BASIC RESEARCH

Cardiac remodelling 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

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Heart 2002;**88**:525–530

Objective: To investigate matrix metalloproteinases (MMP-2 and MMP-9) in heart failure caused by ischaemic and idiopathic dilated cardiomyopathy, and the impact of angiotensin converting enzyme (ACE) inhibition on MMP.

Design and main outcome measures: MMP were extracted from myocardium of patients with heart failure (coronary artery disease, n = 13; idiopathic dilated cardiomyopathy (IDCM), n = 16) and from controls (n = 6). The active form of MMP-2 and MMP-9 was measured by enzyme linked immunosorbent assay; activity of MMPs by zymography; mRNA expression of MMPs by reverse transcriptase polymerase chain reaction.

Results: Active MMP-9 was significantly increased in coronary artery disease (mean (SD) 1.6 (0.35) ng/ml) and IDCM (2.11 (0.54) ng/ml) in comparison with controls (0.53 (0.15) ng/ml). Increased MMP-2 was only found in IDCM (3.68 (0.41) ng/ml). There were corresponding increases in MMP activity but no upregulation of mRNA expression was found. The ACE inhibitors captopril and ramiprilate inhibited MMP-2 and MMP-9 activity in vitro (inhibitory capacity (IC_{50}), in mmol/l: MMP-2: captopril 2.0 (0.16), ramiprilate 2.1 (0.3); MMP-9: captopril 1.65 (0.18), ramiprilate 2.0 (0.3)). Lisinopril inhibited MMP-9 significantly but did not inhibit MMP-2 in vitro (IC_{50} MMP-2: 7.4 (0.88); MMP-9: 7.86 (2.23)). Inhibition of MMP activity by ACE inhibitors was blunted by zinc excess.

Conclusions: Upregulation of MMP-9 activity is common in the failing myocardium, independent of the underlying disease. Missing upregulation of transcription suggests that activation of latent forms of MMP is the source of increased MMP activity, rather than increased de novo synthesis. Some ACE inhibitors may influence MMP activity by a direct effect.

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Accepted 4 July 2002

Recent results from the ELITE-2 (evaluation of losartan in the elderly) study,[1] which was designed to show the superiority of losartan over captopril, failed even to give an assurance that these two agents are of equivalent benefit in heart failure treatment. This result has led to a re-examination of the factors that determine the actions of angiotensin converting enzyme (ACE) inhibitors and sartans in the failing heart. ACE inhibitors inhibit angiotensin converting enzyme, which catalyses the formation of angiotensin II from angiotensin I; sartans are thought to inhibit the ACE system more effectively by angiotensin II receptor antagonism. On the other hand, the haemodynamic consequences of ACE inhibition and angiotensin II receptor antagonism only partially explain their beneficial effects on cardiac remodelling in heart failure.[2] Local mechanisms have been suggested—for example, inhibition of the tissue ACE system and a decrease in the breakdown of bradykinin.[3] Sorbi and colleagues[4] suggested that reduced proteinuria in hypertensive patients treated with captopril reflected a direct effect of captopril on matrix metalloproteinase-2 (MMP-2) and MMP-9 activity, mediated by the sulfydryl group on the ACE inhibitor.

Comparing the effect of ACE and MMP inhibition on cardiac remodelling in a rapid pacing induced heart failure model in pigs, McElmurray and colleagues showed that both MMP and ACE inhibitors significantly reduced the degree of left ventricular dilatation.[5] However, MMP activity in the left ventricular myocardium did not differ between animals treated with MMP inhibitors, ACE inhibitors, or combined treatment. So the question arises as to whether ACE inhibitors have a direct influence on myocardial MMP activity.

In the light of increasing interest in the role of the cardiac proteolytic system, our aim in this study was to investigate the gelatinases MMP-2 and MMP-9 in hearts that had failed because of coronary artery disease or idiopathic dilated cardiomyopathy (IDCM), and the influence of ACE inhibitors on these enzymes.

METHODS

Subjects

Human left ventricular heart tissue was obtained from explanted hearts at the time of heart transplantation. Samples of myocardium from 16 hearts with IDCM, 13 with ischaemic cardiomyopathy, and six brain dead organ donor hearts (which could not be used for heart transplantation) were snap frozen in liquid nitrogen after explantation and stored at –80°C until analysis. IDCM was diagnosed according to recent World Health Organization criteria.[6] The severity of heart failure did not differ between the IDCM and coronary artery disease groups.

The protocol of the study was approved by the ethics commission at the University of Jena.

Abbreviations: ACE, angiotensin converting enzyme; ECM, extracellular matrix; GAPDH, glyceraldehyde-3-phosphodehydrogenase; IDCM, idiopathic dilated cardiomyopathy; MMP, matrix metalloproteinase; RT-PCR, reverse transcriptase polymerase chain reaction assays; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; TIMP, tissue inhibitor of matrix metalloproteinases

Table 1 Primer used to detect mRNA expression by reverse transcriptase polymerase chain reaction

	Forward	Reverse	PCR product	T_A	Accession code
MMP-1	AgCAAACACATCTgACCTAC	TAAAgAACATCACTTCTCCC	564	55.3	X 54925
MMP-2	AgTCTgCTCTgCCTATCCTC	ACACCCATATCTgTCTTCCC	833	59.8	NM00453
MMP-3	ACCCACTCTATCACTCACTCAC	CTgTTACTCTTCAAAgTgTgTgTC	536	56.9	J 03209
MMP-9	CCAgTTTCCATTCATCTTCC	ACAgTAgTggCCgTAgAAgg	479	55.0	NM004994
	CCCTTgTgCTCTTCCCTg (nested)	CCCgTCCTTCCCgTCgAAg (nested)	303	60.0	NM004994
TIMP-2	gAAACgACATTTATggCAAC	gATgTTCTTCTCTgTgACCC	377	58.3	J 05593

MMP, matrix metalloproteinase; PCR, polymerase chain reaction; T_A, annealing temperature; TIMP, tissue inhibitor of metalloproteinases.

Preparation of MMP

Approximately 25 mg of frozen adult left ventricle was washed three or four times with cold saline. Cardiac tissue was then incubated in 1000 µl of extraction buffer (10 mmol/l cacodylic acid at pH 5, 0.15 mol/l NaCl, 1 µmol/l $ZnCl_2$, 20 mmol $CaCl_2$, 1.5 mmol/l NaN_3, and 0.01% (vol/vol) Triton X 100) at 4°C for 72 hours. The extraction buffer was collected and the pH was raised by the addition of 1.5 mol/l Tris HCl buffer (pH 8.8). Aliquots from these samples were loaded directly onto substrate gels.

Total protein in extracts

A Bio-Rad dye binding assay (Palo Alto, California, USA) was used to estimate the total protein concentration in tissue extracts according to Bradford.[7]

Visualisation of gelatinolytic activities on SDS substrate gels (zymography)

Sodium dodecyl sulfate (SDS) substrate gels were prepared as published elsewhere,[8] with modification.[9] Gelatine (porcine skin, 300 bloom from Sigma, St Louis, Missouri, USA) was added to standard Laemmli acrylamide polymerisation mixture at a final concentration of 1 mg/ml. Tissue extract was mixed with substrate gel sample buffer (10% SDS, 0.25 mol/l Tris HCl pH 6.8, and 0.1% wt/vol bromphenol blue) to a final protein concentration of 1000 mg/ml, and 20 µl were loaded under non-reducing conditions immediately without boiling into wells of a 4% (wt/vol) acrylamide Laemmli stacking gel on a cast vertical gel. Gels were run at 15 mA/gel while stacking, and at 20 mA/Gel during the separation phase at room temperature. Following electrophoresis the gels were soaked in 2.5% (wt/vol) Triton X 100 with gentle shaking for 30 minutes at room temperature with one change of detergent solution. The gels were rinsed and incubated overnight at 37°C in substrate buffer (50 mmol/l Tris HCl pH 8, 5 mmol/l $CaCl_2$, and 0.02% wt/vol NaN_3).

After incubation, the gels were stained for three minutes in Coomassie blue R250 in acetic acid:isopropyl alcohol:water (1:3:6 by volume), and destained in water overnight with or without ACE inhibitors (captopril, lisinopril: Sigma; ramiprilate: Aventis, Bad Soden, Germany). Gels were scanned and analysed by densitometry for lysis band intensity (Herolab Imaging system, Wiesloch, Germany). The MMP gelatinolytic activity results are expressed in arbitrary units expressing the videodensitometrically determined ratio of the MMP to the activity of MMP purified standard proteins (Invitek, Berlin, Germany). All experiments were done in triplicate.

Measurement of active MMP

Measurement of active MMP-2 and MMP-9 in human tissue extracts and pleural and pericardial effusion was undertaken using commercially available enzyme linked immunosorbent assay (ELISA) kits (Amersham Life Science, Burlingame, USA).

Western blot

MMP protein was detected by monoclonal antibodies against the proenzyme and active MMP-2 and MMP-9 (Calbiochem, San Diego, California, USA), employing a standard western blot technique.[8]

RNA isolation: cDNA synthesis and quantitative RT-PCR

Total RNA from myocardial tissue was isolated according to the RNeasy protocol from Qiagen (Hilden, Germany) and converted to cDNA using a commercially available kit from Promega (Madison, Wisconsin, USA). The polymerase chain reaction (PCR) MIMIC construction kit from Clontech (Palo Alto, California, USA) was used to produce a DNA fragment of known size and amount, with primer binding sites for the housekeeping gene glyceraldehyde-3-phosphodehydrogenase (GAPDH) as previously reported.[10] To normalise cDNA samples, a competitive PCR from the housekeeping gene GAPDH was undertaken using this competitor fragment, under conditions reported before.[10] Separate reverse transcriptase polymerase chain reaction assays (RT-PCR) from 2 µl of the equilibrated cDNA were done using the GAPDH primer pair (forward: 5′AGC CAC ATC GCT CAG AAC AC; reverse 5′GAG GCA TTG CTG ATG ATC TTG, patent pending) and the primer specified in table 1. The resulting PCR products were separated on 2.0% agarose gel. The MMP mRNA results are given in arbitrary units expressing the videodensitometrically determined ratio of the MMP to the GAPDH RT-PCR products.

Data analysis

Statistical analysis was done using Microsoft Excel data analysis software and SPSS (SPSS Inc, Chicago, Illinois, USA). Differences in the mean value were considered significant at a probability value of $p < 0.05$. Values are presented as mean (SD). Student's *t* test was used to compare baseline characteristics between groups.

RESULTS

MMP-9 activity and mass in failing myocardium

Human cardiac MMPs showed gelatinolytic activity in several bands on the overnight incubated, Coomassie stained, gelatine enriched SDS-PAGE gel. From the known molecular weights of the active forms of MMP-2 and MMP-9, the gelatinolytic bands of the purified proteins MMP-2 and MMP-9, and protein detection using Western blot analysis, active MMP-2 could be identified as a 66 kDa band and MMP-9 as an 86 kDa band at zymography (fig 1). Bands observed in some cases at 92 and 72 kDa should be regarded as gelatinolytic active enzymes, fragments, and proenzymes, partially activated by interaction with SDS-PAGE components.

Concentrations of active forms of MMP-9 measured by ELISA, as well as the gelatinolytic activity of MMP-9, were found to be increased in myocardium from patients with IDCM and coronary artery disease in comparison with the activity in non-failing hearts (table 2). The active form of MMP-2 and its gelatinolytic activity were increased in IDCM hearts, but there were no significant differences in MMP-2 determinations between non-failing and coronary diseased myocardium.

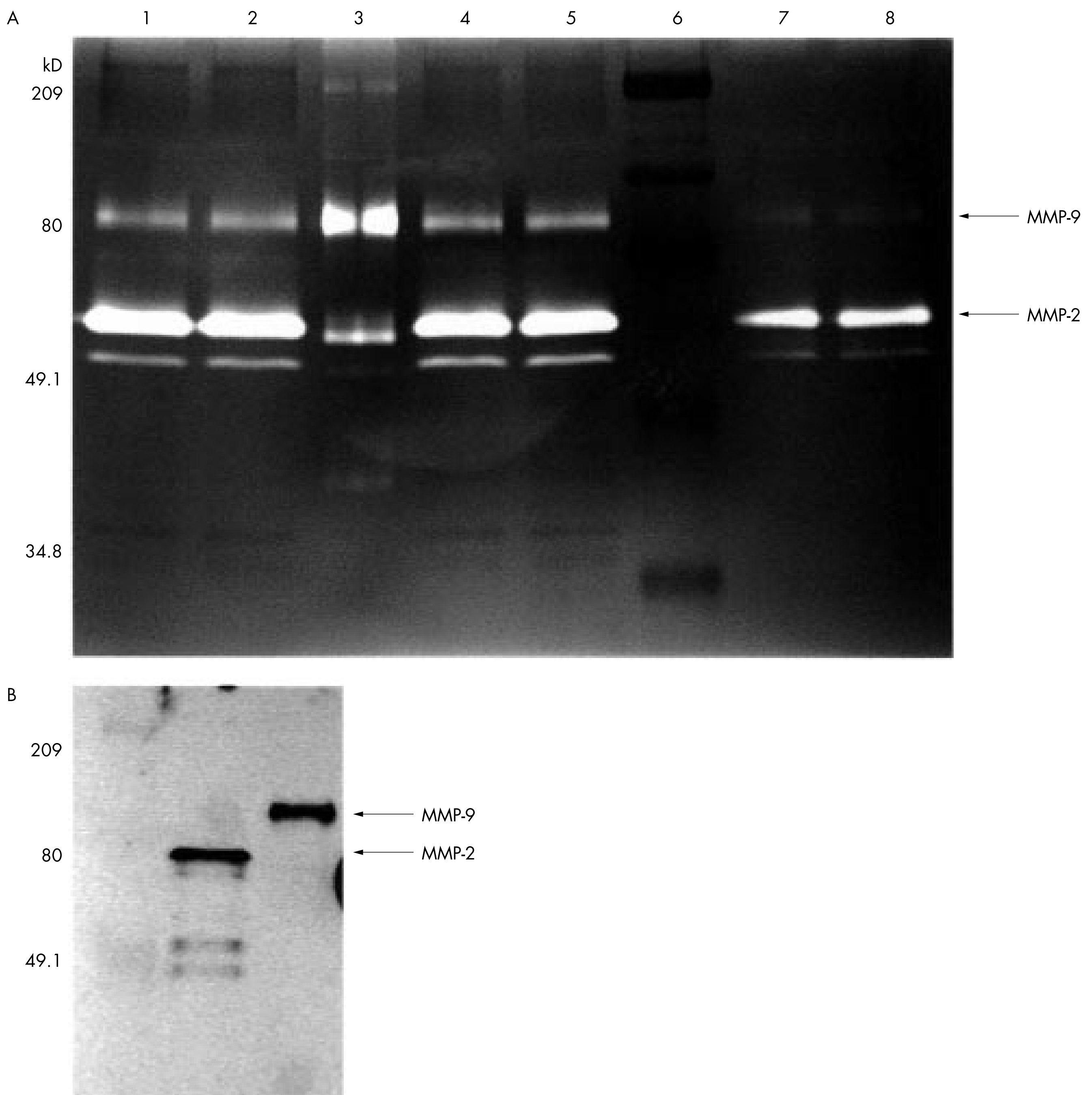

Figure 1 (A) Visualisation of gelatinolytic activities on sodium dodecyl sulphate (SDS) substrate gels (zymography). Extracts were loaded onto a SDS-PAGE gel containing 0.6 mg/ml gelatin under non-reducing conditions. Separation is followed by overnight incubation in substrate buffer, with and without angiotensin converting enzyme (ACE) inhibitor, and staining in Coomassie blue. Lanes 1 and 2, idiopathic dilated cardiomyopathy; lane 3, matrix metalloproteinase (MMP)-2 and MMP-9 purified standard proteins; lanes 4 and 5, coronary artery disease; lane 6, protein molecular weight standard (209, 80, 49.1, and 34.8 kDa bands are indicated); lanes 7 and 8, normal myocardium: arrows show the MMP-2 and MMP-9 bands. Inactive forms of MMP show gelatinolytic activity owing to alterations by SDS and during PAGE passage. (B) Western blot detection of MMP-2 and MMP-9.

Source of increased MMP activity

Expression of MMP-2 mRNA measured by quantitative RT-PCR showed no significant differences between coronary artery disease, IDCM, and non-failing myocardium (table 3). With respect to MMP-9 expression, no increase could be detected in coronary artery disease and IDCM myocardium in comparison with non-failing myocardium. In coronary artery disease, MMP-9 mRNA expression was detectable only by a highly sensitive nested PCR.

Except for the expression of MMP-1 in one patient with IDCM, we could not detect MMP-1 or MMP-3 expression in any of the diseased myocardium samples or in non-failing myocardium. TIMP-2 was highly expressed in all groups, with a tendency to increased expression in the diseased hearts. This did not reach significance because of the highly scattered data in both the IDCM and the coronary artery disease groups.

Effects of captopril, lisinopril, and ramiprilate on human MMP-9 in vitro

The inhibitory capacity of each ACE inhibitor on the MMPs was titrated. Figure 2 shows a representative example of dose dependent inhibition of zymographic activity by captopril. To compare the inhibitory effects of different ACE inhibitors on MMP-2 and MMP-9 in vitro, we titrated MMP inhibition of each ACE inhibitor until the gelatinolytic activity in zymography gel had disappeared. Untreated controls were regarded as

Table 2 Concentration, activity, and mRNA expression of matrix metalloproteinases in idiopathic dilated cardiomyopathy and coronary artery disease

	MMP concentration (ELISA)		Zymographic activity of MMP		mRNA expression (RT-PCR) (MMP/ GAPDH in AU)				
	MMP-2 (ng/ml)	MMP-9 (ng/ml)	MMP-2 (AU)	MMP-9 (AU)	MMP-1/ GAPDH	MMP-2/ GAPDH	MMP-3/ GAPDH	MMP-9/ GAPDH	TIMP-2/ GAPDH
IDCM (n=16)	3.68 (0.41)*	2.11 (0.54)*	1196 (74)*	802 (132)*	0	0.492	0	0.22	1.16
CAD (n=13)	0.7 (0.26)	1.6 (0.35)*	571 (71)	549 (71)*	0	0.329	0	<0.005†	0.6
Control (n=6)	0.89 (0.35)	0.53 (0.15)	989 (158)	245 (58)	0.012	0.7	0	0.033	1.06

Values are mean (SD); mRNA expression is given in arbitrary units expressing the videodensitometrically determined ratio of MMP to GAPDH RT-PCR.
*p<0.05 *v* control.
†Nested reverse transcriptase polymerase chain reaction (RT-PCR).
AU, arbitrary units; CAD, coronary artery disease; ELISA, enzyme linked immunosorbent assay; GAPDH, glyceraldehyde-3-phosphodehydrogenase; IDCM, idiopathic dilated cardiomyopathy; MMP, matrix matalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinases.

Table 3 Clinical and haemodynamic characteristics of patients with end stage heart failure from idiopathic dilated cardiomyopathy or coronary artery disease

Patient number	Group	Age (years)/ sex	Weight (kg)/ height (cm)	NYHA class	Treatment	LVEF (%)	LVEDD (mm)	Creatinine (μmol/l)	CAD	MI
1	IDCM	54/M	70/180	IV	ACEI, DIG, D, DO	10	80	50	–	–
2	IDCM	60/M	70/175	IV	ACEI, BB, D, CA, DO	18	72	110	–	–
3	IDCM	49/M	90/188	IV	ACEI, BB, D	14	70	120	–	–
4	IDCM	41/M	78/176	III	ACEI, DIG, D, DO	18	85	95	–	–
5	IDCM	68/M	87/188	IV	ACEI, BB, DIG, D	15	68	105	–	–
6	IDCM	59/M	91/196	III	AT1, DIG, D, DO	15	68	110	–	–
7	IDCM	41/M	82/176	IV	AT1, DIG, SPIRO, D	20	72	130	–	–
8	IDCM	42/M	105/186	IV	ACEI, BB, DIG, D	29	69	100	–	–
9	IDCM	46/M	81/186	III	ACEI, DIG, D	17	71	96	–	–
10	IDCM	34/M	73/178	III	AT1, BB, D	20	54	86	–	–
11	IDCM	70/M	80/169	III	AT1, BB, D	34	69	170	–	–
12	IDCM	55/M	81/175	III	BB, D	20	73	130	–	–
13	IDCM	66/M	75/176	IV	AT1, D, DO	22	70	68	–	–
14	IDCM	45/M	80/180	IV	BB, D	17	81	79	–	–
15	IDCM	64/M	92/178	III	ACEI, BB, DO	22	77	135	–	–
16	IDCM	68/M	75/169	IV	AT1, BB, DO	12	78	65	–	–
1	CAD	54/M	78/172	IV	AT1, D, DO	23	72	82	1V	A
2	CAD	53/M	78/176	III	ACEI, BB, DIG, D	28	88	100	2V	P
3	CAD	68/M	86/178	III	ACEI, D	24	84	120	3V	A,P
4	CAD	61/M	91/169	IV	ACEI, DIG, D, DO	25	66	140	3V	A
5	CAD	60/M	58/170	IV	ACEI, DIG, D, DO	24	75	60	3V	A, P
6	CAD	58/M	81/190	IV	ACEI, AT1, BB, DIG, D	15	75	180	1V	P
7	CAD	60/M	89/188	III	ACEI, BB, DIG, D	25	82	160	2V	A, P
8	CAD	58/M	82/188	III	ACEI, BB, DIG, D	29	75	150	3V	P, A
9	CAD	67/M	80/178	III	ACEI, AT1, D	20	83	100	2V	P
10	CAD	59/M	79/175	IV	AT1, DIG, D, DO	33	64	76	3V	A
11	CAD	57/M	95/181	III	BB, DIG, D	23	85	100	2V	A
12	CAD	52/M	81/178	IV	ACEI, D, DO	10	88	90	3V	A, P
13	CAD	40/M	88/175	IV	BB, SPIRO, DO	18	78	72	3V	P

A, anterior myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; AT1, angiotensin II type 1 receptor antagonist; BB, β blocker; CA, calcium channel blocker; CAD, coronary artery disease; D, diuretics; DIG, digitalis glycosides; DO, dopamine or dobutamine; IDCM , idiopathic dilated cardiomyopathy; LVEDD, left ventricular end diastolic diameter assessed by echocardiography; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association functional class; P, posterior myocardial infarction; 1–3V, one, two, or three vessel coronary artery disease.

having 100% activity. Table 4 shows the ACE inhibitor concentration that inhibits 50% of the gelatinolytic activity (IC_{50}). Owing to the methodological characteristics of zymography and the fact that we used heart extracts containing several gelatinolytic enzymes, fragments, and activated proenzymes rather than purified enzymes, the IC_{50} value is only approximate. Captopril and ramiprilate significantly inhibited MMP-2 and MMP-9 activity in vitro, while lisinopril inhibited MMP-9 but not MMP-2 (table 4). Inhibition of MMP activity was blunted by excess zinc.

Table 4 IC_{50} (mmol/l): concentration of angiotensin converting enzyme (ACE) inhibitor inhibiting 50% of matrix metalloproteinase (MMP) zymographic activity as a measure of the in vitro MMP inhibitory capacity of different ACE inhibitors

	MMP-2	MMP-9
Captopril	2.00 (0.06)	1.65 (0.18)
Lisinopril	5.40 (0.28)	7.86 (0.43)
Ramipril	2.10 (0.09)	2.01 (0.30)

Values are mean (SD).

DISCUSSION

The extracellular matrix (ECM) is responsible for cardiac cell alignment and myocardial structural integrity. Synthesis and degradation of ECM are balanced and tightly controlled in normal myocardium.[11 12] In pathophysiological processes, an imbalance of proteinase/antiproteinase systems occurs, resulting in quantitative and qualitative alterations in matrix composition.[13] All four categories of proteinases (serine, cysteine, and aspartic proteinases, and metalloproteinases)

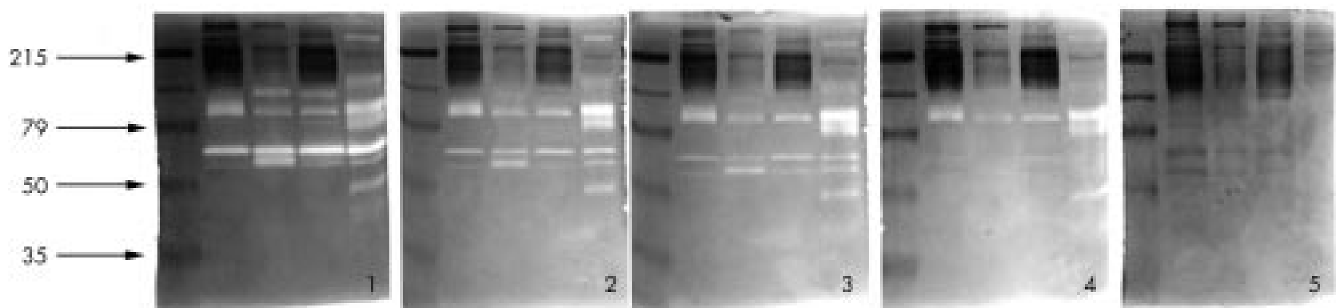

Figure 2 Dose dependent inhibition of matrix metalloproteinases by the angiotensin converting enzyme (ACE) inhibitor captopril in vitro: gel 1, overnight incubation without ACE inhibitor; gel 2, overnight incubation with 4 mM captopril; gel 3, 5 mM captopril; gel 4, 6 mM captopril; gel 5, 7 mM captopril.

have been implicated in the proteolytic process. As collagen represents the major structural protein of ECM, it has long been postulated that collagenolytic MMP plays a pivotal role in cardiac remodelling. Inhibition of the proteolytic activity of MMP has been suggested as a potential therapeutic target in various diseases, including heart failure.[13–21]

The data we present here show different regulatory patterns of MMP depending on the underlying aetiology of heart failure. MMP-9 upregulation is a common feature of matrix activation in terminal heart failure, irrespective of the underlying disease, whereas in our study MMP-2 was upregulated only in IDCM and remained unchanged in coronary artery disease—in line with a previous report.[22]

The fact that we could not detect increased MMP mRNA expression in failing myocardium suggests the presence of additional regulatory mechanisms. In particular, the strikingly low mRNA expression of MMP-9 in coronary diseased myocardium compared with normal myocardium contrasts with the large amount of activated MMP-9 measured by ELISA. A possible explanation for this phenomenon is the circadian synthesis of MMP, with inactive proenzymes kept in stock, implying a chronological imbalance between MMP synthesis and activation.[23 24]

Sources of MMP are fibroblasts, myocytes, endothelial cells, and infiltrating inflammatory cells.[12 25] Monocytes stimulated by tumour necrosis factor α, which have been found to be increased in heart failure, are capable of expressing MMP-9.[26–28] It is possible that these cells may serve as carriers of MMP-9 synthesised before they infiltrate the myocardium. This hypothesis is supported by the observation that in reperfusion of infarcted myocardium, infiltrating neutrophils are the predominant source of MMP-9 and activating enzymes.[25] The source and regulation of MMP activity in normal and diseased myocardium, with a focus on MMP-9 in coronary artery disease, warrants further investigation.

Another interesting question arises: what is the result of the abundant MMP-9 in the myocardium in coronary artery disease and IDCM? Heart failure is a progressive disease. MMP-9 is a key enzyme in matrix component degradation, suggesting a role in matrix remodelling that results in left ventricular enlargement and depression of systolic function. Some of the known substrates of MMP-9 are collagen fragments, gelatin, elastin, aggrecan, versican, and fibronectin. Some of these have important roles in the remodelling process. MMP-9 has been implicated in angiogenesis and apoptosis.[16 29 30] Rouet-Benzineb and colleagues localised MMP-9 immunohistochemically in cardiomyocytes and showed myosin heavy chain cleavage by MMP-9 in vitro, suggesting a direct impairment of the contractile apparatus by MMP-9.[31] There is increasing evidence in studies from transgenic animals that MMP mediates crucial steps in the development of heart failure. The fact that MMP-9 knockout mice survive with no apparent defect has been related to redundancy—expression of related proteins covering for the same function is assumed.[32 33] As the disease progresses, the knockout animals show a decreased ability to adapt or compensate. After experimental myocardial infarction in an MMP-9 knockout model, it was convincingly shown that the targeted deletion of MMP-9 attenuated left ventricular enlargement and collagen accumulation.[32] In another mouse myocardial infarction model it was found that MMP-9 deficiency protected against cardiac rupture.[34]

Except for ACE inhibitors, no other drugs used in the care of heart failure patients have been shown to inhibit MMP activity directly. However, the MMP inhibitory capacity of ACE inhibitors determined by zymographic assay in vitro is not easily transferable to the situation in vivo. There are no data on tissue ACE inhibitor concentrations in human heart, but selective enrichment of ACE inhibitors has been assumed.[35]

Concentrations of ACE inhibitors in zymography are necessarily higher than in blood owing to the need to permeate the SDS-PAGE gel. Other technical points should be mentioned, such as different solubility, different pH, and the application of active metabolites of prodrugs (such as ramiprilate in place of ramipril). However, a non-specific effect of ACE inhibitors on MMP can be excluded by its reversibility by an excess of zinc.

The finding of a direct inhibitory effect of ACE inhibitors on MMP in vitro is of uncertain clinical relevance. The course of the proteolytic activity in the human disease process—from starter event to end stage heart failure—remains unknown. The question of timing arises; do ACE inhibitors affect remodelling more in the earlier stages or in the end stage of heart failure? Do patients who do not respond to ACE inhibition predominantly develop end stage heart failure requiring transplantation?

Conclusions

No definitive statement on the relevance of the interaction of ACE inhibitors and the MMP system is possible. In considering the assumed influence of ACE inhibitors on MMP, we have emphasised the differences in MMP inhibiting capacity between the various different ACE inhibitors.

ACKNOWLEDGEMENTS

This work was supported in part by the German government (Bundesministerium für Bildung und Forschung), grant 2,5 VKF, FKZ 01779602 and National Institutes of Health grant R01-HL-71010. We wish to thank Silke Schreiber and Ulla-Brigitte Köhler for their excellent technical assistance.

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