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Optimal Dose-Setting Study of Curcumin for Improvement of Left Ventricular Systolic Function After Myocardial Infarction in Rats

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Abstract. A natural p300-specific histone acetyltransferase inhibitor, curcumin, may have a therapeutic potential for heart failure. However, a study of curcumin to identify an appropriate dose for heart failure has yet to be performed. Rats were subjected to a left coronary artery ligation. One week later, rats with a moderate severity of myocardial infarction (MI) were randomly assigned to 4 groups receiving the following: a solvent as a control, a low dose of curcumin (0.5 mg·kg^{-1}·day^{-1}), a medium dose of curcumin (5 mg·kg^{-1}·day^{-1}), or a high dose of curcumin (50 mg·kg^{-1}·day^{-1}). Daily oral treatment was continued for 6 weeks. After treatment, left ventricular (LV) fractional shortening was dose-dependently improved in the high-dose (25.2% ± 1.6%, $P < 0.001$ vs. vehicle) and medium-dose (19.6% ± 2.4%) groups, but not in the low-dose group (15.5% ± 1.4%) compared with the vehicle group (15.1% ± 0.8%). The histological cardiomyocyte diameter and perivascular fibrosis as well as echocardiographic LV posterior wall thickness dose-dependently decreased in the groups receiving high and medium doses. The beneficial effects of oral curcumin on the post-MI LV systolic function are lower at 5 compared to 50 mg·kg^{-1}·day^{-1} and disappear at 0.5 mg·kg^{-1}·day^{-1}. To clinically apply curcumin therapy for heart failure patients, a precise, optimal dose-setting study is required.

Keywords: curcumin, heart failure, hypertrophy, dose-dependency, p300

Introduction

Heart failure is an enormous medical and societal burden (1). Patients with heart failure comprise approximately 1% to 2% of the population in developed countries (2). A total of 30% to 40% of patients die from heart failure within 1 year after the diagnosis (3). To overcome this problem, there has been considerable progress in the treatment of chronic heart failure with angiotensin-converting enzyme (ACE) inhibitors (4, 5), aldosterone antagonists (6), beta-receptor blockers (7, 8), and resynchronization therapy (9, 10). Even with the

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very best of modern therapy, however, heart failure is still associated with an annual mortality rate of 10% (10). The search for better treatments is one of the major challenges in cardiology.

Signals of neurohormonal factors activated by hemodynamic overload, such as pressure or volume overload, enter cardiomyocytes via their extracellular receptors, finally reach the nuclei of cardiac myocytes, and change the patterns of gene expressions associated with cardiac hypertrophy. These gene regulations are associated with the activation of hypertrophic-responsive transcriptional factors such as GATA4 (11, 12), MEF2 (13), and SRF (14). Activities of these factors are regulated by histone deacetylases and an intrinsic histone acetyltransferase (HAT), p300 (15, 16). In response to stimuli for cardiomyocyte hypertrophy, p300 HAT activity is enhanced (17, 18). The activation of p300 induces the acetylation of not only histone but also GATA4, increases its DNA-binding capacity, and up-regulates the expression of hypertrophy-promoting genes (19 – 21). On the other hand, in transgenic mice that overexpress intact p300 in the heart, GATA4 acetylation and left ventricular (LV) remodeling after myocardial infarction (MI) have been augmented (19, 22). Such augmentation did not occur in mice that overexpress mutant p300 lacking HAT activity. These findings indicated that the p300 HAT activity is a pharmacological target for heart failure therapy.

The natural compound curcumin, derived from *Curcuma longa*, is an inhibitor of p300 HAT activity (23) and widely employed as a health food. Curcumin possesses diverse pharmacologic properties, including anti-inflammatory, anti-oxidant, anti-proliferative, and anti-angiogenic activities. It has also been reported to exhibit cardioprotective effects on acute injury models in rats such as ischemia/reperfusion (24, 25) and isoproterenol-induced oxidative and ischemic damage (26). In these models, the cardioprotective effects of curcumin are dependent on its anti-inflammatory and anti-oxidative properties. Recently, we reported that native curcumin, at a dose of 50 $mg \cdot kg^{-1}$, prevents deterioration of the systolic function in rat models of chronic hypertension- or MI-induced heart failure (27). Others also reported that curcumin prevents diabetes-induced cardiac hypertrophy in rats (28). Moreover, we have demonstrated the beneficial effects of combination therapy with an ACEI, enalapril, and curcumin on post-MI systolic dysfunction in rats compared with ACEI or curcumin monotherapy (29). These observations suggest that curcumin inhibits maladaptive hypertrophy of cardiomyocytes and exhibits beneficial effects in animal models of chronic heart failure (30, 31). Curcumin's effects of p300 inhibition as well as of anti-inflammation and anti-oxidation will be responsible for these beneficial effects. To clinically apply this therapy for heart failure, information on the optimal dose of curcumin is needed.

Here, we performed an optimal dose-setting study to evaluate the effects of 0.5, 5, and 50 $mg \cdot kg^{-1}$ of curcumin on the post-MI LV function in a rat model of heart failure following MI.

Materials and Methods

Ethical approval

This experiment was performed in accordance with the Guide for the Care and Use of Laboratory Animals by the Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University (registration number MedKyo 07523).

Myocardial infarction model

Male Sprague-Dawley rats weighing 280 – 300 g (SLC Inc., Shizuoka) were tracheally intubated after being anesthetized with ethyl ether gas. Anesthesia was maintained during the operation with 1% to 1.5% isoflurane. MI was created in rats by ligating the proximal left anterior descending (LAD) coronary artery through a left thoracotomy, as described previously (27). The sham procedure was identical except that the LAD coronary artery was not ligated.

Echocardiography and blood pressures

One week after the operation, blood pressures and the cardiac function of all rats were measured, as described previously (29). In brief, blood pressures were measured by the tail-cuff method (BP-98A; Softron, Tokyo) under the awake condition and echocardiography was performed while the rats were lightly anesthetized with ethyl ether gas, and images were recorded using a 10- to 12-MHz phased-array transducer (model 21380A with HP SONOS 5500 imaging system; Agilent Technologies, Santa Clara, CA, USA). All observations were performed in a blinded fashion according to the guidelines of the American Society for Echocardiology and averaged over 3 consecutive cardiac cycles.

Treatments

Curcumin powder and gum arabic for oral administration were purchased from Wako (Osaka). Curcumin was mixed and dissolved in 1% gum arabic solution. After the measurements of blood pressures and echocardiography, 43 rats with moderate MI (left ventricular fractional shortening, LVFS < 40%) were randomly assigned to 4 groups. Groups I and II comprised sham-operated rats treated with vehicle (1% gum arabic, n = 6) as a control or curcumin (50 $mg \cdot kg^{-1} \cdot day^{-1}$, n = 6), respectively. Groups III to VI comprised MI rats treated with

vehicle (n = 11), a low dose of curcumin (0.5 mg·kg^{-1}·day^{-1}, n = 11), medium dose of curcumin (5 mg·kg^{-1}·day^{-1}, n = 10), or high dose of curcumin (50 mg·kg^{-1}·day^{-1}, n = 11), respectively. Daily oral administrations in each group started at 1 week after MI or sham operation and were repeated for 6 weeks.

Histological analysis

The excised hearts were cut into 2 transverse slices, fixed in 10% formalin, embedded in paraffin, sliced into 4-μm-thick sections, and stained with hematoxylin eosin (H&E) and Masson trichrome. The cross-sectional myocardial cell diameter and surface area were measured semiautomatically with the aid of an image analyzer (Image J v.1.46). Fifty cell sections with a crossing central nucleus were selected for the analysis. Perivascular and interstitial fibrosis areas were previously described (29). Quantitative assessments of perivascular and interstitial fibrosis areas and the infarct area were previously described (29). The scale of the measured intramyocardial coronary artery was more than 50 μm in each rat. The wall thickness in each group was measured at three points in the non-MI area of the LV and presented as the average values. The infarct size was calculated by dividing the infarcted area by the total LV area and expressed as a percentage (29).

Statistical analyses

The results are presented as the mean ± S.E.M. Statistical comparisons were performed using ANOVA with Fisher's test. $P < 0.05$ indicated significance.

Results

Blood pressure, body weight, and left ventricular weight

Although the body weight (BW) and heart rate (HR) were comparable at 1 week after coronary artery ligation in all 6 groups, systolic and diastolic blood pressures in the 4 groups with MI were significantly lower than in the sham control and curcumin groups (Table 1). As shown in Table 2, there were no significant differences in the infarct size among the 4 MI groups at 7 weeks after coronary artery ligation. After treatments, BW was comparable in all 6 groups. Curcumin treatment dose-dependently reduced the LV weight to BW ratio (LV/BW), and a significant reduction was obtained with the high dose (50 mg·kg^{-1}·day^{-1}) of curcumin ($P < 0.01$) compared with vehicle treatment with MI. Although there were no differences in hemodynamic and echocardiographic parameters between vehicle and curcumin treatment in sham-operated rats, the systolic blood pressure in the high-dose curcumin group was lower than in the sham vehicle group. However, curcumin treatment did not affect the diastolic blood pressure (Table 2).

Echocardiographic analysis

There were no differences among the 4 groups with MI with respect to any of the parameters examined, including the body weight, blood pressure, LV dimension, LVPWT, and LVFS, at 1 week after coronary artery ligation (Table 1). Representative photographs of M-mode images from vehicle- and 0.5, 5, 50 mg·kg^{-1}·day^{-1} of curcumin-treated MI rats at 6 weeks after treatments

Table 1. BW and hemodynamic parameters before treatment

	n	BW (g)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	LVEDD (mm)	PWT (mm)	LVFS (%)	LVEF (%)
Sham vehicle	6	341 ± 6	127 ± 3	97 ± 4	363 ± 8	8.4 ± 0.3	1.10 ± 0.14	60.6 ± 3.7	93.1 ± 1.9
Sham curcumin, 50 mg·kg^{-1}	6	342 ± 7	122 ± 2	99 ± 6	362 ± 13	8.4 ± 0.4	1.16 ± 0.10	61.6 ± 3.1	93.8 ± 1.3
MI vehicle	11	321 ± 7	112 ± 2*	87 ± 2*	380 ± 9	9.3 ± 0.2*	1.25 ± 0.12*	28.1 ± 2.2*	62.1 ± 3.5*
MI curcumin, 0.5 mg·kg^{-1}	11	332 ± 6	108 ± 4*	80 ± 2*	388 ± 16	9.4 ± 0.3*	1.36 ± 0.08*	25.9 ± 1.4*	58.8 ± 2.4*
MI curcumin, 5 mg·kg^{-1}	10	329 ± 7	113 ± 3*	88 ± 2*	385 ± 11	9.5 ± 0.2*	1.27 ± 0.14*	27.0 ± 1.4*	60.7 ± 2.3*
MI curcumin, 50 mg·kg^{-1}	11	321 ± 6	115 ± 5*	83 ± 5*	402 ± 12	9.6 ± 0.2*	1.31 ± 0.07*	26.1 ± 2.1*	58.7 ± 2.4*

Values are mean ± S.E.M. in each group. BW = Body weight, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVEDD = left ventricular end-diastolic diameter, PWT = posterior wall thickness, LVFS = left ventricular fraction shortening, LVEF = left ventricular ejection fraction. *$P < 0.05$ vs. Sham vehicle.

Table 2. BW, LVW, LVW/BW, and hemodynamic parameters after treatment

	n	BW (g)	LVW (mg)	LV/BW (mg/g)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	Infarct area (%)
Sham vehicle	6	447 ± 12	701 ± 24	1.61 ± 0.04	124 ± 3	96 ± 4	367 ± 16	—
Sham curcumin 50 mg·kg^{-1}	6	449 ± 17	724 ± 12	1.58 ± 0.08	126 ± 4	96 ± 3	358 ± 21	—
MI vehicle	11	446 ± 9	814 ± 25*	1.82 ± 0.03*	117 ± 4	91 ± 4	370 ± 13	8.95 ± 0.91
MI curcumin 0.5 mg·kg^{-1}	11	448 ± 7	809 ± 22*	1.80 ± 0.04*	114 ± 3	92 ± 4	369 ± 23	9.50 ± 1.20
MI curcumin 5 mg·kg^{-1}	10	434 ± 10	756 ± 13$^{\#}$	1.75 ± 0.03*	120 ± 2	94 ± 3	368 ± 10	10.0 ± 1.51
MI curcumin 50 mg·kg^{-1}	11	449 ± 8	755 ± 10$^{\#}$	1.68 ± 0.03†	111 ± 3*	87 ± 5	386 ± 8	10.2 ± 1.63

Values are mean ± S.E.M. in each group. LVW = left ventricle weight. *$P < 0.05$ vs. Sham vehicle, $^{\#}P < 0.05$ vs. MI vehicle, $^{\dagger}P < 0.01$ vs. MI vehicle.

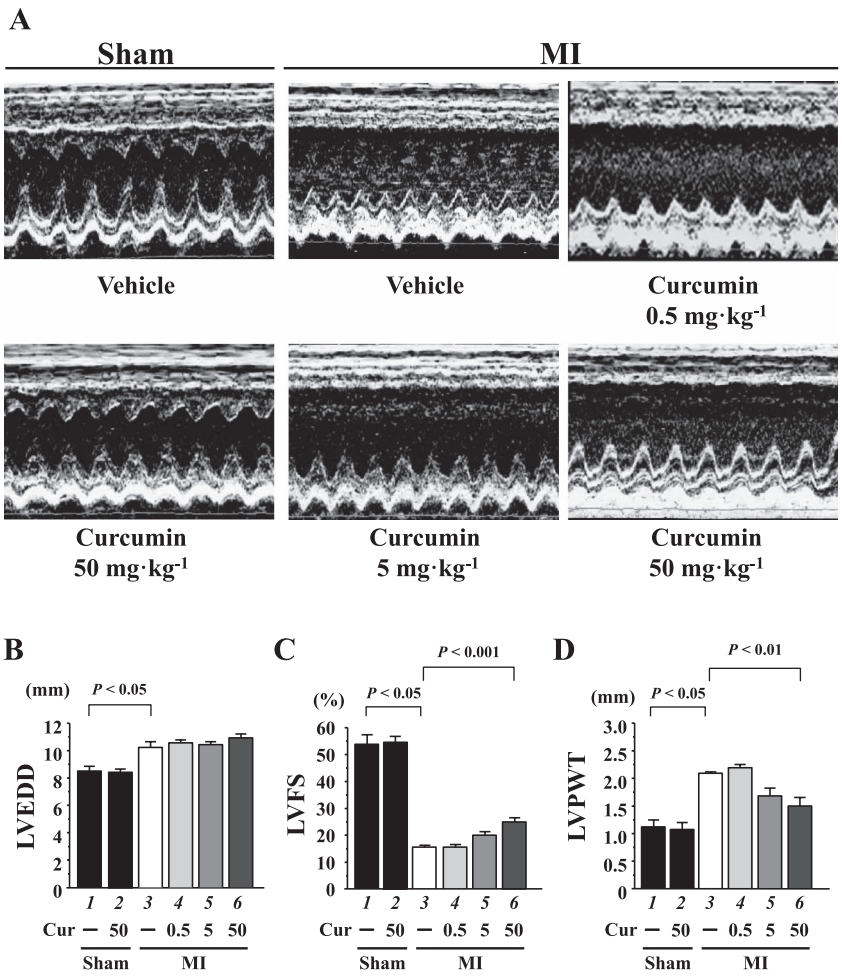

Fig. 1. Curcumin dose-dependently improved LV systolic function on MI in rats. A: Representative photographs of M-mode images from sham- and MI-operated rats with treatments of vehicle or curcumin at a dose of 0.5, 5, or 50 mg·kg^{-1}. B, C, D: The results of echocardiographic parameters. Each value is the mean ± S.E.M. B: LVEDD, C: LVFS, D: LVPWT.

are shown in Fig. 1A. MI significantly increased left ventricle end-diastolic diameter (LVEDD) ($P < 0.05$) and LVPWT ($P < 0.05$) and significantly decreased LVFS ($P < 0.05$). LVEDD in each MI group was comparable (Fig. 1B). The LV systolic function, represented by LVFS, was dose-dependently improved in the high-dose (25.2% ± 1.6%, $P < 0.001$ vs. vehicle) and medium-dose (19.6% ± 2.4%) groups, but not in the low-dose group (15.5% ± 1.4%) compared with the vehicle group (15.5% ± 0.7%) with MI (Fig. 1C). LVPWT was dose-dependently decreased in the high-dose curcumin (1.46 ± 0.11 mm, $P < 0.01$) and medium-dose (1.70 ± 0.13 mm) groups, but not in the low-dose group (2.15 ± 0.13 mm) compared with the vehicle group (2.11 ± 0.02 mm) with MI (Fig. 1D).

Myocardial cell analysis

Representative whole images of the transversely sectioned LV in each group are shown in Fig. 2A. The same configurations of LV tissues as shown in echocardiography could be confirmed. The measurements of the infarct size did not differ among each MI group (Table 2). Treatments with high- and medium-dose curcumin reduced the average wall thickness in the non-MI area compared with the vehicle ($P < 0.05$) (Fig. 2B). Images of myocardial cells in each group are shown in Fig. 3A. MI increased the cross-sectional myocardial cell diameter and surface area ($P < 0.05$) (Fig. 3: B and C, lanes 1 and 3, respectively). These increases were dose-dependently inhibited by curcumin treatment, and significant inhibition was observed in the curcumin high-dose treatment ($P < 0.05$, lanes 3 and 6).

Perivascular fibrosis

Images of perivascular fibrosis in the non-MI area of each group are shown in Fig. 4A. The results of measured perivascular fibrosis areas indicated that they notably expanded after MI ($P < 0.05$) (Fig. 4B, lanes 1 and 3). The perivascular fibrosis area became significantly and dose-dependently smaller in the curcumin groups than the MI vehicle group ($P < 0.05$) (lanes 3, 4, 5, and 6). However, the interstitial fibrosis area was comparable among each MI group (Fig. 4C).

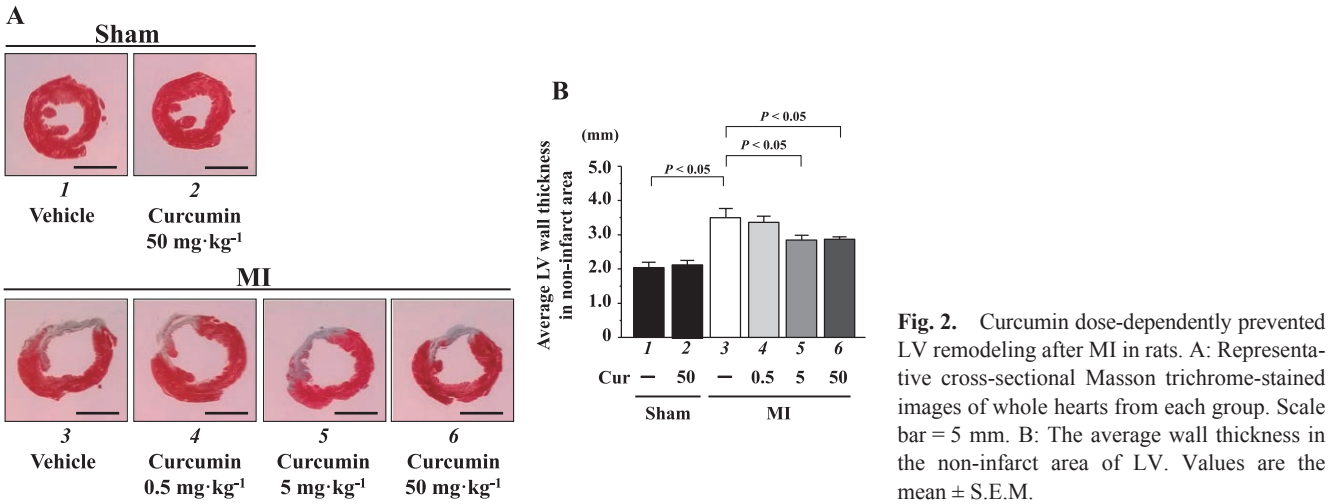

Fig. 2. Curcumin dose-dependently prevented LV remodeling after MI in rats. A: Representative cross-sectional Masson trichrome-stained images of whole hearts from each group. Scale bar = 5 mm. B: The average wall thickness in the non-infarct area of LV. Values are the mean ± S.E.M.

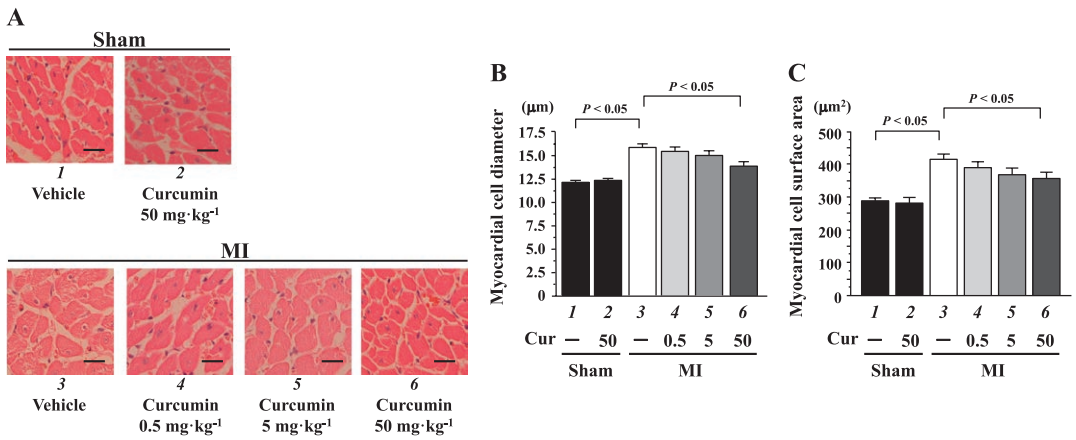

Fig. 3. Curcumin dose-dependently prevented cardiac hypertrophy after MI in rats. A: Representative cross-sectional images of myocardial cells stained with H&E from each rat. Scale bar = 20 μm. B and C: The myocardial cell diameter (B) and surface area (C) were measured in at least 50 cells in each rat. Values are the mean ± S.E.M.

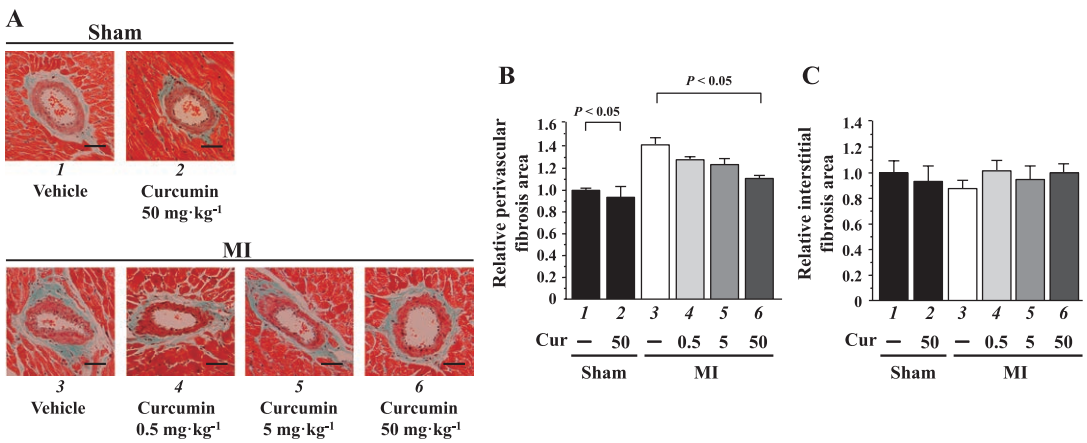

Fig. 4. Curcumin dose-dependently prevented perivascular fibrosis after MI in rats. A: Representative images of Masson trichrome–stained sections of LV from rats in each group. Scale bar = 50 μm. B: The areas of perivascular fibrosis in LV were measured for at least 5 intramyocardial coronary arteries with a lumen size of more than 50 μm. Values are the mean ± S.E.M. C: The areas of interstitial fibrosis in LV were measured. Values are the mean ± S.E.M.

Discussion

The purpose of this study was to examine the dose-dependent effects of curcumin, an active constituent of turmeric, on the cardiac function in an animal model of experimentally induced myocardial infarction. Curcumin suppressed MI-induced fibrosis and cardiomyocyte hypertrophy and prevented the decrease of contractility in the non-infarct area. However, curcumin did not improve wall motion in the infarct area where no cardiomyocytes existed. As indicated in Table 1 and Fig. 1, the improvement of the systolic function by curcumin treatment was modest, compared with the observed improvement of cardiomyocyte hypertrophy. Insufficient improvement of the systolic function in MI rat models is similar between conventional heart failure therapy, such as ACEI (32) and ARB (33), and 50 $mg \cdot kg^{-1} \cdot day^{-1}$ of curcumin. In addition, curcumin treatment did not change LVEDD (Fig. 1B). There is a possibility that related to the improvement of contractility, LVEDD might decrease slowly. In order to further clarify the effects of curcumin on the myocardial infarction model, it is necessary to observe the rats for a longer term. Moreover, a limitation of this experiment was that the heart size was measured by 2D cardiac echography. It is difficult to morphologically estimate the actual volume of the LV cavity after MI in rats. This may be another reason for the modest improvement of the LV systolic function and no decrease of LVEDD due to curcumin in this experiment. Further examination, such as a cardio hemodynamic examination, is needed to clarify this point. Histopathological examinations were also performed to corroborate the overall findings. The results of this study showed that curcumin at high doses (50 $mg \cdot kg^{-1}$) but not at lower doses (0.5, 5 $mg \cdot kg^{-1}$) improved the retardation of the LV systolic function and cardiac hypertrophy after myocardial infarction in rats. Several studies reported oral treatment of 30 to 400 $mg \cdot kg^{-1} \cdot day^{-1}$ of curcumin administrated to cardiac disease models, including ischemia reperfusion injury (24, 25), diabetic cardiomyopathy (28), isoproterenol (ISO)-induced cardiomyopathy (26), and doxorubicin-induced cardiotoxicity (34). These doses had some effects on the heart. However, an optimal curcumin dose for heart disease is unclear. Our previous study demonstrated that survival rates in a hypertension-induced heart failure model using salt-sensitive Dahl rats were not changed with oral administrations of 50 and 200 $mg \cdot kg^{-1}$ of curcumin (Morimoto et al. unpublished data). This indicates that the effects of curcumin at these 2 doses on heart failure are similar. So, we consider that the optimal dose of curcumin for heart failure in rats may be between 5 to 50 $mg \cdot kg^{-1}$.

Although our previous studies indicated that 50 $mg \cdot kg^{-1} \cdot day^{-1}$ of curcumin did not affect the blood pressure in MI and sham rat models (27, 29, 35), treatment with this dose of curcumin significantly reduced the systolic blood pressure of MI rats compared to sham rats in this study. A conclusion regarding the anti-hypertensive effects of curcumin is not possible, since there were no differences in systolic blood pressure between vehicle and curcumin sham groups. Curcumin was reported to favorably affect all leading components of metabolic syndrome, including insulin resistance, obesity, hypertriglyceridemia, decreased HDL-C, and hypertension, and prevent the deleterious complications of metabolic syndrome, including diabetes and cardiovascular disease (36). A few studies demonstrated that curcumin could reduce the blood pressure in a human clinical study and hypertensive rat models (37, 38). Although these hypotensive effects depend on the pathophysiology, reduced blood pressure might maintain cardiac functions during the development of heart failure. Further examinations are needed to clarify the hypotensive effects of curcumin on patients with each condition.

Curcumin has several attractive properties and exhibits diverse pharmacologic effects, including anti-inflammatory, anti-oxidant, anti-proliferative, and anti-angiogenic activities (30). Curcumin has been reported to show protective effects against heart diseases by enhancing anti-oxidant defense against oxidative myocardial injury and attenuating cardiac fibrosis, inflammation, and apoptosis and to have anti-hypertrophic effects and preserve the cardiac function. Some of these depended on the p300 HAT inhibitory effects of curcumin (27). p300 plays crucial roles in cardiac hypertrophy and heart failure in vivo (18, 22). The intracellular protein level of transcription cofactor p300 is strictly limited (30). On the one hand cardiomyocytes enlarge when p300 expression increases (18), but, on the other hand, cardiomyocytes show apoptosis when the p300 protein level decreases (39, 40). Namely, p300 is necessary for both myocardial cell growth and survival. These p300 roles in the heart are mainly dependent on its HAT activity since p300 plays roles in the transcriptional regulation of cardiac hypertrophy and apoptosis (41). Thus, the control of not only protein levels of cardiomyocyte p300 but also its HAT activity may be important for maintaining the homeostasis of cardiomyocytes. It is not favorable for the heart if the inhibitory effects of curcumin, a p300-specific HAT inhibitor, are too weak or too strong. Therefore, the optimal dose setting of curcumin is important for its clinical usage.

Tanwar et al. investigated dose-dependent actions of curcumin on an ISO-induced myocardial damage rat

model (42). Although 100 and 200 $mg \cdot kg^{-1} \cdot day^{-1}$ of orally administered curcumin protected the myocardium against ISO-induced damage, 400 $mg \cdot kg^{-1} \cdot day^{-1}$ of curcumin was ineffective against damage. This may indicate that curcumin augments the endogenous antioxidant system at lower doses but mediates ROS induction at a higher concentration, leading to myocardial damage. Moreover, since this myocardial damage is an acute model and a high level of curcumin is needed compared with chronic models, relatively low-dose curcumin may be sufficient for a chronic heart failure model, such as MI- or hypertension-induced heart failure models. In our previous work, the plasma levels following native curcumin powder administration at 50 $mg \cdot kg^{-1}$ (10.7 ± 1.7 $ng \cdot mL^{-1}$), which was effective for heart failure, were higher than those following highly absorptive curcumin (Theracurmin®) administration at 0.5 $mg \cdot kg^{-1}$ (5.0 ± 2.4 $ng \cdot mL^{-1}$) (35, 43). However, the improvement of the LV systolic function is similar between native curcumin powder at 50 $mg \cdot kg^{-1}$ and Theracurmin® at 0.5 $mg \cdot kg^{-1}$ (27, 35). These data also indicate that plasma curcumin levels between 5.0 ± 2.4 and 10.7 ± 1.7 $ng \cdot mL^{-1}$ show almost the same effects on the systolic function after MI in rats. So, we consider that less than 50 $mg \cdot kg^{-1} \cdot day^{-1}$ of curcumin is sufficient to obtain maximum beneficial effects with fewer side effects. A more precise optimal dose-setting study of curcumin, to achieve maximum effects with fewer side effects, is needed to apply this therapy in a clinical setting (44).

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Conflicts of Interest

There is no conflict of interest in this study.

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