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Release of Matrix Metalloproteinases Following Alcohol Septal Ablation in Hypertrophic Obstructive Cardiomyopathy

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OBJECTIVES This study examined plasma levels of certain matrix metalloproteinase (MMP) and tissue inhibitor of matrix metalloproteinase (TIMP) species before and after alcohol-induced myocardial infarction (MI) in patients with hypertrophic obstructive cardiomyopathy (HOCM).

BACKGROUND Matrix metalloproteinases contribute to tissue remodeling, and endogenous control of MMP activity is achieved by the concordant release and binding of TIMPs. Animal models of MI have demonstrated a role for MMP activation in myocardial remodeling. However, the temporal relationship of MMP and TIMP release following a controlled myocardial injury in humans remains unknown.

METHODS Plasma levels for the gelatinases MMP-2 and MMP-9, and for the collagenases MMP-8 and MMP-13, as well as TIMP-1 profiles were examined (by enzyme-linked immunosorbent assay) at baseline and serially up to 60 h following alcohol injection into the septal perforator artery in order to induce an MI in 51 patients with HOCM (age 55 ± 2 years).

RESULTS Plasma creatine kinase (MB isoform), indicating myocardial injury, increased 2,150% 18 h post-MI ($p < 0.05$). Plasma MMP-9 increased by over 400% and MMP-8 by over 100% from baseline values by 12 h post-MI ($p < 0.05$ vs. baseline). A similar temporal profile was not observed for MMP-2 and MMP-13. In addition, a concomitant increase in plasma TIMP-1 levels did not occur post-MI. As a result, MMP/TIMP stoichiometry (MMP-9/TIMP-1 ratio) increased significantly post-MI, suggestive of reduced TIMP-1 mediated MMP-9 inhibition, which would potentially enhance extracellular myocardial remodeling.

CONCLUSIONS These unique results demonstrated that induction of a controlled myocardial injury in humans, specifically through alcohol-induced MI, caused species- and time-dependent perturbations of MMP/TIMP stoichiometry that would facilitate myocardial remodeling in the early post-MI setting. (J Am Coll Cardiol 2002;40:2165–73) © 2002 by the American College of Cardiology Foundation

An endogenous family of proteolytic enzymes responsible for extracellular protein degradation and tissue remodeling is the matrix metalloproteinases (MMPs). An important control point for MMP activity is a second family of proteins called the tissue inhibitors of matrix metalloproteinases (TIMPs) (1–5). Past clinical studies have demonstrated that MMPs and TIMPs are expressed in normal human left ventricular (LV) myocardium, and changes in MMP expression and activity occur during LV remodeling in patients with heart failure (6–9). Moreover, a cause-effect relationship between the induction of MMPs and LV myocardial remodeling has been established in animal models (2,10–13). For example, increased myocardial MMP activation has been demonstrated to contribute to LV dilation and remodeling in rodent models of myocardial infarction (MI) (2,11). Past clinical studies have reported changes in plasma MMPs in the post-MI period, which suggests that increased synthesis and activation of MMPs occur following myocardial injury and contribute to the myocardial remodeling process (14–16). However, the direct temporal relationship between MMP release and the induction of a specific myocardial injury in patients remains unknown.

Hypertrophic obstructive cardiomyopathy (HOCM) is a genetic disorder most commonly characterized by exuberant myocardial growth of the septal subaortic region of the left ventricular outflow tract (LVOT) (17). Therefore, HOCM can result in hemodynamically significant LVOT obstruction, eventual LV pump dysfunction, and consequent symptoms of LV failure. One current approach for the relief of LVOT obstruction in patients with HOCM is selective induction of an MI within the septal subaortic region (17–20). Through a targeted injection of ethanol into the septal perforator artery, selective destruction of myocardium involved in the LVOT obstruction has been successfully performed in a large number of patients (18–20). Conceptually, this treatment approach causes an alcohol-induced MI and, therefore, provides a unique opportunity to address several critical questions regarding the relationship between MMPs and myocardial injury in patients. First, what is the temporal profile of certain MMP species in the plasma of

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Abbreviations and Acronyms

ANOVA	= analysis of variance
CHF	= congestive heart failure
CK	= creatine kinase
HOCM	= hypertrophic obstructive cardiomyopathy
LV	= left ventricle/ventricular
LVOT	= left ventricular outflow tract
MI	= myocardial infarction
MMP	= matrix metalloproteinases
TIMP	= tissue inhibitor of matrix metalloproteinases

patients following an alcohol-induced MI? Second, is there a relationship between the degree of myocardial injury caused by an alcohol-induced MI and plasma MMP levels? The goal of the present study was to address these specific questions by serially measuring MMP and TIMP plasma levels in patients with HOCM before and after alcohol-induced MI.

METHODS

Patients. Patients (n = 51) diagnosed with HOCM and scheduled for elective alcohol septal ablation were entered into the study after informed consent was obtained. This protocol was reviewed and approved by the Institutional Review Board of Baylor Medical College and the Medical University of South Carolina. Average patient age was 55 ± 2 years and the population consisted of 32 men and 19 women. At catheterization, the baseline LV to aortic pressure gradient was 62 ± 6 mm Hg, indicating a significant LVOT obstruction. The alcohol septal ablation procedure was performed as described previously (18,19). Briefly, a balloon catheter was engaged into the septal perforator artery and 2 to 5 ml of ethanol was injected. The balloon was left inflated for 5 min following injection and then removed. At six weeks post-alcohol injection, repeat catheterization revealed a gradient of 25 ± 4 mm Hg ($p < 0.05$), indicative of a reduction in the LVOT obstruction. The changes in LV function and hemodynamics in patients with HOCM following alcohol-induced MI have been well described (17–20).

Plasma collection. Blood samples (5 cc) were collected from a peripheral vein into chilled ethylenediamine-tetraacetic acid tubes. The samples were centrifuged and the decanted plasma aliquoted and stored at −70°C until assay. Samples were collected at baseline (before catheterization and septal ablation procedure) and at 4- to 6-h intervals for up to 60 h post-alcohol injection.

MMP and TIMP assays. This study focused upon two known classes of MMPs: the interstitial collagenases, which include MMP-8 and MMP-13, and the gelatinases, which include MMP-2 and MMP-9 (1–3). The best-characterized TIMP is TIMP-1 (1,5). Accordingly, measurements of TIMP-1 were also performed in the present study. Quantification of MMP and TIMP species was performed with enzyme-linked immunosorbent assay systems (Amersham Pharmacia Biotech, Buckinghamshire, United Kingdom) using a two-site binding method as described previously (7,21). For MMP-2 (RPN 2617), the antisera used reacts against the proform of MMP-2 (proMMP-2) and does not react against the active form. For MMP-9 (RPN 2614), the antiserum detects the proform of the enzyme (proMMP-9). For MMP-8 (RPN 2619), the antiserum detects both proenzyme and active forms of MMP-8. For MMP-13 (RPN 2621), the antiserum was developed to detect the proform of this enzyme. For TIMP-1, the antiserum was developed in order to detect the functional protein (RPN 2611). The coefficient of variation for these assay systems was 3% to 5%; these systems did not cross-react with other proteases, and the sensitivity was at least 0.02 ng/ml.

Plasma samples were measured in parallel for total plasma creatine kinase (CK) concentrations as well as the concentration of the MB1 isoform using a microparticle enzyme immunoassay procedure (AxSYM, Abbot Laboratories, Chicago, Illinois).

Data analysis. The MMP, TIMP, and CK plasma levels were first examined using an analysis of variance (ANOVA) in which the treatment effect was time following alcohol injection. Following this, the values were computed as a percent change from baseline. These results were subjected to ANOVA and then post-hoc mean separation using a Bonferonni corrected t test for each time point in which the null hypothesis was that the change from baseline was equal to zero. To examine the relationship between the CK and MMP values, the area under the concentration-time curve for each patient was computed using a polygon integration algorithm (SigmaPlot, Jandel, San Rafeal, California). These points were then subjected to linear regression. Values are expressed are expressed as mean ± SEM. All statistical procedures were performed utilizing SYSTAT statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Alcohol injection into the septal perforator artery was successfully performed in all 51 patients with HOCM, and serial blood samples were collected. Baseline CK and MB1 fractions are presented in Table 1. Changes in plasma CK and the MB1 isoform following alcohol injection are shown in Figure 1. A significant rise in plasma total CK and MB1 isoform occurred by 6 h and peaked at approximately 24 h following alcohol injection. Baseline MMP and TIMP-1 plasma levels are summarized in Table 1 and are within the range of plasma levels previously reported for patients (15,21). The changes in plasma MMP-2 and MMP-9 following alcohol injection are shown in Figure 2. A small but statistically significant increase in plasma MMP-2 occurred at 4 h following alcohol injection. In contrast, a robust increase in plasma MMP-9 occurred at 6 h following alcohol injection and remained elevated for up to 50 h post-injection. Plasma MMP-8 levels also increased by 6 h

Table 1. Baseline Plasma CK Enzyme and MMP Levels in Patients Before Alcohol Injection Into the Septal Perforator Artery

	Baseline Value
CK (IU/l)	79.8 ± 6.6
MB1 fraction (IU/l)	2.9 ± 0.4
MMP-9 (ng/ml)	21.0 ± 2.2
MMP-8 (ng/ml)	10.2 ± 1.6
MMP-13 (ng/ml)	0.1 ± 0.1
MMP-2 (ng/ml)	833.9 ± 69.8
TIMP-1 (ng/ml)	1464.7 ± 86.8
MMP-9/TIMP-1	0.019 ± 0.003

CK = creatine kinase; MMP = matrix metalloproteinase; TIMP = tissue inhibitors of matrix metalloproteinase.

post-injection and remained elevated for up to 60 h post-injection (Fig. 3). Plasma MMP-13 levels did not significantly increase at any time point after alcohol injection, but actually decreased with a slight but significant change at 24 h following injection (Fig. 3). Plasma TIMP-1 levels tended to increase at late time points following alcohol injection, but this did not reach statistical significance ($p = 0.15$) (Fig. 4). However, the plasma MMP-9/TIMP-1 ratio increased at 6 h following injection and remained increased for up to 60 h post-alcohol injection (Fig. 4). A similar change occurred for the MMP-8/TIMP-1 ratio, in which this ratio significantly increased following alcohol injection (data not shown). The area under the curve for the plasma CK MB1 and the area under the time curve for MMP-9 were plotted for each patient and are shown in Figure 5. A significant linear relationship was observed between CK MB1 release and that of plasma MMP-9 levels.

DISCUSSION

The LV outflow obstruction caused by HOCM can be relieved through the creation of a targeted myocardial lesion (17–20). Specifically, the injection of ethyl alcohol into the coronary artery supplying the hypertrophic region of the LV causes sclerosis of the vessel and subsequent ischemia/infarction of the targeted myocardium. However, little is known about the cellular and extracellular events contributing to LV remodeling following alcohol-induced MI in patients with HOCM. Changes in the levels of MMPs and TIMPs have been reported in several cardiovascular disease states, such as heart failure and aortic aneurysms (1–3). Moreover, using animal models, a cause-effect relationship has been established between MMP activation and the LV remodeling process (10–13). Accordingly, the present study serially measured changes in the plasma levels of selected MMP and TIMP species in patients with HOCM following alcohol-induced MI. The new and unique findings of the present study were twofold. First, a robust release of certain MMP species (MMP-8 and MMP-9) occurred following intracoronary injection of alcohol in patients with HOCM, which was not accompanied by a concomitant increase in TIMP-1 levels. This resulted in an MMP-TIMP stoichiometry that would favor myocardial matrix degradation. Second, the release of certain MMPs was sustained for up to 48 h following alcohol-induced MI and was related to the degree of myocardial injury. These findings provide a unique temporal profile of MMP and TIMP release following a discrete myocardial injury in humans.

This study is the first to profile plasma MMP and TIMP species levels following alcohol-induced MI in patients. However, past clinical reports have documented changes in plasma MMP levels in patients with acute coronary syndromes (14–16). For example, Kai et al. (16) reported that plasma MMP-9 levels were elevated approximately 24 h following an acute MI in patients. Inokubo et al. (15) demonstrated that the elevation in plasma MMP-9 in patients with acute coronary syndromes was due to a distinct change in the great cardiac vein-aorta gradient, indicating that the source for the elevated MMP-9 was the myocardium. However, these past studies were not able to precisely time the emergence of MMPs with respect to the onset of myocardial injury. In addition, the location and magnitude of the myocardial injury was not precisely defined in these reports. The present study demonstrated that a discrete myocardial injury induced in patients caused a time- and species-dependent plasma release of MMPs. Although the present study provides only temporal associative data regarding myocardial injury and remodeling, past animal studies have clearly demonstrated a cause-effect relationship between myocardial MMP induction and remodeling in the setting of MI (2,11–13). Specifically, using transgenic models in which MMP gene expression has been modified (12,13), or through the use of MMP pharmacologic inhibition (11), it has been demonstrated that the expression, synthesis, and release of MMP species play a fundamental role in the initial wound healing response following MI, as well as the myocardial remodeling that occurs from days to weeks post-MI. Thus, in the present study, emergence of MMPs into the plasma following alcohol-induced MI was likely due to the local release of myocardial MMPs as part of the initial wound healing process. However, it must be recognized that plasma MMP and TIMP profiles were measured following alcohol-induced sclerosis of a septal perforating artery in patients with HOCM. Whether and to what degree this pattern of MMP release occurs in patients with an evolving MI secondary to coronary atherosclerosis/thrombosis remains to be established.

At present, over 20 MMP species have been cloned and cataloged (1–3,5,22). The major classes of MMPs include the interstitial collagenases, such as MMP-1, MMP-13, and MMP-8; the gelatinases, which include MMP-2 and MMP-9; and the membrane-type MMPs. In the present study, preliminary measurements failed to detect MMP-1 within the plasma of patients with HOCM. This finding may have been the result of a relatively low abundance of this particular MMP species in plasma and/or a relatively low sensitivity of this enzyme-linked immunosorbent assay. In past

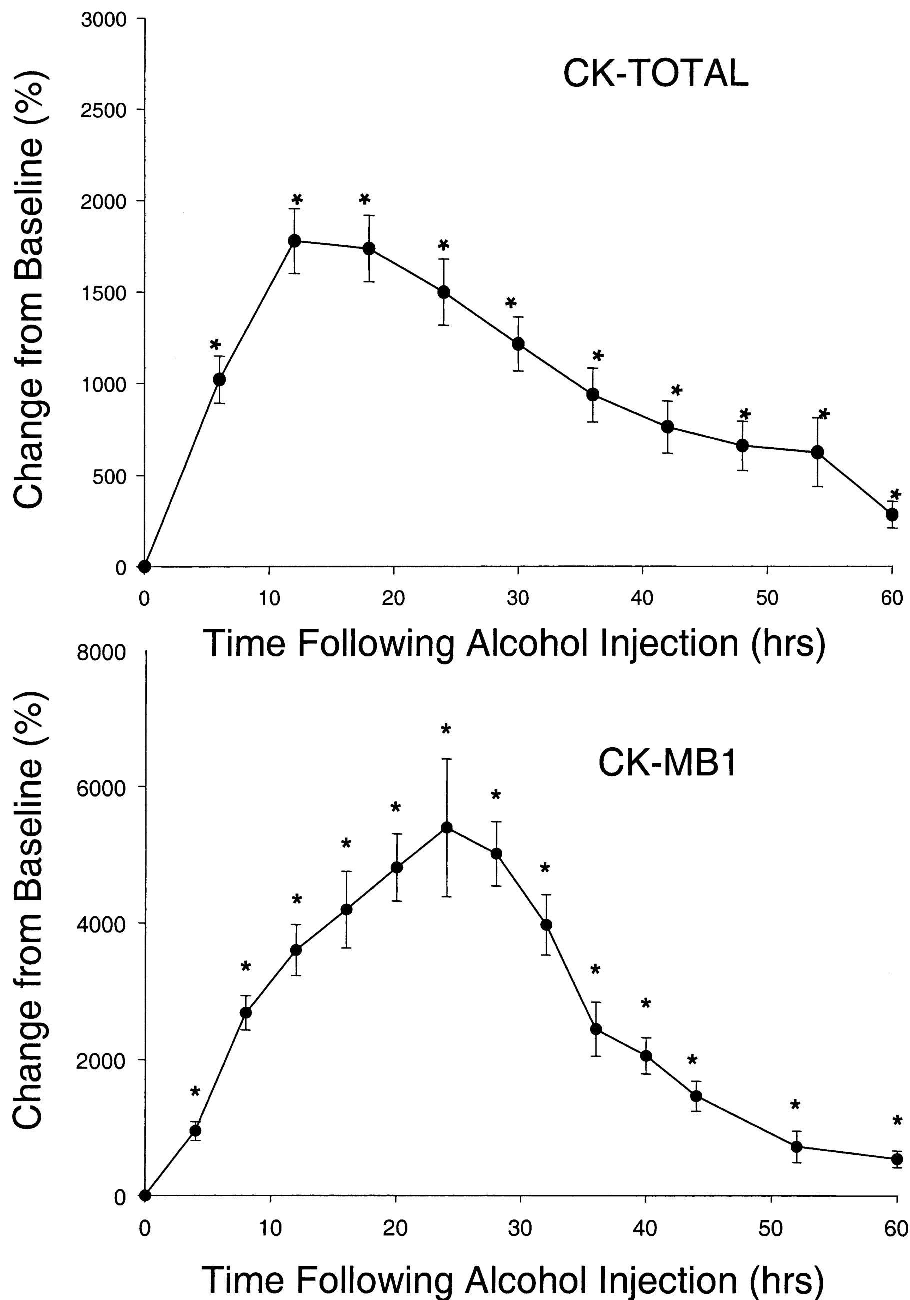

Figure 1. **(Top)** The percent change in plasma total creatine kinase (CK) concentrations following alcohol injection into the septal perforator artery in patients with hypertrophic obstructive cardiomyopathy. Peak plasma CK levels occurred at 10 to 20 h post-injection. **(Bottom)** The percent change in CK MB1 isoform plasma concentrations following alcohol injection. A significant increase in CK-MB1 plasma levels was detected at 4 h and increased until 24 h following alcohol injection. *$p < 0.05$ vs. time 0; baseline values.

reports, myocardial MMP-1 levels were reduced by more than 50% in patients with congestive heart failure (CHF), suggesting that this MMP species may not significantly contribute to the myocardial remodeling process (6,7). Therefore, profiling this particular MMP species was not pursued in the present study. The MT-MMPs are transmembrane proteinases and, therefore, whether this class of MMPs can be detected in plasma is uncertain. Accordingly, the present study focused upon soluble MMPs such as the gelatinases (MMP-2 and MMP-9) and the collagenases (MMP-8, MMP-13) which have been detected in plasma previously (14–16,21). In the early period following alcohol-induced MI, a small increase in MMP-2 plasma levels occurred, but rapidly returned to baseline. This small rise was likely due to the release of intracellular stores of MMP-2 from the area of myocardial injury. Past studies that have measured LV myocardial abundance of MMP-2 in the context of end-stage CHF have been equivocal and appear to depend on the underlying etiology (6–9). An important regulatory point with respect to MMP expression is the induction of transcription factors that bind to promoter

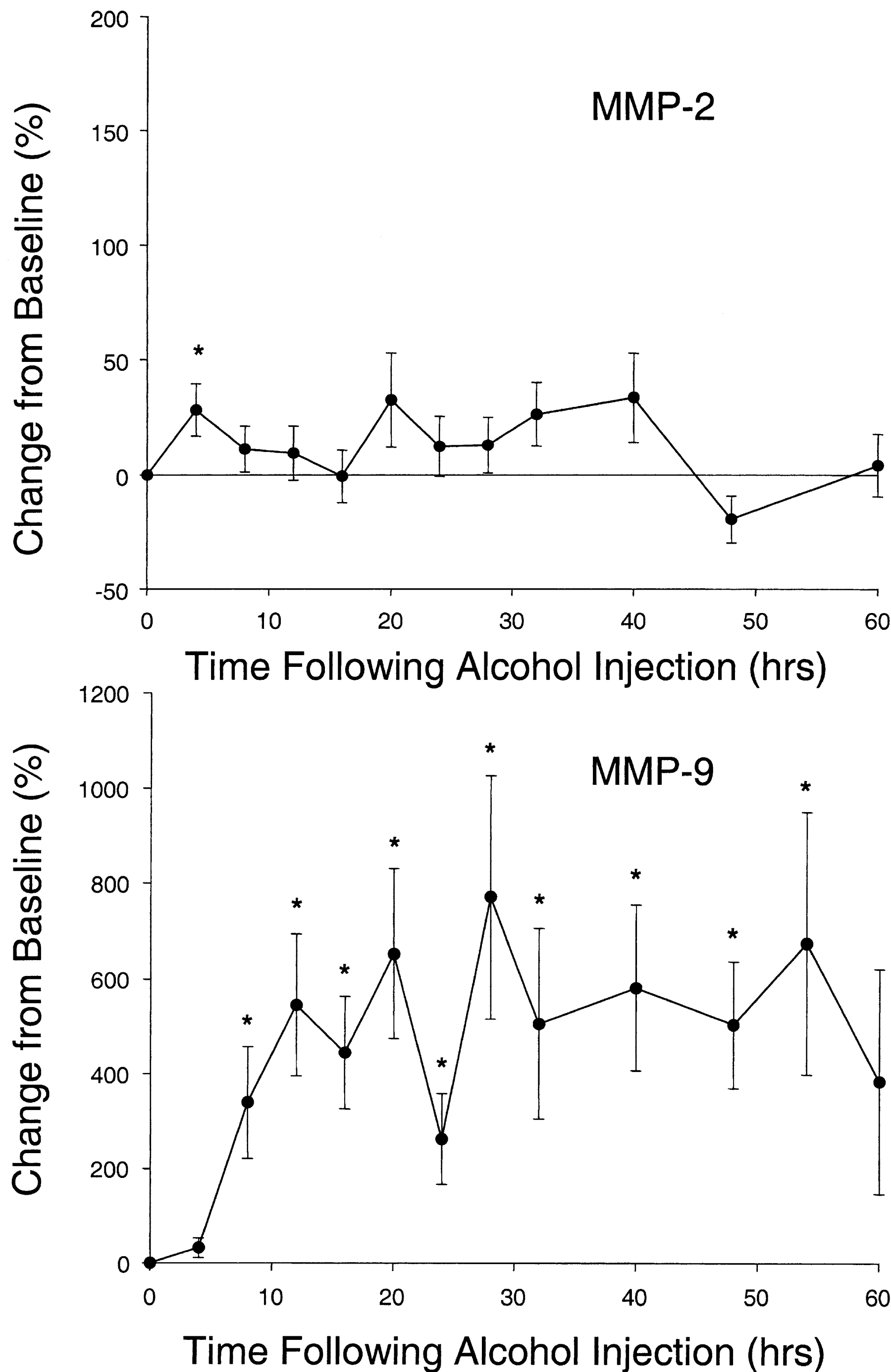

Figure 2. **(Top)** A small but significant change in matrix metalloproteinase (MMP)-2 plasma levels from baseline was observed at 4 h following alcohol injection. **(Bottom)** A significant increase in plasma MMP-9 levels occurred following alcohol injection and appeared to plateau for up to 50 h following injection. *$p < 0.05$ vs. time 0; baseline values.

regions in MMP genes (5,22). The MMP-2 promoter region is relatively devoid of transcription factor binding sites and, therefore, transcriptional regulation of MMP-2 may be minimal. This implies that MMP-2 may be constitutively expressed and not necessarily selectively upregulated with acute pathologic stimuli, such as alcohol-induced MI. In contrast to MMP-2, a robust and persistent increase in plasma levels of MMP-9 occurred following alcohol-induced MI. Past in vitro studies have demonstrated that preformed MMP-9 exists within human platelets and is released with aggregation (23). Furthermore, MMP-9 is synthesized and released by inflammatory cells, such as neutrophils (2–4). Thus, the basis for the acute rise in plasma MMP-9 following alcohol-induced MI was likely the release of MMP-9 from infiltrating neutrophils and platelet aggregation at the site of myocardial injury. Because the immunoassay detected only the proform of MMP-9, the persistently elevated plasma levels of this MMP species suggests that de novo synthesis occurred. In contrast to

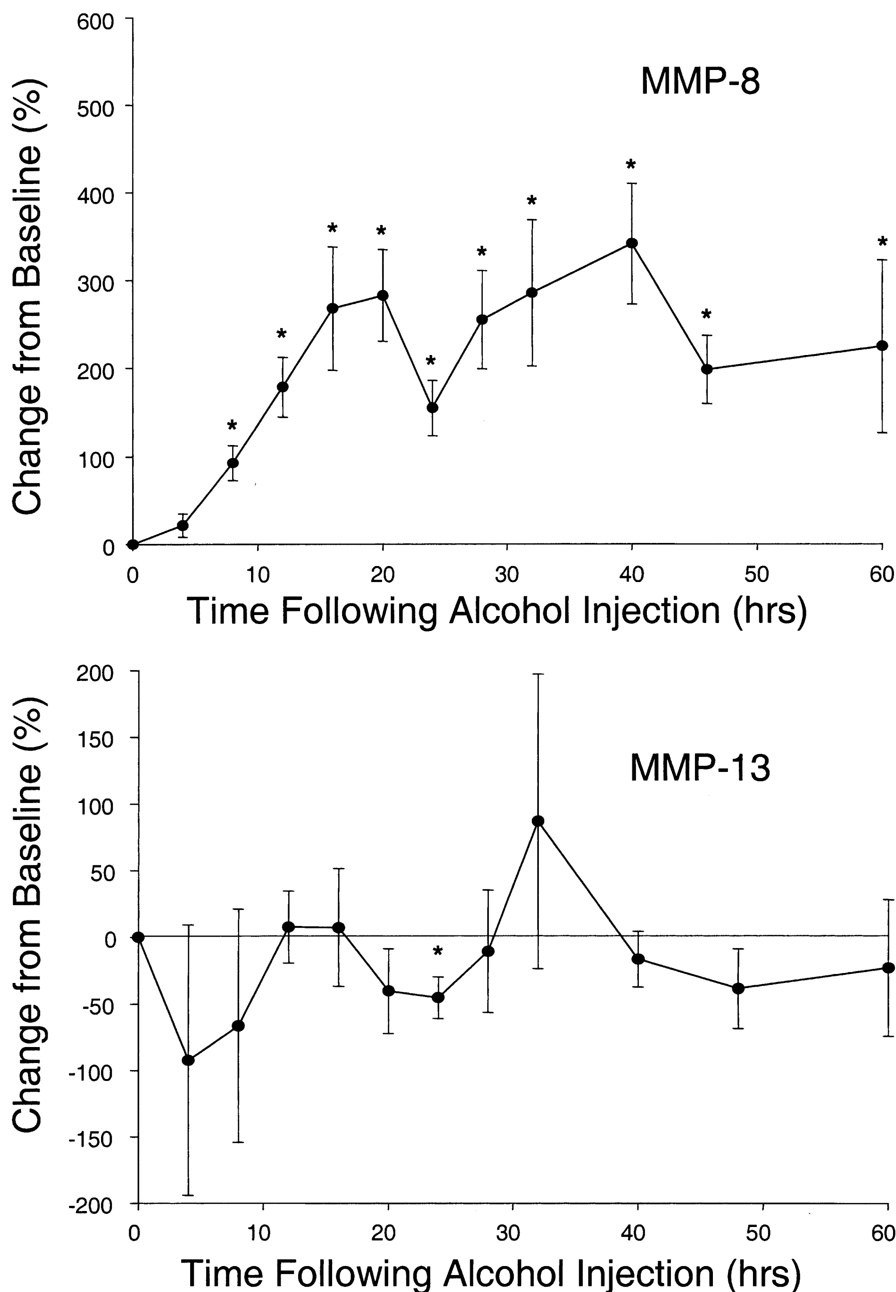

Figure 3. **(Top)** Plasma matrix metalloproteinase (MMP)-8 levels increased in a time-dependent manner up to 24 h following alcohol injection of the septal perforator artery in patients with hypertrophic obstructive cardiomyopathy and plateaued for longer periods following alcohol injection. **(Bottom)** A fall in plasma MMP-13 levels was detected early following alcohol injection and was significant at 24 h. *$p < 0.05$ vs. time 0; baseline values.

MMP-2, the MMP-9 gene contains multiple transcription factor binding sites and is induced in vitro by a number of cytokines (5,22). It has been demonstrated that all cell types can synthesize and release MMP-9 (1–5). For example, oxidative stress has been demonstrated to induce MMP-9 in cardiac fibroblasts (24). In isolated LV myocyte preparations, stimulation with bioactive molecules, such as tumor necrosis factor-alpha, has been shown to induce MMP-9 release (25). MMP-9 proteolytic substrates include the basement membrane components as well as the activation of other MMP species (1,3,4). In transgenic mice, MMP-9 gene deletion has been clearly demonstrated to modify the myocardial remodeling process post-MI (13). Therefore, increased levels of MMP-9 may alter the myocyte interface to the extracellular matrix and thereby facilitate LV remodeling.

The plasma levels of the interstitial collagenase MMP-8 increased markedly following alcohol-induced MI; MMP-8 has been primarily identified within neutrophils (1–5). However, recent data suggest that MMP-8 may be expressed in a number of myocardial cell types (26). Thus, the increased plasma MMP-8 levels following MI induction were likely secondary to the acute inflammatory response as well as

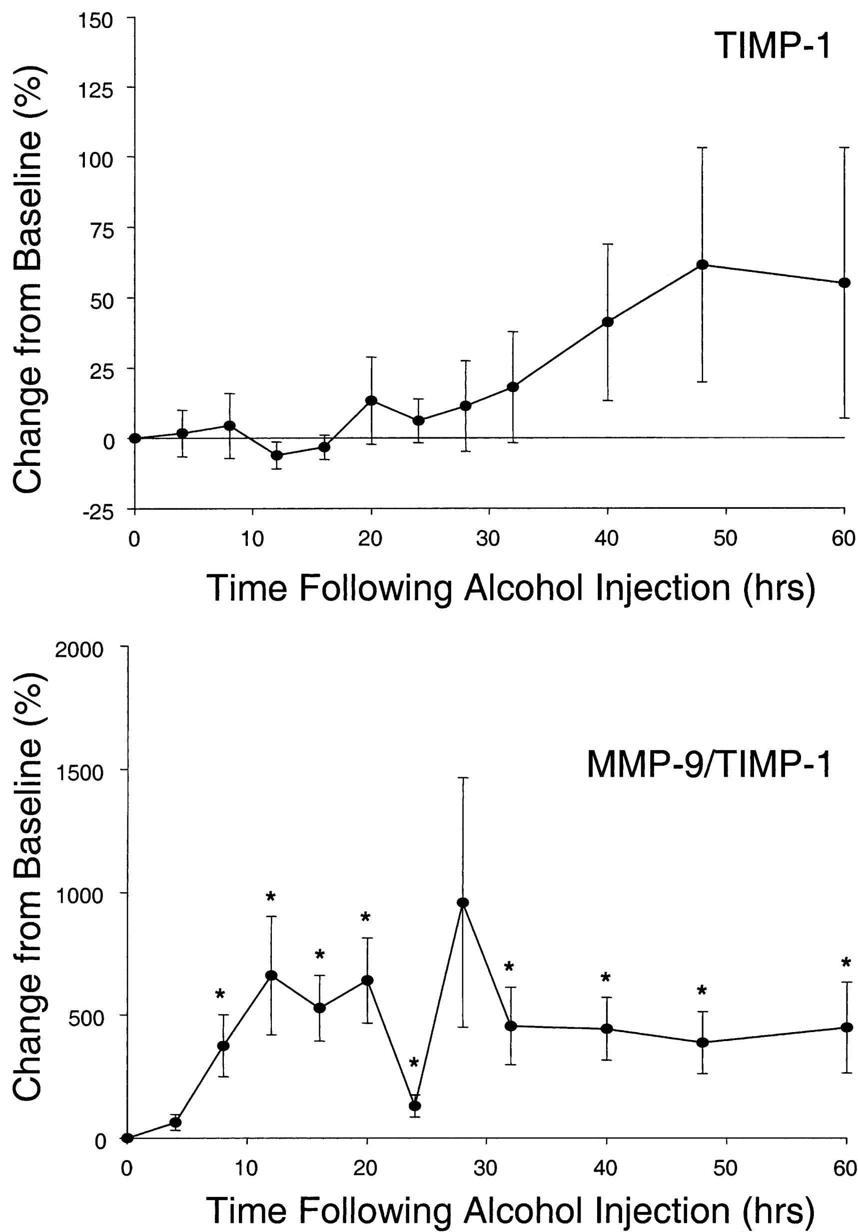

Figure 4. **(Top)** Plasma tissue inhibitor of matrix metalloproteinase (TIMP)-1 levels did not change immediately following alcohol injection, but tended to rise at later time points; however, this did not reach statistical significance ($p = 0.15$). **(Bottom)** The ratio of plasma matrix metalloproteinase (MMP)-9/TIMP-1 levels was computed for each patient and plotted as a change from baseline values. A significant increase in this ratio occurred by 6 h following alcohol injection. *$p > 0.15$ vs. time 0; baseline values.

release from the myocardium. Matrix metalloproteinase-13 has been detected in human LV myocardium and is increased in patients with end-stage CHF (7). The MMP-13 plasma levels fell slightly following alcohol-induced MI and then returned to baseline levels. The immunoassay for MMP-13 was directed against the proform of MMP-13. Thus, the slight fall in circulating MMP-13 was likely due to enhanced activation and subsequent clearance. A number of extracellular proteins have been demonstrated to be substrates for MMP-8 and MMP-13, including the fibrillar collagens. Thus, the activation of this class of MMPs following alcohol-induced MI would significantly alter myocardial extracellular structure and composition.

In the present study, TIMP-1 plasma levels did not significantly change following alcohol-induced MI in patients with HOCM. Computing the relative stoichiometry of MMPs to TIMPs can be used to define net MMP proteolytic capacity (7,27). The stoichiometry for MMP-9/TIMP-1 was computed following MI induction in patients with HOCM. By 12 h post-MI, the plasma MMP-9/TIMP-1 ratio was increased by over 500% from baseline. These alterations in MMP-9/TIMP-1 stoichiometry may favor prolonged MMP-9 activity within the myocardial

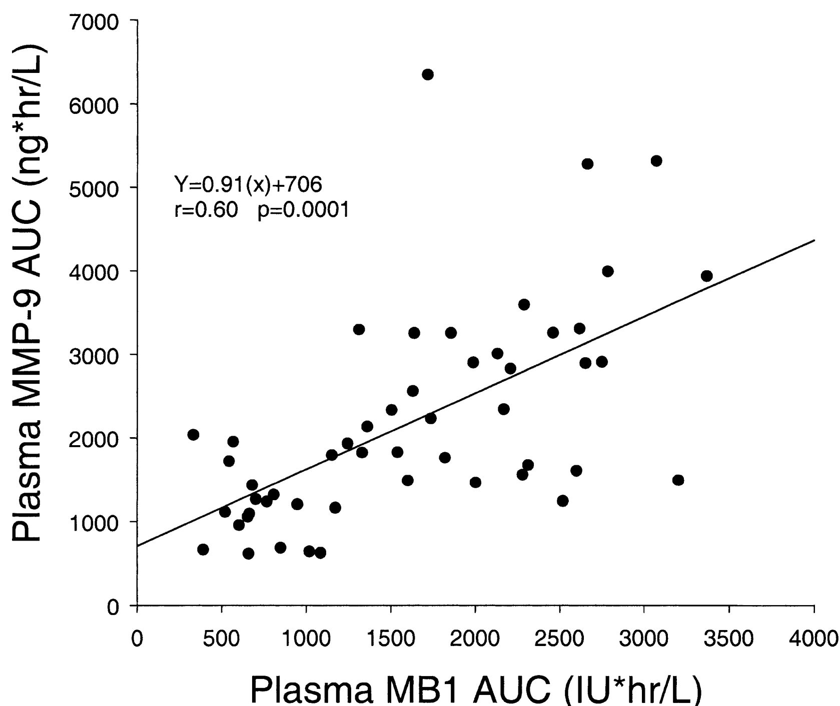

Figure 5. The area under the plasma concentration-time curve (AUC) was computed for each patient (n = 51) with respect to plasma creatine kinase MB1 fraction and matrix metalloproteinase (MMP)-9 levels. A significant linear relationship was observed between these two parameters.

tissue. Although TIMP-1 has been the best-characterized TIMP, all four of the TIMP species have been identified within the human myocardium (6,7,9). Whereas certain TIMPs preferentially bind to certain proforms of MMPs, all TIMPs bind in a 1:1 stoichiometric ratio to activated MMPs. Therefore, whether and to what degree other TIMP species are altered following alcohol-induced MI remains to be established. Because TIMPs are an important endogenous system for regulating local MMP activity, profiling changes in the circulating levels of MMP/TIMP ratios, and how these ratios may serve as a marker of MMP activational states as well as an index of myocardial remodeling, warrant further study.

Study limitations and summary. Even though the present study demonstrated an association between myocardial CK and MMP release following alcohol-induced MI, the relationship between MMP release and the extent of myocardial remodeling directly within the site of the septal lesion was not examined. Past serial studies using magnetic resonance imaging have demonstrated that remodeling of the LVOT continues for several months following alcohol-induced MI (28). Thus, future studies that serially measure LV myocardial geometry and MMP/TIMP plasma levels over an extended follow-up interval are warranted. Past studies have demonstrated that the myocardium is an important source for changes in plasma MMP levels (15,21). Although this study clearly demonstrated that release of certain MMP species into the plasma occurred following alcohol-induced MI, whether and to what degree this release was specific to the injured myocardium or was a more global myocardial process remains to be defined. This is the first study to quantify temporal changes in MMP and TIMP levels following a discrete and defined myocardial injury in humans. However, whether the results from this study with respect to alcohol-induced MI can be extrapolated to myocardial injury from coronary artery disease remains to be established. These limitations notwithstanding, the present study demonstrated a unique profile of MMPs released into the plasma following alcohol-induced MI in patients that was directly related to the degree of myocardial injury. Animal models have clearly demonstrated that MMPs play an important role in the acute wound healing response following MI and that persistent activation of this proteolytic system contributes to the myocardial remodeling process (3,11–13). The results from the present study suggest that monitoring MMP and TIMP profiles may provide a novel approach in monitoring the wound healing and myocardial remodeling process post-MI.

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