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Original Article

Evaluation of the Significance of Positive Troponin I in Patients With Methadone Toxicity

Atoosa Mostafavi[1], MD; Mohammad Hossein Mottaghi[1], MD; Seyed Abdol Hussein Tabatabaei[1*], MD

ABSTRACT

Background: Controversy continues surrounding the relationship between methadone and coronary artery disease (CAD). Given the evidence regarding methadone overdose and elevated high-sensitivity troponin I (hs-TnI) levels, we sought to determine whether elevated hs-TnI was associated with subtle CAD.

Methods: This cross-sectional study was conducted on 100 cases with methadone overdose. Electrocardiography (ECG) was performed on day 1 after admission, and QTc intervals and ST-T segment changes were recorded. The venous level of hs-TnI was checked thrice. Patients aged below 20 years with no risk factors for atherosclerosis were evaluated by stress echocardiography, and the rest underwent coronary angiography.

Results: The mean age of the study population was 41.51 ± 17.82 years. ECG was normal in 48% of the patients, despite elevated levels of hs-TnI. Extensive myocardial infarction was reported in 3% of the study population, and 49% showed ST-T changes. The mean QT-interval was 422.50 ± 77.35 ms in women and 434.28 ± 67.28 in men (P = 0.578). Patients with torsades de pointes had a QT-interval of greater than 500 ms. The mean left ventricular ejection fraction was 55.41 ± 9.85%. All the stress echocardiographic examinations were normal. Twenty-four patients had stenosis exceeding 50% in coronary angiography. The entire study population was older than 40 years of age with more than 1 coronary artery risk factor.

Conclusions: Methadone elevated hs-TnI with and without ST-T changes. Most of our patients had normal coronary arteries in angiography and stress echocardiography. Indeed, even the patients with ST elevation in the anterior leads, combined with a reduced ejection fraction, were ultimately diagnosed as Takotsubo cardiomyopathy. We conclude that elevated hs-TnI in methadone toxicity should not be considered non–ST-segment elevation myocardial infarction. ***(Iranian Heart Journal 2020; 21(3): 119-127)***

KEYWORDS: Methadone, Troponin, Coronary angiography, QT-interval

[1] Department of Cardiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, IR Iran.

***Corresponding Author:** Seyed Abdol Hussein Tabatabaei, MD; Department of Cardiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, IR Iran.
Email: Tabatabaeiseedah@Gmail.com

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Methadone is a synthetic opioid antagonist used for opioid maintenance therapy in cases of opioid dependence and chronic moderate-to-severe pain management. It can be consumed as a powder, a tablet, or a liquid. Methadone may be safer than other narcotics, but the reported cases of overdose have been numerous, underscoring the need for the close monitoring of patients consuming methadone for therapeutic purposes. Indeed, there is evidence not only of the increasing use of methadone by drug addicts but also of first-time suicide attempts among patients on methadone maintenance. As regards methadone abuse, data indicate a significant difference between males and females, with the latter reportedly being more likely to attempt suicide prior to the onset of other forms of abuse. [1]

Opioid abuse is a major concern the world over, and deaths from opioid overdose are on the rise. Methadone overdose is established based on a history of the ingestion of methadone and the presence of at least 2 of the following signs of opioid toxicity: the central nervous system depression, respiratory depression, and myosis. [2]

In recent years, Iran has witnessed an alarming rise in the incidence of methadone poisoning, probably owing to easier access to opioids. [3]

Methadone has some impact on the heart. The prolongation of the QT-interval is deemed a surrogate marker for the development of a fatal arrhythmia called “torsades de pointes (TdP)”. [4] A QT-interval of greater than 500 ms or a greater than 40 ms increase in the QT-interval compared with the baseline is generally accepted to confer a high risk of TdP. Furthermore, methadone-related QT-prolongation is mainly associated with the (R)-enantiomer of methadone, and the mechanism of QT-prolongation TdP is probably the blockage of the human ether-a-go-go-related gene (hERG). [5-7] QT-prolongation can be caused by risk factors such as preexisting QT prolongation; advanced age; female gender; electrolyte abnormalities (eg, hypokalemia and hypomagnesemia); bradycardia; preexisting heart failure or ischemia; and the concomitant use of some drugs including tricyclic antidepressants, antibiotics, fluconazole, and selective serotonin reuptake inhibitors (SSRIs). [8] QT-prolongation can even be associated with the therapeutic levels of methadone. [9] Some other major cardiac effects of methadone include changes in QT-dispersion, Takotsubo cardiomyopathy, and Brugada-like syndrome. [10] Nonetheless, the relationship between methadone and coronary artery disease (CAD) is controversial: Whereas some investigators have reported morbidity and mortality due to cardiovascular disease among methadone users, [11] others have found evidence of the cardioprotective effects of this drug. [12, 13]

Methadone is a potent U-receptor agonist and an N-Methyl-d-aspartate receptor antagonist. [14] A previous study reported that 0.3 mg/kg of methadone before reperfusion could reduce the infarct size and concluded that methadone conferred protection against infarction through the mediating effect of the S-receptor. [13] In contrast, another investigation documented a case of acute myocardial infarction (MI) in a chronic methadone user after the consumption of ASA and concluded that it was in consequence of the paradoxical activation of a major platelet receptor following ASA digestion. [15] Another research reported a higher readmission rate after coronary artery bypass graft surgery secondary to cardiac complications in current opioid users and recommended that the common misconceptions about the beneficial effects of illicit drugs on cardiovascular disease be

addressed. [16] There is also a description of opioid-related ischemia at a younger age. [17]
More than any other marker, high-sensitivity troponin I (hs-TnI) is now widely used for the diagnosis of acute MI. Any elevation exceeding a defined institutional cutoff point can indicate myocyte damage. An abnormal electrocardiogram (ECG) in the presence of a positive marker is strongly indicative of MI. A variety of reasons, however, can elevate hs-TnI levels in the absence of acute coronary syndrome. Moreover, this marker is not specific for the acute thrombotic occlusion of a coronary artery, which is the most common precursor to acute MI.
The existing literature contains no information regarding the high prevalence of detectable hs-TnI among methadone abusers and offers very little concerning the implications of elevated troponin as a result of methadone overdose.
We encountered a higher prevalence rate of detectable hs-TnI among methadone abusers.
The level of hs-TnI can rise in other diseases such as sepsis, atrial fibrillation, heart failure, pulmonary edema, myocarditis, myocardial contusion, renal disease, coronary spasm, direct myocardial damage, acute stroke, and burns. In these patients, elevated hs-TnI does not necessarily indicate myocardial ischemia. [18]
Coronary artery stenosis is detected in different ways, one of which is stress echocardiography. Stress echocardiography is echocardiography combined with a physical, pharmacological, or electrical stress, with the diagnostic endpoint being the induction of the transient exacerbation of the regional function after the induction of stress. [19] Semi-supine exercise is the most frequently used stress test and is the prototype of demand-driven ischemic stress. [19] In cases that cannot exercise or exercise sub-maximally or have uninterpretable ECGs, other forms of stress like pharmacological stress are used.
Myocardial function can have 4 patterns of response to stress: normal, ischemic, viable, and necrotic. A response is defined as normal when a normokinetic myocardium becomes normokinetic or hyperkinetic. If the function of a normokinetic segment worsens into hypokinetic, the response is deemed ischemic. Improvement in the function of a hypokinetic segment qualifies the response as viable. Finally, when an akinetic segment exhibits no change or becomes dyskinetic, the pattern is considered necrotic. [19,20]
Exercise results have sensitivity and specificity of 85% and 79%, respectively, for the detection of CAD (cutoff point > 50% luminal diameter stenosis). [20] Conventional coronary angiography is the gold standard for the detection of coronary stenosis.
In the present study, we sought to determine whether elevated hs-TnI was associated with subtle CAD and to assess the significance of this elevation.

METHODS

This cross-sectional study was conducted on 170 cases with methadone overdose admitted to the Toxicology Ward of Baharlu Hospital, affiliated with Tehran University of Medical Sciences (Tehran, Iran) between March 2017 and March 2018. All patients with methadone overdose, positive urine samples, and elevated troponin were included in this study. The exclusion criteria, with a view to isolating the effects of methadone, were comprised of insufficient data, background liver and renal diseases, and multidrug toxicity or overdose of other opioids.
ECG was performed on day 1 after admission. QT, and if necessary, QTc-intervals were measured and ST-T segment changes were recorded. A QT-interval of greater than 440 ms in men and greater than 460 ms in women was considered abnormal. [21] The level of hs-TnI in venous blood samples was checked thrice: once in the emergency department and twice at 8 and 16 hours subsequently in the ward with a detection limit of 0.06 ng/mL. Cases with

elevated hs-TnI were included in the study. All the specimens were processed by a single laboratory via chemiluminometric technology. Echocardiography was performed with the Esaote MyLab™ClassC ultrasound scanner on the first day, and the left ventricular ejection fraction (LVEF) was measured via the Simpson method.

Ultimately, 100 patients with a diagnosis of isolated methadone overdose and elevated hs-TnI were included in the current study.

The patients were enrolled in the study through the census method, and such different variables as gender, age, route of poisoning, average dose of methadone used, kind of exposure (under methadone maintenance therapy programs, accidental, and intentional), echocardiographic estimation of LVEF, and outcome (surviving or non-surviving) were investigated and recorded in a checklist.

Those aged under 20 years (n = 13) with no known risk factors for atherosclerosis (ie, diabetes, hypertension, dyslipidemia, history of cigarette smoking, and family history of atherosclerotic CAD) were evaluated using exercise stress echocardiography for the detection of possible CAD based on the European guidelines for stress echocardiography. [19] The exercise test was conducted on a treadmill in accordance with the Bruce protocol over approximately a 20-minute period, and all the patients achieved 100% of their maximal predicted heart rate defined as 220 minus age. Four echocardiographic images in the parasternal long-axis, parasternal short-axis, apical 4-chamber, and apical 2-chamber views at rest were compared with the same images at the peak of exercise, and any wall motion abnormalities were recorded. The remaining patients underwent coronary angiography using the Phillips angiography system. Coronary angiography was performed with at least 3 views of the left coronary system and 2 views of the right coronary system. The number of views obtained was at the discretion of the operator. The amount of the contrast used in conventional angiography in each injection was 8 to 10 mL at 4 mL/s for the left coronary system and 6 mL at 3 mL/s for the right coronary system.

The results were divided into 3 groups of normal with no atherosclerosis (stenosis < 30% or slow-flow coronary artery), mild CAD (coronary stenosis: 30%–50%), and significant CAD (coronary stenosis > 50%).

Statistical Analysis

The study was approved by the Ethics Committee of the Research Department of Tehran University of Medical Sciences. The data were analyzed using the SPSS software, version 20, and the frequency and the standard deviation were calculated. First, the Kolmogorov–Smirnov test was run to determine the normal distribution of the quantitative variables; and when the normal distribution of the variables was established, the data were compared using the χ^2 test for the qualitative variables and the *t*-test for the quantitative variables. In the case of non-normal distribution, nonparametric tests such as the Mann–Whitney *U* test and the Wilcoxon signed-rank test were used. Additionally, for the measurement of the strength of the association between 2 variables, the Pearson correlation coefficient was employed. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 170 patients were randomized between March 2017 and March 2018. Seventy patients were excluded due to insufficient data, background liver and renal diseases, and multidrug toxicity or overdose of other opioids. The final analysis was carried out on 100 cases. The patients' characteristics are depicted in Table 1.

Table 1: Baseline patient characteristics

Sex	Female, N (%)	Male (%)	*P* value
Number (%)	12(12%)	88(88%)	
Age (y)	47.08	40.75	NS
First users	7	41	
MMT	5	47	
No risk factor for CAD	7	27	
One risk factor for CAD	3	36	
Two or more risk factors for CAD	3	24	

CAD, Coronary artery disease; MMT, Methadone maintenance therapy; NS, Nonsignificant
Risk factors were comprised of diabetes, hypertension, dyslipidemia, and cigarette smoking.
Values are expressed as N (%) or the mean ± the standard deviation.

Of the 100 cases with methadone overdose admitted to the toxicology ward, 88 (88%) were men (male-to-female ratio: 7.3/1). The mean age of the study population was 41.51 ± 17.82 years (range = 14–82 y). Forty-eight (48%) cases were first users, some of them for attempted suicide, and the rest (52%) were on methadone maintenance therapy. Thirty-nine (39%) cases had 1 CAD risk factor, with the most common risk factor being cigarette smoking (38%); 27 (27%) cases had more than 1 risk factor; and the remaining 34 cases had no cardiac risk factor.

Electrocardiography Findings

The ECG findings are summarized in Table 2.

Table 2: ECG findings

ECG Finding	Frequency	Percentage
Normal	48	48
ST-depression	34	34
ST-depression and inverted T	15	15
ST-elevation	3	3

ECGs were totally normal in 48 (48%) patients, despite elevated levels of hs-TnI. Three patients suffered extensive MI (anterior MI in all 3 cases). The ECGs in 49 patients showed ST-depression, inverted T, or both.

The QTc-interval was between 310 ms and 690 ms. The mean QT-interval was 422.50 ± 77.35 ms in women and 434.28 ± 67.28 in men (*P* = 0.578). Three patients suffered from TdP; all of them had a QT-interval of greater than 500 ms.

Echocardiography Findings

Echocardiography showed no significant valvular heart disease or congenital heart disease. The mean LVEF, measured via the Simpson method, was 55.41 ± 9.85% (25%–69%). The mean LVEF was not significantly different between the male and female cases (*P* = 0.577). The lowest LVEF (25%) was recorded in a 65-year-old diabetic male smoker with an angiographic diagnosis of triple-vessel CAD. The 3 patients with a diagnosis of anterior MI had LVEFs of between 35% and 40%. The patients with significant CAD had lower LVEFs than did the normal group (59.23 ± 7.02% vs 49.54 ± 10.56%, respectively) (*P* = 0.000).

Troponin Level Results

The hs-TnI levels in the study population are summarized in Table 3.

Table 3: Results of the level of hs-TnI

	Number	Minimum	Maximum
TnI 1*	100	0.1	25.00
TnI 2**	99	0.1	18.00
TnI 3***	97	0.7	30.00

*TnI1, hs-TnI in the emergency department; **TnI2, hs-TnI 8 hours later; ***TnI3, hs-TnI 16 hours later
hs-TnI, High-sensitivity troponin I

The highest level of hs-TnI was detected among the patients who suffered ST-elevation myocardial infarction (STEMI), and conventional angiography revealed normal coronary arteries in 2 of these patients.

Stress Echocardiography Results

Stress echocardiography was performed on 13 patients aged below 20 years, all of whom showed no wall motion abnormality indicative of significant coronary artery stenosis at the peak of exercise.

Angiography Results

The patients were divided into 3 groups based on the result of coronary angiography (Table 4).

Table 4: Results of coronary angiography

Angiography Result		
	Number(N)	Percentage (%)
Normal coronary	50	50
Mild CAD	13	13
Significant CAD	24	24

CAD, Coronary artery disease; Normal coronary, Slow flow coronary or stenosis < 30%; Mild CAD, Stenosis between 30% and 50%; Significant CAD, Stenosis > 50%

Twenty-four patients had stenosis exceeding 50% as detected by coronary angiography. All of these patients were older than 40 years and had more than 1 coronary artery risk factor. All the cases with significant CAD had abnormal echocardiography: 1 case had ST-elevation in the precordial leads and the remainder exhibited ST-depression or T-wave inversion. Those with significant CAD had lower LVEFs than did the other 2 groups.

DISCUSSION

Methadone is commonly used for the treatment of opioid addiction and chronic severe pain, especially in cancer, as well as in comorbid delirium in renal failure. [22]

Unfortunately, the rate of acute poisoning by methadone has been on the increase in Tehran Province, [23] which may be due to the significantly low cost of methadone by comparison with the controlled extended-release forms of morphine and also the availability of methadone on the Iranian drug market because of the production of the pharmaceutical forms of this drug since 2003. [21]

Methadone-poisoned patients are commonly men in most studies. In our study, the average age of the patients was 41 years, and there was a male predominance. The main cause of poisoning was drug abuse in our male subjects and suicidal attempts in our female subjects, with most of these suicidal attempts having been made by those in the age range of 14 to 45 years old.

Methadone has a long half-life and tends to accumulate in adipose tissues, particularly after repeated doses; this is a property that increases the likelihood of toxicity, even despite appropriate monitoring. [24]

QT-Prolongation

The QT-interval, which represents the interval during which the myocardial membrane channels are activated in the course of depolarization followed by the repolarization of the ventricles, is known to be prolonged by methadone use. [21,25-28] An arrhythmia called “TdP” might be induced by QT-prolongation. Females have naturally longer QT-intervals and have greater sensitivity to QT-prolongation by drugs; moreover, it has been posited that the sex hormone in males attenuates the drug-induced lengthening of QT. [28] In this study, we did not observe a significant sex dominance in terms of QT-prolongation, which may have been due to the small number of the female sample. A QTc-interval of greater than 500 ms is an accepted threshold for a significant arrhythmia risk. [29]

In our study, 17 patients had QT-intervals exceeding 500 ms, and 3 out of these 17 patients developed TdP. The cases on methadone maintenance therapy had significantly longer QT-intervals than did the first users (456.25 ms vs 416.98 ms; *P* = 0.04), which is due to the known impact of methadone on the QT-interval.

ST-T Changes in Electrocardiography

Methadone can cause T-wave inversion, ST-depression, [29, 30] pathological U waves, and the Brugada pattern on ECGs. [10] ST-depression was more common than was QT-interval prolongation in our study population. Thus far, the importance of such ST-T changes and whether these changes are the main culprit for the increase in mortality and sudden deaths have not been investigated.

Takotsubo cardiomyopathy, also known as "stress cardiomyopathy" and "broken heart syndrome", is a transient cardiac syndrome that involves dramatic LV apical akinesis and mimics anterior MI. It was first described in Japan in 1990 by Sato et al. [31] The clinical presentation of patients ultimately diagnosed with Takotsubo cardiomyopathy is chest pain with ST-elevation on ECG and a significant rise in cardiac hs-TnI. Still, coronary angiography often reveals normal coronary arteries. The scenario is often preceded by physiological or emotional stress. The most common ECG abnormalities are ST-segment elevation (67%–75%) and T-wave inversion (61%). Ninety-five percent of all cases of ST-segment elevation involve the precordial leads and are maximal in leads V_2–V_3. [31] The most acceptable possible mechanism for Takotsubo cardiomyopathy is stress-induced catecholamine release, leading to toxicity and the subsequent stunning of the myocardium. [32] Patients with this diagnosis often have elevated levels of stress hormones or catecholamines in their blood during the time of the incident. [33] Shaikh et al [34] described different time lengths for the recovery of LV systolic dysfunction from 7 days up to 12 weeks.

In this study, STEMI was reported in 3 patients, of whom 2 had normal coronary angiography and 1 had severe multivessel CAD. None of them had recovery of LV dysfunction at 1 month's follow-up.

Echocardiography

The echocardiographic features of methadone-induced Takotsubo cardiomyopathy are well known. [35] The feature in the acute phase is a large area of dysfunctional myocardium not related to the territory of a single coronary artery. This feature encompasses symmetrical regional abnormalities, including the mid-ventricular segments of the anterior, inferior, and lateral walls. A classic pattern is akinesia or hypokinesia in the apical segments with preserved or hypercontractile basal segments. [36] In our study, STEMI was reported in 3 patients. Two of these 3 cases had this typical feature of cardiomyopathy, and none of them had recovery of LV dysfunction at 1 month's follow-up. Heggs et al [37] reported a case of biventricular failure following methadone overdose in a 37-year-old patient with methadone overdose and severe acidosis as well as renal and hepatic failure. We excluded cases with hepatic and renal failure and, as a result, had no cases with biventricular failure.

In our investigation, LVEF ranged between 25% and 69%, and all the cases with a reduced LVEF had concomitant significant CAD except 2 patients, who were diagnosed with Takotsubo cardiomyopathy. The mean LVEF was about 59.23% in the normal coronary artery group and about 49.54% in the patients with abnormal coronary arteries (*P* = 0.000).

Stress echocardiography

Exercise stress echocardiography is a safe and reliable method if performed by an experienced operator. A negative stress echocardiography result has an excellent

negative predictive value concerning cardiovascular morbidity and mortality. [38] The utility of stress echocardiography in patients younger than 20 years is beyond coronary ischemia and is useful in evaluating other areas, including ventricular and coronary reserves, and also in detecting the anomalous origin of native coronary arteries. [39] To the best of our knowledge, the existing literature lacks reports on the assessment of ischemia in patients with positive biomarkers by stress echocardiography; we are, thus, the first to research this area. None of our 13 young patients with negative risk factors for CAD had stress results indicative of coronary artery stenosis.

Coronary Angiography

Coronary angiography is the gold standard for the detection of coronary artery stenosis. Although the angiographic pattern of coronary stenosis in non-STEMI ranges from normal coronary arteries to diffusely diseased coronary arteries, with approximately 20% of these patients having no lesion or nonobstructive lesion in coronary angiography, the guideline still recommends an early invasive strategy in non-STEMI cases who have ST-T changes and/or positive troponin assay on admission. [40] There are reports of conventional coronary angiography in patients with methadone toxicity and echocardiographic evidence of Takotsubo cardiomyopathy. No survey has so far evaluated all patients with methadone overdose and elevated troponin levels. We performed coronary angiography on 87 patients with elevated hs-TnI and found no significant correlation between the amount of hs-TnI rise and either the significance of coronary stenosis (P = 0.690) or QT-interval prolongation (P = 0.094). ST-T changes, either elevation or depression in the ST-segment, had no correlation with the significance of coronary stenosis. Our patients with normal coronary arteries and those with significant CAD both had ST-T changes and elevated cardiac enzymes. This finding shows that elevated troponin levels and ECG changes are probably due to direct cardiac toxicity and drug-induced myocarditis and are not correlated with plaque rupture and thrombosis in coronary arteries, which are the main causes of MI. In the current study, all the patients with significant coronary stenosis were older than 40 years and had 1 or more risk factors for coronary artery stenosis. Accordingly, the general approach to patients with methadone toxicity should be similar to that in the general population with myocarditis, and patients with a low pretest probability of CAD should not be subjected to invasive diagnostic tests like coronary angiography.

CONCLUSIONS

Methadone induces QT-prolongation, but an arrhythmia called “TdP” often happens in QT-intervals exceeding 500 ms. Our results revealed no significant sex dominance vis-à-vis methadone-induced QT-prolongation. Another impact of methadone on the heart among our study population was an elevation in hs-TnI with and without ST-T changes. This rise in hs-TnI is not due to subtle CAD, and most patients will have normal coronary arteries in angiography and stress echocardiography. Even patients with ST-elevation in the anterior leads, combined with a reduced EF, might ultimately be diagnosed as Takotsubo cardiomyopathy. It has been postulated that the reason for such elevations in troponin levels is drug-induced myocarditis. In the present study, patients with significant CAD were older with at least 1 risk factor for CAD.

In light of the results of the current study, it can be concluded that an elevation in hs-TnI in methadone toxicity should not be

considered non-STEMI, and coronary angiography is necessary in selected individuals, not in all patients.

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