Left Ventricular Extracellular Matrix Remodeling in Dogs with Right Ventricular Apical Pacing

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Left Ventricular Remodeling in Pacing Dogs. ***Introduction:*** **Right ventricle (RV) apical pacing is associated with increased incidence of heart failure due to left ventricle (LV) desynchronization. We aim to investigate extracellular matrix (ECM) remodeling of the LV in dogs with atria-sensed RV apical pacing.**

Methods and Results: **Dogs with pacemakers underwent AV nodal ablation. After 12 weeks of atria-sensed obligatory RV pacing, LVs were separated into septum and lateral wall for analysis. Zymographic activity, including matrix metalloproteinase-2 (MMP-2), MMP-9, tissue inhibitors of metalloproteinase-1 (TIMP-1), TIMP-3, collagen transcript expression, and histology were examined in opposite portions of the LV to identify possible ECM remodeling changes by RV apical pacing. Compared with sham-operated dogs, increased interstitial fibrosis and fragmentation of myofibrils was found in the LV lateral wall in the pacing group. Collagen type II mRNA showed a significant 2-fold increase in the LV lateral wall in the pacing group. Although collagen type I mRNA was increased, the difference was not significant. Zymography demonstrated MMP-9 activity was enhanced in both the LV lateral wall and septum in the pacing group, but MMP-2 activity was enhanced in the LV lateral wall. Immunfluorescence stain confirmed the activation of MMP-2 and MMP-9 in the LV lateral wall in the pacing group. Protein expression of TIMP-1 and TIMP-3 showed regional differences in the pacing group and both proteins were increased in the LV lateral wall.**

Conclusion: **LV dyssynchrony by RV apical pacing elicits heterogeneous ECM remodeling in the LV. These findings assist in the elucidation of the pathophysiology of LV desynchronization.** *(J Cardiovasc Electrophysiol, Vol. 21, pp. 1142-1149, October 2010)*

dyssynchrony, heart failure, matrix metalloproteinase, remodeling, ventricular pacing

Introduction

Left ventricular (LV) dyssynchrony continues to be an important issue in heart failure management despite the myriad of reports regarding the success of cardiac resynchronization therapy.[1,2] Several clinical studies have addressed the deleterious effect of LV desynchronization in heart failure patients;[3] however, whether LV desynchronization on a structurally normal heart elicits adverse tissue remodeling is not well understood. Artificial right ventricle (RV) apical pacing creates LV desynchronization by initiating impulse from local myocardium and bypassing His-Purkinje system. The consequence of abnormal impulses conduction is LV septum contracts first and stretches the not-yet-activated remote LV lateral wall. The stretched LV lateral wall requires more energy to contract and stretch the other regions that are already activated.[4] This abnormal stretching is a key mediator of the adverse tissue remodeling process.

RV apical pacing as a treatment modality for bradyarrhythmia has demonstrated to increase the incidence of heart failure hospitalization in many long-term clinical studies.[5,6] The MOST trial demonstrated that the risks of heart failure development were proportional to cumulative ventricular pacing burden regardless of pacing mode.[7] This study also reported traditional RV apical pacing resulted in a reduction in the LV ejection fraction and adverse LV remodeling in patient with preexisting normal systolic function, and these effects were prevented by biventricular pacing.[8] These clinical findings implicate that ventricular desynchronization by RV apical pacing is associated with a higher incidence of heart failure development. But molecular evidence of RV-associated adverse effects based on a structurally normal heart model is still lacking.

Cardiac remodeling involves the replacement of cardiomyocytes with fibrotic tissue and extracellular matrix (ECM) remodeling. Matrix metalloproteinases (MMPs), zinc-dependent ECM-degrading endopeptidases, and tissue inhibitors of metalloproteinases (TIMPs) are both important regulators of tissue remodeling.[9-11] In this study, an atrium-sensed obligatory RV pacing canine model was employed to investigate ECM remodeling of the LV with desynchronization. It was hypothesized that ECM remodeling is evident in

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the late-activated and stretched portion of the LV by dyssynchronous pacing.

Materials and Methods

Animal Preparation

Ten adult mongrel dogs weighing 12.3 ± 1.6 kg were randomly divided into a pacing group ($n = 6$) and a sham group ($n = 4$). All dogs were anesthetized with sodium phenobarbital (30 mg/kg, i.v.) and then intubated. Oxygen saturation and expiratory CO_2 were monitored and maintained with mechanical ventilation within physiologic range throughout the procedure. A DDD permanent pacemaker (Medtronics, Minneapolis, MN, USA) was implanted via the right internal jugular vein using the venous cut-down method. The ventricular and atrial leads were positioned at the apex of the RV and the right atrium with screw-in leads, respectively. The 6 dogs in the pacing group received radiofrequency ablation of the AV node under fluoroscopic guidance and the DDD pacemaker was programmed to VDD mode after complete AV block was achieved. The 4 dogs in the sham group received the same pacemaker implantation procedure with pacemakers maintained in an "off " status without AV nodal ablation. Both pacing and sham groups were dependent on their own intrinsic sinus rhythm. The only difference between the 2 groups was discordant ventricular contraction by RV apical pacing in the pacing group.

Twelve weeks post-pacemaker implantation, the dogs were again anesthetized and humanely euthanized. The hearts of all dogs were removed, retroperfused with cold cardioplegia, excised, and dissected into various parts for further measurements. All procedures followed the protocols approved by the Animal Care and Use Committee of the National Taiwan University.

Echocardiographic Study and Assessment of Electrical and Mechanical Dyssynchrony

Echocardiography was performed at baseline and 12 weeks after pacing to evaluate cardiac chamber size and LV contractility. Twelve-lead surface ECG was also performed at baseline and 12 weeks after pacing and the QRS wave duration was measured to assess the electrical dyssynchrony. The intraventricular mechanical dyssynchrony of the LV was assessed with speckle tracking technique. The high frame 2-dimensional images were taken and analyzed with an echocardiographic machine (Vivid 7, General Electric-Vingmed, Milwaukee, WI, USA). Peak longitudinal strain was recorded using apical 4-chamber views. After gating with the onset of the QRS complex, the time to peak longitudinal strain (Ts, in ms) was measured and averaged for at least 3 consecutive beats at the middle and basal segments of septum and lateral wall of LV.

Western Blot Analysis

Frozen LV tissues were homogenized in lysis buffer (Cell Signaling Technology, Danvers, MA, USA) and equivalent samples (confirmed by co-probing for glyceraldhyde-3-phosphate dehydrogenase, GAPDH) were loaded for gel electrophoresis. After transfer to nitrocellulose membrane, the membranes were blocked and probed overnight at 4°C with primary antibodies for TIMP-1 and TIMP-3 (Chemicon, Souffelweyersheim, France). Membranes were incubated with HRP-conjugated secondary antibodies for 1 h at room temperature. The expressed protein levels were detected by chemiluminescence and autoradiography.

Immunofluorescence and Confocal Study

The ventricular tissue sections were incubated with primary antibody (diluted 1:100 in PBS) for 1 hour at room temperature and then washed 3 times and incubated with secondary antibody in 1% BSA for 1 hour. The sections were then incubated with DAPI (diluted 1:10,000; Invitrogen, Carlsbad, CA, USA)) for DNA staining for 5 minutes and washed with PBS before being examined by laser scanning confocal microscopy. The primary antibodies were mouse antihuman MMP-2 (Millipore, Billierica, MA, USA) and rabbit antihuman MMP-9 (Assay Designs, Ann Arbor, MI, USA). The secondary antibodies were goat antimouse (Invitrogen), red color for MMP-2 and goat antirabbit, green color for MMP-9. The area of immunofluorescence stining in digital images was quantified by Image-Pro Plus software.[12]

Histologic Examination

LV tissue was cut into 3- to 5-mm slices and fixed for 7 days in buffered formalin containing 0.1 M sodium phosphate (pH 7.5) before paraffin embedding. Tissue blocks were cut into 6-μm sections and deparaffinized for Masson's trichrome stain. Five random fields were photographed under a microscope (400×). Tissue representing collagen and muscle was identified and the collagen fraction area of each was calculated by Image-Pro Plus software. The operator was blinded to the experimental groups during the analysis.

Endocardium and inner half of myocardium derived from LV lateral wall and LV septum were measured for comparison of fibrosis between LV septum and lateral wall. The epicardium and outer half of myocardium derived from LV lateral wall and RV septum were also measured for evaluation of transmural fibrotic changes.

Gelatin Zymography

Gelatin zymography was performed as previously described after myocardial extracts were isolated from frozen cardiac samples.[12] After staining with Coomassie brilliant blue, gelatinase activity were identified as clear zones against a blue background. Gelatinase activity in the gel slabs were quantified using Image-Pro Plus software (NIH, Bethesda, MD, USA).

Quantification of Gene Expression

To prepare a cDNA pool from each RNA sample, 3 μg of total RNA was reverse transcribed using MMLV reverse transcriptase (Promega, San Luis Obispo, CA, USA). Each cDNA pool was stored at −20 °C until further real-time PCR analysis. The TaqMan probe assay with forward and reverse primers and MGB probe were purchased from ABI (collagen type I, Cat. Cf02741579; collagen type II, Cat. Cf02622862; Applied Biosystems, Carlsbad, CA, USA) for real-time PCR assays. The real-time PCR reactions were performed on the Roche LightCycler Instrument 1.5 using LightCycler® FastStart DNA Master^{PLUS} Hvprobe kit (Roche, Castle Hill, Australia).

TABLE 1
Electrocardiographic and Echocardiographic Measurements

	Pacing Group (n = 6)		Sham Group (n = 4)		
	Baseline	**Post 12 weeks**	**Baseline**	**Post 12 weeks**	**P value**
Electrocardiography					
QRS wave (ms)	67 ± 2	113 ± 5	69 ± 6	69 ± 5	<0.05
Echocardiography					
LA diameter (mm)	13 ± 2	12 ± 2	12 ± 2	13 ± 2	NS
LV end-diastole diameter(mm)	30 ± 2	31 ± 3	34 ± 3	34 ± 3	NS
LV end-systole diameter (mm)	22 ± 1	21 ± 2	24 ± 2	23 ± 2	NS
LV ejection fraction (%)	58 ± 2	60 ± 4	58 ± 2	57 ± 1	NS

LA = left atrium; LV = left ventricle; NS = nonsignificant; P value from pacing group versus sham group at 12 weeks.

Statistical Analysis

All values are presented as mean ± standard deviation (SD). Paired 2-tailed *t*-test was used to assess the significance of expression differences. A value of $P < 0.05$ was considered statistically significant.

Results

After 12 weeks of obligatory RV apical pacing, transthoracic echocardiography was performed. Cardiac measurements of pacing dogs were not different from the sham dogs (Table 1). Twelve-lead surface electrocardiography showed significant widening of QRS wave in the pacing dogs compared to sham group. (QRS 113 ± 5 ms in pacing group versus QRS 69 ± 5 ms in sham group, $P < 0.05$). Measurement of mechanical dyssynchrony between the lateral wall and septum of LV by speckle-tracking image also demonstrated a significant time delay of contraction of LV lateral wall compared to LV septum in the pacing group (Table 2).

Histologic Analysis

After 12 weeks of obligatory dyssynchronous RV pacing, the LVs were dissected and separated into lateral wall and septum. The LV lateral wall from dyssynchronous pacing dogs contained cardiomyocytes associated with thinning myofibril bundles, myolysis, and an increased perinuclear space within the myofibrils (Fig. 1A and B). Masson's trichrome staining showed that myocardial ECM accumulated markedly in the interstitial space in dyssynchronous pacing dogs (Fig. 1C and D). The cardiomyocyte and ECM changes were not obvious in either the LV septum of dyssynchronous pacing dogs or the wall or septum of the LVs isolated from sham dogs.

The extent of ECM-reactive staining was measured in the lateral wall and septum of the LV. The amount of fibrosis in the LV lateral wall of the dyssynchronous pacing group was significantly greater than in the sham group (8.3 ± 1.5% in pacing group vs 3.9 ± 0.9% in sham group, $P < 0.01$); however, the difference was not significant in LV septum (4.2 ± 1.1% in pacing group vs 3.6 ± 1.3% in sham group). (Fig. 1E).

The transmural fibrosis in pacing group showed a trend of decrease toward epicardium in LV lateral wall, but the difference is insignificant (8.3 ± 1.5% in endo/myocardium vs 7.0 ± 1.1% in epi/myocardium). However, the fibrosis extent between LV septum and RV septum is similar in pacing group (4.2 ± 1.1% in LV septum vs 4.3 ± 1.2% in RV septum).

TABLE 2
Comparison of Values of Ts in the Lateral Wall and Septum of Left Ventricle Between Pacing and Sham Groups after 12 Weeks

	Pacing Group	**Sham Group**	**P value**
Heart rate (bpm)	97 ± 6	99 ± 9	NS
Ts value			
Ts basal septum	243 ± 15	218 ± 26	NS
Ts mid septum	243 ± 15	218 ± 26	NS
Ts basal lateral	313 ± 15*	208 ± 22	<0.001
Ts mid lateral	313 ± 15*	208 ± 22	<0.001

NS = nonsignificant; Ts = time to peak strain from QRS wave onset; *P < 0.05 for Ts of middle/basal lateral wall versus Ts of middle/basal septum.

Altered Expression of Collagen-Encoding Genes

Expression of ECM coding proteins was measured using quantitative real-time RT-PCR (TaqMan) technology. Two different type of collagen-coding genes, type I (1A1) and type II (2A1), were investigated. Collagen type II gene showed a 2.10 ± 0.70 fold increase in expression in the LV lateral wall of pacing dogs compared to levels measured in the sham dogs. In contrast, no significant change of expression was found in the LV septum between the pacing and sham groups. Expression of collagen type I was not different between the LV lateral wall or septum between 2 groups (Fig. 2).

Gene expression data from real-time, reverse transcription PCR, and cDNA microarray were quite similar and consistent. Specifically, collagen type II gene expression was about increased approximately 2-fold in the LV lateral wall of pacing dogs than sham dogs by both methods (i.e., real-time, reverse transcription PCR, and cDNA microarray). The average expression of collagen type I showed a trend toward an increased expression in the LV lateral wall of pacing dogs than sham group using real-time RT-PCR method, but this difference failed to reach significance due to the high variance between the pacing and sham groups.

Gelatin Zymography

To determine whether MMP activity is changed in LV myocardium after 12 weeks of dyssynchronous RV pacing, MMP zymographic gelatinase activity was examined. Gelatin zymography showed 2 predominant regions of gelatinase activity: one at 72 kDa and the other at 92 kDa. These

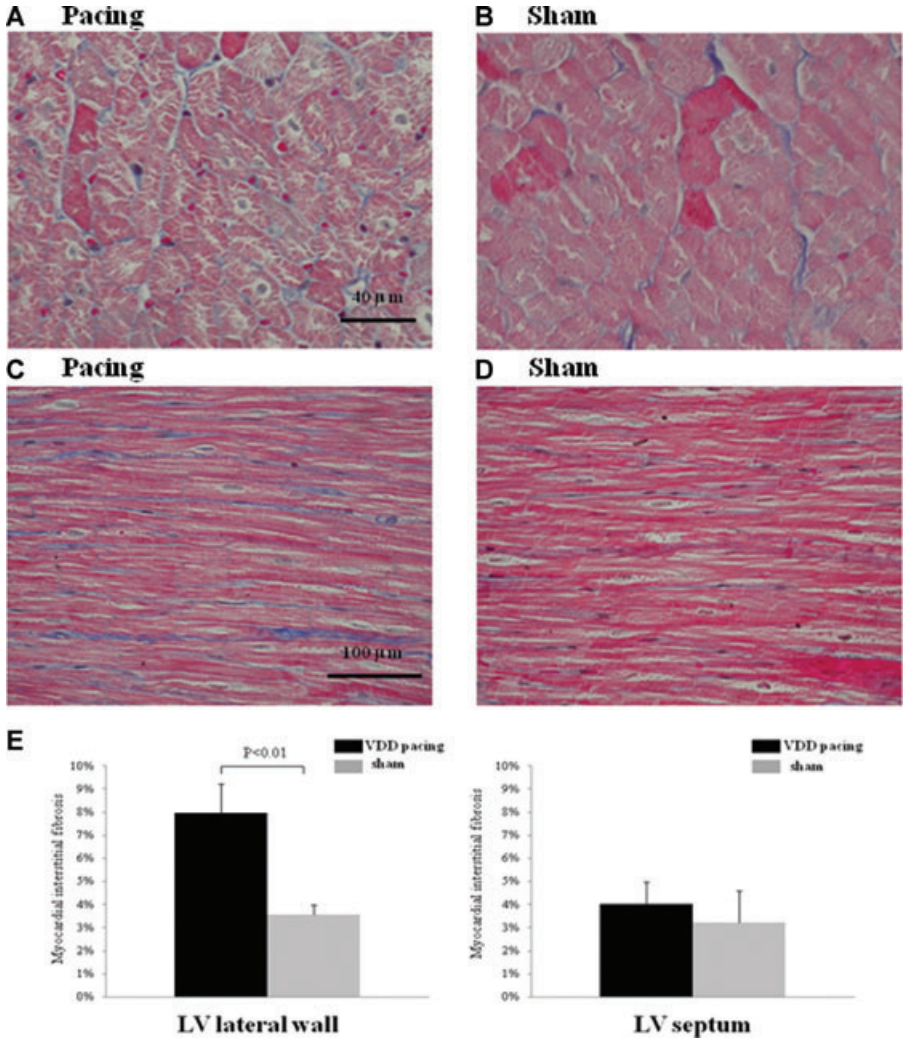

Figure 1. *Histological staining with Masson's trichrome of the lateral wall of the left ventricle (LV) in cross-section with magnification 400× (A and B) and longitudinal section with magnification 100× (C and D) isolated from the pacing (A and C) and sham groups (B and D). Area (%) of myocardial fibrosis in the LV lateral wall and LV septum of the pacing group ($n = 6$) and sham groups ($n = 4$) were measured and compared (E). Data are expressed as mean ± SD.*

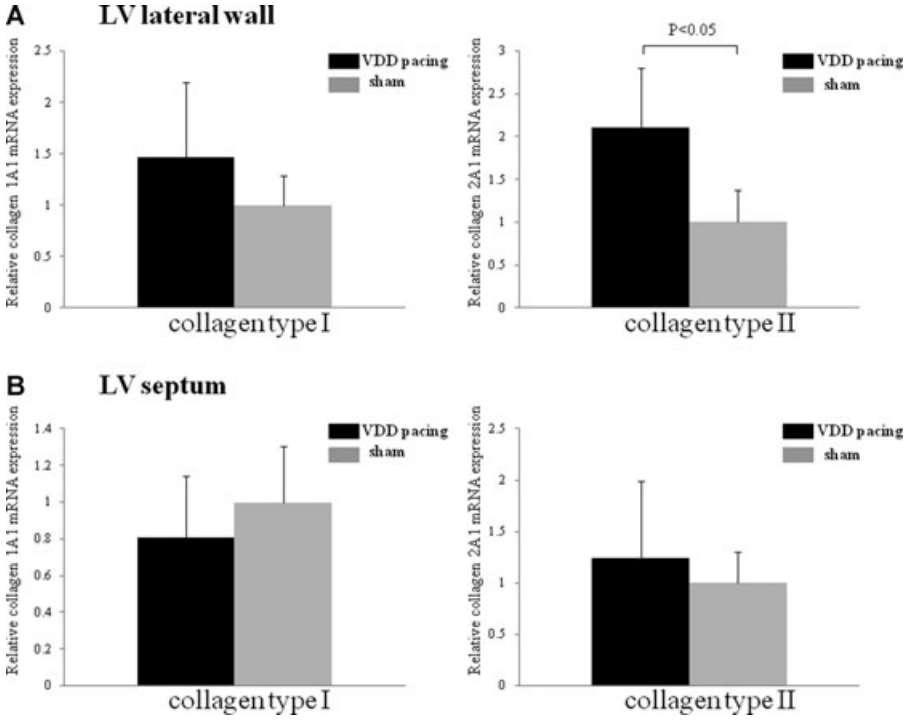

Figure 2. *Relative mRNA expression of collagen type I and type II in the lateral wall of the left ventricle (LV, A) and LV septum (B) from the pacing and sham groups. Data are expressed as mean ± SD.*

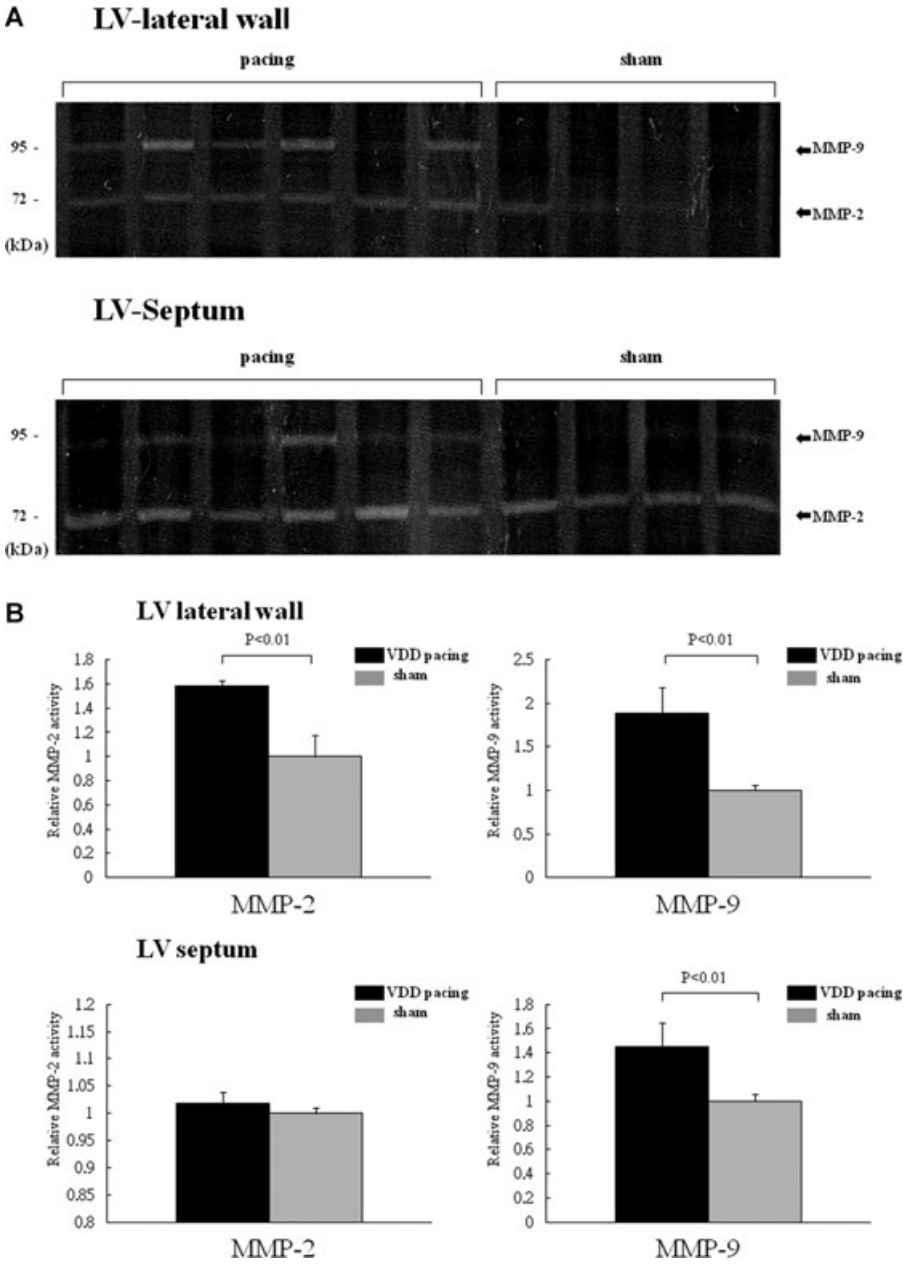

Figure 3. *(A) Zymographic activity of gelatinases in myocardial tissue. The upper panel and lower panel show activities in the lateral wall of the left ventricle (LV) and LV septum, respectively. A gelatinolytic band at 72 kDa represents MMP-2 activity while the gelatinolytic band at 95 kDa represents MMP-9 activity. Lanes on the left are extracts from the pacing group (n = 6), whereas the lanes on the right are extracts from the sham group (n = 4). (B) Relative MMP-2 and MMP-9 activity quantified via densitometry. Data are expressed as mean ± SD. MMP-9 activity was significantly increased in both the lateral wall and septum of the left ventricles (LVs) from the pacing group; however, MMP-2 activity was only significantly increased in the LV lateral wall of the pacing group.*

correspond to MMP-2 and MMP-9 activity, respectively (Fig. 3A).

Zymographic activity was quantified by densitometric analysis. Compared with the sham group, MMP-2 activity in the LV lateral wall by RV apical pacing was increased by 1.58 ± 0.04 fold ($P < 0.01$). Similar changes in MMP-2 activity in the pacing group were not observed in the LV septum (1.01 ± 0.03, nonsignificant). MMP-9 activity increased by 1.88 ± 0.29 fold ($P < 0.01$) in the LV lateral wall and 1.45 ± 0.19 fold ($P < 0.01$) in the LV septum of the pacing group compared with the sham group (Fig. 3B). MMP-9 activity was prominently elevated in both the LV lateral wall and septum, but a prominent increase in MMP-2 activity was only found in the LV lateral wall after RV apical pacing.

Immunofluorescence Staining of MMP-2 and MMP-9

Immunofluorescence staining for MMP-2 and MMP-9 was performed. MMP-2 staining with red fluorescence was abundant in the LV lateral wall of the pacing group, but scarce in the LV lateral wall of the sham group. Similarly, MMP-9 staining with green fluorescence showed increased expression in the LV lateral wall of pacing dogs compared to the expression levels observed in the sham dogs (Fig. 4). The distribution of MMP-2 and MMP-9 staining was quite different in that MMP-2 staining was mainly intracellular and MMP-9 was primarily extracellular.

Expression of TIMP-1 and TIMP-3

The protein expression of TIMP-1 and TIMP-3 was assessed by Western blotting. Both TIMP-1 and TIMP-3 expression were significantly increased in the LV lateral wall of the pacing group by 1.23 ± 0.16 ($P < 0.05$) and 1.98 ± 0.27 ($P < 0.01$) fold compared with those detected in the sham group. In LV septum, only TIMP-3 expression (1.16 ± 0.06 fold, $P < 0.01$), but not TIMP-1, was significantly different between the pacing and sham groups (Fig. 5).

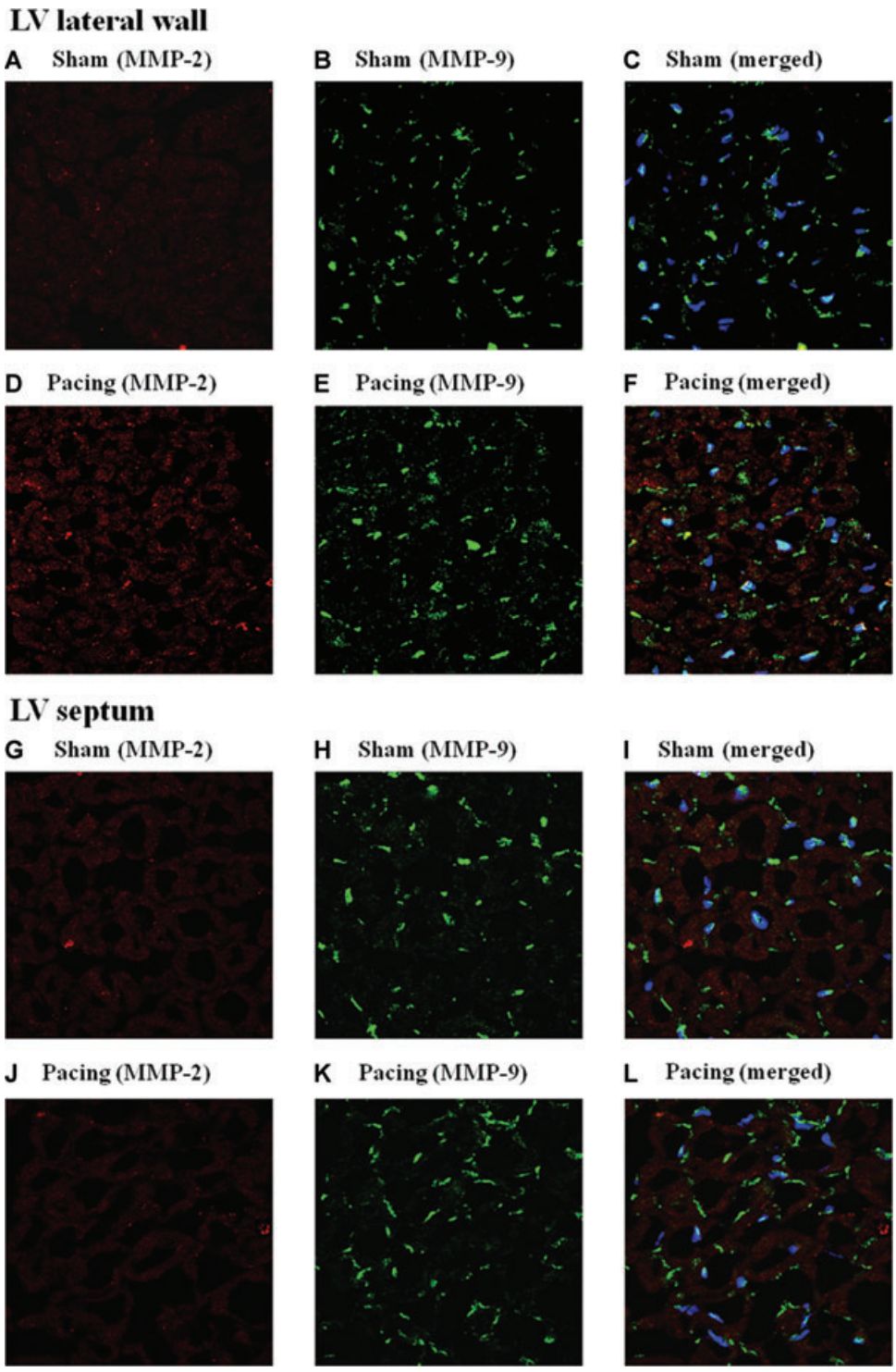

Figure 4. *Localization of MMP-2 and MMP-9 activities in the lateral wall of the left ventricle (LV) (upper panel) and in the septum of LV (lower panel) via immunofluorescence staining. Staining for both the sham (A, B, C; G, H, I) and pacing groups (D, E, F; J, K, L) are presented. Positive staining is red for MMP-2 and green for MMP-9. Nuclei are counterstained with blue (DAPI). Figure panels (C), (F), (I), and (L) show the merged images.*

Discussion

Pathophysiological changes of heart failure include both cardiomyocyte dedifferentiation and degeneration of cells with fibrosis.[13] The remodeling process of the LV triggered by RV pacing is rarely reported. A retrospective study has demonstrated ultrastructural changes including mitochondrial disorganization and fatty-fibrous tissue infiltration in young patients with long-term pacing.[14] Spragg *et al.* reported gradient changes of protein expression in the late-activated lateral wall using an atrial tachycardia pacing canine model;[15] however, the molecular evidence of RV pacing-associated adverse effects is based on heart failure model.

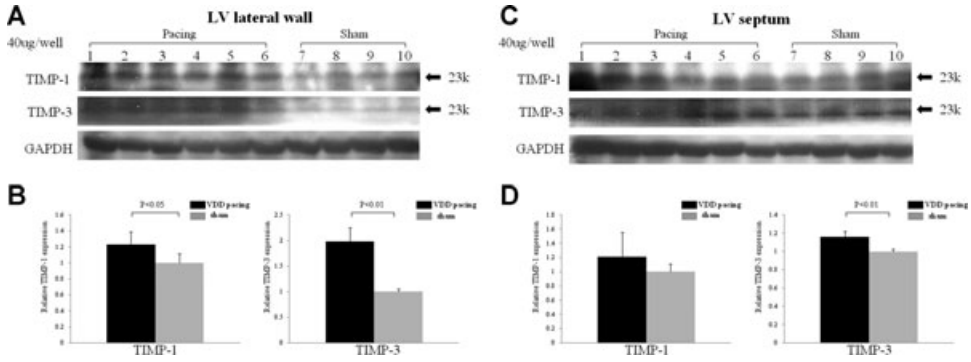

Figure 5. *Immunoblots (A and C) and relative expression (B and D) of TMIP-1 and TIMP-3 in lateral wall (A and B) and septum (C and D) of the left ventricle (LV). GADPH was used as an internal control. Data were expressed as mean ± SD.*

Interstitial fibrosis is the cardinal feature of tissue remodeling in heart failure and this study found that these changes occurred in the late-activated site (i.e., lateral wall) of the LV following RV pacing. MMPs and TIMPs, the key regulators of ECM remodeling, were differentially activated and expressed in opposite portions of the LV (i.e., late-activated lateral wall vs. early-activated septum) in RV apical pacing dogs. These 2 distinct findings confirmed LV remodeling induced by RV pacing.

Another important result generated by this study is the identification of heterogeneous tissue remodeling in the LV. These changes are considered concordant with the physiological response of asynchronous activation of the LV. The late-activated site of the LV has to create more force to contract and therefore more tissue remodeling occurred at that site than the early-activated site of the LV during RV apical pacing. Myocardial interstitial fibrosis and changes in activity of ECM-regulated MMPs were both more evident in the late-activated lateral wall of the LV than the early-activated LV septum thereby contributing to heterogeneous LV remodeling.

MMPs are a large family of ECM degrading enzymes. Which of the MMPs contribute to LV remodeling remains unclear. Several clinical and experimental studies have demonstrated altered expression of gelatinases (MMP-2 and MMP-9) related to cardiac remodeling and failure.[16,17] Genetic knockout mice (either MMP-2 or MMP-9) proved to be resistant to cardiac rupture postmyocardial infarction and showed reduced dilatation.[18,19] The differences between MMP-2 and MMP-9 on LV remodeling are unclear; however, it seems that MMP-9 plays a more important role in LV dilatation than MMP-2. Specifically, MMP-9 activity was significantly increased in a systolic heart failure model with LV dilatation,[20] and Ducharme *et al*. reported that LV dilatation was attenuated even with enhanced expression of MMP-2 after myocardial infarction in MMP-9 knockout mice.[18]

The pro-form of MMP-9 can accumulate on the cell surface and form a high-affinity complex ready for activation by specific proteinases.[21] In this study, we also found that the majority of MMP-9 deposition among the ECM suggesting that MMP-9 could serve as an extracellular pro-enzyme pool for local and rapid activation of MMP-9. In addition, this study showed enhanced MMP-9 activity in both the LV lateral wall and septum, with a more pronounced increase in the LV lateral wall. This finding is not unexpected because both the LV septum and lateral wall were sequentially under abnormal passive stretch during cardiac contraction. In contrast, MMP-2 activity was only enhanced in the LV lateral wall and not the septum. It is therefore possible that MMP-9 activity is more sensitive to abnormal mechanical stretch than MMP-2.

The activity of MMPs is inhibited by binding with TIMPs to form inactive complexes and regulate/control ECM degradation. TIMP-1 and TIMP-3 are highly inducible and more relevant to cardiac remodeling among the TIMP family.[22,23] Notably, TIMP-3 is ECM bound and recognized as a more potent inhibitor of MMP-9 than the other TIMPs.[24] TIMP-3 deficiency caused an elevation in myocardial MMP-9 zymographic activity level, leading to dilated cardiomyopathy.[25]

Together, these data support the contention that TIMP-1 and -3 are both important mediators in cardiac remodeling. A significant increase of TIMP-1 expression of the LV lateral wall was found in RV pacing dogs compared to the sham group in this study. Similarly, the enhanced expression of TIMP-3 in the LV lateral wall was more notable in the pacing group than the sham group. Interestingly, the enhanced TIMP-3 expression in both the LV lateral wall and septum of the pacing group corresponded to the changes in MMP-9 activity. It appears that the activity of TIMP-3 and MMP-9 are closely related and that TIMP-3 is a more sensitive biomarker of remodeling than other TIMPs.

In addition to inhibiting MMPs, TIMPs also play a role in promoting cell growth, inhibiting angiogenesis, and inducing apoptosis.[26] The expression of MMPs and TIMPs were simultaneously elevated in regional LV by RV apical pacing. This condition was different from prior observations in heart failure induced by myocardial infarction where expression of MMPs was up-regulated and TIMPs were down-regulated.[22,23,27] Simultaneously elevated plasma levels of TIMP-1 and MMP-9 were also reported in hypertensive patients with diastolic dysfunction and fibrosis.[28] This different pattern of ECM-regulated enzyme activation implies that the tissue remodeling process in local LV by RV pacing more closely resembles tissue remodeling in hypertension than other model systems.

Thus, both myocardial fibrosis and ECM remodeling were identified in the LV induced via the atria-sensed RV apical pacing model. Theoretically, activation of MMP activity should decrease various components of the ECM, including collagen. In this study, cardiac remodeling was associated with collagen accumulation and an alteration in various components of the ECM, including activation of MMPs. This phenomenon has been demonstrated in many studies of heart failure development.[20,23,27] Except for MMP-2 and MMP-9,

the activity of other MMPs was not studied in this study. That said, other MMPs are potentially involved in ECM remodeling and are worthy of further investigation. Enhanced activity of TIMP-1 and TIMP-3 may also obviate the effects of MMPs on collagen degradation and could modulate ECM degradation. Importantly, recent studies have indicated MMP-9 not only contributes to ECM degradation, but also modulates activation of transforming growth factor-β1 and ECM-bound vascular epithelial growth factor.[29,30] Regulation of these specific cytokines is closely linked to cardiac fibrosis development. Finally, gene expression of collagen type II was significantly increased (and collagen type I also increased, but the difference was not significant) in pacing dogs in this study. These gene expression changes together with histological findings confirm the presence of regional fibrosis in the LV by RV apical pacing.

Conclusion

In summary, this study demonstrated regional LV remodeling and changes in ECM-regulated protein expression in an RV apical pacing model in dogs. Specifically, LV dyssynchrony is associated with heterogeneous adverse tissue remodeling. These findings help cardiac researchers understand the pathophysiology of the development of heart failure caused by LV dyssynchrony and identify possible therapeutic targets to reduce cardiac remodeling in the future.

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