Enhanced cardiac production of matrix metalloproteinase-2 and -9 and its attenuation associated with pravastatin treatment in patients with acute myocardial infarction

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ABSTRACT

Previous experimental studies have demonstrated that MMPs (matrix metalloproteinases) contribute to LV (left ventricular) remodelling. We hypothesized that cardiac MMPs are activated in patients with AMI (acute myocardial infarction) and, if so, MMP production may be attenuated by statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) through their cardiovascular protective actions. We studied 30 patients, ten control patients with stable angina pectoris and 20 patients with AMI, in whom LV catheterization at the chronic stage was performed 22 ± 12 days (value is mean $\pm$ S.D.) after the onset of AMI. Blood samples were collected from the CS (coronary sinus) and a peripheral artery. In patients with AMI, the levels of MMP-2 and MMP-9 were significantly ($P < 0.05$) higher in the CS than the peripheral artery (MMP-2, 853 ± 199 compared with 716 ± 127 ng/ml; MMP-9, 165 ± 129 compared with 98 ± 82 ng/ml), whereas no significant differences were observed in the patients with angina pectoris. The CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with BNP (brain natriuretic peptide) levels (MMP-2, $R = 0.68$, $P < 0.01$; MMP-9, $R = 0.59$, $P < 0.05$) and LV end-diastolic volume index (MMP-2, $R = 0.70$, $P < 0.01$; MMP-9, $R = 0.70$, $P < 0.01$). When patients with AMI treated with 10 mg of pravastatin or without ($n = 10$ in each group) were compared, this statin therapy significantly ($P < 0.05$) decreased the CS–arterial concentration gradients of MMP-2 (69 ± 43 compared with 213 ± 185 ng/ml) and MMP-9 (14 ± 27 compared with 119 ± 84 ng/ml). In conclusion, the enhanced production of cardiac MMP-2 and MMP-9 is associated with LV enlargement and elevated BNP levels in patients with AMI. A pleiotropic effect of statins appears to be associated with the modulation of cardiac MMP activation, which may be potentially beneficial in the attenuation of post-infarction LV remodelling.

Key words: acute myocardial infarction, angina pectoris, brain natriuretic peptide (BNP), metalloproteinase (MMP), remodelling, statin, tissue inhibitor of metalloproteinases (TIMP).

Abbreviations: ACE-I, angiotension-converting enzyme inhibitor; AMI, acute myocardial infarction; Ang II, angiotensin II; AP, angina pectoris; BNP, brain natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; CS, coronary sinus; LDL, low-density lipoprotein; LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinases; WBC, white blood cell.

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INTRODUCTION

The loss of myocytes as a consequence of AMI (acute myocardial infarction) results in progressive changes in ventricular architecture [1,2]. This process, defined as post-infarction ventricular remodelling, is associated with a higher mortality and a higher incidence of complications, such as the development of heart failure, aneurysm formation and ventricular rupture [3,4]. During the remodelling process, as well as intrinsic changes in cardiac myocytes, it has been recognized that important alterations also occur within the extracellular matrix of the myocardium [5,6].

MMPs (matrix metalloproteinases) belong to a family of zinc-containing endoproteinases responsible for extracellular protein degradation, and are inhibited by specific tissue inhibitors [TIMP (tissue inhibitor of metalloproteinases)] [5,6]. In experimental myocardial infarction, MMPs are up-regulated in myocardial tissues, and are the driving force in extracellular matrix remodelling and infarct expansion [7,8]. Among the MMPs, the importance of MMP-9 during the processes of infarct healing and LV (left ventricular) remodelling has been demonstrated in previous studies using genetically modified mice [9,10]. Infarcted mice with the targeted deletion of MMP-9 had a decreased incidence of early myocardial rupture [9] and progressive LV dilation [10]. However, in the clinical setting, there has been little evidence regarding the production of MMPs in the infarcted human heart.

Statins have various cardiovascular protective actions, including anti-inflammatory and anti-apoptotic actions, independent of their effects on cholesterol levels. A study using a mouse AMI model demonstrated that statin treatment attenuated LV remodelling [11], which was associated with decreased MMP activity [12].

In the present study, we hypothesized that cardiac MMP activation may be associated with the degree of LV enlargement and the level of BNP (brain natriuretic peptide), a biochemical marker of post-infarction remodelling [13,14]. If so, MMP production may be attenuated by statin treatment in patients with AMI.

MATERIALS AND METHODS

Patients

This study included 30 male patients. All of the patients gave their written informed consent prior to participation in the study. The Institutional Ethical Committee on Human Research approved the study protocol. Patients with the following disorders were excluded from the study: prior myocardial infarction, and liver (elevated activities of aminotransferases), kidney (elevated level of creatinine or urea) or lung dysfunction (restrictive or obstructive pattern in spirometry).

The control group consisted of ten patients with stable AP (angina pectoris), who complained of symptoms consistent with Canadian Cardiovascular Society Classification of angina level I, II or III, with evidence of myocardial ischaemia. All of the control patients had no evidence of a previous AMI, and had severe coronary artery stenosis and therefore underwent coronary angioplasty (with adjunctive stenting in five patients). The treated sites were the left anterior descending artery in four patients (40 %), the right or left circumflex artery in four patients (40 %), and both the left anterior descending and right coronary arteries in two patients (20 %).

We also studied 20 patients with AMI who fulfilled the following criteria: typical chest pain >30 min of duration, ST segment elevation > 0.1 mV in two or more ECG leads with the subsequent evolution of a typical infarct pattern, and increased serum CK (creatine kinase) level. A total of 14 patients underwent PTCA (percutaneous transluminal coronary angioplasty) of the infarct-related artery (with adjunctive stenting in nine patients), and the remaining six patients received an intravenous administration of a tissue-type plasminogen activator and/or heparin in the acute phase. In all the patients, coronary angiography immediately after treatment showed a TIMI 3 grade flow in the infarct-related artery. The elapsed time to reperfusion was 4.6 h on average. The infarct sites were in the anterior wall in ten patients (50 %), the inferior wall in seven patients (35 %) and the postero-lateral wall in three patients (15 %). In this study, all of the patients with AMI were treated with the ACE-I (angiotension-converting enzyme inhibitor) enalapril (5 mg) after their hospital admission. Among them, ten patients with hyperlipidaemia (total cholesterol level > 220 mg/dl) were treated with 10 mg of pravastatin; the remaining ten patients did not have hyperlipidaemia and thus did not receive pravastatin. A recent Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial [14a] has shown a similar decrease in coronary artery disease incidence following treatment with 10–20 mg of pravastatin used in Asia to that observed for 20–40 mg doses used in Europe and the United States.

Cardiac catheterization and analysis of LV function

In patients with AMI, chronic-stage cardiac catheterization was repeated approx. 3–4 weeks after the onset of AMI. A 5 French multipurpose catheter (Cathex) was introduced into the CS (coronary sinus) through the left subclavian vein under fluoroscopic guidance [14]. The position of the catheter tip was confirmed by the injection of contrast medium. Blood samples were collected from the CS before the intravenous administration of heparin. Following the collection of blood samples from the right brachial artery (as peripheral blood samples) through a 6 French sheath, heparin was administered and coronary

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angiography and left ventriculography were performed, according to the conventional Judkins' technique. LV pressure was measured using a 2 French high-fidelity micromanometer catheter (Miller Instruments) advanced into the left ventricle via the lumen of a 6 French pig-tail catheter. The restenosis of a treated artery was defined as an arterial narrowing of $>75\%$, as determined by coronary angiography.

LV volume was evaluated angiographically by a cardiologist who was blinded to the results of the biochemical assays. Ventricular silhouettes in a 30° right anterior oblique projection were digitized using an ANCHOR ventriculography analysis system (Siemens-Elema). Using the area-length method, LV end-systolic volume index, LVEDVI (LV end-diastolic volume index) and LVEF (LV ejection fraction) were calculated.

Biochemical assessment

Blood samples were centrifuged and serum was stored at $-80\,^{\circ}C$ until assay. A sandwich enzyme immunoassay was performed to determine MMP-2 level (Fuji Chemical Industries) [15]. In addition, the level of MMP-9, another gelatinase-like MMP-2, and that of MMP-13, an interstitial collagenase, were analysed using MMP Biotrak enzyme-linked immunoadsorbent assay kits (Amersham Biosciences). The levels were back-calculated from the standard curve determined with the enzyme-linked immunoadsorbent assay kits using a 96-well microplate reader (Emax; Molecular Devices). These kits detect the pro-enzyme and the pro-enzyme complexed with TIMP. The detection limits were 0.5 ng/ml for MMP-2, 0.6 ng/ml for MMP-9 and 0.03 ng/ml for MMP-13.

We also measured levels of TIMP-1 (Fuji Chemical Industries) and TIMP-2 (Amersham Biosciences) using sandwich enzyme immunoassays [15]. The detection limits for TIMP-1 and TIMP-2 were 1.2 and 8.0 ng/ml respectively.

BNP was measured using specific immunoradiometric assay kits (Shionogi). The sensitivity of these kits was 2 pg/ml. Ang II (angiotensin II) and TGF-β (transforming growth factor-β) levels were also measured, as reported previously [16].

The serum CRP (C-reactive protein) level was measured by N Latex CRP II monoassay using a nephelometric analyser (BN II; Dade Behring). The lower detection limit of this test was 0.06 mg/dl. Total cholesterol, triacylglycerol (triglyceride) and HDL (high-density lipoprotein) cholesterol concentrations were determined by enzymatic methods using a Toshiba TBA 80M analyser. LDL (low-density lipoprotein) was calculated using Fredewald's formula. We also measured WBC (white blood cell) number.

Statistical analysis

The two groups were compared by Student's t test. Measurements from the CS and the peripheral artery were compared within a group by ANOVA. When a significant difference among groups was indicated by the initial analysis, individual paired comparisons were determined using the Student–Newman–Keuls method. A linear regression line was calculated by the least-square method to assess the correlation between two parameters. To investigate independent predictors, we used multivariate logistic regression analysis. In all cases, differences were considered significant at $P<0.05$. Results are presented as means $\pm$ S.D., or medians.

Table 1 Clinical characteristics

$^{*}P=0.05$ and $^{**}P<0.01$ compared with control (patients with stable AP).

Characteristic	Patients with AMI ($n=20$)	Patients with stable AP ($n=10$)
Age (years)	66 ± 9	67 ± 6
Peak CK (units/l)	1986 (801–8574)	—
Cardiac function		
LVEF (%)	$48\pm7^{**}$	58 ± 7
LVEDVI (ml/m^2)	$95\pm18^{**}$	55 ± 21
Vessels $>75\%$ stenosed (n)	1.5 ± 0.7	1.6 ± 0.7
Risk factors (n)		
Hypertension	11 (55%)	7 (70%)
Diabetes mellitus	15 (75%)	6 (60%)
Hyperlipidaemia	10 (50%)	6 (60%)
Smoking	12 (60%)	6 (60%)
Biochemical parameters†		
Total cholesterol (mg/dl)	193 ± 27	198 ± 20
LDL (mg/dl)	120 ± 30	122 ± 31
WBC count (cells/μl)	6615 ± 1571	5600 ± 1063
CRP (mg/dl)	$0.34\pm0.33^{*}$	0.13 ± 0.06
Medication used (n)		
ACE-I	20 (100%)	4 (40%)
β-Blockers	11 (55%)	6 (60%)
Statins	10 (50%)	6 (60%)
Calcium antagonists	7 (35%)	5 (50%)
Nitrates	4 (20%)	2 (20%)
Aspirin	20 (100%)	10 (100%)

† Data obtained on the day when cardiac catheterization was performed.

RESULTS

The baseline clinical characteristics of the patients with AMI and the control patients with AP (without evidence of AMI) are summarized in Table 1. In the patients with AMI, cardiac function data were obtained at chronic-stage cardiac catheterization performed 22 ± 12 days after the onset of AMI. Coronary angiography revealed 90% stenosis of the infarct-related artery in two patients and 100% stenosis in three patients. These five patients with restenosis had received intravenous thrombolysis alone in the acute stage. In the remaining 15 patients, the treated

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Table 2 Comparisons of BNP, MMP and TIMP levels in the CS and peripheral artery

*$P < 0.05$ compared with levels in artery; †$P < 0.05$ compared with control (patients with stable AP).

	Patients with AMI ($n = 20$)		Patients with stable AP ($n = 10$)	
Peptide	CS	Artery	CS	Artery
BNP (pg/ml)	400 ± 376*†	126 ± 176	54 ± 25	52 ± 25
MMP-2 (ng/ml)	853 ± 199*†	716 ± 127	631 ± 44	630 ± 46
MMP-9 (ng/ml)	165 ± 129*†	98 ± 82	68 ± 25	71 ± 24
MMP-13 (ng/ml)	0.05 ± 0.04	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02
TIMP-1 (ng/ml)	155 ± 59	150 ± 53	130 ± 33	134 ± 32
TIMP-2 (ng/ml)	112 ± 18	108 ± 14	94 ± 11	97 ± 16

sites remained patent. With the exception of cardiac function (LVEF and LVEDVI) and the prevalence of ACE-I use, clinical characteristics were similar between patients with AMI and AP.

Enhancement of cardiac MMP production in patients with AMI

Table 2 shows the comparison of BNP, MMP and TIMP levels between blood samples from the CS and peripheral artery. In patients with AMI, levels of BNP, MMP-2 and MMP-9 were significantly ($P < 0.05$) higher in the CS than in the peripheral artery, whereas the levels of MMP-13, TIMP-1 and TIMP-2 were similar. In control patients with AP, no significant differences in the levels of BNP, MMPs and TIMPs were observed between the CS and peripheral artery. These findings indicate that the production of MMP-2 and MMP-9, as well as that of BNP, is enhanced in an infarcted heart.

Correlation of cardiac MMP production with post-infarction LV remodelling

In patients with AMI, the CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with those of BNP and LVEDVI respectively (Figure 1), but not with LVEF, peak CK level and circulating WBC counts. These myocardial gradients were not different between patients with and without progression to restenosis (MMP-2, 87 ± 32 compared with 152 ± 173 ng/ml; MMP-9, 83 ± 86 compared with 61 ± 82 ng/ml).

Comparisons between pravastatin-treated patients with AMI and non-pravastatin-treated patients with AMI

We then compared levels of MMPs between ten patients treated with 10 mg of pravastatin and ten patients not treated with pravastatin (Table 3). Although the total cholesterol level before treatment was higher ($P < 0.05$) in the pravastatin-treated patients with AMI (223 ± 7 mg/dl in treated patients compared with 195 ± 17 mg/dl in

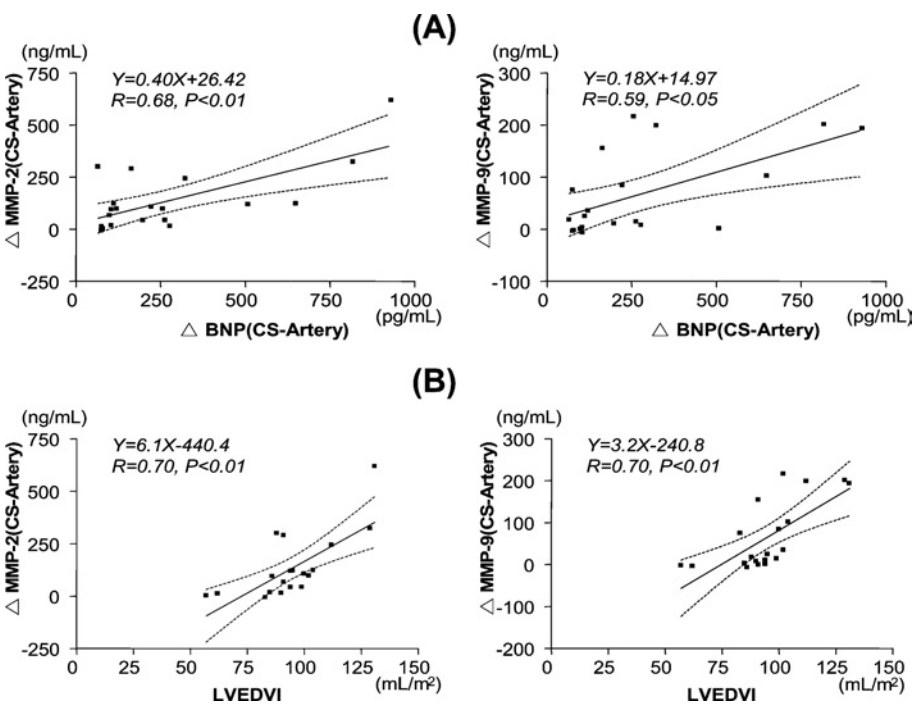

Figure 1 Correlations between CS–arterial concentration gradients of MMP-2 and -9 and BNP (A) and LVEDVI (B) in 20 patients with AMI

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Table 3 Comparisons of MMPs between pravastatin-treated and non-pravastatin-treated patients

*$P < 0.05$ compared with levels in artery; †$P < 0.05$ compared with levels in non-pravastatin-treated patients. CS–artery, CS–arterial concentration gradient.

	Patients with AMI						Patients with stable AP					
	Pravastatin-treated ($n = 10$)			Non-pravastatin-treated ($n = 10$)			Pravastatin-treated ($n = 6$)			Non-pravastatin-treated ($n = 4$)		
MMP (ng/ml)	CS	Artery	CS–artery	CS	Artery	CS–artery	CS	Artery	CS–artery	CS	Artery	CS–artery
MMP-2	808 ± 182	739 ± 158	69 ± 43†	897 ± 216*	684 ± 84	213 ± 185	631 ± 53	624 ± 51	7 ± 23	629 ± 32	639 ± 43	−9 ± 53
MMP-9	94 ± 61†	80 ± 59	14 ± 27†	236 ± 142*	117 ± 100	119 ± 84	68 ± 20	72 ± 16	−4 ± 4	68 ± 20	69 ± 29	0 ± 5
MMP-13	0.06 ± 0.06	0.03 ± 0.03	0.03 ± 0.06	0.03 ± 0.02	0.05 ± 0.03	−0.01 ± 0.03	0.03 ± 0.04	0.04 ± 0.02	−0.01 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	0.01 ± 0.03

non-treated patients), no significant differences were observed after treatment between the two groups (183 ± 31 mg/dl in treated patients compared with 201 ± 20 mg/dl in non-treated patients). Levels of CRP (0.18 ± 0.13 mg/dl in treated patients compared with 0.50 ± 0.40 mg/dl in non-treated patients; $P = 0.03$) and the CS–arterial concentration gradients of MMP-2 and MMP-9 (Table 3) were significantly different between the two groups. However, the concentration gradients of TGF-β and Ang-II were similar between patients treated with pravastatin and those not treated (Ang-II, 19.5 ± 20.2 compared with 36.9 ± 32.4 pg/ml respectively; TGF-β, 1.2 ± 3.3 compared with 2.1 ± 4.7 pg/ml respectively).

We then performed multivariate analysis for the predictors of CS–arterial concentration gradients of MMP levels, including age, sex, coronary risk factors, peak CK, infarct site (anterior wall), CRP, TIMP, pravastatin treatment, LVEF and LVEDVI. The association between pravastatin treatment and cardiac MMP-2 production was modest, with an odds ratio of 0.074 (95 % confidence interval, 0.005–1.109; $P = 0.06$), and did not reach statistical significance.

DISCUSSION

The major findings of the present clinical study are that after AMI, the cardiac production of MMP-2 and MMP-9 is enhanced and associated with LV enlargement and BNP secretion, and that the pleiotropic effect of statins appears to be associated with the modulation of cardiac MMP activation.

Among the MMP species, MMP-2 and MMP-9 play an important role in LV remodelling, as these MMPs are activated in the myocardium and it has been reported that the targeted deletion of these MMPs prevents post-infarction cardiac dysfunction and rupture [9,10]. In the clinical setting, circulating MMP-2 and MMP-9 levels have been measured in previous studies of patients with AMI [17–19]; however, these results were conflicting. Squire et al. [17] reported that circulating MMP levels were inversely correlated with LV dilatation, whereas Matsunage et al. [18] and Nakaya et al. [19] found that serum MMP levels and activity were positively correlated with LV dilatation. In addition, circulating MMP levels could be affected at the acute stage following reperfusion therapy and by the clinically vulnerable state [20–23]. In the present study, we focused on cardiac production of MMP [14], and the measurement was performed at the clinically stable stage following AMI. As shown in Table 2, despite similar levels of TIMPs, significant differences in levels of BNP, MMP-2 and MMP-9 were observed between the CS and the peripheral artery in patients with AMI. To our knowledge, this is the first study demonstrating the enhanced production of MMP-2 and MMP-9 in a human infarcted heart. Moreover, as shown

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in Figure 1, the CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with those of BNP and LVEDVI. Taking into account the delicate balance between MMPs and TIMPs in tissue remodelling, the present findings indicate that excessive cardiac production of MMPs may play an important pathological role in the progression of post-infarction LV dysfunction.

A previous experimental study of an AMI model using BNP-transgenic mice demonstrated a potential interaction of BNP with inflammation [24]. The overexpression of BNP leads to neutrophil infiltration and MMP-9 expression in the infarct region and increases the incidence of cardiac rupture. These findings suggest the significance of inflammatory reaction in the heart accompanied by changes in LV function. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors, such as statins, exert various cardiovascular protective effects beyond their lipid-level lowering actions [12,25]. These pleiotropic effects include the inhibition of inflammatory responses. In the present study, we have shown that the CS–arterial concentration gradients of MMP-2 and MMP-9 were smaller in the pravastatin-treated group than in the non-pravastatin-treated group, which was accompanied by a decrease in CRP level. These findings indicate that pravastatin may modulate cardiac MMP production in patients with AMI, probably via its anti-inflammatory effects. Similar observations of decreased circulating MMP-2 levels in patients with AMI treated with 10 mg of paravastain have been reported previously [19].

There are several potential limitations of the present study. First, this study was not randomized. Pravastatin was administered to a small number of patients with AMI with hyperlipidaemia. In such a pro-inflammatory state, tissue MMPs might have been activated before treatment [26], which could affect the results. Therefore prospective studies will be required to determine if pravastatin has a causal role in reducing cardiac MMP production in patients with AMI. Secondly, the present study was carried out over the short term, whereas ventricular remodelling is known to progress over months or years. Thirdly, previous studies have shown that the renin–angiotensin system is also involved in the induction of post-infarction ventricular remodelling [27] and can be inhibited by statins [28,29]. However, we have shown that the CS–arterial concentration gradients of Ang II were similar between pravastatin-treated patients and non-pravastatin-treated patients. This may be related, in part, to the fact that all our patients with AMI had been treated with 5 mg of enalapril.

In conclusion, the present study demonstrates the enhancement of MMP production in an infarcted heart. Pleiotropic effects of statins may be associated with the modulation of cardiac MMP activation, which is potentially beneficial in the attenuation of post-infarction LV remodelling.

REFERENCES

1 Sutton, M. G. and Sharpe, N. (2000) Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation **101**, 2981–2988
2 Yousef, Z. R., Redwood, S. R. and Marber, M. S. (2000) Postinfarction left ventricular remodelling: where are the theories and trials leading us? Heart **83**, 76–80
3 White, H. D., Norris, R. M., Brown, M. A., Brandt, P. W., Whitlock, R. M. and Wild, C. J. (1987) Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation **76**, 44–51
4 Weisman, H. F. and Healy, B. (1987) Myocardial infarct expansion, infarct extension, and reinfarction: pathophysiologic concepts. Prog. Cardiovasc. Dis. **30**, 73–110
5 Creemers, E. E., Cleutjens, J. P., Smits, J. F. and Daemen, M. J. (2001) Matrix metalloproteinase inhibition after myocardial infarction: a new approach to prevent heart failure? Circ. Res. **89**, 201–210
6 Spinale, F. G. (2002) Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ. Res. **90**, 520–530
7 Cleutjens, J. P., Kandala, J. C., Guarda, E., Guntaka, R. V. and Weber, K. T. (1995) Regulation of collagen degradation in the rat myocardium after infarction. J. Mol. Cell. Cardiol. **27**, 1281–1292
8 Rohde, L. E., Ducharme, A., Arroyo, L. H. et al. (1999) Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. Circulation **99**, 3063–3070
9 Heymans, S., Luttun, A., Nuyens, D. et al. (1999) Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure. Nat. Med. **5**, 1135–1142
10 Ducharme, A., Frantz, S., Aikawa, M. et al. (2000) Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J. Clin. Invest. **106**, 55–62
11 Nahrendorf, M., Hu, K., Hiller, K. H. et al. (2002) Impact of hydroxymethylglutaryl coenzyme a reductase inhibition on left ventricular remodeling after myocardial infarction: an experimental serial cardiac magnetic resonance imaging study. J. Am. Coll. Cardiol. **40**, 1695–1700
12 Hayashidani, S., Tsutsui, H., Shiomi, T. et al. (2002) Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation **105**, 868–873
13 Nagaya, N., Nishikimi, T., Goto, Y. et al. (1998) Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am. Heart J. **135**, 21–28
14 Yasuda, S., Goto, Y., Baba, T. et al. (2000) Enhanced secretion of cardiac hepatocyte growth factor from an infarct region is associated with less severe ventricular enlargement and improved cardiac function. J. Am. Coll. Cardiol. **36**, 115–121
14a Nakamura, H., Arakawa, K., Itakura, H. et al. (2006) Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised control trial. Lancet **368**, 1155–1163
15 Fujimoto, N. and Iwata, K. (2001) Use of EIA to measure MMPs and TIMPs. Methods Mol. Biol. **151**, 347–358
16 Yasuda, S., Goto, Y., Sumida, H. et al. (1999) Angiotensin-converting enzyme inhibition restores hepatocyte growth factor production in patients with congestive heart failure. Hypertension **33**, 1374–1378
17 Squire, I. B., Evans, J., Ng, L. L., Loftus, I. M. and Thompson, M. M. (2004) Plasma MMP-9 and MMP-2 following acute myocardial infarction in man: correlation with echocardiographic and neurohumoral parameters of left ventricular dysfunction. J. Card. Failure **10**, 328–333

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18 Matsunaga, T., Abe, N., Kameda, K. et al. (2005) Circulating level of gelatinase activity predicts ventricular remodeling in patients with acute myocardial infarction. Int. J. Cardiol. **105**, 203–208
19 Nakaya, R., Uzui, H., Shimizu, H. et al. (2005) Pravastatin suppresses the increase in matrix metalloproteinase-2 levels after acute myocardial infarction. Int. J. Cardiol. **105**, 67–73
20 Wagner, D. R., Delagardelle, C., Ernens, I., Rouy, D., Vaillant, M. and Beissel, J. (2006) Matrix metalloproteinase-9 is a marker of heart failure after acute myocardial infarction. J. Card. Failure **12**, 66–72
21 Higo, S., Uematsu, M., Yamagishi, M. et al. (2005) Elevation of plasma matrix metalloproteinase-9 in the culprit coronary artery in patients with acute myocardial infarction: clinical evidence from distal protection. Circ. J. **69**, 1180–1185
22 Kai, H., Ikeda, H., Yasukawa, H. et al. (1998) Peripheral blood levels of matrix metalloproteases-2 and -9 are elevated in patients with acute coronary syndromes. J. Am. Coll. Cardiol. **32**, 368–372
23 Fukuda, D., Shimada, K., Tanaka, A. et al. (2006) Comparison of levels of serum matrix metalloproteinase-9 in patients with acute myocardial infarction versus unstable angina pectoris versus stable angina pectoris. Am. J. Cardiol. **97**, 175–180
24 Kawakami, R., Saito, Y., Kishimoto, I. et al. (2004) Overexpression of brain natriuretic peptide facilitates neutrophil infiltration and cardiac matrix metalloproteinase-9 expression after acute myocardial infarction. Circulation **110**, 3306–3312
25 Davignon, J. (2004) Beneficial cardiovascular pleiotropic effects of statins. Circulation **109**, III39–III43
26 El Messal, M., Beaudeux, J. L., Drissi, A. et al. (2005) Elevated serum levels of proinflammatory cytokines and biomarkers of matrix remodeling in never-treated patients with familial hypercholesterolemia. Clin. Chim. Acta **366**, 185–189
27 Bader, M. (2002) Role of the local renin-angiotensin system in cardiac damage: a minireview focusing on transgenic animal models. J. Mol. Cell. Cardiol. **34**, 1455–1462
28 Dechend, R., Fiebler, A., Lindschau, C. et al. (2001) Modulating angiotensin II-induced inflammation by HMG Co-A reductase inhibition. Am. J. Hypertens. **14**, 55S–61S
29 Luo, J. D., Zhang, W. W., Zhang, G. P., Guan, J. X. and Chen, X. (1999) Simvastatin inhibits cardiac hypertrophy and angiotensin-converting enzyme activity in rats with aortic stenosis. Clin. Exp. Pharmacol. Physiol. **26**, 903–908

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