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Captopril Attenuates Matrix Metalloproteinase-2 and -9 in Monocrotaline-Induced Right Ventricular Hypertrophy in Rats

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Abstract. Little is known about the influence of angiotensin converting enzyme (ACE) inhibitors on matrix metalloproteinase (MMP) in right ventricular remodeling. We investigated the effect of captopril, an ACE inhibitor, on MMP-2 and MMP-9 in monocrotaline-induced right ventricular hypertrophy. Six-week-old male Wistar rats were injected intraperitoneally with monocrotaline (60 mg/kg) or saline. The rats were administrated captopril (30 mg/kg per day) or a vehicle orally for 24 days from the day of monocrotaline injection. At day 25, echocardiography was performed and hearts were excised. Expressions and activities of MMP-2 and MMP-9 were measured by Western blotting and by gelatin zymography, respectively. In monocrotaline-injected rats, right ventricular weight/tail length ratio increased significantly. Histological analysis revealed cardiomyocyte hypertrophy and fibrosis in right ventricular sections. Echocardiography showed right ventricular dysfunction compared with saline-injected rats. The right ventricular hypertrophy, fibrosis, and dysfunction were inhibited by captopril. However, captopril did not attenuate an increase in pulmonary artery pressure. MMP-2 and MMP-9 expressions and activities in right ventricles increased significantly in monocrotaline-injected rats and captopril inhibited them. These findings indicate that captopril attenuates the development of monocrotaline-induced right ventricular hypertrophy in association with inhibition of MMP-2 and MMP-9 in rats.

Keywords: angiotensin-converting enzyme inhibitor, captopril, matrix metalloproteinase, monocrotaline, right ventricular hypertrophy

Introduction

Heart failure or myocardial dysfunction is a major contributor to morbidity and mortality. The myocardial dysfunction and the attendant reduction of forward cardiac output lead to stimulation of neurohumoral systems, particularly the autonomic nervous and renin-angiotensin systems. These compensatory responses maintain blood flow to organs by increasing ventricular preload, enhancing myocardial contractility, and increasing arterial tone (1). However, each of these compensatory responses would also promote disease progression. The neurohumoral factors such as noradrenaline and angiotensin II may act directly on the myocardium to promote unfavorable remodeling by causing cardiomyocyte hypertrophy, fibrosis, and apoptosis (2). Inhibition of the renin-angiotensin system by angiotensin-converting enzyme (ACE) inhibitors can decrease pathological ventricular remodeling and mortality in patients with heart failure (3).

Matrix metalloproteinases (MMPs), a family of zinc-dependent proteinases, have an important role in the development of clinical and experimental cardiac diseases models through degradation of the extracellular matrix, whose functions include maintenance of tissue structure and retention of bioactive molecules (4, 5). Inhibition of MMPs by ACE inhibitors, MMP inhibitor, and gene deletion attenuated left ventricular remodeling (6 – 9). However, so far there is no direct evidence for a relationship between MMPs and ACE inhibitors in right

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ventricular remodeling.

Monocrotaline produces pulmonary hypertension by impairing the endothelium of pulmonary artery. The increased pulmonary arterial pressure by monocrotaline evokes right ventricular hypertrophy, fibrosis, and dysfunction (10 – 13). The development of monocrotaline-induced right ventricular hypertrophy was ameliorated by ACE inhibitors (14). MMP-2 and MMP-9 immunoreactivities were augmented in right ventricular hypertrophy induced by monocrotaline treatment in rats (15).

We hypothesized that ACE inhibitors might attenuate MMPs in monocrotaline-induced right ventricular hypertrophy. Therefore, the purpose of the present study was to evaluate the influence of captopril, a prototypical ACE inhibitor, on expressions and activities of MMP-2 and MMP-9 during the monocrotaline-induced right ventricular hypertrophy.

Materials and Methods

Animal models

All animals were cared for in accordance with the Kitasato University guidelines for animal treatment, which meet international guiding principles of laboratory animal care. Six-week-old male Wistar rats (Clea Japan, Inc., Tokyo) maintained on a standard laboratory diet and tap water and exposed to a 12/12 h light-dark cycle at 23°C were used in the experiments. Rats received a single intraperitoneal injection of monocrotaline (60 mg/kg; Wako Pure Chemical Industries, Ltd., Osaka). Monocrotaline was dissolved in 1 N HCl and neutralized with 1 N NaOH. Control rats were injected with saline (2.5 ml/kg). From the day of monocrotaline injection, captopril (30 mg/kg per day, Wako Pure Chemical Industries, Ltd.) or distilled water (1 ml/kg per day, as a vehicle) were administrated orally for 24 days.

Echocardiography

Echocardiography was performed at day 25 after monocrotaline injection under pentobarbital (50 mg/kg i.p.) anesthesia using SONOS 5500 (Hewlett-Packard Co., Andover, MA, USA) with a dynamically focused S12 probe (5 – 12 MHz. Hewlett Packard Co.). Pulsed Doppler of pulmonary artery flow velocity was recorded in the short axis view at the level of the aortic valve. Acceleration time was measured as the time it takes to reach the peak velocity from the starting velocity. Ejection time is the time period from the beginning to the end of pulmonary artery flow. Acceleration time/ejection time ratio was calculated as the index of pulmonary hypertension and right ventricular hypertrophy. Tricuspid annular plane systolic excursion, a parameter for right ventricular systolic function, was also measured. Briefly, tricuspid annular plane systolic excursion was measured in the M-mode from the apical four chamber view and it expresses the motion of tricuspid annulus.

Pulmonary artery pressure measurements

Pulmonary artery pressure was measured by the method of Rabinovitch et al. (16). Briefly, rats were anesthetized with pentobarbital (50 mg/kg, i.p.) and then the right jugular vein was exteriorized. Then catheter filled with a heparin-saline solution was inserted into right ventricle through the right jugular vein with a small incision and advanced into the pulmonary artery. The catheter was connected to the MLT0670 disposable BP transducer (ADInstruments, Colorado Springs, CO, USA), and pulmonary artery pressure was measured using a ML117 BP Amp (ADInstruments) and a ML825 PowerLab 2/25 (ADInstruments) system.

Histology

After echocardiographic examination, hearts were excised for histological and biochemical examinations. The hearts were separated into right and left atrial or ventricular tissues. Isolated ventricular tissues were weighed and fixed in 10% neutral buffered formalin, dehydrated, and embedded in paraffin. Thin tissue sections (2 μm) were made and deparaffinized by the standard procedure. Hematoxylin and eosin (H&E) staining and Azan staining were performed. For Azan staining, deparaffinized sections were immersed in 5% potassium dichromate solution for 30 min and stained with azocarmine G for 20 min. Then sections were immersed in 12-tungsto-(VI)-phosphoric acid n-hydrate solution for 1 h and stained with aniline blue-orange G for 30 min.

Western blot analysis

Western blotting was performed as described previously (17). Right ventricular samples were homogenized in lysis buffer [20 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM EDTA-2Na, 1 mM EGTA, 1% Triton, 2.5 mM sodium pyrophosphate, 1 mM β-glycerophosphate, 1 mM Na_3VO_4, 1 mg/ml leupeptin; Cell Signaling Technology Inc., Danvers, MA, USA] containing 1% protease inhibitor cocktail (Nacalai Tesque, Inc., Kyoto). The homogenates were centrifuged and the supernatant was used as soluble proteins. The soluble proteins (20 μg) were separated on 7.5% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a nitrocellulose membrane (Pall Co., Ann Arbor, MI, USA). After block-

Table 1. Effects of captopril on body weight, tail length, right ventricular weight, right ventricular weight / tail length ratio, left ventricular + interventricular septum weight, left ventricular + interventricular septum weight / tail length, and lung wet weight in control, monocrotaline-, monocrotaline + captopril-, and captopril-treated groups

	Control (n = 13)	Monocrotaline (n = 19)	Monocrotaline + Captopril (n = 17)	Captopril (n = 13)
Body weight (g)	307 ± 6	249 ± 5*	254 ± 4*	288 ± 4*,†
Tail length (cm)	16.0 ± 0.2	15.4 ± 0.1*	15.4 ± 0.1*	15.9 ± 0.1†
Right ventricular weight (mg)	160 ± 5	330 ± 13*	230 ± 11*,†	149 ± 4†
Right ventricular weight / tail length ratio (mg/cm)	10.0 ± 0.3	21.4 ± 0.9*	14.9 ± 0.7*,†	9.3 ± 0.2†
Left ventricular + interventricular septum weight (mg)	686 ± 14	664 ± 14	612 ± 12*,†	607 ± 11*,†
Left ventricular + interventricular septum weight / tail length ratio (mg/cm)	42.9 ± 0.7	43.2 ± 0.9	39.8 ± 0.8*,†	38.1 ± 0.6*,†
Lung wet weight (mg)	1219 ± 20	2200 ± 108*	1870 ± 70*,†	1158 ± 20†

Data are presented as the mean ± S.E.M. *P<0.05, compared with control; †P<0.05, compared with monocrotaline.

ing with 0.5% skim milk, the membranes were incubated with rabbit polyclonal antibodies against MMP-2 (Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA), MMP-9 (Millipore Co., Billerica, MA, USA), and mouse monoclonal antibody against actin (Sigma-Aldrich Co., St. Louis, MO, USA). HRP-conjugated anti rabbit IgG or anti mouse IgG was used for the secondary antibody. Signal detection was achieved using the ECL plus western blotting detection reagents (GE Healthcare Ltd., Buckinghamshire, UK) in the ATTO light capture system (AE-6972; ATTO Co., Tokyo).

Gelatin zymography

Soluble proteins (10 μg) were separated on 7.5% SDS-PAGE containing 1.8 mg/ml gelatin under non-reducing conditions. After incubating for 1 h in washing buffer [50 mM Tris-HCl (pH 7.5), 2.5% Triton X-100, 5 mM $CaCl_2$, 1 μM $ZnCl_2$] at room temperature, gels were incubated overnight in incubation buffer [50 mM Tris-HCl (pH 7.5), 5 mM $CaCl_2$, 1 μM $ZnCl_2$] at 37°C. Then the gels were stained with 0.1% Coomassie Blue G-250 and destained with ion-exchanged water until bands were visible. MMP activity was presented as an unstained band in comparison with MMP standards (Sigma-Aldrich Co.).

Statistical analyses

All values are expressed as means ± S.E.M. Statistical analyses were performed by one-way ANOVA followed by Tukey's post-hoc test. A value of P<0.05 was considered significant.

Results

Biometrical changes

Table 1 shows the biometrical changes of the animals at day 25 after monocrotaline-injection. Body weights decreased significantly in the monocrotaline group compared with the control (P<0.05). Captopril treatment did not prevent the body weight loss (P<0.05 *vs* control). Body weight in the captopril alone group was less than that in the control (P<0.05), but significantly higher than that in the monocrotaline group (P<0.05). Right ventricular weight was corrected by tail length. Right ventricular weight/tail length ratio increased by about 2-fold in the monocrotaline group compared with the control (P<0.05). Right ventricular weight/tail length ratio for captopril alone was similar to the control. This ratio was significantly decreased with monocrotaline + captopril (P<0.05 *vs* monocrotaline). While the sum of left ventricular and interventricular septum weight / tail length ratio was not different between the control and monocrotaline group, it significantly decreased with monocrotaline + captopril or captopril alone (P<0.05 *vs* control). Lung wet weight increased in the monocrotaline group (P<0.05 *vs* control) but not in the captopril alone group compared with the control. This increase was significantly prevented in the group treated with monocrotaline + captopril (P<0.05 *vs* monocrotaline).

Histological analysis

H&E and Azan staining in the sections revealed that hypertrophy and fibrosis of right ventricular myocardium were induced by monocrotaline (Fig. 1: C and D). Captopril treatment inhibited hypertrophy (Fig. 1E) and attenuated fibrosis (Fig. 1F). No histological abnormality was observed in the captopril alone group (Fig. 1: G and H).

Echocardiography

Assessment of right ventricular functional change was done by echocardiography. Acceleration of pulmonary artery flow velocity was a characteristic change of the wave form in the monocrotaline group (Fig. 2a: B). The

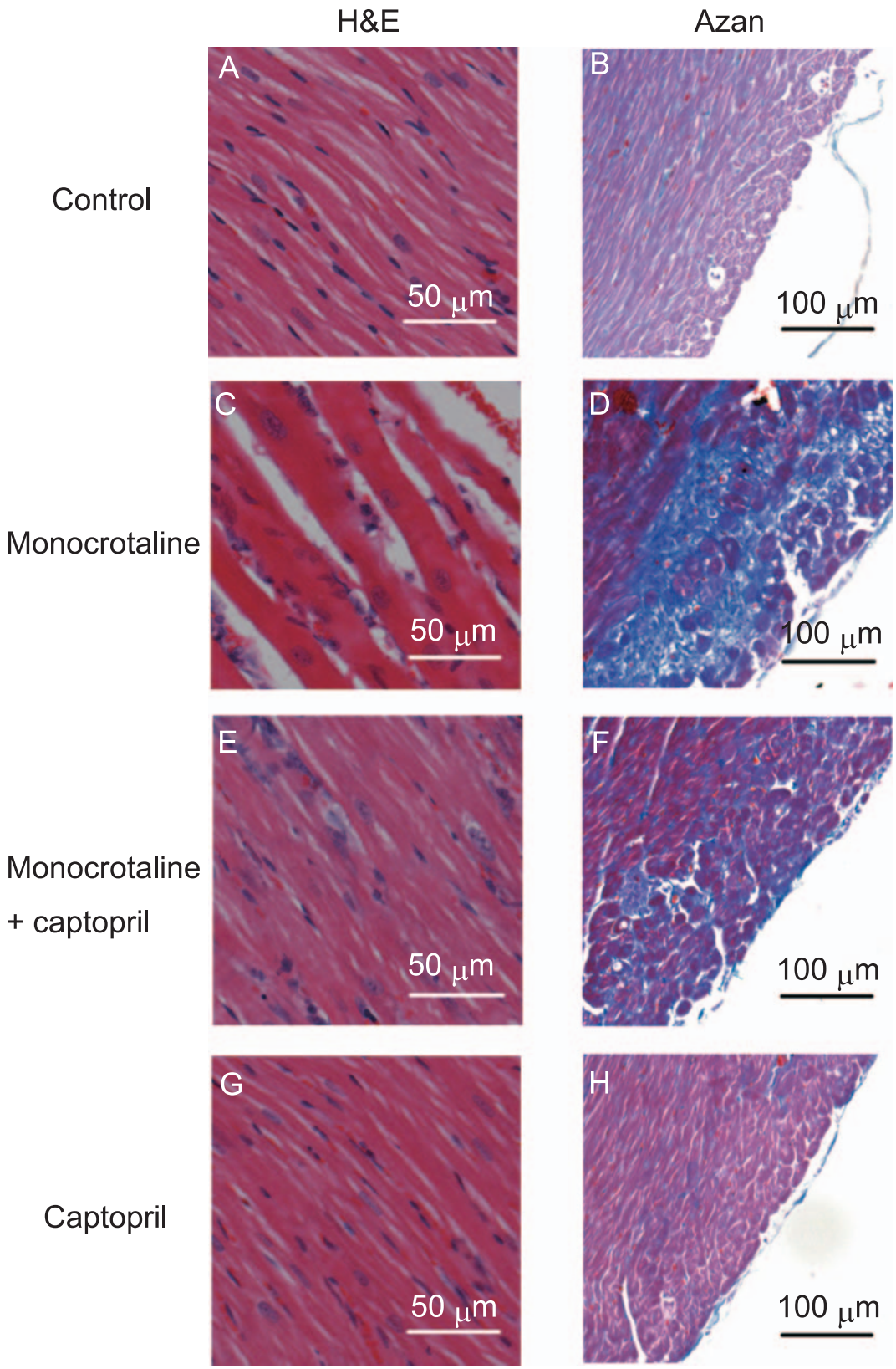

Fig. 1. Effect of captopril on monocrotaline-induced cardiomyocyte hypertrophy and fibrosis in rat right ventricle. Representative sections from the right ventricle of control (A and B), monocrotaline-treated (C and D), monocrotaline + captopril-treated (E and F), and captopril alone-treated (G and H) groups are shown. A, C, E, and G were stained with Hematoxylin and eosin (H&E) (Scale bars represent 50 μm). B, D, F, and H were stained with Azan (Scale bars represent 100 μm).

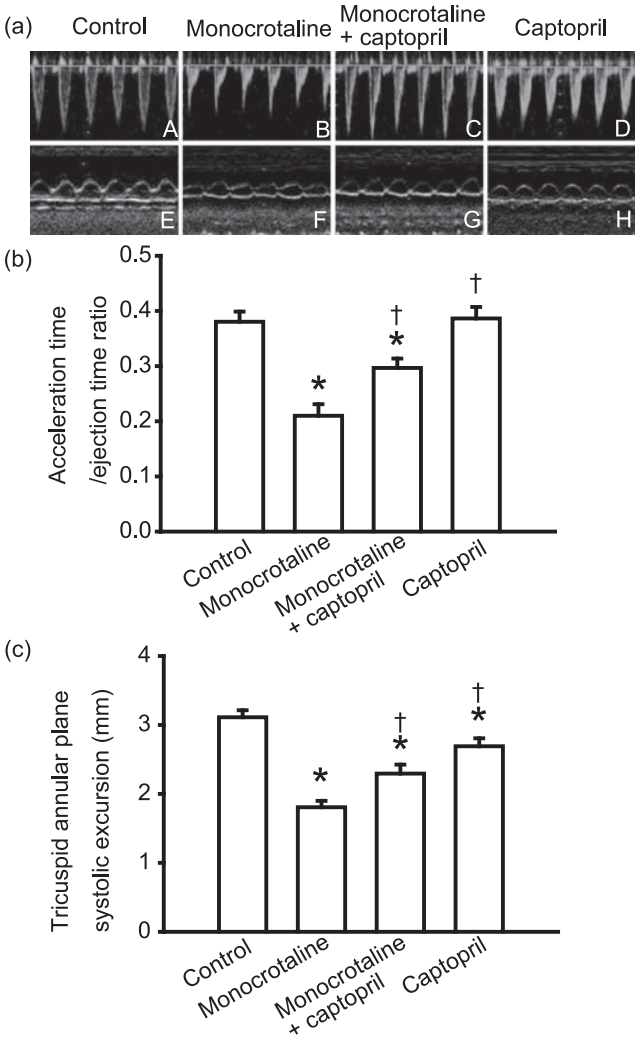

Fig. 2. Effect of captopril on monocrotaline-induced right ventricular dysfunction. a: Representative pulsed Doppler of pulmonary artery flow in the short axis view at the level of the aortic valve (A – D) and the motion of tricuspid annulus in M-mode echocardiography from the apical four chamber view (E – H) in control (A and E), monocrotaline-treated (B and F), monocrotaline + captopril-treated (C and G), and captopril alone-treated (D and H) groups. b: Acceleration time/ejection time ratio of pulmonary artery flow (control, n = 14; monocrotaline, n = 12; monocrotaline + captopril, n = 15; captopril, n = 13). c: Tricuspid annular plane systolic excursion (control, n = 14; monocrotaline, n = 10; monocrotaline + captopril, n = 13; captopril, n = 11). Data are shown as means ± S.E.M. **P*<0.05, compared with the control; †*P*<0.05, compared with monocrotaline.

wave forms in the monocrotaline + captopril group and captopril alone group were similar to those in the control (Fig. 2a: C and D). Acceleration time/ejection time ratio in the group treated with monocrotaline (0.210 ± 0.021, n = 12, *P*<0.05) decreased significantly compared with the control (0.380 ± 0.018, n = 14). In monocrotaline + captopril group, acceleration time/ejection time ratio significantly increased compared with monocrotaline (0.300 ± 0.017, n = 15, *P*<0.05 *vs* monocrotaline). Acceleration time/ejection time ratio in the group treated with captopril alone was similar to the control (0.386 ± 0.021, n = 13) (Fig. 2b). We next examined tricuspid annular plane systolic excursion to assess right ventricular systolic function (Fig. 2a: E – H). Tricuspid annular plane systolic excursion decreased significantly in monocrotaline group (1.81 ± 0.09 mm, n = 10, *P*<0.05) compared with the control (3.11 ± 0.10 mm, n = 14). This decrease was inhibited significantly in the monocrotaline + captopril group (2.29 ± 0.13 mm, n = 13, *P*<0.05 *vs* monocrotaline). Tricuspid annular plane systolic excursion in the group treated with captopril alone was decreased significantly compared with the control (2.69 ± 0.12 mm, n = 11, *P*<0.05) (Fig. 2c).

Pulmonary artery pressure

Pulmonary artery pressure was increased significantly in the monocrotaline group (41.4 ± 0.8 mmHg, n = 4, *P*<0.05) compared with the control (23.0 ± 0.8 mmHg, n = 6). Captopril did not attenuate the increase in pulmonary artery pressure by monocrotaline (39.2 ± 1.2 mmHg, n = 3). Captopril alone had no effect on pulmonary artery pressure (21.6 ± 1.3 mmHg, n = 5).

MMP-2 and MMP-9 expressions

Western blot analysis showed that MMP-2 and MMP-9 expressions increased significantly in the monocrotaline group (408 ± 41% and 248 ± 35% respectively, n = 19, *P*<0.05) compared with the control (n = 13). Captopril treatment significantly inhibited MMP-2 expression (277 ± 44%, n = 17, *P*<0.05 *vs* monocrotaline) and reversed MMP-9 expression (153 ± 22%, n = 17, *P*<0.05 *vs* monocrotaline) to a similar level in the control. Captopril alone had no effect on MMP-2 and MMP-9 expressions (116 ± 18% and 84 ± 8% respectively, n = 13) (Fig. 3.).

MMP-2 and MMP-9 activities

Gelatin zymography was used to determine the effect of captopril on MMP-2 and MMP-9 activities in monocrotaline-induced right ventricular hypertrophy. Both MMP-2 and MMP-9 activities increased significantly with monocrotaline (149 ± 5% and 268 ± 23% respectively, n = 19, *P*<0.05), compared with the control (n = 13). The increased MMP-9 activity was significantly decreased by captopril to a similar level in the control (148 ± 17%, n = 17, *P*<0.05 *vs* monocrotaline). The increased MMP-2 activity tended to decline by captopril treatment (132 ± 6%, n = 17), but the effect was not significant. Captopril alone had no effect on MMP-2 and MMP-9 activities (111 ± 7% and 91 ± 7%, n = 13) (Fig. 4.).

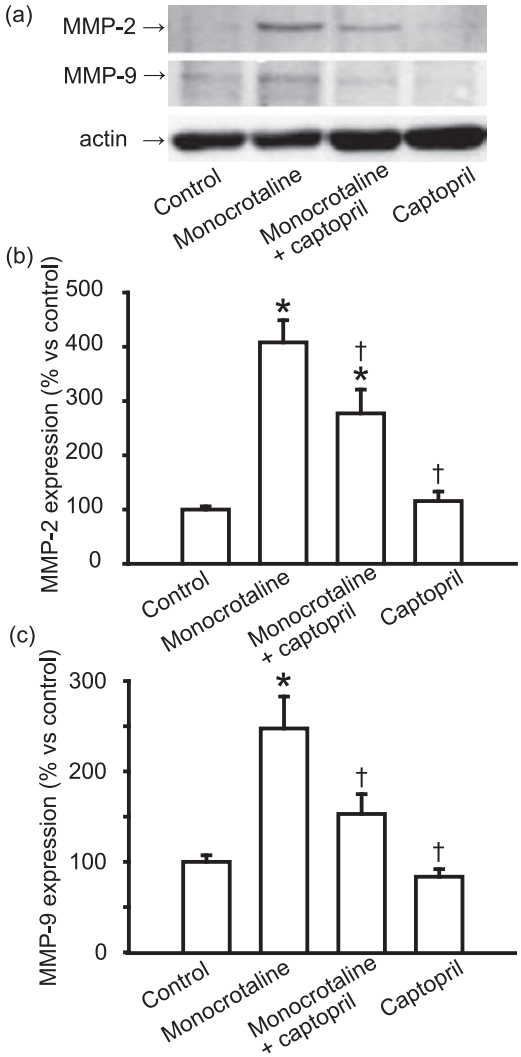

Fig. 3. Effect of captopril on monocrotaline-induced MMP-2 and MMP-9 expressions in rat right ventricle. a: Representative blots for MMP-2 and MMP-9 in control, monocrotaline-treated, monocrotaline + captopril-treated, and captopril alone-treated groups are shown. Equal loading of protein was confirmed with anti-actin antibody. Levels of MMP-2 (b) and MMP-9 (c) expressions relative to the control are shown as means ± S.E.M. (control, n = 13; monocrotaline, n = 19; monocrotaline + captopril, n = 17; captopril, n = 13). **P*<0.05, compared with control; †*P*<0.05, compared with monocrotaline.

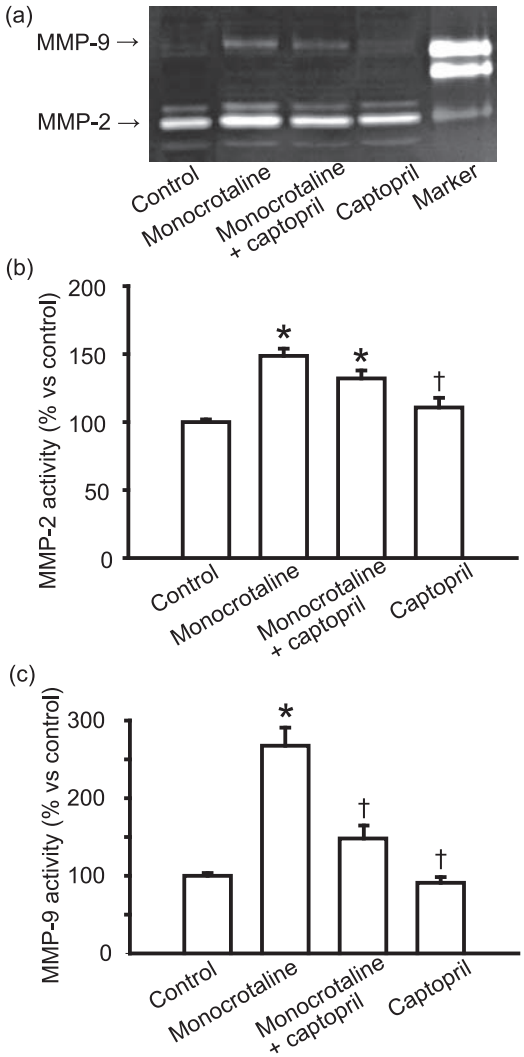

Fig. 4. Effect of captopril on monocrotaline-induced MMP-2 and MMP-9 activities in rat right ventricle. a: Representative zymograms for MMP-2 and MMP-9 in control, monocrotaline-treated, monocrotaline + captopril-treated, and captopril alone-treated groups. Marker: Positive control of MMP-2 and MMP-9. Activities of MMP-2 (b) and MMP-9 (c) relative to the control are shown as means ± S.E.M. (control, n = 13; monocrotaline, n = 19; monocrotaline + captopril, n = 17; captopril, n = 13). **P*<0.05, compared with control; †*P*<0.05, compared with monocrotaline.

Discussion

The main findings of this study are that increased expressions and activities of MMP-2 and MMP-9 in monocrotaline-induced hypertrophied right ventricle in rats are attenuated by long-term treatment with captopril. Consistently, captopril suppressed monocrotaline-induced right ventricular hypertrophy, fibrosis, and dysfunction. Thus we suggest that captopril may attenuate MMP-2 and MMP-9 during the development of monocrotaline-induced right ventricular hypertrophy in rats. To the best of our knowledge, this is a novel finding about the effects of captopril against MMPs in monocrotaline-induced right ventricular hypertrophy.

Right ventricular hypertrophy induced by single intraperitoneal injection of 60 mg/kg monocrotaline is confirmed by the increases in right ventricular weight/tail length ratio and lung wet weight. Histological analysis further revealed the cardiomyocyte hypertrophy and fibrosis in the right ventricles of monocrotaline-treated rats. These features are generally confirmative of the previous reports (10 – 13, 18 – 20).

Additionally, it has been reported that enalapril, an ACE inhibitor, attenuated monocrotaline-induced right ventricular hypertrophy (14). Consistent with the reports, the present results showed that captopril inhibits monocrotaline-induced right ventricular hypertrophy as well as fibrosis. Left ventricle + interventricular septum weight / tail length ratio was decreased by captopril in our experiment, which might be due to decrease in the body weight by captopril. In fact, the ratio of left ventricle + interventricular septum weight/body weight was similar to that of the control (data not shown).

Pulsed Doppler images revealed acceleration of pulmonary artery flow velocity and significant decrease in acceleration time/ejection time ratio in the monocrotaline-injected rats. Jones et al. (18) observed similar acceleration of pulmonary artery flow velocity in the monocrotaline-induced rat right ventricular hypertrophy model. They suggested that this acceleration is a characteristic feature of pulmonary hypertension. Shortening of acceleration time/ejection time ratio is used for a marker of pulmonary hypertension and it well correlates with the degree of right ventricular hypertrophy (19). Hardziyenka et al. (20) demonstrated that tricuspid annular plane systolic excursion was significantly decreased in monocrotaline-induced right ventricular failure in rats. Right ventricular systolic function was evaluated by measuring tricuspid annular plane systolic excursion in our experiment. Monocrotaline significantly decreased tricuspid annular plane systolic excursion. Captopril treatment suppressed this change. There are controversial reports about the influence of ACE inhibitor on monocrotaline-induced pulmonary hypertension. van Suylen et al. (21) reported that captopril has no significant effect on pulmonary artery pressure in monocrotaline-treated rats. On the other hand, Kanno et al. (14) reported that enalapril attenuated pulmonary hypertension. The present study showed that increased mean pulmonary artery pressure by monocrotaline was not attenuated by captopril. From these results, it is suggested that captopril may attenuate monocrotaline-induced right ventricular hypertrophy and functional disorder without affecting pulmonary artery pressure. Captopril itself decreased tricuspid annular plane systolic excursion in the present study. Although the decrease might be derived from reduction in body weight, the precise mechanisms remain unclear.

Several studies have reported that MMPs have critical roles in the development of cardiac hypertrophy and heart failure via extracellular matrix remodeling (22 – 25). MMP-2 and MMP-9 degrade many components of extracellular matrices, including type IV collagen, laminin, and fibronectin. MMP-2 and MMP-9 are highly expressed in the process of ventricular remodeling in several cardiovascular diseases, including heart failure, cardiomyopathy, and ventricular hypertrophy (5). A recent study showed that MMP-2 and MMP-9 immunoreactivities are upregulated in monocrotaline-induced hypertrophied right ventricles (15). Consistent with the reports, we found that MMP-2 and MMP-9 protein expressions as well as activities were significantly increased in monocrotaline-induced hypertrophied right ventricular tissues. Various agents including bioactive molecules, cytokines, chemokines, and growth factors stimulate induction of MMPs (26). Angiotensin II is one of the major bioactive molecules in cardiac remodeling. Angiotensin II elicits biologic functions via binding to AT1 receptor. Activation of AT1 receptor leads to the stimulation of transcription factors such as activator protein-1 (AP-1) and nuclear factor-kappaB (NF-κB) (26). In addition, both MMP-2 and MMP-9 genes have AP-1 and NF-κB binding sites in their promoters (27 – 29). Thus it is possible to speculate that angiotensin II activates MMP transcription during cardiac remodeling and that ACE inhibitors prevent MMP induction via inhibiting angiotensin II production. On the other hand, recent studies suggest that ACE inhibitors prevent MMP-2 and MMP-9 activities directly (9, 30). We demonstrated that captopril treatment significantly inhibits the expression and activity of MMP-9 and the expression of MMP-2. It has not also been clarified whether ACE inhibitors directly affect the heart or indirectly influence it by improving hemodynamics in cardiac disease (31). In the present study, captopril attenuated monocrotaline-induced cardiac hypertrophy without affecting pulmonary artery pressure. Thus captopril may directly inhibit MMP-2 and MMP-9 during the development of monocrotaline-induced right ventricular hypertrophy.

In summary, captopril attenuates MMP-2 and MMP-9 expressions and activities during monocrotaline-induced right ventricular hypertrophy, fibrosis, and dysfunction in rats. Further study is necessary to elucidate the mechanisms through which captopril attenuates these MMPs.

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References

1 Willenbrock R, Philipp S, Mitrovic V, Dietz R. Neurohumoral blockade in CHF management. J Renin Angiotensin Aldosterone Syst. 2000;Suppl 1:24–30.

2 Zhu YC, Zhu YZ, Lu N, Wang MJ, Wang YX, Yao T. Role of angiotensin AT1 and AT2 receptors in cardiac hypertrophy and cardiac remodeling. Clin Exp Pharmacol Physiol. 2003;30:911–918.
3 Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation. 1998;97:1411–1420.
4 Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases structure, function, and biochemistry. Circ Res. 2003;92:827–839.
5 Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev. 2007;87:1285–1342.
6 Peterson JT, Hallak H, Johnson L, Li H, O'Brien PM, Sliskovic DR, et al. Matrix metalloproteinase inhibition attenuates left ventricular remodeling and dysfunction in a rat model of progressive heart failure. Circulation. 2001;103:2303–2309.
7 Reinhardt D, Sigusch HH, Hensse J, Tyagi SC, Körfer R, Figulla HR. Cardiac remodeling in end stage heart failure: upregulation of matrix metalloproteinase (MMP) irrespective of the underlying disease, and evidence for a direct inhibitory effect of ACE inhibitors on MMP. Heart. 2002;88:525–530.
8 Hayashidani S, Tsutsui H, Ikeuchi M, Shiomi T, Matsusaka H, Kubota T, et al. Targeted deletion of MMP-2 attenuates early LV rupture and late remodeling after experimental myocardial infarction. Am J Physiol Heart Circ Physiol. 2003;285:H1229–H1235.
9 Brower GL, Levick SP, Janicki JS. Inhibition of matrix metalloproteinase activity by ACE inhibitors prevents left ventricular remodeling in a rat model of heart failure. Am J Physiol Heart Circ Physiol. 2007;292:H3057–H3064.
10 Ghodsi F, Will JA. Changes in pulmonary structure and function induced by monocrotaline intoxication. Am J Physiol. 1981;240:H149–H155.
11 Chen L, Gan XT, Haist JV, Feng Q, Lu X, Chakrabarti S, et al. Attenuation of compensatory right ventricular hypertrophy and heart failure following monocrotaline-induced pulmonary vascular injury by the Na^+-H^+ exchange inhibitor cariporide. J Pharmacol Exp Ther. 2001;298:469–476.
12 Kögler H, Hartmann O, Leineweber K, Nguyen van P, Schott P, Brodde OE, et al. Mechanical load-dependent regulation of gene expression in monocrotaline-induced right ventricular hypertrophy in the rat. Circ Res. 2003;93:230–237.
13 Hessel MH, Steendijk P, den Adel B, Schutte CI, van der Laarse A. Characterization of right ventricular function after monocrotaline-induced pulmonary hypertension in the intact rat. Am J Physiol Heart Circ Physiol. 2006;291:H2424–H2430.
14 Kanno S, Wu YJ, Lee PC, Billiar TR, Ho C. Angiotensin-converting enzyme inhibitor preserves p21 and endothelial nitric oxide synthase expression in monocrotaline-induced pulmonary arterial hypertension in rats. Circulation. 2001;104:945–950.
15 Umar S, Hessel M, Steendijk P, Bax W, Shutte C, Schalij M, et al. Activation of signaling molecules and matrix metalloproteinases in right ventricular myocardium of rats with pulmonary hypertension. Pathol Res Pract. 2007;203:863–872.
16 Rabinovitch M, Gamble W, Nadas AS, Miettinen OS, Reid L. Rat pulmonary circulation after chronic hypoxia: hemodynamic and structural features. Am J Physiol. 1979;236:H818–H827.
17 Yamawaki H, Iwai N. Cytotoxicity of water-soluble fullerene in vascular endothelial cells. Am J Physiol Cell Physiol. 2006;290:C1495–C1502.
18 Jones JE, Mendes L, Rudd MA, Russo G, Loscalzo J, Zhang YY. Serial noninvasive assessment of progressive pulmonary hypertension in a rat model. Am J Physiol Heart Circ Physiol. 2002;283:H364–H371.
19 Kato Y, Iwase M, Kanazawa H, Kawata N, Yoshimori Y, Hashimoto K, et al. Progressive development of pulmonary hypertension leading to right ventricular hypertrophy assessed by echocardiography in rats. Exp Anim. 2003;52:285–294.
20 Hardziyenka M, Campian ME, de Bruin-Bon HA, Michel MC, Tan HL. Sequence of echocardiographic changes during development of right ventricular failure in rat. J Am Soc Echocardiogr. 2006;19:1272–1279.
21 van Suylen RJ, Smits JF, Daemen MJ. Pulmonary artery remodeling differs in hypoxia- and monocrotaline-induced pulmonary hypertension. Am J Respir Crit Care Med. 1998;157:1423–1428.
22 Spinale FG, Coker ML, Heung LJ, Bond BR, Gunasinghe HR, Etoh T, et al. A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure. Circulation. 2000;102:1944–1949.
23 Polyakova V, Hein S, Kostin S, Ziegelhoeffer T, Schaper J. Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression. J Am Coll Cardiol. 2004;44:1609–1618.
24 Kizaki K, Ito R, Okada M, Yoshioka K, Uchide T, Temma K, et al. Enhanced gene expression of myocardial matrix metalloproteinases 2 and 9 after acute treatment with doxorubicin in mice. Pharmacol Res. 2006;53:341–346.
25 Graham HK, Trafford AW. Spatial disruption and enhanced degradation of collagen with the transition from compensated ventricular hypertrophy to symptomatic congestive heart failure. Am J Physiol Heart Circ Physiol. 2007;292:H1364–H1372.
26 Deschamps AM, Spinale FG. Pathways of matrix metalloproteinase induction in heart failure: bioactive molecules and transcriptional regulation. Cardiovasc Res. 2006;69:666–676.
27 Bergman MR, Cheng S, Honbo N, Piacentini L, Karliner JS, Lovett DH. A functional activating protein 1 (AP-1) site regulates matrix metalloproteinase 2 (MMP-2) transcription by cardiac cells through interactions with JunB-Fra1 and JunB-FosB heterodimers. Biochem J. 2003;369:485–496.
28 Xie Z, Singh M, Singh K. Differential regulation of matrix metalloproteinase-2 and -9 expression and activity in adult rat cardiac fibroblasts in response to interleukin-1β. J Biol Chem. 2004;279:39513–39519.
29 Suh SJ, Jin UH, Kim SH, Chang HW, Son JK, Lee SH, et al. Ochnaflavone inhibits TNF-α-induced human VSMC proliferation via regulation of cell cycle, ERK1/2, and MMP-9. J Cell Biochem. 2006;99:1298–1307.
30 Takai S, Yamamoto D, Jin D, Inagaki S, Yoshikawa K, Tanaka K, et al. Inhibition of matrix metalloproteinase-9 activity by lisinopril after myocardial infarction in hamsters. Eur J Pharmacol. 2007;568:231–233.
31 Miyazaki M, Takai S. Tissue angiotensin II generating system by angiotensin-converting enzyme and chymase. J Pharmacol Sci. 2006;100:391–397.