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The Effects of Curcumin on Mechanical Functions and Cardiac Contractility in Isolated Rat Hearts

Kurkuminin İzole Sıçan Kalbinde Mekanik Fonksiyonlar ve Kardiyak Kontraktilite Üzerine Etkisi

ABSTRACT

Objective: Curcumin is a bioactive compound that has well-known pharmacological activities. Numerous studies have shown that curcumin provides potential cardiovascular benefits through a variety of mechanisms.The present study aims to discuss different concentrations of curcumin's impact on mechanical functions and cardiac contractility in isolated perfused rat hearts.

Methods: The hearts were isolated under sodium thiopental (50 mg/kg) anesthesia and perfused with a modified Krebs-Henseleit solution (mK-Hs). After stabilization, curcumin was applied in concentrations of 0.1, 1, and 10 μM. In isolated rat hearts, indexes of + dP / dt max, LVDP, MAP, and LVEDP were evaluated for cardiac contractility and ventricular function.

Results: All curcumin concentrations reduced $+dP/dt_{max}$ and LVDP. Ten μM curcumin also significantly decreased heart rate. Curcumin (1 and 10 μM) increased LVEDP and reduced MAP amplitude with a concomitant increase in MAP duration. Curcumin at all concentrations did not affect dMAPdtmax and dMAPdtmin.

Conclusion: Our results might suggest that curcumin at higher concentrations (≥ 1 μM) increases LVEDP with a negative chronotropic effect and decreases MAP amplitude with an increase in MAP duration. There is sufficient evidence from this study that Curcumin possesses an adverse inotropic action. Different disease models should support the pathophysiological role of Curcumin on cardiac contraction.

Keywords: Cardiac contractility, curcumin, heart rate, isolated rat heart, left ventricular end-diastolic pressure

ÖZET

Amaç: Kurkumin, iyi bilinen farmakolojik aktiviteleri olan biyoaktif bir bileşiktir. Kurkuminin çeşitli mekanizmalar yoluyla potansiyel kardiyovasküler faydalar sağladığı çok sayıda çalışma ile gösterilmiştir. Bu çalışma, izole perfüze edilmiş sıçan kalplerinde farklı kurkumin konsantrasyonlarının mekanik fonksiyonlar ve kardiyak kontraktilite üzerindeki etkisini tartışmayı amaçlamaktadır.

Yöntem: Kalpler, sodyum tiyopental (50 mg/kg) anestezisi altında izole edildi ve modifiye edilmiş bir Krebs-Henseleit solüsyonu (mK-Hs) ile perfüze edildi. Stabilizasyondan sonra 0,1, 1 ve 10 μM konsantrasyonlarda kurkumin uygulandı. +dP/dt max, LVDP, MAP ve LVEDP indeksleri izole sıçan kalplerinde kardiyak kontraktilite ve ventriküler fonksiyon açısından değerlendirildi.

Bulgular: Tüm kurkumin konsantrasyonları +dP/dtmax ve LVDP'yi azalttı. On μM kurkumin de kalp atış hızını önemli ölçüde azalttı. Kurkumin (1 ve 10 μM), MAP süresinde bir artışla birlikte LVEDP'yi arttırdı ve MAP amplitüdünü azalttı. Tüm konsantrasyonlardaki kurkumin, dMAPdtmax ve dMAPdtmin'i etkilemedi.

Sonuç: Sonuçlarımız, kurkuminin daha yüksek konsantrasyonlarda (≥ 1 μM) negatif kronotropik etki ile LVEDP'yi arttırdığını ve MAP süresindeki artışla MAP amplitüdünü azalttığını düşündürebilir. Bu çalışmada kurkuminin negatif bir inotropik etkiye sahip olduğuna dair yeterli kanıt bulunmaktadır. Kurkuminin kalp kasılması üzerindeki patofizyolojik rolü, farklı hastalık modelleri ile desteklenmelidir.

Anahtar Kelimeler: İzole sıçan kalbi, kalp hızı, kardiyak kasılma, kurkumin, sol ventrikül diyastol sonu basıncı

Polyphenolic phytochemical curcumin is the main ingredient of the traditional Southeast Asian and Indian herb *Curcuma longa* (turmeric). Curcumin has been used not only as a traditional spice but also used in Asian medical treatments because

ORIGINAL ARTICLE
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of its potent biochemical and biological features such as antibacterial, anti-viral, anti-inflammatory, antimicrobial, hypoglycemic, antioxidant, and anticancer activities.[1-3] These actions were mediated by growth factors, transcription factors, protein kinases, cyclooxygenase 2,5-lipoxygenase, and inflammatory cytokines.[3] Curcumin has been applied therapeutically in treating many diseases with these properties, such as diabetes, neurological diseases, cancer, and cardiovascular diseases.[2]

Curcumin has recently received attention for its protective effects on the cardiovascular system, such as the down-regulation of blood pressure[4] and inhibition of the progression of atherosclerosis.[5] Recent ischemia/reperfusion studies have shown that curcumin attenuates the infarcted area. It has a curative effect on heart functions after ischemia[6-9] and reduces maladaptive cardiac repair in rats.[6] Likewise, curcumin prevents heart failure and the development of cardiac hypertrophy.[10] In another study, the ability of curcumin to inhibit the contractility of the isolated goat detrusor muscle was pointed out.[11] Another research group showed that curcumin has a beneficial protective effect on smooth muscle tissue.[12] Additionally, it has been reported that curcumin has protective effects on the myocardium against Dox-induced injury via suppressing oxidative stress and apoptosis.[13]

Given the potential beneficial effects of curcumin on cardiovascular function, there is still limited information about the effects of curcumin on dose-dependent mechanical functions. It is known that an increase in LVEDP or end-diastolic volume could characterize the function of the failing ventricle. On the other hand, increasing $+dP/dt_{max}$ values indicate improving cardiac contractility. Therefore, this study was aimed to determine the following hemodynamic responses: left ventricular developed pressure (LVDP), maximal rate of pressure development ($+dP/dt_{max}$), heart rate, left ventricular end-diastolic pressure (LVEDP), monophasic action potential amplitude (MAPamp), and MAP duration at 90% repolarization (MAP90).

Materials and Methods

Ethical Approval

All animal procedures by the Eskişehir Osmangazi University Animal Experiments Ethics Committee were followed (Approval number: 2842012).

Isolated Heart Preparation and Perfusion

Male Sprague–Dawley rats g) (275-350 g and 10 weeks of age) were randomly divided into 4 weight-matched groups (n=7/group): control, curcumin (0.1 μM), curcumin (1 μM), curcumin (10 μM). During the experiment, the rats were fed with standard feed and kept 12:12 h light-dark in cages at 20-25˚C. Previous studies testing the effect of curcumin in animal models of the isolated perfused heart and cultured cardiomyocytes have used doses ranging from 0.25 to 10 μM.[14-16] However, our pilot studies showed that 0.1 μM curcumin is effective in isolated rat hearts. Therefore, this low dose of curcumin was used, and other curcumin doses were chosen based on previous studies.

The intraperitoneal injection of sodium thiopental (50 mg/kg) was used to anesthetize the animals, along with heparin (1000 IU). After removing the heart quickly, it was submerged in ice-cold modified Krebs–Henseleit solution (mK-Hs). The heart was then moved to the Langendorff apparatus while perfusing with mK-Hs. The non-circulating Langendorff model was used to perform retrograde perfusion. The experiment was carried out under constant pressure (60 mmHg). This research pursued the same method as He and Downey[17] to measure the cardiac contractile force. Accordingly, a water-filled latex balloon was set to reach a stable left ventricular end-diastolic pressure of 8 mmHg. Then, it was inserted into the left ventricle through the mitral valve, which was then linked to a pressure transducer. A data acquisition and analysis system (Isoheart Software, Germany) was used to perform data acquisition to decide on the pressure measurements. As for the contractility index, the main parameters monitored were LVDP and $+dP/dt_{max}$. The MAP electrodes ($Ag/AgCl_2$) were used to calculate MAPamp and MAP90 recordings. To this end, we applied the contact electrode technique.

Infusion of Curcumin

After a 30-min stabilization period, curcumin at 0.1, 1, and 10 μM concentrations was infused into the heart by using an infusion pump (Graseby Medical, Model 3400, Watford Herts, England) for 30 minutes at a rate of 0.2 mL/min during all of the experiments. Each concentration was applied to a different group of hearts. All values were recorded in the control and experimental groups at the 10th, 20th, and 30th minute of a 30-minute observation period. Our preliminary studies indicated no changes were detected in the cardiac variables after repeated infusions of perfusion solutions that did not contain curcumin.

Drugs and Chemicals

Curcumin was obtained from Sigma (St. Louis, USA). Dimethyl sulfoxide (DMSO) was purchased from Carlo Erba (Val De Reuil, France). Curcumin is difficult to prepare, and it was dissolved in DMSO (20 mg/ml), stored at –20˚C, and diluted with mK-Hs immediately before the infusions. The final DMSO concentration in mK-Hs was <0.1, which did not affect cardiac parameters. Sodium thiopental (Pental sodium) and heparin sodium were obtained from I. E. Ulagay Pharmaceutical Industry (Istanbul, Türkiye) and Koçak Farma Pharmaceutical and Chemical Industry (Tekirdag, Türkiye), respectively.

Statistical Analysis

In this study, the sample size was calculated using one-way analysis of variance (ANOVA) with 0.05 significance level, $f=0.60$ effect size, and 0.80 power, and the sample consisting of 28 rats was sufficient will be determined. Statistical analyses were assessed with Statistical Package for Social Sciences version

ABBREVIATIONS

$+dP/d_{tmax}$	Maximal rate of pressure development
ANOVA	Analysis of variance
cAMP	Cyclic adenosine monophosphate
$dMAPd_{tmax}$	Maximum upstroke velocity
$dMAPd_{tmin}$	Maximum downstroke velocity
DMSO	Dimethyl sulfoxide
LVDP	Left ventricular developed pressure
LVEDP	Left ventricular end-diastolic pressure
MAP	Monophasic action potential
MAPamp	Monophasic action potential amplitude
mK-Hs	Modified Krebs–Henseleit solution
PKA	Protein kinase

Table 1. Control Values of LVDP, +dP/dt_{max}, Heart Rate, LVEDP, MAP Amplitude, MAP Duration, dMAPdt_{max}, and dMAPdt_{min} (n=7).

	0th Minute	10th Minute	20th Minute	30th Minute
LVDP (mmHg)	89.71 ± 3.64	85.14 ± 4.64	79.14 ± 4.56	75.57 ± 4.67
+dP/dt_{max} (mmHg s^{-1})	3950.71 ± 188.58	3680.85 ± 194.7	3531.85 ± 171.1	3385.57 ± 254.96
Heart rate (beats/min)	325.33 ± 20.43	294.5 ± 24.12	285.66 ± 23.81	287.16 ± 27.04
LVEDP (mmHg)	7 ± 0.26	6.5 ± 0.42	6.3 ± 0.33	6.16 ± 0.31
MAP amplitude (mV)	16.1 ± 1.52	13.65 ± 1.23	13.4 ± 1.29	10.66 ± 1.07
MAP duration (ms)	202.16 ± 13.24	229.16 ± 21.16	243.16 ± 22	268.5 ± 22.93
dMAPdt_{max} (V/s)	5.33 ± 0.49	3.33 ± 0.33	2 ± 0.25	1.66 ± 0.33
dMAPdt_{min} (V/s)	-2.83 ± 0.3	-2.33 ± 0.42	-2.16 ± 0.3	-1.7 ± 0.33

dMAPdt_{max}, maximum upstroke velocity; dMAPdt_{min}, maximum downstroke velocity +dP/dt_{max}, maximal rate of pressure development; LVDP, left ventricular developed pressure; LVEDP, left ventricular end-diastolic pressure, MAP, monophasic action potential.

13.0 (SPSS Inc., Chicago, Ill, USA). Shapiro–Wilk test was used to evaluate data distribution normality, and the Kolmogorov–Smirnov test for Lilliefors correction. Finally, a one-way ANOVA and Tukey-HSD multiple comparisons tests were used for data analysis. Data were expressed as mean ± standard error of the mean and $P < 0.05$ was considered significant.

Results

Control values of LVDP, +dP/dt_{max}, heart rate, LVEDP, MAP amplitude, MAP duration, dMAPdt_{max}, and dMAPdt_{min} are shown in Table 1. Infusion of curcumin at a concentration of 0.1, 1, and 10 μM markedly decreased LVDP and +dP/dt_{max} in a concentration-dependent manner ($P < 0.001$). A significant decline in LVDP and +dP/dt_{max} was seen 10 minutes after the initiation of infusions. The decrease in these parameters was higher at 20th and 30th minute of the observation period and the maximal decrease for 3 concentrations occurred 30 minutes after the administration of curcumin (Figures 1 and 2).

Either 0.1 or 1 μM curcumin did not alter heart rate; however, 10 μM curcumin significantly decreased it compared to control values ($P < 0.001$). The maximal decrease in heart rate was seen in 30th minute of infusion (Figure 3).

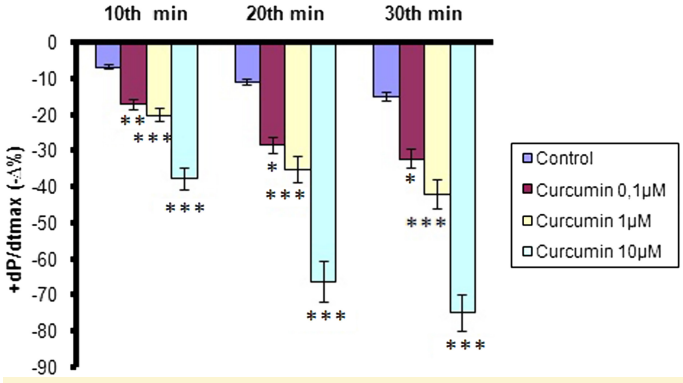

Figure 2. Concentration-dependent effect of curcumin on +dP/dt_{max}. -Δ% is the percent decrease according to the value obtained prior to the infusion of curcumin in curcumin groups and percent decrease according to the value obtained prior to the infusion of mK-Hs (the 0th minute value) in the control group. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ statistically significant according to control (n=7).

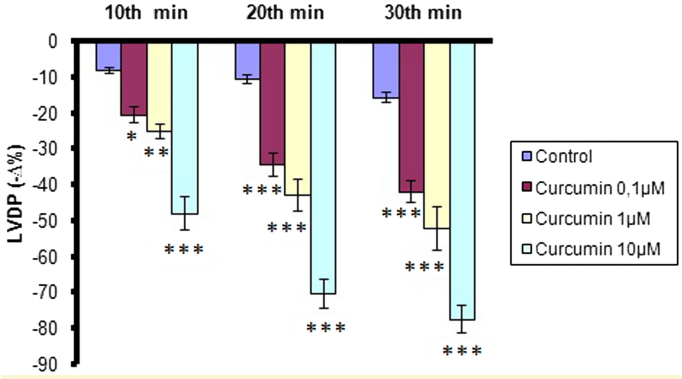

Figure 1. Concentration-dependent effect of curcumin on LVDP. -Δ% is the percent decrease according to the value obtained prior to the infusion of curcumin in curcumin groups and percent decrease according to the value obtained prior to the infusion of mK-Hs (the 0th minute value) in the control group. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ statistically significant according to control (n=7).

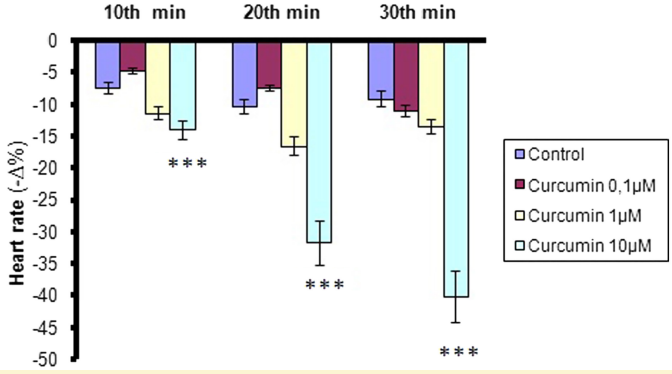

Figure 3. Concentration-dependent effect of curcumin on heart rate. -Δ% is the percent decrease according to the value obtained prior to the infusion of curcumin in curcumin groups and percent decrease according to the value obtained prior to the infusion of mK-Hs in the control group. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ statistically significant according to control (n=7).

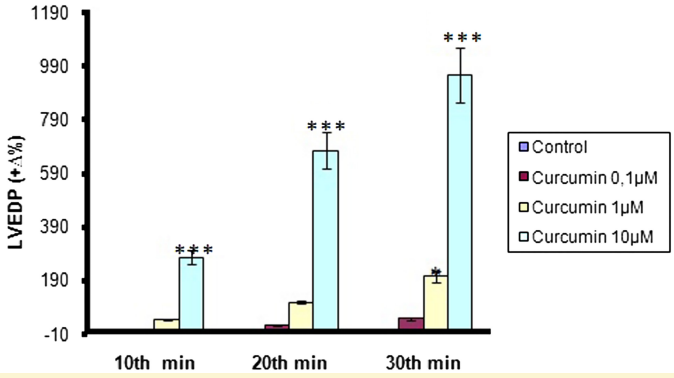

Figure 4. Concentration-dependent effect of curcumin on LVEDP. +Δ% is the percent increase according to the value obtained prior to the infusion of curcumin groups and percent increase according to the value obtained prior to the infusion of mK-Hs (the 0th minute value) in control group. -Δ% values of control group are -7 ± 0.85, -11.83 ± 1.04, and -12.3 ± 1.3 for 10th minute, 20th minute, and 30th minute, respectively. +Δ% value of 0.1 μM curcumin group is 4.66 ± 0.55 for 10th minute (data are not shown).

As illustrated in Figure 4, curcumin at a concentration of 0.1 μM did not affect LVEDP. There was a tendency toward an increase in LVEDP, but this increase was not statistically significant. Compared to control values, 1 μM curcumin increased LVEDP only at 30th minute ($P < 0.05$). A total of 10 μM curcumin induced a marked increase in this variable ($P < 0.001$), with a maximal increase occurring 30 minutes after the start of infusions.

Curcumin (0.1 μM) did not significantly change the amplitude and duration of MAP. One and 10 μM concentrations of curcumin decreased MAP amplitude ($P < 0.01$ for 1 μM and $P < 0.001$ for 10 μM) and increased MAP duration ($P < 0.05$ for 1 μM and $P < 0.001$ for 10 μM). The maximum effect of curcumin on both MAP amplitude and MAP duration was observed 30 minutes after initial exposure (Table 2). Curcumin at all doses had no significant effect on dMAPdt_{max} and dMAPdt_{min} (Table 3). Furthermore, after the infusion of curcumin was stopped, all parameters remained below the control values.

Discussion

In this study, we observed that curcumin reduces cardiac contractility and heart rate; the findings are similar to a previous study.[18] These researchers reported that curcumin induces negative inotropic and chronotropic effects on isolated perfused rabbit hearts. Consistent with our results, another researcher found that curcumin had a bradycardic effect in rats.[19] It is known that the inositol-1,4,5-trisphosphate (IP_3) receptor is a Ca^{2+} channel on the endoplasmic reticulum membrane and activation of this receptor by IP_3 induces an increase in cytosolic Ca^{2+} concentration.[20] Curcumin inhibits Ca^{2+} release via IP3-sensitive Ca^{2+} channels from IP_3-sensitive Ca^{2+} stores in porcine cerebellar microsomes.[21] Besides, curcumin inhibits extracellular Ca^{2+} influx through voltage-operated channels in rat mesenteric arteries.[22] Thus, the negative inotropic effect shown in this study may be due to a decrease in cytosolic Ca^{2+} concentration due to the blockade of IP3-sensitive and voltage-operated Ca^{2+} channels.

Beta-adrenergic stimulation of the heart activates the cyclic AMP-dependent protein kinase A (PKA), and phosphorylation of myofibrillar proteins by PKA increases cardiac contractility[22] Moreover, protein kinase C (PKC) is another peptide that may also enhance cardiac contractility in isolated perfused rat hearts.[23] Curcumin inhibits PKC and the catalytic subunit of PKA.[24] It has been reported that curcumin also inhibits the PKC pathway in macrophages induced by phorbol 12 myristate 13-acetate.[25] Therefore, curcumin-induced negative inotropy may also depend on cyclic adenosine monophosphate (cAMP) dependent protein kinase and PKC inhibition. Contrary to our findings, some researchers demonstrated that curcumin improves cardiac contractility determined by echocardiography in rats in an ischemia/reperfusion model. These investigators administered 150 mg/kg/day of curcumin (orally), and they used an experimental model which was different from the Langendorrf technique.[6,26]

Left ventricular end-diastolic pressure is a valuable measurement in evaluating the left ventricular function of patients with various cardiac disorders. It is affected by several factors, such as afterload, preload, heart rate, pleural or pericardial pressure, inotropic state, and diastolic properties of the left ventricle.[27] Left ventricular end-diastolic pressure is the most important

Table 2. Time-Dependent Effect of Curcumin on MAP Amplitude and MAP Duration

MAP Amplitude (-Δ %)	10th Minute	20th Minute	30th Minute
Control	-14.83 ± 1.35	-16.1 6 ± 1.7	-34.66 ± 3.6
0.1 μM Curcumin	-18.83 ± 1.88	--34.33 ± 3.63	-49 ± 4.09
1 μM curcumin	-19.5 ± 1.78	-39.16 ± 4.04 *	-64.3 ± 6.68 **
10 μM curcumin	-40 ± 4.16 ***	-73.83 ± 7.58 ***	-82.6 ± 6 ***
MAP Duration (+Δ %)	**10th Minute**	**20th Minute**	**30th Minute**
Control	12.66 ± 0.95	18.66 ± 1.89	31.16 ± 3.51
0.1 μM curcumin	13.83 ± 1.01	19.5 ± 1.72	41.16 ± 4.25
1 μM curcumin	16.66 ± 1.6	24.16 ± 2.24	60.16 ± 6.07*
10 μM curcumin	18 ± 1.82	84 ± 8.01***	121.66 ± 10.38***

MAP, monophasic action potential.
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ significantly different from the respective control (n=7).

Table 3. Time-Dependent Effect of Curcumin on dMAPdt_{max} and dMAPdt_{min} (n =7).

dMAPdt_{max} (-Δ %)	**10th Minute**	**20th Minute**	**30th Minute**
Control	-40.83 ± 3.86	-60.66 ± 5.37	-71.83 ± 6.6
0.1 μM curcumin	-35.16 ± 2.28	-54.5 ± 4.02	-59.5 ± 3.97
1 μM curcumin	-51.33 ± 3.79	-62.66 ± 5.75	-75.66 ± 7.16
10 μM curcumin	-55 ± 5.24	-80.83 ± 5.79	-85.33 ± 2.69
dMAPdt_{min} (-Δ %)	**10th Minute**	**20th Minute**	**30th Minute**
Control	-30.5 ± 2.27	-46.5 ± 2.93	-47.83 ± 7.04
0.1 μM curcumin	-28.16 ± 2.13	-44.83 ± 3.52	-46.16 ± 4.74
1 μM curcumin	-29 ± 2.46	-49.66 ± 2.95	-54.5 ± 4.28
10 μM curcumin	-36.16 ± 1.68	-59.66 ± 4.63	-69.33 ± 7.11

dMAPdt_{max}, maximum upstroke velocity; dMAPdt_{min}, maximum downstroke velocity.

index of left ventricular contractility and is generally elevated in patients with poor left ventricle function. Left ventricular dysfunction increases the amount of blood in left ventricle which in turn causes elevations in LVEDP and increased LVEDP may lead to pulmonary congestion.[28] In our study, we showed that 1 and 10 μM curcumin increased LVEDP in isolated heart rats in accordance with the results of Rao et al.[29]

In contrast to transmembrane action potential, which can be recorded with a glass microelectrode placed into a cell, MAP is recorded using the contact electrode technique from the endocardium and epicardium of beating hearts. Monophasic action potential records are helpful in evaluating the characteristics of an action potential, the repolarization process.[22,26] The contact electrode technique has wide experimental and clinical utility due to its safety and simplicity.[29] Monophasic action potential amplitude typically changes from 5 to 50 mV when the contact electrode technique is used. The variations of MAP amplitude depend on the contact pressure and tissue type,[30] and MAP amplitude tends to decrease during a prolonged recording period from a single site.[29] Monophasic action potential amplitude also depends upon the sodium channel current during phase 0 of the MAP.[26] It is possible that curcumin may inhibit the sodium channel current, and in the present study, the decrease in MAP amplitude may be related to inhibition of sodium channel current.

We also demonstrate that the duration of the MAP along with decreasing heart rate is prolonged. These findings can be explained with the frequency dependence of MAP duration. This phenomenon means that under physiological conditions, increases in heart rate lead to a shortening of MAP duration. A balance between inward and outward currents during the plateau phase of MAP determines the length of MAP duration.[26] The delayed rectifier K+ current (IK) plays a significant role in the late repolarization phase of MAP and regulates MAP duration.[31] In HEK293 cells stably expressing hERG channels, curcumin inhibits hERG K^+ current, which is the rapid component of I_K. Inhibition of hERG K^+ current results in prolonging of cardiac repolarization and the QT interval.[10] It is possible that the inhibition of hERG K^+ current by curcumin may contribute to the increase of MAP duration in this study. It is known that L-type Ca^2 current (I_{CaL}) is responsible for the plateau of a cardiac action potential. An increase in I_{CaL} lengthens MAP duration and blockade of I_{CaL} shortens it.[32] Curcumin selectively inhibits I_{CaL} in cultured rat hippocampal neurons.[33] Since the blockade of I_{CaL} reduces MAP duration, the increased MAP duration observed in our experiments might not be related to curcumin-induced inhibition of $I_{CaL.}$

Conclusions

Our data have demonstrated that a higher concentration of curcumin led to negative chronotropic action while increased LVEDP. Our results also show for the first time that a high concentration of curcumin reduces MAP amplitude with a concomitant increase in MAP duration. Curcumin has a reducing effect on cardiac contractility and therefore shows myocardial depressant in isolated rat hearts. The effect of curcumin on cardiac contractility may be pathological and this claim about curcumin should be supported in future studies.

Ethics Committee Approval: All animal procedures by the Eskişehir Osmangazi University Animal Experiments Ethics Committee were followed (Approval number: 2842012).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.K., B.K.; Design - Ö.K., B.K.; Data Collection or Processing Ö.K., B.K.; Analysis or Interpretation - Ö.K., B.K., A.K.A.; Literature Search - Ö.K., B.K., A.K.A.; Writing - Ö.K., B.K.; A.K.A. Critical Review Ö.K., B.K., A.K.A.

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Declaration of Interests: The authors declare that they have no conflict of interest.

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