Matrix Metalloproteinase Levels Identify Heart Failure Patients with Higher Burden of Atrial Fibrillation

Toshimasa Okabe*, Avinash Chandra*, Shaw R. Natan#, Suzanne Adams*, Jocelyn A. Sendecki*, Melissa M. McCarey*, Reginald T. Ho*, Behzad B. Pavri*, Arnold J. Greenspon*, Daniel R. Frisch*

*Department of Medicine, Thomas Jefferson University Hospital, Philadelphia PA; #Center for Cardiac and Vascular Care, Saint Elizabeth's Medical Center, Boston, MA

INTRODUCTION/HYPOTHESIS

- Adverse cardiac remodeling and fibrosis provide an arrhythmic substrate for atrial fibrillation (AF), but the role of **matrix metalloproteinases (MMPs)** as a biomarker is not well understood. MMPs are zinc-dependent endopeptidases known to degrade substrates such as elastin, gelatin and collagen.
- In excised human atrial tissue, MMP 2 and 9 levels rise as the AF burden increases from sinus rhythm ("No AF") to non-permanent AF ("Non-Prm AF") to permanent AF ("PrmAF"). Higher plasma levels of MMPs are also associated with recurrent AF after cardioversion.
- This study sought to elucidate 1) the relationship of these biomarker levels with AF burden and 2) the predictive value of biomarkers for future AF episode in patients with severely reduced left ventricular ejection fraction (LVEF) and implantable cardioverter-defibrillators (ICDs)

METHODS

- From 2006 to 2008 we obtained **MMP 2, 3, and 9** levels from HF patients with an ICD and a reduced LVEF (<0.4) across the AF spectrum (No AF, Non-Prm AF, and PrmAF).
- We hypothesized that higher levels of MMP 2, 3 and 9 would predict new or recurrent AF during a three-year follow-up period.
  1. First, we compared the biomarker levels between the three patient groups (No AF, Non-Prm AF, and PrmAF).
  2. Second, we compared the biomarker levels between patients with and without recurrent AF during the follow-up period.
- All the available electrocardiograms and device-based diagnostics were analyzed to determine an incidence of AF. Any device-detected atrial tachyarrhythmia was classified as AF.
- Patients were classified to 6 groups based on a prior history of AF, rhythm at the time of blood draw and an incidence of AF during the follow-up period (Table 1).

Table 1. Patient classification

Group classification		Number of patients	History of AF prior to blood draw	AF at the time of blood draw	AF during follow-up
1 "No AF"		19	No	No	No
2 "Prm AF"		6	Yes	Yes	Yes
3 "New AF"		1	No	No	Yes
4 "No AF recurrence"	"Non-Prm AF"	4	Yes	No	No
5 "AF recurrence"	"Non-Prm AF"	12	Yes	No	Yes
6 "At least one AF episode"	"Non-Prm AF"	3	Yes	Data N/A	Data N/A

Table 2. MMP levels between No AF, PrmAF and Non-Prm AF

	Group 1 (n=19) "No AF"		Group 2 (n=6) "Prm AF"		Group 4-6 (n=20) "Non-Prm AF"		p-values			
	Median	IQR	Median	IQR	Median	IQR	Overall	1 vs 2*	1 vs 4-6*	2 vs 4-6*
MMP2	112.0	60.6	228.8	126.2	146.1	140.4	0.0212	0.0495#	0.1041	0.2709
MMP3	20.3	33.4	0.7	13.9	0.9	27.0	0.5414	0.5870	0.5870	0.5870
MMP9	282.6	1288.9	190.0	139.6	166.2	1033.9	0.6109	0.6520	0.6520	0.6520

*p-values adjusted for multiple comparisons
statistically significant

Figure 1. MMP2, 3, 9 levels by group

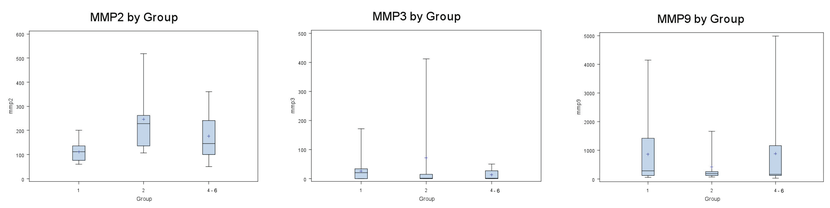

Table 3. MMP levels according to AF recurrence during the follow-up

	Group 4 (n=4) "No AF recurrence"		Group 5 (n=12) "AF recurrence"		p-value
	Median	IQR	Median	IQR	
MMP2	100.9	139.8	135.7	148.8	0.3775
MMP3	14.5	36.1	3.1	17.3	0.9525
MMP9	163.3	880.5	231.5	1428.3	0.3190

RESULTS

- MMP biomarker levels and clinical information were available in 45 patients (No AF: n=20, Non-Prm AF: n=19, PrmAF: n=6). There was only one patient with no history of AF who developed AF during the follow-up period, and the patient was excluded from the analysis. Only MMP2 was statistically higher in PrmAF compared to No AF. (median 229 ng/ml, [interquartile range 136.0, 262.2], vs 112 ng/ml [interquartile range 75.3, 135.9], p=0.0495). This finding was not seen with MMP 3, or 9. (Table 2 and Figure 1)
- Among patients with a history of paroxysmal AF, but no AF at the time of blood draw, there were no significant differences in biomarker levels between patients with recurrent AF (n=12) and without recurrent AF (n=4) during the follow-up period. (Table 3)

CONCLUSION

- In this pilot study, HF patients with a reduced EF and an ICD, MMP 2 was statistically higher in those with PrmAF compared to patients without AF.
- In this population with a reduced EF, MMP 2, 3, and 9 levels did not predict new or recurrent AF during the three-year follow-up.

DISCLOSURES
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