Original Article

Comparison of Serum proBNP and Apelin Levels in Hypertensive Crisis Versus Controlled Hypertension: Impact of Opium Addiction Status

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Abstract

Background: Hypertension (HTN) is associated with the risk of cardiovascular diseases (CVDs) and mortality. It is estimated that by 2025, 1.6 billion people worldwide will suffer from HTN. HTN crisis is characterized by severe HTN exceeding 180/120 mmHg, leading to acute myocardial infarction (AMI), acute left ventricular failure, and intracerebral hemorrhage. Apelin and N-terminal proBNP (NT-proBNP) play a role in cardiovascular homeostasis. Opium addiction has been reported to increase the risk of CVD. In this study, we compared the serum apelin and NT-proBNP levels in HTN crisis and controlled HTN, considering the impact of addiction status among patients referred to Kerman hospitals from 2018 to 2019.

Methods: Eighty-nine patients with HTN crisis and 111 controlled HTN subjects as the control group were enrolled. Each group was further divided into two subgroups: non-addicts and opium addicts. Demographic data were recorded, and serum apelin and NT-proBNP levels were measured using the ELISA method.

Findings: Our results indicated that patients with HTN crisis had higher apelin levels than controlled HTN individuals ($\beta = 2.08$, $P < 0.001$). Among the patients with controlled HTN, diastolic blood pressure (DBP) was higher in opium-addicted subjects compared to their non-addicted counterparts ($P = 0.035$). NT-proBNP levels were higher in opium-addicted patients with HTN crisis but higher in non-addicted patients with controlled HTN. Furthermore, mean age, SBP, DBP, HR, CR, and apelin were higher in patients with HTN crisis than those with controlled HTN, which was also statistically significant ($P < 0.05$). However, regarding NT-proBNP levels, there was no significant difference between the two groups ($P = 0.175$).

Conclusion: Contrary to the general belief that opium addiction has cardioprotective effects, we found that opium addiction in controlled HTN subjects was associated with higher DBP and proBNP levels were elevated in addicts with HTN crisis, indicating potential cardiac damage.

Keywords: Hypertension, Hypertension crisis, Opium addiction, Apelin, NT-proBNP

Introduction

HTN is one of the most common risk factors for cardiovascular disease (CVD)[1,2] and is associated with coronary artery disease (CAD), heart failure (HF), kidney damage, and cerebrovascular events.[3,4] Hypertension (HTN) crisis is characterized by a severe and acute increase in blood pressure, typically exceeding 180/120 mmHg. It is divided into two categories: urgent hypertensive (without organ damage) and emergency hypertensive (with organ damage).[5] Potential complications include acute myocardial infarction (AMI), acute left ventricular failure with pulmonary edema, intracerebral hemorrhage, acute ischemic stroke, and acute kidney failure.[6]

Damaged and abnormal vascular structures are one of the causes of HTN, which can be accompanied by increased vascular resistance. Mediators and signaling pathways play a pivotal role in regulating the function of the cardiovascular system (CVS).[7] Apelin is an important polypeptide in CVS with multiple functions, including preventing the development and progression of CVD, regulating energy metabolism, and maintaining the homeostasis of body fluids.[8,9] The Apelin receptor (APJ) is expressed in the vascular system, and apelin acts through nitric oxide (NO), causing vasodilation. Reduced

circulating apelin has been significantly associated with an increased risk of HTN. The integrity of the vascular endothelium is critical for apelin to exert its hypotensive effect.[7] Interestingly, due to the similarity of APJ with angiotensin receptor 1 (ATR1), the apelin-APJ system can have mutual effects on the renin-angiotensin-aldosterone system (RAAS) and showed opposite physiological effects compared to RAAS.[9,10]

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are produced in cardiomyocytes and serve as biomarkers for chronic heart damage, promoting damage caused by increased volume or pressure. Their elevation is associated with increased cardiovascular complications.[11,12]

Opium addiction has been reported as a risk factor for CVD and may be associated with HTN incidence.[13,14] On the other hand, opioids are implicated in the pathogenesis of HTN.[15-17] In Iran, opium is the most commonly used substance, and approximately 3% of the general population is addicted to it. Opium contains over 40 alkaloids and more than 70 types of substances.[18,19] Opioid receptors are categorized into three groups: mu (μ), delta (δ), and kappa (κ), which belong to the G protein-coupled receptor (GPCR) family.[20,21] and expressed in the CVS. Endogenous opioids and their receptors are crucial to regulating the CVS, including electrophysiological activity, heart rate (HR), and vascular tone regulation.[20] APJ and κ opioid receptors form a heterodimer that enhances the positive inotropic effects of apelin on the heart, reinforcing each other's physiological effects [21].

Apelin levels have been found to be inversely related to systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP).[22,23] Furthermore, apelin levels are lower in patients with HTN.[24] Ye et al demonstrated that apelin levels were lower in hypertensive patients with evidence of left ventricular hypertrophy (LVH) than those without LVH.[25] In a study by Baysal et al, serum apelin levels increased in individuals newly diagnosed with HTN and treated with medication for one month.[26]

According to McKie and colleagues' study, proBNP levels above 80% in early-stage HF patients (stage A/B) have been associated with a higher risk of cerebrovascular events, myocardial infarction (MI), advanced stages of HF, and death.[27] El Maraghi et al showed that BNP levels increased in subjects with HTN crisis and measuring BNP levels can be used as a diagnostic marker for emergency HTN.[28] In the study conducted by Phelan et al, who examined BNP levels in individuals with HTN, high BNP levels were associated with subclinical cardiac damage and ventricular remodeling.[29]

Reports showed that the prevalence of HTN is higher in opium addicts, while some other studies hold the opposite opinion.[30,31] NT-ProBNP is a biomarker that indicates cardiac complications, and its measurement can be used as a quick method to investigate organ damage in cases of emergency HTN.[32-34] Apelin is an important hormone in the CVS with protective properties. Given the high prevalence of HTN and its complications, especially emergency cases of HTN, and considering the similarity of opioid receptors and APJ and their mutual effects on each other, it may be possible to further investigate the serum levels of apelin and NT-proBNP in opium addicts and compare them with non-addicted subjects to identify the complications of HTN and explore the potential use of apelin in treating or reducing the complications of emergency HTN cases. Therefore, in the present study, we compared the serum levels of proBNP and apelin in HTN crisis with controlled HTN while considering opium addiction status.

Materials and Methods
Study population
The current research is a case-control study on HTN patients referred to Kerman city hospitals between 2018 and 2019. The target population for this study consists of patients with HTN crises and those with controlled HTN. Patients with HTN crisis were selected by convenience sampling among the patients referred to the cardiac emergency departments of educational hospitals in Kerman as the case group, and the control group was selected in outpatient settings with controlled HTN.

Considering the information presented in the study[27] and with $\alpha = 0.05$ and $\beta = 0.2$ as the parameters, the sample size for each group was determined to be 48. This indicates that the sample size for individuals experiencing an HTN crisis was 96, with 48 in the opium addict and 48 in the non-addict group. The sample size for individuals with controlled HTN was also 96, consisting of 48 patients in each opium addict and non-addict group. Finally, 89 patients with HTN crisis were selected and divided into two subgroups: opium addicts (n = 55) and non-addicts (n = 34). Additionally, 111 patients were chosen as a control group from subjects with controlled HTN, and they were divided into two subgroups: opium addicts (n = 32) and non-addicts (n = 79).

Exclusion criteria
Patients below 20 and above 90 were not included in the study. Additionally, participants with inflammatory and chronic diseases, including rheumatic diseases, malignancy, a history of previous MI, cardiomyopathies, HF, kidney or liver failure, thyroid diseases, cardiac arrhythmias, and pulmonary diseases, pregnant women, and those using oral corticosteroids were excluded from the study. Individuals who did not meet the exclusion criteria were included in the study.[24,28]

Demographic and clinical measurements
Blood pressure measurements were taken after a

10-minute rest in a sitting position. If, throughout two or more visits, the systolic blood pressure exceeds 140 mmHg or the diastolic blood pressure exceeds 90 mmHg, it is clinically considered HTN. Controlled HTN is defined clinically as SBP < 140 mm Hg and DBP < 90 mm Hg, achieved through treatment, lifestyle modification, or pharmacologic therapy.[35,36]

In sum, patients with chronic HTN defined as controlled HTN with values < 140/90 on antihypertensive medications were considered the control group, while values exceeding > 180/120 mm Hg were considered indicative of HTN crisis. The smoking status of participants was recorded as non-smoker or current smoker based on self-reported cigarette smoking. Drug history was documented by inquiring about the type of drugs used. Participants were recorded as non-opium addict or opium addict based on self-reports. Patients with a history of opium addiction for at least 12 months were selected, and people with addiction to other substances, such as methadone or opium tincture, were excluded. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). BMI levels higher than 30 kg/m² were considered obese. BMIs between 25 and 29.9 kg/m² and below 25 kg/m² were considered overweight and normal, respectively. Opium addiction was defined according to the DSM-IV criteria (American Psychiatric Association, 2022).[13,14,37]

This study used a checklist to collect data. The checklist consisted of three parts. The first part included demographic information such as age, sex, opium addiction, history of HTN, medication, and other relevant details. The second part contained information on SBP, DBP, HR, blood urea nitrogen (BUN), and serum creatinine (Cr) levels. The third part involved measuring and recording serum levels of apelin and NT-proBNP.[14]

Sample collection and biochemical measurements
A whole blood sample was obtained from participants who had fasted for 10 hours. The blood sample was left undisturbed at room temperature to clot for 30 minutes. It was then centrifuged at 4000 rpm for 10 minutes, and the serum was promptly collected in a microtube and stored at -80 ˚C. Apelin and NT-proBNP levels were determined using specific ELISA kits as per the manufacturer's instruction (Human NT-ProBNP ELISA Kit (catalog No. RK09256) and Human Apelin (APLN) ELISA Kit (catalog No. RK10311) were used in this study. Blood samples were obtained at a specific time of day to mitigate the impact of circadian rhythm on apelin secretion. BUN was calculated by dividing blood urea levels (mg/dL) by 2.143, and Cr levels were quantified by Jaffe's reaction for all participants.

Statistical analysis
Data were analyzed using SPSS software (version 22).

Descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to characterize the demographic and clinical data. Independent t tests were conducted to examine differences in quantitative variables between the two groups. Chi-square and Fisher's exact tests were applied to compare qualitative variables. A linear regression analysis was carried out to investigate the effect of the demographic variables on the levels of apelin and proBNP. A significance level of 0.05 was considered for all tests.

Results
In the group with controlled HTN (n = 111), 32 participants were opium addicts (28.9%), and 79 were non-addicts (71.1%). Of these, 18 opium addicts and 47 non-addicts were female (56.3% and 59.5%, respectively). The proportion of participants over 50 years was higher in opium addicts (22, 68.8%) compared to non-addicts (39, 49.4%). The BMI in most non-opium addicts was between 25 and 29.9 (23, 41.1%) while in opium addicts it was greater than 30 (11, 52.4%). The frequency of LVH did not have a significant difference between opium addict and non-addict groups in controlled HTN (non-addicts: 13 (16.5%) vs opium addicts: 5 (15.6%) ($P = 0.914$, Table 1).

In the HTN crisis patient group (n = 89), 55 were opium addicts (61.8%), and 34 were non-addicts (38.2%). Among the opium addicts, 40 (72.7%) were over 50 years old. However, 22 (64.7%) of the non-addicts were over 50 years old. Male participants made up 63.6% of opium addicts and 73.5% of non-addicts. Among non-opium addicts, 17 had BMIs between 25 and 29.9 (50.0%), while 25 opium addicts had BMIs greater than 30 (45.5%). Additionally, family histories of HTN were reported in 28 (50.9%) opium addicts and 19 (55.9%) non-addicts. LVH was similar in patients with HTN crises in two groups (27 [79.4%] in non-addicts vs 43 [78.2%] in opium addicts) and the difference was not statistically significant ($P = 0.802$) (Table 1).

The mean age, SBP, DBP, HR, and Cr were higher in the HTN crisis group compared to the controlled HTN group, all statistically significant ($P < 0.05$). Although NT-proBNP and BUN levels were higher in patients with HTN crisis than those with controlled HTN, and the differences were not statistically significant ($P > 0.05$). In addition, apelin levels were higher in the HTN crisis than in the controlled HTN group (8.7 ± 4.3 vs 7.5 ± 1.5) ($P = 0.010$). Although NT-proBNP levels were higher in patients with HTN crisis (132.9 ± 21.8) than in those with controlled HTN (128.3 ± 23.1), this difference was not statistically significant ($P = 0.175$). LVH was significantly higher in the HTN crisis group than in the HTN control group ($P < 0.001$) (Table 2).

In patients with HTN crisis, the mean value of SBP was higher in non-addicts compared to opium addicts

Table 1. Characteristics of patients referring to the emergency unit

Covariates	Levels of covariates	HTN crisis			Controlled HTN		
		Non-opium addict (n = 34)	Opium addict (n = 55)	*P* value	Non-opium addict (n = 79)	Opium addict (n = 32)	*P* value
Age	20–35	-	-	0.514	1 (1.3)	-	0.161
	36–50	12 (35.3)	15 (27.3)		39 (49.4)	10 (31.3)	
	Above 50	22 (64.7)	40 (72.7)		39 (49.4)	22 (68.8)	
Gender	Male	25 (73.5)	35 (63.6)	0.231	32 (40.5)	14 (43.8)	0.753
	Female	9 (26.5)	20 (36.4)		47 (59.5)	18 (56.3)	
Education	Under high school diploma	17 (50.0)	32 (58.2)	0.810	23 (29.1)	7 (21.9)	0.671
	High school diploma and higher	17 (50.0)	23 (41.8)		56 (70.9)	25 (78.1)	
BMI	≤24.9	4 (11.8)	6 (10.9)	0.615	11 (19.6)	4 (19.0)	0.536
	25–29.9	17 (50.0)	24 (43.6)		23 (41.1)	6 (28.6)	
	≥30	13 (38.2)	25 (45.5)		22 (39.3)	11 (52.4)	
Smoking	No	32 (94.1)	54 (98.2)	0.324	77 (97.5)	31 (96.9)	0.861
	Yes	2 (5.9)	1 (1.8)		2 (2.5)	1 (3.1)	
HTN family history	No	15 (44.1)	27 (49.1)	0.346	40 (50.6)	14 (43.8)	0.511
	Yes	19 (55.9)	28 (50.9)		39 (49.4)	18 (56.3)	
Symptoms	Chest pain	10 (29.4)	19 (34.5)	0.310	-	-	
	Dyspnea	9 (26.5)	6 (10.9)		-	-	
	Epistasis	2 (5.9)	7 (12.7)		-	-	
	Neurologic	8 (23.5)	18 (32.7)		-	-	
	Blurred vision	5 (14.7)	4 (7.3)		-	-	
	No symptom	0	1 (1.8)		79 (100.0)	32 (100.0)	
Regular medication	No	31 (91.2)	49 (89.1)	0.698	12 (15.2)	6 (18.8)	0.645
	Yes	3 (8.8)	6 (10.9)		67 (84.8)	26 (81.3)	
Medication	ACEI	4 (11.8)	7 (12.7)	0.910	10 (12.7)	4 (12.5)	0.933
	ARB	23 (67.6)	34 (61.8)		61 (77.2)	25 (78.1)	
	Calcium blocker	3 (8.8)	6 (10.9)		6 (7.6)	2 (6.3)	
	No	4 (11.8)	8 (14.5)		2 (2.5)	1 (3.1)	
CPK	Normal	31 (91.2)	49 (89.1)	0.698	76 (96.2)	32 (100.0)	0.264
	Not checked	3 (8.8)	6 (10.9)		3 (3.8)	-	
ECG	LVH	15 (44.1)	25 (45.5)	0.412	8 (10.1)	6 (18.8)	0.389
	Normal	15 (52.9)	25 (45.5)		70 (88.6)	26 (81.3)	
	ST change	1 (2.9)	5 (9.1)		1 (1.3)	-	
LVH	No	7 (20.6)	12 (21.8)	0.802	66 (83.5)	27 (84.4)	0.914
	Yes	27 (79.4)	43 (78.2)		13 (16.5)	5 (15.6)	
Diastolic dysfunction	1	23 (67.6)	33 (60.0)	0.530	47 (59.5)	21 (65.6)	0.627
	2	11 (32.4)	22 (40.0)		3 (3.8)	2 (6.3)	
	No	-	-		29 (36.7)	9 (28.1)	

HTN: hypertension; BMI: body mass index; LVH: left ventricular hypertrophy.
Note: Data presented as *n* (%) and compared using chi-square test and Fisher's exact test.

(219.2 ± 15.8 vs 212.1 ± 17.7) (*P* > 0.05). However, DBP in the HTN control group was higher in addicts than non-addicts (79.8 ± 6.0 vs 77.1 ± 6.0, *P* = 0.035). The levels of apelin and NT-proBNP based on addict status did not significantly differ between the HTN crisis and HTN control groups (*P* > 0.05) (Table 3).

Multivariable linear regression analysis revealed an inverse relationship between age and apelin levels (β = -0.07, *P* = 0.02). Patients with HTN crisis had significantly higher levels of apelin than the controlled HTN group (β = 2.08, *P* < 0.001). Moreover, NT-proBNP levels were lower in individuals with a family history of HTN compared to those without (β = -8.76, *P* = 0.013). LVH was found to have no significant effect on apelin and

Table 2. Comparison of age and biochemical characteristics of patients referring to the emergency unit in two groups: HTN crisis and controlled HTN

		HTN crisis	Controlled HTN	*P* value
Age[a]		56.4±10.1	52.5±8.1	0.002*
SBP[a]		214.8±17.3	132.4±9.3	<0.001*
DBP[a]		115.8±10.1	77.9±6.1	<0.001*
HR[a]		85.1±8.3	81.4±7.2	<0.001*
BUN[a]		46.7±13.6	44.1±13.3	0.189
Cr[a]		1.01±0.1	0.96±0.1	0.034*
Apelin[a]		8.7±4.3	7.5±1.5	0.010*
NT-proBNP		132.9±21.8	128.3±23.1	0.175
LVH[b]	No	19	93	<0.001
	Yes	70	18	
Family history[b]	No	42	54	0.838
	Yes	47	57	

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; BUN: blood urea nitrogen; Cr: creatinine; HR: Heart rate.
[a] Independent *t*-test; [b] The chi-square test and Fisher's exact test.

NT-proBNP levels ($P > 0.05$) (Table 4).

Discussion

This study examined the serum levels of pro-BNP and apelin in HTN crisis with controlled HTN while considering opium addiction status. Our results indicated that apelin, HR, and Cr levels were elevated in HTN crisis patients compared to those with controlled HTN. Additionally, we observed that DBP was higher in opium-addicted subjects with controlled HTN compared to non-addicts; however, this difference was not significant among HTN crisis patients. Our findings revealed that apelin levels in HTN crisis patients were higher than those with controlled HTN.

We found a remarkable prevalence of opium use among individuals over 50 years old, consistent with previous studies conducted in Kerman, suggesting an increasing trend of opium use in older demographics.[14] Among HTN crisis patients, opium addiction was more common in men, whereas women had higher rates of opium addiction in the controlled HTN group. This trend is consistent with earlier findings indicating greater overall opium addiction rates among men,[13,14] suggesting that misconceptions about opium's beneficial effects may contribute to its increased use among women, particularly in chronic disease contexts.

Our findings revealed significantly elevated serum apelin levels in HTN crisis patients compared to those with controlled HTN. Previous literature documented that decreased apelin levels can exacerbate HTN and promote cardiac complications.[38] Apelin is known to reduce exercise-induced cardiac hypertrophy[39] and regulate blood pressure via the Akt/eNOS pathway, influencing both pathological and non-pathological

cardiac hypertrophy.[39,40] In patients with LVH, plasma apelin levels increase while myocardial apelin expression is reduced.[41] Thus, the observed elevation in apelin levels among patients experiencing HTN crisis likely reflects a physiological response to combat acute blood pressure elevation despite cardiac dysfunction.

The apelin/APJ (apelin receptor) signaling pathway is crucial in cardiovascular health as the intrinsic ligand for the G protein-coupled APJ receptors. Research has highlighted the complex and sometimes contradictory role of apelin/APJ in cardiac hypertrophy. While some studies suggest that apelin may reduce hypertrophy caused by angiotensin II and oxidative stress, other investigations have indicated that apelin's central administration could paradoxically stimulate cardiac hypertrophy.[39] Our data indicate substantial differences in cardiovascular metrics between patients experiencing HTN crises and those with controlled HTN. Notably, the prevalence of LVH was significantly higher in the HTN crisis group.

Additionally, apelin levels were elevated in HTN crisis patients compared to controlled HTN subjects. These findings regarding LVH and apelin confirmed previous studies by Lu et al and Falcão-Pires et al,[39,41] as Lu et al found that apelin/APJ can promote cardiomyocyte hypertrophy[39] and Falcão-Pires et al noted that while myocardial apelin levels may decline during LVH, plasma concentrations could rise, potentially functioning as a compensatory response to maintain cardiac output amid pressure overload.[41] Additionally, Ye et al demonstrated a correlation between apelin levels and LVH, suggesting that serum apelin could predict hypertrophy in hypertensive patients.[25] The elevated apelin levels in our hypertensive crisis patients, alongside significant LVH presence, indicate a more complex pathological context. This suggests a maladaptive cardiac response despite elevated apelin levels, usually associated with cardioprotective functions.

Interestingly, Ashley et al provided evidence that apelin administration can induce vasodilation and enhance cardiac output without leading to hypertrophy.[42] This finding does not align with our results, implying a lack of a direct correlation between apelin levels and LVH. Additionally, Przewlocka-Kosmala et al reported reduced serum apelin levels in hypertensive individuals compared to controls,[24] contradicting our observations of increased apelin in HTN crisis patients.

NT-proBNP levels were elevated across all study participants (exceeded 100 pg/mL), marking potential cardiac damage. Previous research has shown that elevated BNP levels (exceeding 90 pg/mL) denote underlying cardiac stress in HTN, suggesting their utility as diagnostic markers in emergency settings.[28] In contrast to prevailing beliefs regarding opium's protective effects in HTN, our results reaffirm that opium addiction does not confer benefits against CVD risks. Notably, patients who were

Table 3. Comparison of age and biochemical characteristics of patients referring to the emergency unit based on the addict's status

Covariates	HTN crisis			Controlled HTN		
	Non-opium addict	Opium addict	P value	Non-opium addict	Opium addict	P value
Age	55.9±10.4	56.8±9.9	0.66	52.2±8.5	53.1±6.8	0.615
SBP	219.2±15.8	212.1±17.7	0.09	132.1±9.1	133.1±9.8	0.622
DBP	116.2±10.3	115.5±10.1	0.965	77.1±6.0	79.8±6.0	0.035*
HR	85.8±8.3	84.7±8.4	0.501	81.6±7.2	80.8±7.4	0.613
BUN	46.7±14.1	46.6±13.4	0.715	44.2±13.4	44.0±13.4	0.937
Cr	0.9±0.1	1.0±0.2	0.331	0.9±0.1	0.9±0.1	0.611
Apelin	9.1±4.3	8.5±4.4	0.497	7.4±1.3	7.6±1.9	0.578
NT-proBNP	132.1±22.3	133.4±21.7	0.825	130.4±22.7	122.9±23.4	0.182

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension; BUN: blood urea nitrogen; Cr: creatinine; HR: Heart rate
Independent t-test.

Table 4. The effect of demographic variables on apelin and NT-proBNP according to the multivariable linear regression

Covariates		Apelin		NT-proBNP	
		Regression coefficient (β)	P value	Regression coefficient (β)	P value
Age		-0.07	0.020*	-0.20	0.290
Group	Chronic HTN	Reference		Reference	
	HTN crisis	2.08	<0.001*	3.37	0.358
Gender	Male	Reference		Reference	
	Female	-0.138	0.799	3.09	0.388
Family history of HTN	No	Reference		Reference	
	Yes	-0.262	0.694	-8.76	0.013*
Opium addict	No	Reference		Reference	
	Yes	-0.220	0.619	6.64	0.07
LVH	No	Reference		Reference	
	Yes	-1.07	0.092	-7.11	0.091

LVH: left ventricular hypertrophy; HTN: hypertension.

opium addicts exhibited similar or worse cardiovascular risk parameters compared to non-addicts,[13,14] and this holds true for CAD risk factors as well.[30,43]

APJ and κ opioid receptors can form a heterodimer and initiate similar signaling pathways within the CVS. Activation of both receptors results in decreased arterial pressure.[15,21,44] However, our study revealed that opium consumption has no effect on SBP but leads to an increase in DBP in the controlled HTN group of opium addicts. Yeganeh-Hajahmadi et al also validated the interaction between the opioid receptor and APJ.[44] In our study, the use of opium in the HTN crisis group did not cause significant changes. Of course, it should be considered that Yeganeh-hajahmadi et al injected different doses of apelin, and their study was experimental, which may partially account for the observed differences.

A significant limitation of this study is the relatively small sample size, which should be addressed in future research by including a larger cohort. Furthermore, the absence of a control group with normal blood pressure restricts a comprehensive evaluation of the observed relationships. Therefore, the specific effects of opium on serum apelin warrant further investigation.

Conclusion

This study emphasizes that regardless of opium addiction, LVH is more prevalent in individuals with HTN crises versus those with controlled HTN. The fluctuation in serum apelin levels in patients with cardiac dysfunction is not easily predictable, reflecting its involvement in both pathological and protective mechanisms. Moreover, the significant high apelin and elevated NT-proBNP (>100 pg/mL) levels in our patients indicate potential cardiac damage. Ultimately, our findings reject the widely held belief in the protective effects of opium consumption.

Authors' Contribution
Conceptualization: Shirin Jafari.
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Investigation: Mansour Moazenzadeh.
Methodology: Shirin Jafari.
Project administration: Mansour Moazenzadeh.
Resources: Hamidreza Nasri.
Software: Shirin Jafari, Parya Jangipour Afshar.
Validation: Parya Jangipour Afshar.

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Competing Interests
The authors affirm that they do not have any competing interests.

Ethical Approval
All methodologies employed in this study involving human participants strictly adhered to the ethical standards set forth by the Research Committee of Kerman Cardiovascular Research Center (code: IR.KMU.REC.1399.541). Before the initiation of research procedures, written informed consent was obtained from all participants, ensuring their right to withdraw from the project at any stage without facing any adverse consequences. The entire study was conducted in strict accordance with relevant guidelines, regulations, and the principles outlined in the Declaration of Helsinki.

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