Role of matrix metalloproteinase-9 in endothelial apoptosis in chronic heart failure in mice

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Ovechkin, Alexander V., Neetu Tyagi, Walter E. Rodriguez, Melvin R. Hayden, Karni S. Moshal, and Suresh C. Tyagi. Role of matrix metalloproteinase-9 in endothelial apoptosis in chronic heart failure in mice. J Appl Physiol 99: 2398–2405, 2005.—Accumulation of oxidized extracellular matrix between endothelium and muscle is an important risk factor in the endothelium-myocytes uncoupling in congestive heart failure. Although ventricular remodeling is accompanied by increased matrix metalloproteinase (MMP)-9 activity, it is unclear whether MMP-9 plays a role in endothelial apoptosis in chronic volume overload congestive heart failure. We tested the hypothesis that, in chronic volume overload, myocardial dysfunction involves endocardial endothelial (EE) apoptosis in response to MMP-9 activation, extracellular matrix accumulation, and endothelium-myocytes uncoupling. Arteriovenous fistula (AVF) was created in control (FVB/J) and MMP-9 knockout (MMP-9KO; FVB.Cg-Mmp9tm1Tvu/J) mice. Sham surgery was used as control. Mice were grouped as follows: wild type, n = 3 (sham control); MMP-9KO, n = 3 (sham); AVF, n = 3; and MMP-9KO + AVF (n = 3). Heart function was analyzed by M-mode and Doppler echocardiography, and with a pressure-tipped Millar catheter placed in the left ventricle of anesthetized mice 8 wk after AVF. Apoptosis was detected by measuring caspase-3, transerase-mediated dUTP nick-end labeling (TUNEL), and CD-31 by immunolabeling. Protease-activated receptors-1, connexin-43, and a disintegrin and metalloproteinase (ADAM)-12 expression were measured by Western blot analyses. MMP-2 and MMP-9 are the most robustly increased during the early and late phase of CHF, respectively (28).

Different stimuli, including cardiac mechanical stress and overload, have been found to increase the rate of myocardial apoptosis, a process of programmed cell death (10). It has been found that myocyte apoptosis is one of the factors in developing CHF, but the role of endothelial apoptosis in progression of cardiac dysfunction remains controversial (17). The capillary endothelium, strategically located between flowing blood and underlying cardiac muscle, plays an important role in controlling myocardial performance (19). In fact, 16% of the myocardium consists of capillaries, including lumen and endothelium (11). We hypothesized that, in a chronic heart volume overload model and the late phase of CHF, myocardial dysfunction involves endothelial apoptosis in response to MMP-9 activation, ECM accumulation, and endothelial-myocyte (E-M) uncoupling.

Previously, our laboratory demonstrated that tissue inhibitor of metalloproteinase-4 (TIMP-4) ameliorated the endothelial cell apoptosis in part by inhibiting MMPs (22). To demonstrate a direct role of MMP in apoptosis, we tested the hypothesis that ablation of the MMP-9 gene can also alleviate the endothelial cell apoptosis in heart failure.

MATERIALS AND METHODS

All mice were exposed to a similar environment and all animal procedures were approved by the Institutional Animal Care and Use Committee of the University of Louisville Medical Center. Male mice aged 8–12 wk, MMP-9 knockout (MMP-9KO; FVB.Cg-Mmp9tm1Tvu) and FVB/NJ controls (2), were obtained from Jackson Laboratories (Bar Harbor, ME). An arteriovenous fistula (AVF) was created between the aorta and the caudal vena cava ~0.5 cm below the left kidney with the use of a 30-gauge needle as described (7) in tribromoethanol-anesthetized mice (100 mg/kg ip; n = 12) (16). Mice were divided into four groups: 1) WT (FVB/NJ control); 2) WT plus AVF; 3) MMP-9KO; and 4) MMP-9KO + AVF (n = 3 in each group). Because it is known that the heart became decompensated after 8–10 wk of AVF-induced chronic volume overload (21), mice were anes-

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were collected (5). LV size and the thickness of LV wall were measured. Only M-mode echocardiography with a Hewlett-Packard Sonos 7770 echocardiographic system equipped with a 15-MHz shallow-focus 15-6L phased-array transducer was used for measurements of LV function. The transducer probe was placed on the left hemithorax of the mice in the partial left decubitus position. Two-dimensionally targeted M-mode echocardiograms were obtained from a short-axis view of the LV at or just below the tip of the mitral-valve leaflet. LV size and the thickness of LV wall were measured. Only M-mode echocardiography with well-defined continuous interfaces of the septum and posterior wall were collected (5).

**Measurements of aortic and LV blood pressure.** The Millar transducer was calibrated manually using a mercury manometer. The arterial blood pressure, heart rate, and systolic and diastolic blood pressures were measured by a pressure-tipped Millar transducer (SPR-249A) inserted into the right common carotid artery. Ten minutes after stabilization, the aortic pressure was measured by advancing the catheter into the LV. The catheter was connected to a pressure transducer (Micro-Med) positioned at the level of the heart. Ten minutes after the insertion of the catheter, LV variables were measured (4). LVESP, LVEDP, and +dP/dt/MAP were measured. At the end of the experiment, the anesthetized mice were prepared for the excision of the lungs and arrested heart.

**MMPs activity.** Zymography using 1% gelatin gels were performed on LV tissue homogenates as described (29).

**Table 1. Gravimetric and hemodynamic data**

<table>
<thead>
<tr>
<th></th>
<th>WT (n = 3)</th>
<th>MMP-9KO (n = 3)</th>
<th>AVF (n = 3)</th>
<th>MMP-9KO+AVF (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>27.3 ± 0.4</td>
<td>26.2 ± 0.5</td>
<td>27.1 ± 0.6</td>
<td>26.3 ± 0.3</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>0.15 ± 0.012</td>
<td>0.16 ± 0.013</td>
<td>0.232 ± 0.025*</td>
<td>0.18 ± 0.014</td>
</tr>
<tr>
<td>Lungs weight, g</td>
<td>0.3 ± 0.04</td>
<td>0.31 ± 0.05</td>
<td>0.54 ± 0.07*</td>
<td>0.39 ± 0.06</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>409.2 ± 9.5</td>
<td>428.3 ± 8.9</td>
<td>398.5 ± 10.1</td>
<td>399.2 ± 7.4</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>1.2 ± 0.6</td>
<td>1.4 ± 1.0</td>
<td>8.4 ± 2.9*</td>
<td>2.6 ± 0.8</td>
</tr>
<tr>
<td>LVESP, mmHg</td>
<td>112.7 ± 1.6</td>
<td>110.9 ± 2.0</td>
<td>96.4 ± 1.8*</td>
<td>99.6 ± 1.3</td>
</tr>
<tr>
<td>LVESP/heart weight</td>
<td>746.7 ± 133.3</td>
<td>687.5 ± 153.9</td>
<td>414.4 ± 72*</td>
<td>559.7 ± 92.3</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>69.8 ± 0.7</td>
<td>67.7 ± 0.6</td>
<td>71.8 ± 1.1</td>
<td>62.3 ± 0.7</td>
</tr>
<tr>
<td>−dP/dt, mmHg/s</td>
<td>5491 ± 201</td>
<td>4838 ± 288</td>
<td>3156 ± 243*</td>
<td>4391 ± 298</td>
</tr>
<tr>
<td>+dP/dt, mmHg/s</td>
<td>9050 ± 435</td>
<td>8236 ± 378</td>
<td>7666 ± 443</td>
<td>7997 ± 478</td>
</tr>
<tr>
<td>(--dP/dt)/MAP, s⁻¹</td>
<td>81.7 ± 6.3</td>
<td>82.4 ± 3.2</td>
<td>40.4 ± 4.1*</td>
<td>68.9 ± 8.3</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>2.81 ± 0.08</td>
<td>2.78 ± 0.07</td>
<td>3.91 ± 0.11*</td>
<td>2.91 ± 0.08</td>
</tr>
<tr>
<td>LVEDs, mm</td>
<td>1.69 ± 0.07</td>
<td>1.65 ± 0.07</td>
<td>2.79 ± 0.12*</td>
<td>1.83 ± 0.09</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>0.74 ± 0.03</td>
<td>0.72 ± 0.04</td>
<td>0.85 ± 0.05*</td>
<td>0.79 ± 0.05</td>
</tr>
<tr>
<td>LVPWs, mm</td>
<td>1.12 ± 0.03</td>
<td>1.08 ± 0.03</td>
<td>1.29 ± 0.04*</td>
<td>1.08 ± 0.03</td>
</tr>
<tr>
<td>FS, %</td>
<td>39.86 ± 0.85</td>
<td>40.65 ± 1.1</td>
<td>28.65 ± 1.03*</td>
<td>37.45 ± 1.33</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of animals. MMP, matrix metalloproteinase; AVF, arteriovenous fistula; LVEDP and LVESP, left ventricular end-diastolic and end-systolic pressure, respectively; MAP, mean arterial pressure; LVEDd and LVEDs, left ventricular end-diastolic and end-systolic diameter, respectively; LVPWd and LVPWs, left ventricular end-diastolic and end-systolic wall thickness, respectively; FS, fractional shortening. *P < 0.05. Note that there were no significant differences between the data obtained from control (WT), MMP-9 knockout (MMP-9KO), and MMP-9KO+AVF groups.

**Fig. 1.** Histological analysis of left ventricle (LV) at 8 wk after arteriovenous fistula (AVF). Frozen tissue sections were labeled with trichrome for collagen. A: control (WT) mice; B: AVF mice. Arrows indicate deposition of collagen (blue). Note that the heart with AVF is hypertrophic. Insets: ×20 magnification. C: WT mice; D: AVF mice. Note greater collagen expression in overloaded heart.
cDNA by RT. The RNA samples were incubated (70°C, 5 min) with 1 μl of oligoprimers in a final volume of 5 μl. Samples then were incubated in 15 μl of a reaction buffer. Expression level of the RNA was determined from 2 μl of each cDNA sample for amplification of the housekeeping gene, glycerol aldehyde phosphate dehydrogenase (mouse GAPDH: GenBank accession no.: NM-008084). Upstream (5'-TACATTTCCTTCCCTTACT-3') and downstream (3'-CCA-CATTGACGTCCAGAGA-5') primers for MMP-2 and -9 were synthesized based on the mouse MMP-2 and -9 mRNA sequences (GenBank). Denaturation step was set for 30 s at 94°C, annealing for 60 s at 60°C, and extension for 90-s cycles at 72°C. Glucose-3-phosphate dehydrogenase samples were taken after 30 cycles, and MMPs samples were taken after 35 cycles. PCR reactions were performed with a thermal cycler (Perkin-Elmer 9600) in 50 μl of 1× PCR buffer, 1.5 mM MgCl2, each primer at 0.2 μM, 200 μM deoxynucleotide triphosphate, and 1 U of Taq DNA polymerase (Invitrogen). Amplification mixtures were analyzed by 1% agarose gel electrophoresis.

Western blot analysis of protease-activated receptors-1, a disintegrin and metalloproteinase-12, connexin-43, and caspase-3. LV tissue homogenates were prepared, analyzed on 10% SDS-PAGE, and transferred to polyvinylidene difluoride membranes. Twenty-five micrograms of total protein were loaded onto each lane. The membranes were blotted with anti-caspase-3, protease-activated receptor-1 (PAR-1), a disintegrin and metalloproteinase-12 (ADAM-12), or connexin-43 monoclonal antibodies (Cell Signaling and Chemicon) as previously described (4). The secondary IgG-alkaline phosphatase was used for detection. Actin blots were used as a loading control. The bands were scanned and normalized with actin intensity. The gels were stained with Commassie blue for protein.

Fig. 2. Effects of AVF on total matrix metalloproteinase (MMP) activity (A). MMP-9 (B) and MMP-2 gene expression (C) in the LV by quantitative RT-PCR analysis. Values are means ± SE. AU, arbitrary units. *p < 0.05 compared with all groups. †p < 0.05 compared with all groups except MMP-9KO group. Mr, molecular marker.

Fig. 3. Comparison of effects of AVF on protease-activated receptor-1 (PAR-1) expression in LV by Western blot analysis. Values are means ± SE; n = 3 in each group. *p < 0.05 compared with all groups. †p < 0.05 compared with all groups except AVF. Note that increased PAR-1 expression in AVF group was prevented in MMP-9KO + AVF group.

Fig. 4. Comparison of effects of AVF on ADAM-12 expression in LV by Western blot analysis. Values are means ± SE; n = 3 in each group. *p < 0.05. Note that increased ADAM-12 expression in AVF group was prevented in MMP-9KO + AVF group.
Transferase-mediated dUTP nick-end labeling and CD-31 immunohistochemical labeling. To determine whether CHF caused endothelial and endocardial injury, 5-μm serial heart tissue sections from snap-frozen blocks were labeled with transferase-mediated dUTP nick-end labeling (TUNEL: Upstate Cell Signaling Solutions, Lake Placid, NY) according to the instructions of the manufacturer for apoptosis identification by nicked DNA labeling. Endothelial cells were marked using FITC-labeled anti-mouse CD31/PECAM-1 antibody (Southern Biotech, Birmingham, AL) on serial tissue sections from the same frozen blocks. Quantitative analysis was performed using Image Pro program (IMAGE-PRO Media Cybernetics, Silver Spring, MD), and data was expressed in marker area (pixels²) averaged form five randomly selected fields per slide.

Statistical analysis. Values are reported as means ± SE. Differences between groups were compared by one-way ANOVA with repeated measurements and multiple comparisons (consideration given to within-sample variability of observations). A probability level of \( P < 0.05 \) was used to indicate statistical significance.

RESULTS

Hemodynamic variables. Mean arterial blood pressure and heart rate (67.9 ± 0.8 mmHg, \( n = 3 \) and 408.8 ± 9 beats/min, \( n = 3 \), respectively) were not significantly different between all groups (12 animals). Although the body weight (26.7 ± 0.5 g) was not significantly different between all groups, the heart weight was significantly increased in AVF mice compared with controls (WT and MMP9KO groups) (Table 1), suggesting cardiac hypertrophy in mice with chronic volume overload. The histological data revealed biventricular hypertrophy in AVF mice. In addition, compared with WT, the focal fibrosis...
was also increased in LV and right ventricle in the animals from the AVF group (Fig. 1). In contrast, there was no hypertrophy or focal fibrosis in WT, MMP-9KO, and MMP-9KO + AVF mice.

In AVF animals, compared with controls, LVESP was decreased and LVEDP was increased. In those animals, the $-\frac{dP}{dt}$ normalized by mean arterial pressure was significantly decreased, suggesting that LV diastolic relaxation is decreased in AVF animals compared with controls (Table 1). LV systolic dysfunction in AVF animals was shown by LVESP-to-heart weight ratio (Table 1). In contrast, both diastolic and systolic dysfunctions were prevented in MMP-9KO + AVF mice (Table 1).

**Role of MMP-9 in cardiac remodeling.** Total MMP activity in heart tissue was significantly increased in the AVF group compared with WT. The quantitative RT-PCR data also showed increased MMP-9 mRNA expression in heart tissue from AVF animals (Fig. 2). Although the basal levels of MMP-2 were higher in MMP-9$^{-/-}$ mice than in WT mice, there was a significant increase in MMP-2 expression in AVF compared with both WT and MMP-9KO groups (Fig. 2). Compared with WT, the level of PAR-1 expression was significantly increased in AVF animals, but ablation of MMP-9 in animals that underwent AVF ameliorated the increase (Fig. 3). Similarly, the heart tissue expressions of ADAM-12 and connexin-43, which significantly increased in the AVF group, were attenuated in MMP-9KO + AVF animals (Figs. 4 and 5). These data suggest that AVF-induced MMP-9 is involved in PAR-1, ADAM-12, and connexin-43 overexpression.

**Cardiac function.** The LV dilatation and LV wall thickness measured by echocardiography revealed that the LV wall-to/LV end-diastolic diameter (EEDD) ratio was significantly decreased in the AVF group compared with controls, and ablation of MMP-9 in MMP-9KO + AVF animals prevented this decrease (Fig. 6). These data suggest a role of MMP-9 in cardiac dilatation in CHF.
Endothelial and myocyte apoptosis. There was significant induction of caspase-3 in AVF hearts compared with WT or MMP-9KO, with or without AVF (Fig. 7). There were higher numbers of TUNEL-positive cells (Fig. 8) in heart tissue of AVF animals compared with controls. Although the general morphological appearance of the MMP-9KO/AVF heart tissue (Fig. 8C) may appear to be different from WT, there was no quantitative or qualitative difference when compared with MMP-9KO alone (no AVF) or WT. The increase in caspase-3 activation and TUNEL was prevented in MMP-9KO + AVF animals. The colabeling of TUNEL and CD-31, as a marker for endothelial cells in serial heart tissue sections, demonstrated that endothelial cells underwent apoptosis (Fig. 9). Based on TUNEL-positive and CD-31 positive vs. CD-31-negative cells, we estimated that 75% of TUNEL-positive cells were endothelial origin (Table 2). Besides those cells, there were other TUNEL-positive cells, suggesting that endothelial, as well as myocyte apoptosis, is involved in this chronic heart failure model (Table 2). The induction of caspase-3 and in situ TUNEL in the LV of AVF suggest involvement of MMP-9 in transduction of apoptosis.

DISCUSSION

We and others suggested the role of endocardial apoptosis in the cardiac dysfunction in CHF (27, 31). However, the mechanism of this phenomenon is still unknown (1, 18). The results of the present study show that impaired cardiac function in chronic volume overload CHF is associated with endothelial and myocyte apoptosis and is accompanied by endothelial-myocyte uncoupling in response to MMP-9 activation. MMPs are potential mediators of cardiac remodeling and progression to heart failure. Previously, we showed that, during the compensatory phase of CHF, MMP-2 is increased and MMP-9 is overexpressed (23). Others have suggested that targeted deletion of MMP genes in mice attenuates cardiac remodeling in acute (6, 9, 26) and in LV pressure overload chronic heart failure models (10). In the present study, we demonstrated molecular and cellular mechanisms that mediate the pathogenesis of chronic heart failure and the involvement of MMPs in cardiac remodeling and dysfunction.

The histological and gravimetical data suggested that cardiac hypertrophy in mice with chronic volume overload heart failure were associated with ECM accumulation (Fig. 1). We obtained histological data on MMP-9KO similar to the data obtained by others (6) and found that there was no significant difference in MMP-9KO (control and AVF). The total MMP-2 and MMP-9 expressions were significantly increased in animals from the AVF group (Fig. 2). We measured total MMP and MMP-9 expression in MMP-9KO animals (control and AVF) and found that there was no expression of MMP-9 in control and AVF. However, there was increased MMP-2 expression (Fig. 2). This finding is in part due to a compensatory response to MMP-9 ablation (6). In addition, the lung weight from the AVF animals was significantly higher than controls, suggesting pulmonary edema (Table 1). A significant decrease in the LV wall-to-LV EDD ratio, changes in LVESP and LVEDP, and decrease in LV contraction and relaxation suggested that cardiac function in those animals was also impaired (Table 1 and Fig. 6). The ablation of MMP-9 in animals with AVF significantly normalized LV parameters and clearly indicates that MMP-9 plays a crucial role in pathogenesis of chronic heart failure. These results are consistent with previous reports that MMP-9 inhibition, or targeted deletion of the MMP-9 gene in mice, attenuates LV dilation and decreases

Fig. 10. Overall hypothesis: stress and progression of congestive heart failure are associated with activation of latent MMP, which activates PAR receptors and subsequently activate ADAM-12. This, in turn, induces MMP-9- and ADAM-12-dependent oxidized extracellular matrix (ECM) accumulation, leading to endothelial-myocyte (E-M) uncoupling and endothelial apoptosis. EC, endothelial cell; MC, myocyte cell.

Table 2. Morphological data

<table>
<thead>
<tr>
<th></th>
<th>WT (n = 3)</th>
<th>MMP-9KO (n = 3)</th>
<th>AVF (n = 3)</th>
<th>MMP-9KO + AVF (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD31-positive cells/field</td>
<td>2,456±232</td>
<td>2,277±256</td>
<td>1,845±296</td>
<td>1,978±273</td>
</tr>
<tr>
<td>TUNEL-positive cells/field</td>
<td>103±23</td>
<td>87±26</td>
<td>978±32*</td>
<td>198±39†</td>
</tr>
<tr>
<td>CD31/TUNEL colocalized cells/field</td>
<td>63±15</td>
<td>56±18</td>
<td>645±22*</td>
<td>135±26†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of animals. *P < 0.05 compared with all groups. †P < 0.05 compared with WT or MMP-9KO group.
collagen accumulation in the infarcted area after experimental myocardial infarction (6), after AVF (3), or after pressure overload (10).

Our hypothesis was that impaired cardiac function in CHF could be the consequence of endothelial apoptosis in response to E-M uncoupling due to ECM accumulation in the myocardium (Fig. 10). We found that the levels of caspase-3 activation and numbers of TUNEL-positive cells in heart tissue of AVF animals were significantly higher than in controls (Figs. 7 and 8). Serial heart tissue sections were immunochemically developed with CD-31 antibody as a label for endothelial cells and TUNEL for apoptosis. This TUNEL/CD-31 colabeling showed that endothelial as well as myocyte apoptosis is involved in pathogenesis of CHF (Fig. 9). Previously, our laboratory reported that activated PAR-1 led to cardiac remodeling (21) and that inhibition of MMPs prevented connexin-43 degradation and ameliorated heart failure (13). In the present study, we found that, other than increased expression of PAR-1, ADAM-12, an enzyme involved in cell adhesion and myoblast differentiation and fusion (15), was also overexpressed in AVF animals. This finding suggests that increased activity of PAR-1 could lead to activation of several proteolytic events. It was shown previously that reduced connexin-43 expression produces uncoupling between myocytes (24). In our model, increased expression of connexin-43 might be associated with E-M uncoupling due to a compensatory response to cell disintegration by ADAM-12. However, further studies are needed to confirm the relationship between PAR-1 and connexin-43 remodeling by ADAM-12. The results of our experiments show that, in animals from MMP-9KO + AVF, the increase in the levels of apoptosis was prevented (Figs. 8 and 9). In addition, PAR-1, ADAM-12, and connexin-43 expressions were also normalized (Figs. 3–5).

Limitations. TUNEL detection alone is not enough to confirm apoptotic death (12, 25, 30). Therefore, we measured the levels of caspase-3 and showed that a caspase-3 inhibitor ameliorated the endothelial cell apoptosis (22). Here, we suggested that caspase-3 was significantly induced in AVF hearts compared with the sham or the MMP-9−/− mouse hearts with and without AVF (Fig. 7). These results suggested apoptosis in the AVF hearts, in part, due to activation of caspase-3.

The connection between PAR-1 and connexin-43 may not be strong. However, in light of our human heart end-stage failure data, in which we showed that connexin-43 synthesis and degradation both were increased and MMPs were activated in CHF (22). It is a logical extension of the idea that volume overload stress activated the MMP that, in turn, activated PAR-1, leading to induction of connexin-43 in AVF.

In summary, the results of the present study demonstrate that, in chronic volume overload model of CHF in mice, impaired cardiac function is associated with endothelial and myocyte apoptosis. The mechanism of these phenomena involves activation of MMP-9, leading to cardiac remodeling and E-M uncoupling. Our study also shows that MMP-9 has a major role in ventricular remodeling associated with endothelial and myocyte apoptosis (Fig. 10).

GRANTS

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REFERENCES


