study tried to investigate the angiographic anatomy of 347 MI patients, divided into three subgroups: diabetic and khat chewers, khat chewers and non diabetic, and diabetic and non-khat users (6). This study showed that, 58% of the second investigated group (khat chewers and non diabetic) had *non significant* lesions, including normal coronary arteries (44%) compared to the other two groups who were diabetic (6). Although, these findings are related to MI, the correlation between khat chewing with non obstructive lesions demonstrates the vasospastic mechanism of khat amines (cathinone and cathine) in inducing of ischemia.

Pharma codynamical and patho physiological effects of khat on the cardiovascular system are related to the actions of the most active khat alkaloids, cathinone and cathine. The amphetamine-like compounds are responsible for the sympathomimetic and catecholamine effects, that play an essential role in the pathogenesis of Khat-induced cardiovascular complications, particularly ACS. These mechanisms include Khat induced tachycardia and arterial hypertension, Khat induced vasospasm and thrombogenicity, cathinone effect of catecholamine-induced platelet aggregation, hypercoagulability and premature coronary atherosclerosis.**(3,7,10,11, 14, 26, 29, 30)**.

Khat-induced coronary spasm was primarily hypothesized and supported by the fact that compounds similar to cathinone, like amphetamine, cocaine, and ecstasy, have been shown to induce coronary artery spasm and ACS (33). However, previous animal studies demonstrated the direct coronary vasoconstriction. It was found that cathinone infusion produces a marked vasoconstriction of the coronary vasculature of isolated guinea pig hearts **(5)**.Baker and others demonstrated in an experimental study, that cathinone-induced coronary vasoconstriction of porcine arteries has been blocked by the α1-adrenoceptor antagonist prazocin or by the neuronal uptake inhibitor cocaine. **(7)**

We could suggest, that chronic khat use is a possible cause of nonobstructive ACS, induced by vasospasm. Probably, this is due to a long-term exposure to hyper catecholamines, systemically released during cathinone metabolism. At this point, we accept the coronary vasospasm as a possible cause of non obstructive ACS in khat chewers presenting with UA/NSEMI, who had ≤50% stenosis. Majority of these patients were relatively older non diabetic men with evidence of long standing khat chewing.

In summary, we can characterize our study sub group patients with detectable atherosclerosis(stenosis 20-50%) as distinct group that differ entirely from patients with stenosis less than 20%. Patients with non obstructive detectable atherosclerosiswere relatively older males, with an increasing frequency of non diabetic, with a history of chronic heavy chewing and with a worse prognosis, during long term evaluation.

Limitations

Our data have been collected retrospectively, so procedural and operative data on coronary angiography were limited. Lack of advanced coronary investigations locally is associated with limited evaluation of some performed procedures and measurements. However, well-designed study plan, and the availability of full sized previous clinical patients' records are supporting factors for conduction of our study. Furthermore,we had an easy contact with the other centers engaged with the invasive investigations of our patients. Future prospective studies, involving patients from multiple hospitals and cardiac centers are needed.

Conclusions

1. Patients with non obstructive ACS were approximately 14 % of all ACS patients, screened during the study period.
2. Patients with stenosis 20-50% almost were older male, with an increasing frequency of non diabetic khat chewers.
3. The prognosis of patients with non obstructive ACS seems to be better than that of patients with critical obstructive ACS; although patients with stenosis 20%-50% had a worse prognosis than did those with normal coronary arteries or stenosis less than 20%.

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المتلازمة الإكليلية الحادة غير الانسدادية وتعاطي القات

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DOI: https://doi.org/10.47372/uajnas.2016.n2.a16

الملخص

تحدث المتلازمة الاكليلية الحادة غير الانسدادية في 10%- 25% من المرضى الذين يجرون قسطرة إكليلية وما يربوعلى6% من مرضى المتلازمةالإكليليةالحادة موجبيالتروبونين. على الرغم من انَها لم تحز على الاهتمام الكافي غير أنَ الأهمية السريرية تكمن في أنَ هذه المتلازمة مرتبطة بمضاعفات خطيرة منها حدوث الاحتشاء القلبي والوفاة بعد أقل من عام من تشخيصها. لقد قُيمت دراسات سابقة النتائج على مرضى احتشاء قلبي يمنيين متعاطيين للقات بإصابات غير انسدادية وهو أمر معروف سلفا. بيد أن العلاقة بين المتلازمة الإكليلية الحادة غير الانسدادية وتناول القات لم يدرس حتى الأن.هدفت دراستنا الى دراسة المميزات السريرية والتنبؤية للمرضى الذين يعانون من الذبحة الصدرية غير مستقرة والاحتشاء غير المصاحب لارتفاع STوالذين بينت القسطرة وجود آفة إكليلة غير انسدادية (انسداد أقل من 50%) حيث يتم مقارنتهم بمرضى الانسداد الحرج. و هدفت الدراسة الى دراسة العلاقة بين المتلازمة الإكليلية الحادة غير الانسدادية وتعاطي القات المزمن. جرت الدراسة في مركزنا الخاص حيث يتم تقديم الرعاية الصحية لمرضى القلب والأمراض الداخلية لموظفي شركة النفط اليمنية عدن من 2005 حتى 2010. عينة الدراسة شملت 114 مريضاً ممن بينت القسطرة اعتلالاً إكليلياً بانسداد وعائي أقل من 50%. وشملت العينة الاختبارية 213 مريضا بانسداد وعائي حرج اعلى من 50%0 تم تقسيم عينة الدراسة إلى مجموعتين:

1. المرضى الذين بينت القسطرة وجود أوعية قلبية طبيعيةأوانسداد وعائي أقل من 20%.
2. المجموعة الثانية تحتوي على المرضي الذين لديهم انسداد من 20% إلى 50%.

بيَنت الدراسة ان المرضى في مجموعة الدراسة في الأغلب أقل سناً و من الإناث و بأقل عوامل الخطورة للإصابة؛ على خلاف المرضى من العينة الاختبارية . حدث كل من الاحتشاء والقسطرة العلاجية بنسبة 1.7% و3.5% في مرضى المتلازمة غير الانسدادية وبنسبة 5.16% و17.37% في مرضى المتلازمة الإكليلية الانسدادية الحرجة. نتائج تقسيم المرضى الى مجموعتين بينت أن المجموعة الثانية التي تشمل المرضي بانسداد من 20 % الى 50% تتكون في الأغلب من مرضى رجال بسن عمرية متقدمة ونسبة محدودة من مرضى السكري ومرتفعة جدا من المتعاطيين للقات،وذلك على عكس المجموعة الأولي. نتائج المتابعة بيَنت أن عدد الوفيات بلغ حالتين في المرضي الذين لديهم انسداد أكثر من 20 % وأقل من 50% (المجموعة الأولى) في حين لم تحدث أية وفيات في المجموعة الأولى. و لوحظ ان الاحتشاء والقسطرة العلاجية لم يحدث إلا في المجموعة الثانية. أخيرا استنتجنا أنه على الرغم من أنَ التنبؤ لدى المرضي المصابين بآفات غير انسدادية (انسداد أقل من 50%) أفضل مقارنة بالمرضى الذين يعانون من انسداد حرج لكن حالات المرضى بانسداد من 20%الى 50%تميزوا بمؤشرات تنبؤ سيئة مقارنة بالمرضى بانسداد أقل من 20% أو ممن اوعيتهم طبيعية دون انسداد.

الكلمات المفتاحية: المتلازمة الإكليلية الحادة ، تعاطي القات، تضيق غير انسدادي، لانسداد الحرج.