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Interrelationship Between Inflammatory Biomarkers and Collagen Remodeling Proteins in Atrial Fibrillation

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Abstract

Introduction: Atrial Fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide. Inflammation and structural remodeling of the left atrium are thought to be involved in the pathogenesis of AF. This study explores collagen remodeling and inflammatory biomarkers in AF patients compared to healthy controls to discern their role in AF.

Materials and Methods: Plasma samples were collected from AF patients undergoing first AF ablation (n = 72) and compared with commercially available human plasma samples from healthy subjects (n = 62). The collagen remodeling biomarkers and inflammatory biomarkers in the AF patients and control population were quantified using sandwich ELISA kits. GraphPad prism was used to perform statistical analyses.

Results: There was a statistically significant elevation in all the collagen remodeling biomarkers and inflammatory biomarkers in the AF patients compared to healthy controls. Spearman correlation analysis demonstrated significant correlations between inflammatory and collagen remodeling biomarkers, and among the collagen biomarkers. Of note, CRP was found to be correlated with TIMP-1, ICTP and PIIINP. IL6 and TIMP-1 were also found to be intercorrelated. Furthermore, correlations were noted among the different collagen remodeling peptides, and between TNFα and IL6, two of the inflammatory markers explored in this study.

Conclusions: The elevation of the inflammatory biomarkers and collagen remodeling proteins in AF patients is suggestive of inflammation and increased collagen turnover. The association between inflammatory biomarkers and collagen remodeling proteins may contribute to their regulation and role in the remodeling process.

Keywords

atrial fibrillation, collagen remodeling, inflammation, biomarkers

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Introduction

Atrial Fibrillation (AF) has become the most prevalent cardiac arrhythmia seen around the world.[1,2] The incidence of AF has been growing, partly due to the increased number of older adults. It is estimated that the prevalence of AF will rise to 12.1 million Americans by 2030.[3] AF patients have a two-fold higher risk of mortality in part due to the hypercoagulable state induced by this disease.[4,5] Due to the increased number of AF cases and a higher mortality rate, it is paramount to develop better ways to diagnose, manage and prevent this disorder. Currently, the complete pathophysiology of AF is not fully understood. A multifactorial pathogenesis is highly

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likely that includes cardiac structural remodeling and inflammation.[6] Since inflammation and structural remodeling play a role in the pathogenesis of AF, the biomarkers of inflammation and collagen metabolism may have a role in understanding the pathophysiology and further risk stratification.

Atrial structural remodeling is one of the key mediators in the development and progression of AF. Specifically, fibrosis in the left atrium, a form of structural remodeling, contributes to AF manifestation.[7] Atrial fibrosis occurs when collagen and extracellular matrix (ECM) proteins are deposited in the atria which impairs atrial contraction.[8] Fibrosis occurs due to an imbalance between ECM deposition and degradation within cardiac tissue. Studies have shown that there is a positive association between the extent of fibrosis and AF persistence.[9] In AF, the fibroblasts may proliferate and produce more extracellular matrix which leads to slower conduction.[10] This increase in the ECM volume can disrupt the continuity between cardiomyocytes and cause major pathological implications, such as the disruption of electrical conduction leading to the arrhythmogenic state associated with AF.

Since collagen turnover is one of the key mediators of atrial fibrosis, biomarker analysis can help assess the extent of collagen turnover. Procollagen is processed into collagen before collagen can be used by the body, releasing collagen degradation products into the plasma.[11] This process is mediated via matrix metalloproteases (MMPs) and the tissue inhibitors of the matrix metalloproteases (TIMPs). If the plasma levels of collagen degradation products or MMPs are elevated, that could indicate an increase in collagen turnover.[12] Because many different collagen remodeling biomarkers exist in the plasma, they may potentially be used to noninvasively monitor the progression of AF.

Table 1. Patient Demographics of the Atrial Fibrillation Cohort.

Demographic categories	
Age (years ± SD)	62.8 ± 11.1
Gender; N (%)	
Male	42 (71.2%)
Female	17 (28.8%)
BMI ± SD	31.97 ± 5
Smoking status; N (%)	
No smoking history	37 (62.7%)
Former Smoker	20 (33.9%)
Current smoker	1 (1.7%)
Anticoagulation Status; N (%)	
Not on anticoagulation	6 (10.2%)
On anticoagulation	53 (89.8%)
Comorbidities; N (%)	
Diabetes Mellitus	10 (16.9%)
Hypertension	36 (61.0%)
Acute Coronary Syndrome	2 (3.7%)
Stroke/TIA	4 (6.8%)
Peripheral Artery Disease	2 (3.4%)
Chronic Kidney Disease	3 (5.1%)
Heart Failure	4 (6.8%)
Dyslipidemia	33 (55.9%)

Abbreviations: SD, standard deviation; BMI, body mass index; TIA, transient ischemic attack.

Inflammatory processes are another major contributing mechanism involved in the pathogenesis of AF. Atrial fibrosis, impaired conduction, and endothelial damage in AF cause amplified inflammatory responses.[13,14] AF patients express a higher level of inflammatory biomarkers[15] than unaffected individuals, e.g., tumor necrosis factor alpha (TNFα), an inflammatory cytokine, is significantly elevated during AF.[15] TNFα plays a role in the activation of the TGFβ1 pathway involved in collagen synthesis.[16] This suggests that a positive feedback loop is involved in the pathogenesis of AF. An increased inflammatory response causes more fibrosis through the TNFα/TFGβ1 pathway, which further upregulates the inflammatory response.

Many other pro-inflammatory cytokines, such as interleukin 1-beta (IL-1β), IL-18, and IL-6, may also be implicated in the pathogenesis of AF. After IL-1β and IL-18 are released by immune cells, they can recruit more immune cells and activate fibroblasts.[14] The subsequent activation of fibroblasts could induce increased collagen deposition in the atria. Furthermore, in a previous study, a cross-sectional analysis was performed which showed that IL-6 was significantly associated with AF.[17] Measuring the plasma levels of inflammatory cytokines in AF patients may be a useful noninvasive tool used for risk stratification.

The objectives of this study were (1) to quantify the plasma concentration of collagen remodeling biomarkers and inflammatory biomarkers in the AF patients and a control population and (2) to determine if there is a correlation between the collagen remodeling biomarkers and inflammatory biomarkers. We hypothesized that the inflammatory and collagen remodeling biomarkers would be elevated in the AF patients compared to healthy controls and that there would be a correlation between inflammatory and collagen remodeling biomarkers, reinforcing the positive feedback cycle between inflammation and atrial fibrosis believed to be involved in the pathogenesis of AF.

Materials and Methods

Patients with paroxysmal or persistent AF undergoing first AF ablation (n = 72) were prospectively enrolled in this study. This study was designed to evaluate the imaging and biomarker characteristics of patients undergoing first ablation and their impact on AF recurrence after ablation. Patients were excluded if they were not undergoing ablation or having repeat ablation. The reason for AF ablation was based on patient's clinical status and shared decision making between patients and their physicians. In the current paper, we only report the biomarker analysis. This study was approved by the institutional review board of Loyola University Medical Center. Blood samples were collected from patients prior to AF ablation. The demographic information of the AF cohort is presented in Table 1. The blood samples were obtained in tubes containing 3.2% sodium citrate. The tubes were subsequently centrifuged at 3000 X g for 15 min. We separated the plasma supernatant, aliquoted and then froze the samples at −80 °C until they were analyzed. The samples were identified by each patient's study number and no patient identifying information was labeled on the vials. We then blindly analyzed the samples in the

Hemostasis and Thrombosis Research Laboratories at the Loyola University Medical Center. The control group in our study consisted of 62 normal human plasma samples (healthy, non-smoking volunteers) purchased from a commercial vendor, George King Biomedical (Overland Park, Kansas).

To quantify the collagen remodeling and inflammatory biomarkers, we used commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits. The collagen remodeling biomarkers included Type I collagen degradation product (ICTP), procollagen I aminoterminal propeptide (PINP), procollagen I carboxyterminal propeptide (PICP), procollagen III aminoterminal propeptide (PIIINP), procollagen III carboxyterminal propeptide (PIIICP), tissue inhibitor of metalloproteinases-1 (TIMP-1), tissue inhibitor of metalloproteinases-2 (TIMP-2), matrix metalloproteinase-1 (MMP-1), and matrix metalloproteinase- 2 (MMP-2). The inflammatory biomarkers we focused on in our study were tumor necrosis factor-alpha (TNFα), C-reactive protein (CRP), and interleukin 6 (IL-6). If there was an inadequate supply of plasma remaining for any of the healthy controls or AF patients, they were excluded from the ELISA analysis. The ELISA kits were purchased from R&D Systems (Minneapolis, Minnesota), Aviva Systems Biology (San Diego, California, Neobiolabs (Cambridge, Massachusetts) and Antibodies On-line.

Statistical analyses were carried out using Microsoft Excel, the QI Macros Statistical Software, and the GraphPad Prism Software. The mean ± SEM for each biomarker was calculated for both the AF samples and the healthy controls. Standard deviations were calculated too. The percent change between the AF mean and the healthy control mean was calculated for each biomarker and then we used the Mann-Whitney U test to analyze for a significant difference between the two cohorts. A *P*-value of <.05 was considered statistically significant for the Mann-Whitney U test. Then, the medians and interquartile ranges (IQRs) were also calculated for each biomarker. The Mood's median test was used to assess for a significant difference between the medians of the AF cohort and the healthy control group. We set a statistically significant *P*-value for the Mood's median test as < .05. After that, we performed a spearman correlation analysis to assess for the interrelationship between the biomarkers.

Results

Collagen Metabolism Biomarkers

Table 2 shows biomarker results on all the individual biomarkers measured in the study groups. All the collagen turnover biomarkers were upregulated in the AF group compared to NHP. The most pronounced increases were noted in PIIINP and PIIICP.

A comparison of the collagen turnover biomarkers in the AF population (n = 61 to 73) with normal human plasma (n = 50) is shown in Figure 1. The collagen turnover proteins, PICP, PINP, ICTP, PIIICP, and PIIINP, were significantly elevated in the AF patients. The AF cohort showed a wider range in each of the biomarkers compared to the healthy controls. The medians and IQRs for each collagen remodeling biomarker, with the associated *P*-values, are summarized in Table 3. All the collagen remodeling biomarkers in the AF group displayed higher medians and IQRs compared to the healthy controls. There was a statistically significant higher median in PICP, PINP, ICTP, PIIICP, and PIIINP in the AF group compared to the healthy control cohort.

Figure 2 illustrates the comparison of MMP-1, MMP-2, TIMP-1, and TIMP-2, in the AF patients and healthy controls. A significant increase in the metalloproteases and tissue inhibitors of metalloproteases in the AF group was noted. The AF cohort displayed a wide range in these biomarkers compared to the healthy controls, as shown in Table 3. The medians and IQRs for MMP-1, MMP-2, TIMP-1, and TIMP-2 are provided in Table 3. TIMP-2 was the only collagen remodeling biomarker to not have a statistically significant difference between the medians of the AF and healthy control populations. MMP-1, MMP-2, and TIMP-1 had statistically significant increases in the median concentration of each biomarker in the AF population compared to the healthy controls.

Table 2. Comparison of the Collagen Remodeling Biomarkers and Inflammatory Biomarkers Between the Atrial Fibrillation and Healthy Control Groups.

Biomarker	Atrial fibrillation mean ± SEM (SD)	Healthy controls mean ± SEM (SD)	*P*-values	AF versus healthy controls % Change
MMP-1 (ng/mL)	1.347 ± 0.19 (1.519)	0.55 ± 0.07 (0.495)	<.0001	146.25%
MMP-2 (ng/mL)	263.5 ± 6.41 (55.17)	183.4 ± 5.58 (39.45)	<.0001	43.70%
TIMP-1 (ng/mL)	125.9 ± 9.0 (76.45)	63.97 ± 3.99 (28.18)	<.0001	96.80%
TIMP-2 (ng/mL)	68.79 ± 2.1 (17.8)	61.64 ± 1.7 (12.05)	.0328	11.60%
ICTP (ng/mL)	4.0 ± 0.13 (1.083)	1.4 ± 0.07 (0.4611)	<.0001	186.20%
PICP (ng/mL)	1.40 ± 0.29 (2.287)	0.68 ± 0.08 (0.5847)	.0042	104.80%
PINP (ng/mL)	422.3 ± 43.8 (350.3)	159.9 ± 9.6 (67.94)	<.0001	164.10%
PIIICP (pg/mL)	1435 ± 288 (2461)	147.8 ± 39.2 (277.1)	<.0001	870.90%
PIIINP (ng/mL)	26.36 ± 4.3 (36.1)	2.82 ± 0.35 (2.484)	<.0001	833.80%
TNFα (pg/mL)	1.911 ± 0.085 (0.65)	0.793 ± 0.087 (0.38)	<.0001	141.04%
IL6 (pg/mL)	30.41 ± 10.13 (70.88)	2.94 ± 2.44 (19.2)	.0029	1034.35%
CRP (ug/mL)	3.786 ± 0.457 (3.423)	0.648 ± 0.146 (0.946)	<.0001	584.26%

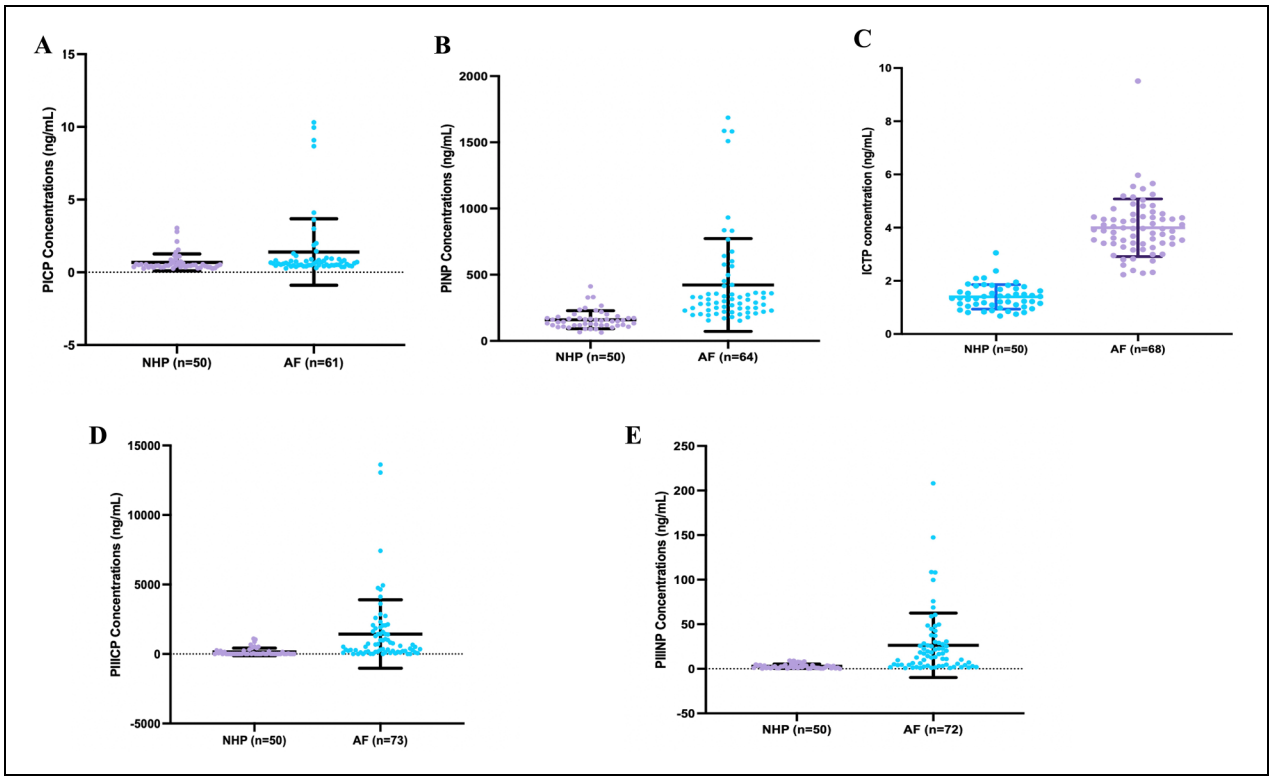

Figure 1. A comparison of plasma concentrations of some of the collagen turnover biomarkers in the AF cohort compared to NHP represented as scatter plots. Results are reported as means (center horizontal line) with the errors bars representing the standard deviation. Each colored dot represents one sample. (A) represents the comparison of PICP; (B) shows the comparison of PINP; (C) demonstrates the comparison of ICTP; (D) shows the comparison of PIIICP; and (E) represents the comparison of PIIINP. Abbreviations: NHP, normal human plasma; AF, atrial fibrillation; PICP, procollagen I carboxyterminal propeptide; PIIICP, procollagen III carboxyterminal propeptide; PINP, procollagen I aminoterminal propeptide; PIIINP, procollagen III aminoterminal propeptide; ICTP, type I collagen degradation product.

Table 3. Comparison of the medians and Interquartile Range (IQR) of the Inflammatory Biomarkers and Collagen Remodeling Biomarkers in the Atrial Fibrillation and Healthy Control Groups.

Biomarker	Atrial fibrillation Median (IQR)	Healthy controls Median (IQR)	*P*-values
MMP-1 (ng/mL)	0.86 (0.54 to 1.49)	0.36 (0.2 to 0.79)	<.001
MMP-2 (ng/mL)	249 (228 to 303)	177 (159 to 200)	<.0001
TIMP-1 (ng/mL)	106 (85.6 to 143.2)	56 (45.8 to 72.6)	<.0001
TIMP-2 (ng/mL)	68.5 (53.7 to 81.3)	64.5 (50.9 to 70.4)	.091
ICTP (ng/mL)	3.9 (3.4 to 4.4)	1.3 (1.1 to 1.7)	<.0001
PICP (ng/mL)	0.61 (0.49 to 0.9)	0.48 (0.37 to 0.68)	.028
PINP (ng/mL)	305.2 (229 to 422)	149.2 (117 to 175)	<.0001
PIIICP (pg/mL)	520.8 (149 to 1733)	0 (0 to 204)	<.0001
PIIINP (ng/mL)	15.3 (4.1 to 29.9)	2.1 (0.8 to 4.1)	<.0001
TNFα (pg/mL)	1.82 (1.43 to 2.3)	0.74 (0.4 to 0.9)	<.0001
IL6 (pg/mL)	0 (0 to 13.4)	0 (0 to 0.26)	.02
CRP (ug/mL)	2.7 (0.79 to 6.1)	0.14 (0 to 1.1)	<.0001

Inflammatory Biomarkers

A comparison of IL6, TNFα, and CRP levels in the AF cohort and healthy controls is illustrated in Figure 3, which shows that TNFα, IL6, and CRP were significantly elevated in the AF population. The mean concentrations of IL6, CRP, and TNFα, with the associated percent changes, are shown in Table 2. Among all the biomarkers, IL6 showed the most pronounced increase of greater than ten-fold in AF patients compared to healthy controls. According to Table 3, the AF cohort displayed a wider range in the inflammatory biomarkers, compared to NHP. The medians and IQRs of each inflammatory biomarker were increased in the AF group compared to the healthy controls.

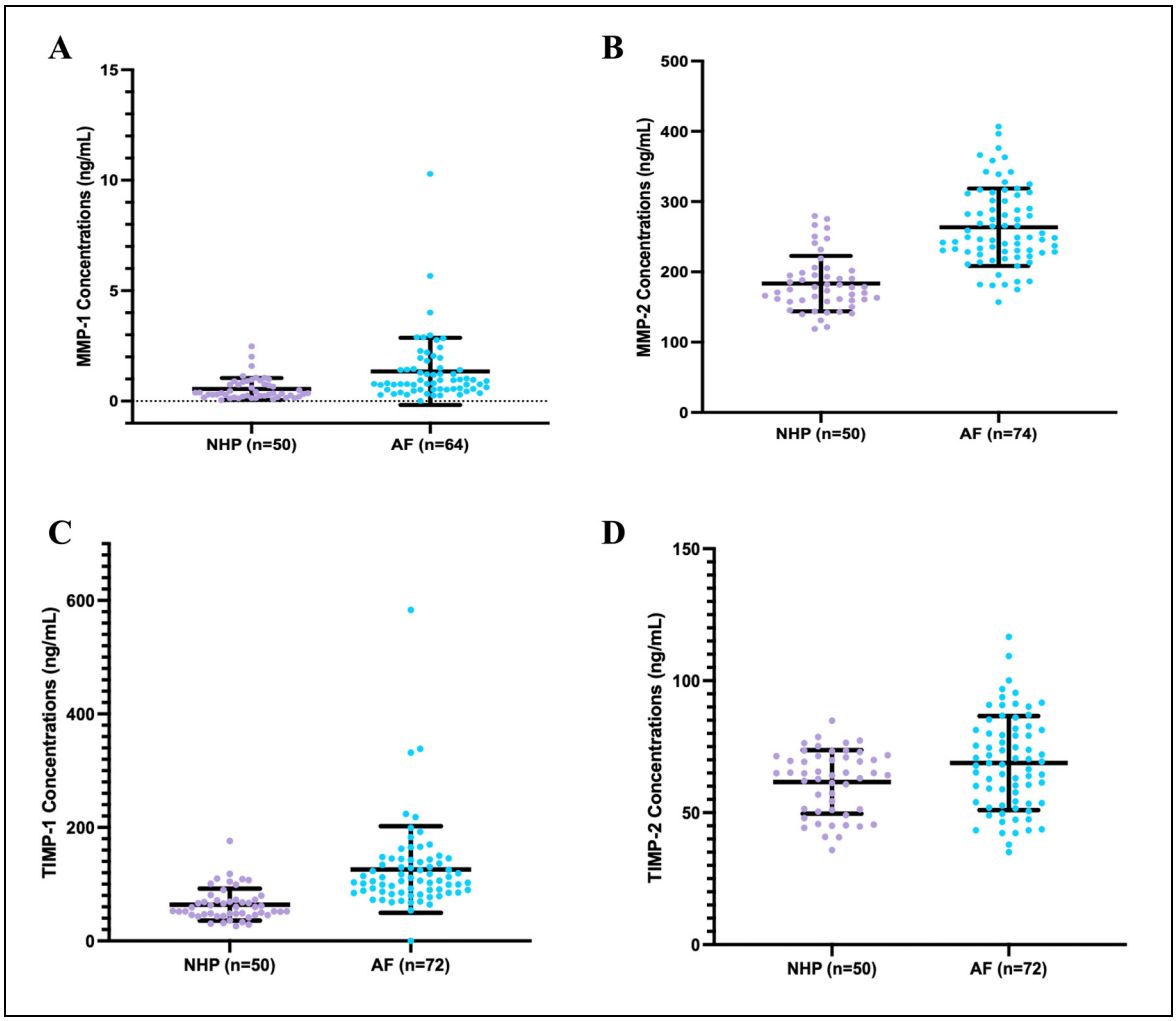

Figure 2. A comparison of plasma concentrations of the metalloproteases and tissue inhibitors of metalloproteases in the AF group compared to NHP represented in the form of scatter plots. Results are reported as means (center horizontal line) with the errors bars representing the standard deviation. Each colored dot represented one patient. (A) represents the comparison of MMP-1; (B) shows the comparison of MMP-2; (C) demonstrates the comparison of TIMP-1; and (D) shows the comparison of TIMP-2. Abbreviations: NHP, normal human plasma; AF, atrial fibrillation; MMP-1, matrix metalloproteinase 1; MMP-2, matrix metalloproteinase 2; TIMP-1, tissue inhibitor of matrix metalloproteinase 1; and TIMP-2, tissue inhibitor of matrix metalloproteinase 2.

There was a statistically significant elevation in the median concentration of TNFα, CRP, and IL6 in the AF cohort compared to the healthy controls.

Spearman Correlation Analysis

Figure 4 represents a spearman correlation matrix comparing all the biomarkers in the AF cohort. Several statistically significant correlations were found between the inflammatory and collagen remodeling biomarkers. CRP and TIMP-1 ($r = 0.301$, $P = .012$), CRP and ICTP ($r = 0.331$, $P = .007$), CRP and PIIINP ($r = 0.3$, $P = .012$), and IL6 and TIMP-1 ($r = 0.276$, $P = .029$) were all found to be interrelated. Many significant correlations were seen among the collagen remodeling proteins: MMP-2 and TIMP-2 ($r = 0.492$, $P < .0001$), TIMP-1 and PIIINP ($r = 0.305$, $P = .011$), ICTP and PIIINP ($r = 0.631$, $P < .0001$), ICTP and PINP ($r = 0.302$, $P = .016$), PICP and PINP ($r = 0.616$, $P < .0001$), and PIIINP and PINP ($r = 0.46$, $P < .001$). An interrelationship was also noted between TNFα and IL6 ($r = 0.322$, $P = .01$).

Discussion

This was a prospective study evaluating the biomarkers of inflammation and collagen turnover in AF patients undergoing first clinically indicated ablation in comparison with healthy controls. We found a statistically significant increase in all the collagen turnover biomarkers in the AF population compared to the healthy control group. These findings are in accordance with the previous studies that demonstrated an upregulation of collagen and collagen degradation biomarkers in patients with AF.[18–23] Some of the collagen remodeling biomarkers

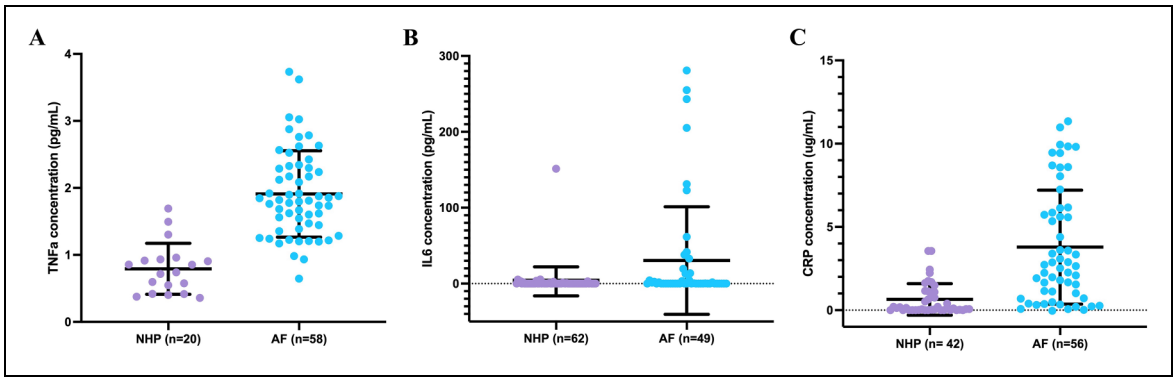

Figure 3. A comparison of plasma concentrations of the inflammatory biomarkers in the AF patients compared to NHP represented as scatter plots. Results are reported as means (center horizontal line) with the errors bars representing the standard deviation. Each colored dot represents one patient. (A) represents the comparison of TNFα, (B) shows the comparison of IL6 and (C) demonstrates the comparison of CRP. Abbreviations: NHP, normal human plasma; AF, atrial fibrillation; TNFα, tumor necrosis factor alpha; IL6, interleukin 6; CRP, C-Reactive Protein.

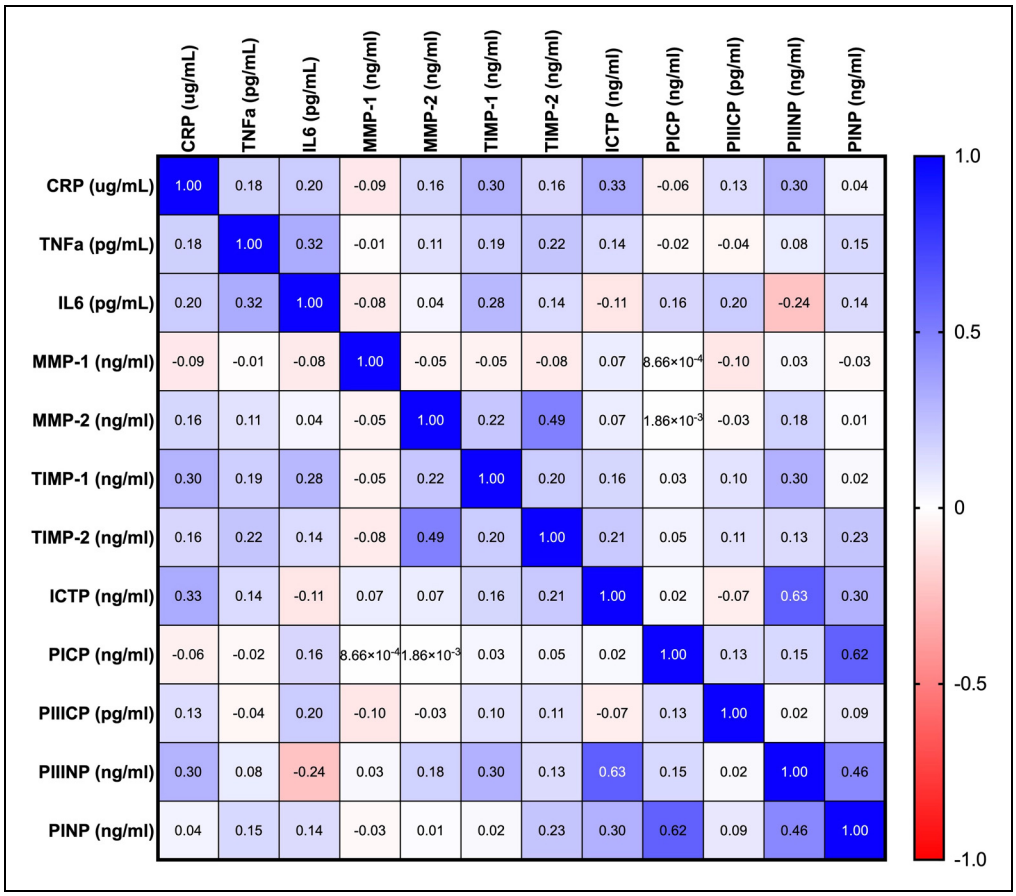

Figure 4. Spearman correlation matrix between different biomarkers. Blue boxes indicate positive correlations, while red boxes indicate negative correlations. The intensity of the color within the box represents the strength of the correlation. The numbers in the box represent the *r* value, otherwise known as the correlation coefficient.

were much more significantly elevated than other biomarkers; eg, the greatest percent increase among the collagen turnover biomarkers was seen in PIIINP and PIIICP, demonstrating greater than an 8-fold increase compared to the healthy control population. PINP and PICP also increased about 1–2 fold in the AF group. A possible explanation for this finding is that collagen type III may play a more significant role in AF pathogenesis compared to collagen type I. Overall, these

findings help reinforce the role of collagen turnover in the pathogenesis of AF.

We also found a statistically significant elevation in the plasma levels of inflammatory biomarkers TNFα, CRP and IL6 in the AF population compared to healthy controls. Among all biomarkers, IL6 demonstrated the highest, greater than a 10-fold increase in the AF population compared to the healthy controls. These findings are in line with previous studies showing an elevation of inflammatory biomarkers in AF patients compared to the control groups.[17,24–26] Our findings further contribute to the theory that inflammation is a major mechanism involved in AF.

MMP-2 and TIMP-2, TIMP-1 and PIIINP, ICTP and PIIINP, ICTP and PINP, PICP and PINP, PIIINP and PINP were all found to be correlated with each other. Since all these biomarkers are involved in collagen metabolism, it was expected that some correlations would exist between them. Furthermore, an association was found between TNFα and IL6 ($r = 0.322$), likely due to both being inflammatory cytokines. Interestingly, multiple statistically significant correlations were found between the collagen turnover biomarkers and inflammatory biomarkers. Although they are modest associations, it could help support the hypothesis that a positive feedback mechanism between inflammation and fibrosis is involved in the pathogenesis of AF.

Previous studies have shown increased levels of collagen remodeling biomarkers in AF patients compared to control populations. Polyakova et al demonstrated that ICTP, TIMP-1, MMP-2, PINP, and PIIINP levels were increased in the atrial samples obtained from the AF patients compared to patients in normal sinus rhythm (NSR).[27] Another experiment from Chinese investigators illustrated that higher levels of collagens I and III were found in patients who had AF and mitral valve disease compared to those with mitral valve disease without AF.[21] Moreover, in the Multi-Ethnic Study of Atherosclerosis, higher baseline levels of ICTP and PIIINP in patients with no overt cardiovascular disease predicted a new onset of AF over the next 10 years.[18] Furthermore, a previous study demonstrated that collagen I was increased by 48% in right atrial appendages and 69% in the right atrial free walls of the AF patients compared to the patients without AF.[23] Our study adds to the literature on this subject and reinforces the hypothesis that collagen turnover could be a contributing mechanism to the AF pathogenesis and may have a role in the assessment and risk stratification of AF patients.

In addition to atrial structural remodeling, inflammation has also been shown to be involved in the pathogenesis of AF.[13–15] As discussed earlier, there seems to be an interrelationship between the role of inflammation and collagen remodeling in the development of AF. Increased inflammation is thought to cause fibrotic changes in myocardial tissue.[28] Increased fibrosis then triggers a stronger inflammatory response.[13,14] This vicious cycle continues to occur leading to worsening fibrosis and inflammation in AF patients. Although it is unknown whether AF is a cause or effect of excess inflammation, inflammatory biomarkers may serve as a useful tool in predicting or risk stratifying AF thus aiding in clinical management. Many previous studies have reported an association between inflammation and AF, and an association between inflammation and AF-associated mortality. One study showed that IL6 was an independent predictor for the development of AF in patients with chronic kidney disease.[24] Another study illustrated that IL6 levels were a significant predictor of a stroke or death in patients that had AF, even after the researchers adjusted for age.[29] Similarly, in the ARISTOTLE trial, blood samples were obtained from 4830 patients at randomization and at 2 months. The researchers found that higher IL6 levels at 2-months were independently associated with increased mortality.[30] Overall, there is an abundance of evidence that inflammation is associated with AF. An amplified inflammatory response in AF patients could also be a marker for increased morbidity and mortality. Inflammatory biomarkers may serve as a noninvasive prognostic marker to monitor or modify the progression of AF.

We have previously reported the upregulation of collagen turnover biomarkers and metalloproteases in AF.[31] The current study extends these findings highlighting the combined role of inflammation and collagen metabolism in patients with AF. Matrix degradation and cellular and tissue remodeling in cardiac muscles and endothelial lining may contribute to the increased collagen remodeling process. It is likely that inflammatory processes triggered by ongoing pathophysiologic changes may result in the induction of matrix degrading proteins, as evidenced by increased metalloproteases in the AF cohort, which may be responsible for the degradation of collagen. Although, in our studies, we have not addressed the dysregulation of coagulation and the complement system in relation to its contribution to the pathogenesis of AF, several previous reports have provided supportive data on the dysregulation of these processes which lead to tissue damage and a hypercoagulable state.[32–36]

Besides the electrophysiologic evaluation, imaging techniques such as MRI have become very useful in understanding the structural pathophysiology of AF.[37,38] The data on the collagen remodeling proteins and inflammatory biomarkers reported herein may have a complimentary role to the structural remodeling data obtained with imaging techniques. To our knowledge, such a study has not been carried out in the past. MRI analysis of imaging data and its relevance may shed light into the molecular pathogenesis of AF, with reference to collagen remodeling peptides and inflammatory biomarkers.

This study has a few limitations, including small cohort size, and nonavailability of an age and gender-matched control population. There is a significantly higher number of males than females in the AF population. Additionally, the analysis performed represents a single sample obtained prior to the ablation procedure in a heterogeneous AF population. Furthermore, the profiling of these markers was carried out on a select number of biomarkers and may have benefitted from extending the scope of the study to include additional biomarkers, including coagulation markers and complement proteins. Additionally, the patients' comorbidities, such as hypertension, may also impact atrial structural remodeling. This may impact the

biomarkers of inflammation and collagen metabolism. A similar effect may be seen with obesity, diabetes mellitus and other comorbidities that are risk factors for atrial fibrillation. These comorbid conditions including hypertension are very prevalent in AF population and coexist in individual patients and hence it is challenging to evaluate the impact of each condition on biomarker results.

In conclusion, our study demonstrated a significant elevation in inflammatory biomarkers and collagen remodeling biomarkers in AF patients compared to healthy controls. Profiling of these biomarkers may serve as a useful tool in understanding the pathophysiology of structural remodeling and may assist in the risk stratification and management of AF patients.

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Declaration of Conflicting Interests

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