SELÇUK TIP DERGİSİ
SELCUK MEDICAL JOURNAL

Araştırma Makalesi / Research Article

Selcuk Med J 2022;38(3): 128-135
DOI: 10.30733/std.2022.01558

NEÜ YAYINEVİ

Does Experimental Morphine Addiction in Rats Change Physiological and Histological Characteristics of the Heart?

Sıçanlarda Deneysel Morfin Bağımlılığı Kalbin Fizyolojik ve Histolojik Özelliklerini Değiştirir mi?

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Geliş Tarihi/Received: *28 January 2022*
Kabul Tarihi/Accepted: *11 July 2022*

Öz

Amaç: Morfin, kronik ağrı tedavisinde tercih edilen opioidlerdendir. Tekrarlayan kullanımı bağımlılığa neden olabilir. Opioid bağımlılığının kalp kontraksiyonuna olan etkilerini araştırmak amacıyla deneysel morfin bağımlılığı/yoksunluğu oluşturulan sıçanlarda miyokardiyal kontraktilite/histolojik değişiklikler araştırıldı.
Gereçler ve Yöntem: Resmi olarak 28.05.2021'de tamamlanan çalışmada kullanılan 32 yetişkin erkek Wistar albino sıçan, Kontrol(C), Morfin(M), Morfin+Nalokson(MN) gruplarına ayrıldı. GrupC'ye 10mg/kg %0,9 NaCl, GrupM'ye 10mg/kg morfin 7 gün subkutan uygulandı. Son morfin uygulamasından sonra C-M gruplarına 3mg/kg NaCl, GrupMN'ye 3mg/kg nalokson intraperitoneal verildi. 30dk morfin yoksunluğu belirtileri puanlandı. 3-4mm atriyum şeritleri izole organ banyosu haznelerine asıldı. 2g gerimle adrenalin kaynaklı kasılmalar(0,001M) gözlemlendi. Gerim değişiklikleri kaydedildi. İstatistiksel analizde SAS University Edition 9.4 programı kullanıldı.
Bulgular: MN grubunda morfin yoksunluğu davranışları gözlendi. GrupM-MN'de adrenalin öncesi gerim değerleri GrupC'ye göre daha yüksekti. Adrenalin kaynaklı verilerden 15 dakika öncesi/sonrası kasılmadaki en büyük artış GrupC'de tesbit edildi.
Sonuç: Morfin bağımlılığı-yoksunluğu, sıçanlarda inotropik/kronotropik etkilerde değişikliğe neden olmadı. Mast hücrelerinde histolojik farklılık gözlenmedi. Çalışma morfin bağımlılarında, sistem analizi açısından kalp için olumlu bir kaynak oluşturabilir.

Anahtar Kelimeler: İzole organ banyosu, sıçan, miyokardiyal kasılma, morfin bağımlılığı, morfin çekilmesi

Abstract

Aim: Morphine is one of the most preferred opioids in treatment of chronic pain. Recurrent use can cause addiction. There is no consensus on cardiovascular system treatment/side effects of opioids. In order to investigate effects of opioid addiction on heart, myocardial contractility/histological changes were investigated in rats via experimental morphine addiction/withdrawal.
Materials and Methods: 32 adult male Wistar albino rats used for study, which was officially completed on 28-05-2021, were divided into Control(C), Morphine(M), Morphine+Naloxone(MN) groups randomly. In GroupC 10mg/kg 0.9% NaCl solution, in GroupM-MN 10mg/kg morphine were administered subcutaneously for 7 days. After the last administration of morphine, 3mg/kg NaCl was given to GroupC-M, 3mg/kg naloxone was given to GroupMN intraperitoneally. Signs of morphine withdrawal were observed for 30 minutes and scored. 3-4mm strips of atria were hung in isolated organ bath chambers. Tension was adjusted to 2g. Adrenaline-induced contractions (0.001M) were observed. Changes in tension were recorded. SAS University Edition 9.4 program was used for statistical analysis.
Results: Morphine withdrawal behaviours were observed in GroupMN. There was no statistically significant difference between atrial contractility tension values of GroupC-M-MN($p>0.05$). Pre-adrenaline tension values were higher in GroupM-MN than in GroupC. But the greatest contraction increase between 15minutes before/after adrenaline-induced data was in GroupC.
Conclusion: Morphine addiction/withdrawal didn't cause inotropic/chronotropic changes. No histological differences were observed in mast cells. These results may constitute a positive resource for the heart for systems analysis in morphine addicts.

Key words: Isolated organ bath;rat, myocardial contractility, morphine addiction, morphine withdrawal.

Cite this article as: Caglayan H, Solak Gormus ZI, Solak H, Ozen Koca R, Gultekin B. Does Experimental Morphine Addiction in Rats Change Physiological and Histological Characteristics of the Heart? Selcuk Med J 2022;38(3): 128-135

Disclosure: *None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. All authors have agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Morphine is a powerful analgesic and a natural opioid. Opium (poppy) plant is the dried form of the juice obtained by drawing the fresh fruit capsule (13). Morphine, which is a Mu receptor agonist, is one of the most preferred opioids in the treatment of chronic pain. When used repeatedly, they can cause addiction (9). Naloxone is an opioid antagonist used to reverse the effects of opioid overdose. It causes withdrawal syndrome (5).

Specific receptors to which opioids bind in the central nervous system are also found in many organs including cardiovascular tissue. The heart controlled by the autonomic nervous system has a cardiac nervous system composed of cardiac ganglia, sensory afferents, pre- and postganglionic parasympathetic and postganglionic sympathetic efferents. It has been observed in rats that μ, κ, δ receptors are expressed as mRNA and converted into specific receptor proteins on different components of the cardiac nervous system (28).

Morphine is used for pain relief during postoperative cardiac surgery and myocardial ischemia. Due to the high affinity for mu receptors, stimulation of mu opioid receptors is responsible for respiratory and cardiovascular side effects (7). The mechanism of opioids in the pathogenesis of cardiovascular disease is unclear. It is said that long-term opioid intake causes cardiovascular risk. Studies have found a relationship between cardiovascular death, MI, and opioid use. In recent studies, when prescription opioid use and non-steroidal anti-inflammatory drugs were compared, it was stated that the risk of coronary artery revascularization and MI risk increased, and cardiac death was higher in those treated with opioids. After MI, opioids affect myocardial conduction, reperfusion, and contractility (2).

Morphine and its analogues decrease sympathetic activity and increase parasympathetic activity. It causes hypotension and cardiac arrhythmias by histamine release from mast cells. In addition, morphine causes peripheral vasodilation and orthostatic hypotension. With naloxone deprivation, heart rate and systolic pressure increased with a decrease in cardiac vagal tone (14). The riskiest cardiac side effect of opioids is prolongation of the QT interval, as it causes Torsades de Pointes (a specific type of ventricular tachycardia), which can result in sudden death (2).

The effects of opioids vary according to the duration of use. acute and chronic opioid use does not have the same cardiac effect (4). Morphine was frequently preferred in the treatment of heart failure and heart attack in the previous periods. It is said that this improves myocardial function by relieving pain, decreasing respiratory rate, effective in anxiety, and dilating venous vessels. Also, long-term use of opioids is a risk factor for acute myocardial infarction. Because of its pain-relieving properties, it hides the symptoms, leads to the progression of the lesion and causes the development of coronary atherosclerosis (17). Although there are few studies on chronic activation of these receptors, it has been reported that chronic morphine use has cardioprotective effects. Morphine has been shown to have a cardioprotective role with delta-1 opioid receptor agonists. Recent studies have shown that other opioids such as morphine can exert a protective effect in ischemia induced heart (26). By administering intrathecal morphine to rats with ischemia-reperfusion damage, infarction decreased as a result of activation of central opioid receptors, resulting in cardioprotective effects (35).

While there are many studies on addiction and tolerance in the central nervous system, there are not enough studies yet on the effects of opioid addiction on cardiac functions. Data regarding the cardiac side effects of chronic opioid administration are currently limited. The aim of the present study is to examine the chronotropic, inotropic effects and myocardial histology in rats with a morphine dependence and withdrawal model.

MATERIALS AND METHODS

Ethics Statement

The protocols of animal experiments were approved by the Local Ethics Committee of Application and Research Center of Experimental Medicine, Necmettin Erbakan Universty No. 2020-006, on 16.01.2020.

In this study, 32 adult (300-350gr), male Wistar albino rats were randomly divided into 3 different groups. The care and feeding of the rats were done at Experimental Medicine Application and Research Center. They were housed in plastic cages where they could move freely with food and water containers, their food and water were given as ad-libitum. The animals were stored at room temperature 22 ± 1˚C for 12 hours light/dark period under standard laboratory conditions.

Creation and evaluation of morphine addiction

Control group (Group C, n=10): 10mg/kg saline solution (0.9% NaCl solution) was injected subcutaneously once a day for 7 days. On the 7th day

at 08:00, 2 hours after the last saline administration a single dose of 3 mg/kg saline was administered intraperitoneally, and the behavior of the animals was observed.

Morphine group (Group M, n=11): 10mg/kg of morphine was injected subcutaneously once a day for 7 days. On the 7th day at 08:00, 2 hours after the last dose of morphine was administered, a single dose of 3 mg/kg saline (0.9% NaCl solution) was administered intraperitoneally, and the behavior of the animals was observed.

Morphine+Naloxone group (Group MN, n=11): 10mg/kg of morphine was injected subcutaneously once a day for 7 days. On the 7th day at 08:00, 2 hours after the last dose of morphine was administered, a single dose of 3 mg/kg naloxone was administered intraperitoneally and the behavior of the animals was observed (18).

After naloxone and saline injection, the animals were placed in plexiglass transparent cylinder observation cages with a diameter of 25 cm and a height of 65 cm and were observed for 30 minutes. Their weight was included in the scoring by measuring 1.5 hours before and half an hour after the naloxone and saline (0.9% NaCl solution) injections. The Withdrawal score was calculated for each animal using the modified Gellert and Holtzman scale (Table 1) (8). The numbers of withdrawal behaviors were compared between groups. Later, cervical dislocation was applied to the rats under mild ether anesthesia. The heart was included in Krebs-Henseleit solution [composed of (mM): NaCl 119, MgSO4 1.50, KCl 4.70, CaCl2 2.50, KH2PO4 1.20, Glucose 11, NaHCO3 25].

Preparation of isolated Organ Bath

3-4 millimeters long incisions were made from the atrium. Tissues were hung in the isolated organ bath with silk thread. Its tension was set to 2g. The krebs solution temperature is 37˚C and is continuously gassed (95% O_2 and 5% CO_2). Isometric tension values of the atrium sections were recorded with a transducer (MAY IOBS 99 Isolated Tissue Bath Stand Set Integrated Tissue Bath System, Turkey). After a 45-minute adaptation period, spontaneous isometric contractions were observed. 1 hour after hanging, contractions were induced with 0.001 M adrenaline solution. Tensions at the 15th minute before the administration of adrenaline and the 15th, 30th and 45th minutes after the administration were evaluated.

Histological Evaluation

The heart tissue of the rats was taken and placed in 10% formaldehyde. Tissue samples were embedded in paraffin. 5 µm thick sections were taken with microtom. Hematoxylene Eosin and Toluidine blue staining methods were applied to the sections. The prepared preparations were examined with light microscopy. The sections were histologically examined for myofibril loss in heart muscle, intracytoplasmic vacuolization, eosinophilic stained, picnotic nucleated cells and congestion. Mast cell and degranulation were investigated in preparations stained with Toluidine blue.

Statistical Method

Atrial contractions and withdrawal behaviors were evaluated. Mean and standard deviations were given for symmetrically distributed numeric data, while median values (25. percentile- 75. percentile) were given for non-symmetric numeric data. A mixed effect model was created to analyze the change of tension values between groups and over time. Group, Time and Group×Time effects were investigated. Poisson mixed effect models were used in the analysis of withdrawal findings. SAS University Edition 9.4 program was used for analyzes. $p<0.05$ was considered statistically significant.

RESULTS

Morphine Withdrawal Findings

In the analysis of morphine withdrawal score, a

Table 1. Modified Gellert and Holtzman Behavior Scale

Behavior or finding	Score	Behavior or finding	Score
1% body weight loss for each	1	Abnormal postures	3
Escape attempts 2-4 times	1	Squinting eyes	1
Escape attempts 5-9 times	2	Sneeze	1
Escape attempts 10-∞ times	3	Rolling movements	2
Wet dog shaking 1-2 times	2	Rearing	1
Wet dog shaking 3-4 times	4	Jumping	2
The number of defecations (diarrhea) per each	2	Body grooming	1
		Profuse salivations	7
Teeth chattering	2		

significant increase was observed in the comparison of the Group MN with the Group C and Group M (p<0.001). In the weight loss analysis, a significant increase was observed in the Group MN compared to the Group M (p<0.05). In the defecation number analysis, a significant increase was observed in the Group MN compared to the Group M and Group C (p <0.001). A significant increase was observed in the MN group compared to the Group C and Group M in the analysis of the number of cracking teeth (p <0.001). No significant differences were seen between the groups in the number of prancing, embellishment and escape attempts (p>0.05) There was an increase in the number of eyes squint in the Group MN compared to the Group M and Group C (p<0.05). An increase was seen in the comparison of the Group MN with the Group M and Group C in the number of abnormal posture (p<0.001). The number of genital grooming was higher in the Group MN than in the Group C and Group M (p<0.05). Wet dog shaking and rolling movements were more observed in the Group MN. But it was not statistically significant (p>0.05). Profuse salivations and sneeze were not observed in Group K and Group M, and were observed in Group MN. But it was not statistically significant (p>0.05) (Table 2).

Isolated Organ Bath Findings

The tension values before adrenaline administration were found to be higher in the Group M and Group MN compared to the Group C. However, the highest increase in the tension value between the 15th minute before induction with adrenaline and the 15th minute after the induction was in the Group C. In the other two groups, the amount of increase in these time periods and the tension value at the 15th minute after adrenaline were observed less (Fig. 1). There was no statistically significant difference in inotropic and chronotropic effects in the Group C, Group M and Group MN. As a result of the mixed effect model analysis, p=0.7085 for group-time, p=0.0005 for time, and p=0.9383 for the group, the result shows that the groups were similar to each other.

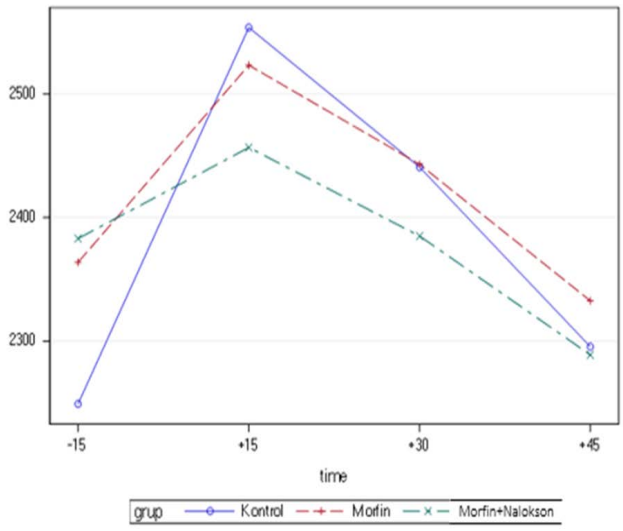

Figure 1. Comparison of induced in vitro atrial contractility in the Group C, Group M and Group MN by time.

Histological Findings

The heart muscle of Group C was monitored in a normal histological view (Fig. 2a). The heart muscle in the Group M and Group MN showed similar

Table 2. Social and demographic characteristics of the individuals.

	Control (10)	Morphine (11)	Morphine + naloxone (11)
Weight	258,60±41	302,55±25,99	303,64±33,95
Weight loss (g)	8,40±7,76	4,45±3,11	10,18±3,89
Escape Attempt	7,80±6	9,91±6,55	5,18±2,32
Wet dog shaking	0,00(0,00-0,00)	0,00±0,00	1,82±1,17
Defecation	1,50(0-3)	0,00(0,00-0,00)	7,73±3,04
Teeth chattering	0,00(0,00-0,00)	0,00(0,00-0,00)	4,91±1,92
Rolling movements	0,00±0,00	0,00(0,00-0,00)	0,00(0-1,00)
Profuse salivations	0,00±0,00	0,00±0,00	0,00(0,00-2,00)
Rearing	2,20±2,20	2,00(0-4,00)	0,00(0,00-0,00)
Body Grooming	5,10±1,60	3,18±1,66	4,09±2,47
Squinting eyes	1,80±1,48	1,00(0-2,00)	5,45±2,07
Sneeze	0,00±0,00	0,00±0,00	0,00(0-1,00)
Abnormal postures	0,00(0,00-0,00)	1,00(0-1,00)	3,09±1,30
Genital grooming	0,00(0,00-0,00)	0,00(0,00-0,00)	2,27±1,90
Withdrawal Score	14,80±6,05	10,64±2,62	34,09±4,28

Values are expressed as mean ± standard error.

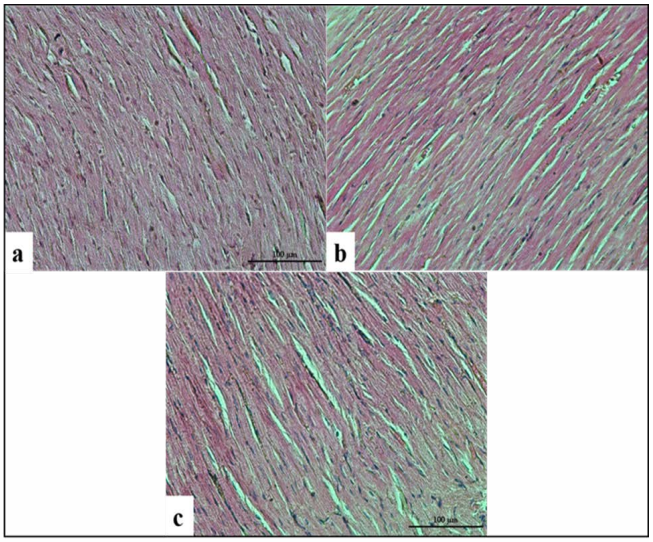

Figure 2. Hematoxylin-Eosin image **a)** Group C, **b)** Group M, **c)** Group MN

characteristics to the Group C (Fig. 2b, c). In Toluidine blue-dyed preparations, there was no difference in the number of mast cells of the Group C (Fig. 3a), Group M (Fig. 3b) and Group MN (Figure 3c). Degranulated mast cells were found in the Group MN (Fig. 3c).

DISCUSSION

The cardiovascular effects of opioids are controversial. Due to the connection between the heart and the central nervous system, adaptive changes that drugs make in the brain affect the heart pathways, neurotransmitters and adrenergic receptors expressed in the heart. Heart also has an intrinsic cardiac plexus that works independently, taking inferences from the cardiac sympathetic nervous system and the parasympathetic nervous system. Cardiac changes that occur after medication may be due to changes in intrinsic cardiac neurons (16).

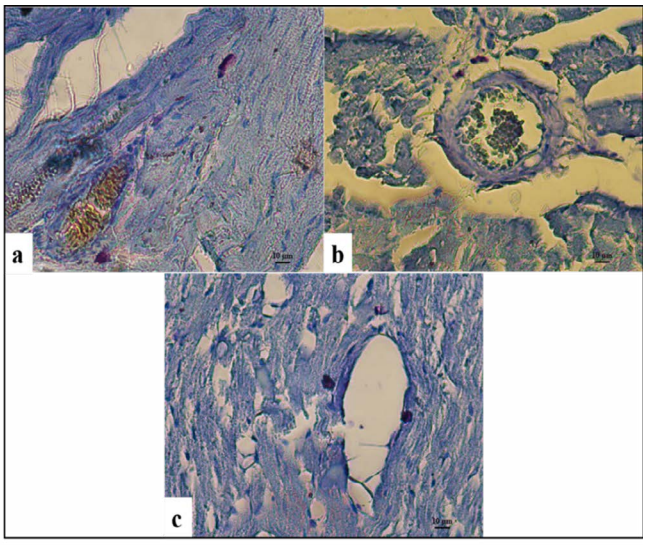

Figure 3. Toluidine Blue image **a)** Group C **b)** Group M **c)** Group MN

Scientific research about morphine is mostly in the central nervous system. In recent years, interest in the cardiovascular system has increased due to the cardioprotective effect of opioid endogenous and exogenous compounds in ischemic preconditioning (IPC). Opioids cause IPC, reduce apoptosis and ischemic reperfusion injury in myocytes. Thus, it improves ventricular function by reducing the infarct. In addition, μ-opioid receptor stimulation supports improvement of myocardial contractility in the post-ischemia period. Despite this therapeutic and protective effects during ischemic event, the chronic consumption effects of opioids are complicated (20).

Morphine is responsible for cardiovascular complications with histamine release. It leads to decreased cardiac output, hypotension, vasodilation, bradycardia (3). In the study conducted on dogs, it has been observed that morphine caused a decrease in systemic blood pressure, cardiac output, heart rate with histamine release and increased vagal effect (6).

There is evidence of a negative or positive inotropic effect of opioid receptor agonists on the myocardial function (31). There are also studies that say there is no direct effect on myocardial contractility (25). The inotropic effect that morphine does not alter contractions has been said to be unique to Kappa-type opioid agonists. It has been said that μ and δ opioid receptor agonists have no effect on contraction, whereas stimulation of κ opioid receptors reduces contraction through g (i/o) proteins (34). In another study, it has been observed that δ and κ opioid receptor agonists had a negative inotropic effect on left ventricular myocytes by causing changes in cell Ca homeostasis and IP3 production. It has been said that μ-opioid receptor stimulation has no significant effect on contractility (32).

There are also studies stating that μ-opioid receptor activation decreases the frequency of myocardial infarction with increased action potential duration and negative inotropic effects (21). In the study where morphine and noradrenaline were given cumulatively

to the atrium preparation in an isolated organ bath, it has been recorded that morphine increased the power of noradrenaline. It has been concluded that morphine acts presynaptically to increase noradrenaline release (30).

Morphine and heroin have been administered to the rabbit heart perfused in Langendorff device. It has been said that there is no significant change in contractility, chronotropic effect, systolic and diastolic ventricular pressure (6). It has been said that most opioids do not have a direct effect on cardiac contractility (4). While the endogenous opioid system is active in cardiac hypertrophy, it has been found that opioid receptor antagonists are not effective on contractility (33).

Morphine did not significantly affect inotropy and action potential in guinea pig, rabbit and human ventricular preparations. In a previous study examining the effects of morphine on rabbits, a small negative inotropic effect was observed that was eliminated by the addition of naloxone. However, morphine-induced negative inotropy was not seen in the presence of atenolol. Based on these results, it has been said that the effect of morphine on cardiac contractility mediates presynaptically by affecting the release of noradrenaline or acetylcholine from nerve termin. Another study has showed that the negative inotropic effects induced by opioids given in cumulative doses in organ baths were not antagonized by opioid antagonists. Thus, it has been suggested that cardiac effects are not mediated by opioid receptors and these effects may be due to sodium channel blocking actions (15).

It has been found that the cumulatively administered morphine in the organ bath does not cause a significant electrophysiological effect, but has little negative inotropic effect. Morphine has been thought to have no direct cardiac effects (11). In a study comparing the inotropic effects of morphine and ketamine on the canine right ventricle, it has been recorded that morphine did not make any significant inotropic changes even at high concentrations (29). In our study, morphine dependence and morphine withdrawal were performed in rats. Rat hearts were studied in an isolated organ bath. There was no statistically significant difference in myocardial contractility. It did not cause changes in chronotropic and inotropic effects.

Opioids have different arrhythmogenicity and data on morphine are scarce. Most of the studies confirm its safety for cardiac electrical activity when used in routine doses and are said to be low risk (3). There are also studies saying that morphine causes minimal cardiac arrhythmias and coagulation abnormalities by inducing histamine release (10). The frequency of atrial contraction has been investigated by intravenous administration of 30 mg/kg of morphine on the last day to rats treated with implantation of pellets (75 mg of morphine) for 7 days. It was concluded that acute administration of morphine to rats treated with morphine reduced the frequency of atrial contraction by leading to inhibition of neuronal catecholamine activity in the heart (23). No difference was observed in our study.

In a study, slight irregularities in the atrial and ventricular structures were observed in histological specimens, both after heroin and after administration of morphine (19). As a result of chronic opioid exposure, decreased sensitivity of the neurons in the respiratory center in the brainstem has caused a decrease in respiratory rate. Hypoxia has been observed in the heart tissue due to this decrease. Thus, the accumulation of fibrous connective tissue has caused thickening of the walls and stiffness of the tissue, leading to impairment cardiac contractility (27). In our study, the heart muscle was seen in normal histological appearance in all three groups. However, degranulated mast cells were found in places in the group that we created withdrawal.

Naloxone administration increased heart rate, mean aortic pressure, cardiac output, and myocardial contractility in dogs with congestive heart failure (12). In another study, two in vitro models were used to test the hypothesis that naloxone has a direct positive inotropic effect on heart muscle. In the first experiment, the isolated perfused rat heart has been given naloxone to the isolated rat atrium in the organ bath in the other. Both have been observed to provide a significant increase in the contraction amplitude. It has been said that this effect of naloxone is not related to opioid receptors, as it is not affected by pre-treatment with morphine (24).

While the main effects of opioids are on the autonomic and central nervous system, they affect many organ systems, including the respiratory and cardiovascular systems. The treatment and side effects of opioids on cardiovascular system are discussed. However, there are not many studies done to prove or refute these ideas (1). In a comprehensive animal model study by Schultz and Gross, it has been proven that finding different opioid receptors in the heart and minimizing the cardioprotective effects and

infarction size of opioid drugs such as morphine (26). However, many different studies have been stated that opioid use is a strong risk factor for cardiovascular problems (22).

CONCLUSION

Different opinions have been put forward in studies on the effect of opioids on myocardial contractility. Studies on the effect of opioids given in cumulative doses in organ baths on myocardium are available in the literature. However, there are deficiencies in the literature regarding the investigation of myocardiums with morphine addiction and withdrawal. In the present study, a morphine dependence model was established with 7 days of morphine administration and withdrawal with a single dose of naloxone administration. Chronotropic and inotropic effects, myocardial histology, behavioral changes caused by withdrawal were examined. Morphine withdrawal behaviors were seen in naloxone-treated rats. There were no statistically significant differences in inotropic and chronotropic effects. The heart muscle of the groups was observed in normal histological appearance. No change was seen in the number of mast cells. However, degranulated mast cells were found in places in the group that we created withdrawal.

It is thought that different results could be obtained by increasing the number of days and dose of morphine. The present study can provide insight into the literature as a primary source of inotropic chronotropic effects of opioid dependence and withdrawal on the cardiovascular system. These results may constitute a positive resource for the heart for systems analysis in morphine addicts. Further more and different scientific researches should be carried out with different parameters in order to obtain further information about the effects of addiction on the heart.

Conflict of interest: *Authors declare that there is no conflict of interest between the authors of the article.*

Financial conflict of interest: *Authors declare that they did not receive any financial support in this study.*

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