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High Plasma Concentrations of Transforming Growth Factor-β and Tissue Inhibitor of Metalloproteinase-1

– Potential Non-Invasive Predictors for Electroanatomical Remodeling of Atrium in Patients With Non-Valvular Atrial Fibrillation –

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Background: The degree of electroanatomical remodeling of the left atrial (LA) affects the clinical outcome after rhythm control of atrial fibrillation (AF). Our hypothesis was that plasma concentrations of transforming growth factor (TGF)-β and tissue inhibitor of metalloproteinase (TIMP)-1 reflect LA voltage and structural remodeling in patients with non-valvular AF.

Methods and Results: In the study, 242 patients (male 79.4%, 55.1±11.0 years old) with AF (155 paroxysmal AF, 87 persistent AF) underwent catheter ablation. Pre-ablation plasma concentrations of TGF-β and TIMP-1 and the degree of electroanatomical remodeling quantified by LA voltage map (NavX) and 3D-CT were evaluated. The mean LA voltage and volume were compared in patients with high TGF-β (≥10.0 ng/ml, H-TGF) vs. low TGF-β (<10.0 ng/ml, L-TGF) and high TIMP-1 (≥1.1 ng/ml, H-TIMP) vs. low TIMP-1 (<1.1 ng/ml, L-TIMP). Patients with H-TGF had lower mean LA voltage (P=0.014) and greater LA volume (P=0.022), particularly, posterior venous LA volume (P=0.005) than those with L-TGF. In patients with H-TIMP, the mean LA voltage (P=0.019) was lower than those with L-TIMP. LA volume was significantly higher (P<0.001) in patients with ejection fraction ≤58% than those with >58%.

Conclusions: In patients with non-valvular AF, high plasma concentrations TGF-β and TIMP-1 and low ejection fraction were closely related with electroanatomical remodeling of LA. (*Circ J* 2011; **75:** 557–564)

Key Words: Atrial fibrillation; Left atrium; Remodeling; Tissue inhibitor of metalloproteinase; Transforming growth factor-β

Atrial fibrillation (AF), one of the most common arrhythmias in clinical practice, is related to increasingly high mortality and disability.[1] Several studies have shown that AF changes the electrophysiologic properties of atrial myocardium and causes alterations in the structure of atrial tissue.[2,3] The longer the duration of AF is, the more persistent AF becomes because of atrial remodeling. Both electrical remodeling and structural remodeling beget AF, so that an increase in AF burden leads to a more vulnerable substrate.[4] The electrical remodeling is presented by shortened atrial refractory period and slow conduction velocity in the atrium.[2,4] The structural remodeling is related to the interstitial fibrosis, downregulation of the density of gap junction, and enlargement of atrial chamber size (critical mass).[5,6] While the electrical remodeling might be able to be reversed by maintaining the sinus rhythm, structural substrate remodeling might persist even after rhythm control.[7] The degree of structural remodeling measured by left atrial (LA) size[8] or multiple serologic markers[9,10] affects the clinical outcome of rhythm control in patients with AF. Therefore, non-invasive predictor of electroanatomical remodeling might be valuable to select appropriate patients with AF for rhythm control and improve their clinical outcome. Transforming growth factor (TGF)-β is central to signaling cascades implicated in the genesis of cardiac fibrosis.[11] The balancing of matrix metalloproteinase (MMP) and tissue inhibitor of

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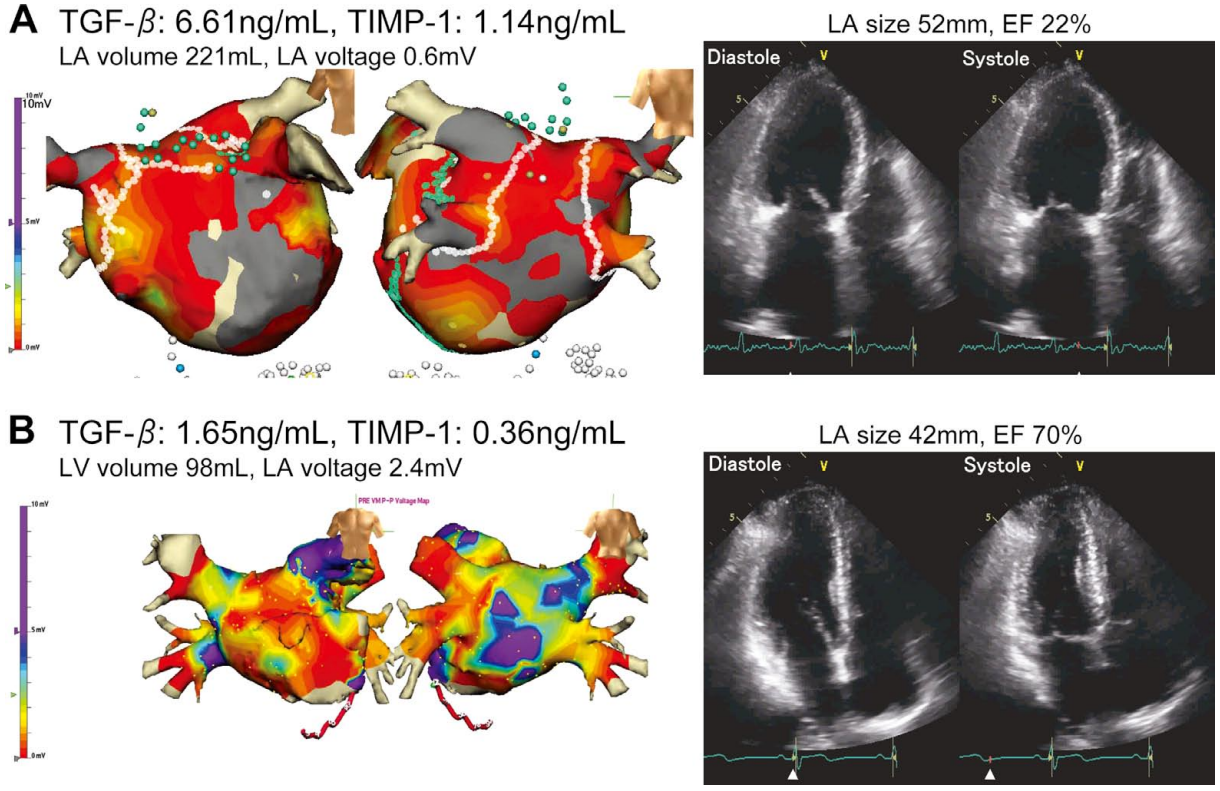

Figure. (**A**) 3D-spiral computed tomography merged NavX electroanatomical voltage map of left atrium (LA) and apical 4-chamber views of echocardiography in patients with high plasma concentrations of transforming growth factor (TGF)-β and TIMP-1. (**B**) NavX electroanatomical voltage map of LA and echocardiography in patients with low plasma concentrations of TGF-β and tissue inhibitor of metalloproteinase (TIMP)-1. In patients with high plasma concentrations of TGF-β, LA is significantly enlarged with low voltage remodeling, and LA size in echocardiography was larger in patients with low ejection fraction (EF).

metalloproteinase (TIMP) regulate extracellular matrix turnover.[12–14] Therefore, we hypothesized that plasma concentrations of TGF-β and TIMP-1 can be used to predict LA voltage and LA structural remodeling in patients with non-valvular AF. The purpose of the current study was to define the association of non-invasive parameters to the degree of electroanatomical remodeling (voltage and volume) of LA.

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Methods

Patient Selection

The study protocol was approved by the Institutional Review Board and adhered to the declaration of Helsinki. All patients provided written informed consent. We included 242 AF patients (male 79.4%, 55.1±11.0 years old) who underwent radiofrequency catheter ablation (RFCA) guided by computed tomography (CT) merged 3D NavX map. Among them, 87 patients had persistent AF (PeAF) and 155 had paroxysmal AF (PAF). We excluded the following patients: (1) permanent AF refractory to the electrical cardioversion; (2) LA size >55 mm measured on echocardiogram; (3) aortic aneurysm or dissection; (4) AF with rheumatic valvular disease; or (5) previous AF ablation. All patients maintained optimal anticoagulation and stopped taking all anti-arrhythmic drugs for 5 half-lives of each drug. We examined all patients with 3D spiral CT (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Netherlands) to visually define the anatomy of LA.

Electrophysiological Mapping

Intracardiac electrograms were recorded using a Prucka CardioLab™ Electrophysiology system (General Electric Health Care System Inc, Milwaukee, WI, USA). We generated 3D-spiral CT merged 3D electroanatomical mapping (NavX system, St. Jude Medical Inc, Minneapolis, MN, USA) for RFCA. Before the catheter ablation, we generated a LA 3D voltage map by obtaining contact bipolar electrograms from 250 to 350 points of the LA endocardium during high right atrial (RA) pacing (pacing cycle length 500 ms) utilizing a deflectable 3.5-mm tip 7-Fr open irrigation tip ablation catheter (Celsius, Johnson & Johnson Inc, Diamond Bar, CA, USA). The bipolar electrograms were filtered from 32 to 300 Hz. For patients with initial rhythm of AF during the procedure, we generated voltage during pacing after internal electrical cardioversion (2–10 J, biphasic shocks with R wave synchronization, anodal decapolar catheter in high RA to cathodal duo-decapolar catheter inside of the coronary sinus (CS), Lifepak12, Physiocontrol Ltd). We did not obtain an LA voltage map, if frequently re-initiating AF required electrical cardioversion more than 3 times.

Table 1. Clinical and Electroanatomical Characteristics According to Plasma Concentrations of TGF-β

	TGF-β ≥10.0 ng/ml (n=121)	TGF-β <10.0 ng/ml (n=121)	P value
Clinical findings			
Age (years)	55.04±10.87	55.63±11.60	0.3452
Sex (Male %)	82.6	79.1	0.2523
PAF (%)	63.5	71.3	0.1036
EF (%)	59.5±8.8	58.4±7.7	0.1650
LA size (mm; Echo)	42.2±5.5	40.9±7.1	0.0652
Recurrence (%)	17.6	20.0	0.3446
ACEI/ARB	33.1%	39.7%	0.2125
ACE (ng/ml)	133.37±44.80	126.49±44.36	0.2763
Angiotensin II (ng/ml)	3.98±3.72	1.86±1.42	0.0066
LA voltage (mV)			
Mean LA	1.35±0.61	1.65±0.82	0.0344
LA ant wall	1.23±0.48	1.42±0.65	0.0751
Septum	1.24±0.60	1.25±0.62	0.4885
LAA	2.48±1.34	3.05±1.78	0.0606
Venous atrium	1.08±0.89	1.80±1.34	0.0051
Post-inferior LA	1.31±0.70	1.57±0.92	0.0808
Lt lateral isthmus	1.02±0.89	1.45±0.93	0.0208
LA volume (ml)			
Mean LA	132.0±53.1	113.0±38.4	0.0220
Venous atrium	42.9±17.9	34.9±11.6	0.0046
LAA	12.7±5.6	9.9±4.6	0.0035
Anterior LA	76.3±35.2	68.3±27.7	0.1019

TGF-β, transforming growth factor-β; PAF, paroxysmal atrial fibrillation; EF, ejection fraction; LA, left atrium; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAA, left atrial appendage.

Off-Line Analyses of Color-Coded 3D Voltage Map of LA

Color-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage. We analyzed the color-coded LA electroanatomical voltage maps in the anterior-posterior and posterior-anterior views. The low voltage areas ≤0.2 mV were marked in gray, and the high voltage areas >5.0 mV in purple. The reference distance was measured by the inter-electrode distances of CS catheters (duodecapolar catheter, St. Jude Medical Inc, Minnetonka, MN, USA). The voltage areas in the pulmonary veins were excluded. To quantify the mean voltage of the LA, the percent area of each color was calculated by customized software (Image Pro) referenced to a color scale bar as described before.[15]

Curvilinear and Volumetric Analyses of 3D-Spiral CT Image

We measured the LA volume by CT. The 3D-spiral CT images of LA were analyzed on an imaging processing workstation (Aquarius, Terarecon Inc, USA) as described before.[16] Each LA image was divided into portions by embryological origin[17] as follows: the venous LA (posterior LA including the antrum and posterior wall), anterior LA (excluding the LA appendage (LAA) and venous LA), and LAA. Although both LAA and anterior LA are embryological primordial atrial origin, they are different in geometry, myocardial fiber orientations, and distribution of autonomic innervations.[16,18] Therefore, we separated LAA and anterior LA, and referenced them to the points of inflection on 3D spiral CT image. We calculated and compared the absolute and relative volumes of their portions.

Biochemical Analyses

We took peripheral blood samples before the procedure, and measured the plasma concentrations of TGF-β, TIMP-1, angiotensin converting enzyme (ACE), angiotensin II, and MMP-1, 2, and 9 by ELISA kits (R&D Systems, Minneapolis, MN, USA).

Data Analyses

We evaluated the degree of electroanatomical remodeling by the mean and regional LA voltage and the mean and regional LA volume. The degree of electroanatomical remodeling was compared with clinical parameters, and the plasma concentrations of multiple biological markers. Comparisons between groups were analyzed by the Mann–Whitney test or the t-test. All values were expressed as mean±SD. All statistical analyses were performed using SPSS version 12.0 and a P-value of <0.05 was considered significant.

Results

High Plasma Concentration of TGF-β Associated With Electroanatomical Remodeling of LA

Figure shows the representative examples of 3D-spiral CT merged electroanatomical map and apical 4-chamber view of echocardiogram in patients with high TGF-β (Figure A) and low TGF-β (Figure B). Patients with high TGF-β (Figure A) had an enlarged atrium with a relatively low voltage and low ejection fraction (EF) of left ventricle compared to those with low TGF-β (Figure B). Table 1 summarizes the comparisons of clinical and electroanatomical characteristics according to plasma concentrations of TGF-β in patients with AF. We divided patients into those with TGF-β ≥10.0 ng/ml and those with TGF-β <10.0 ng/ml, based on the median value rounded to zero decimal places and validated it by receiver operating characteristic (ROC) curve analysis. There was no significant difference in baseline characteristics between the 2 groups. Patients with TGF-β ≥10.0 ng/ml had a lower mean LA

Table 2. Clinical and Electroanatomical Characteristics According to Plasma Concentration of TIMP-1

	TIMP-1 ≥1.1 ng/ml (n=128)	TIMP-1 <1.1 ng/ml (n=114)	P value
Clinical findings			
Age (years)	56.7±10.3	53.2±11.8	0.0072
Sex (Male %)	78.9	82.3	0.2544
PAF (%)	64.1	68.1	0.2534
EF (%)	59.2±9.4	57.4±7.8	0.0573
LA Size (mm; Echo)	41.8±5.6	41.4±7.3	0.3183
Recurrence (%)	20.8	17.8	0.3005
ACEI/ARB (%)	39.1%	33.3%	0.2374
ACE (ng/ml)	122.85±43.86	131.74±44.73	0.2634
Angiotensin II (ng/ml)	4.39±3.64	2.35±2.50	0.0211
LA voltage (mV)			
Mean LA	1.26±0.54	1.80±0.83	0.0006
LA ant wall	1.17±0.50	1.53±0.61	0.0003
Septum	1.11±0.53	1.43±0.64	0.0095
LAA	2.34±1.22	3.33±1.83	0.0028
Venous atrium	1.11±0.90	1.87±1.46	0.0032
Post-inferior LA	1.34±0.83	1.56±0.81	0.1260
Lt lateral isthmus	0.99±0.87	1.54±0.92	0.0042
LA volume (ml)			
Mean LA	114.0±40.0	122.1±49.6	0.0964
Venous atrium	36.7±13.8	38.6±16.0	0.1791
LAA	9.4±5.3	11.0±5.3	0.0185
Anterior LA	68.2±26.6	71.7±35.0	0.2076

TIMP, tissue inhibitor of metalloproteinase. Other abbreviations see in Table 1.

Table 3. LA Volume and Voltage According to EF

	EF ≤58% (n=120)	EF >58% (n=122)	P value
LA volume (ml)			
LA size (mm; Echo)	42.3±6.3	41.0±6.6	0.0420
Mean LA	128.2±47.9	107.2±37.9	0.0002
Venous atrium	40.2±14.8	34.8±14.1	0.0038
LAA	11.6±5.5	8.6±4.3	<0.0001
Anterior LA	76.7±34.4	63.2±24.9	0.0005
LA voltage (mV)			
Mean LA	1.78±0.87	1.34±0.56	0.0038
Anterior LA	1.48±0.65	1.23±0.48	0.0250
Septum	1.39±0.68	1.18±0.53	0.0654
LAA	3.33±1.87	2.53±1.35	0.0139
Venous atrium	1.90±1.43	1.16±0.95	0.0032
Post-inferior LA	1.60±0.82	1.32±0.79	0.0621
Lt lateral isthmus	1.61±1.00	1.01±0.86	0.0027
Serologic biomarkers			
TGF-β (ng/ml)	9.45±7.33	13.34±8.88	0.0002
MMP-1 (ng/ml)	0.23±0.24	0.23±0.24	0.4723
MMP-2 (ng/ml)	90.83±20.73	96.01±16.69	0.3451
MMP-9 (ng/ml)	37.67±28.23	48.10±17.03	0.1368
TIMP-1 (ng/ml)	1.12±0.60	1.48±0.75	<0.0001
ACEI (ng/ml)	132.34±45.74	113.36±31.00	0.1315
Angiotensin II (ng/ml)	2.55±2.18	2.88±3.01	0.4609

MMP, matrix metalloproteinase. Other abbreviations see in Tables 1, 2.

voltage (1.35±0.61 mV vs. 1.65±0.82 mV, P=0.0344) and a greater mean LA volume measured by 3D-spiral CT (132.0±53.1 ml vs. 113.0±38.4 ml, P=0.0220) compared to those with <10.0 ng/ml (Table 1). Regional voltage was lower at the venous atrium (P<0.0051) and left lateral isthmus area (P=0.0208) that is surrounded by lower border of venous atrium, distal CS, and LAA, and the regional volume was significantly enlarged at the venous atrium (P=0.0046) and LAA (P=0.0035) in patients with high TGF-β group (Table 1). Although the proportion of patients who were taking ACE

Table 4. LA Volume and Voltage According to ACEI/ARB

	No ACEI/ARB (n=154)	ACEI/ARB (n=88)	P value
Clinical findings			
Age (years)	53.24±11.24	58.46±9.99	0.0003
Sex (Male %)	83.97%	75.95%	0.0687
PAF (%)	65.39%	64.56%	0.4402
EF (%)	59.11%	57.02%	0.0258
LA size (mm; Echo)	40.71±5.99	43.98±6.99	0.0001
Recurrence (%)	17.97%	22.03%	0.2575
LA volume (ml)			
Mean LA	114.7±43.7	129.2±47.53	0.0140
Venous atrium	37.1±13.7	40.3±16.9	0.0714
LAA	9.9±5.0	11.16±5.87	0.0467
Anterior LA	67.2±32.5	78.35±28.74	0.0073
LA voltage (mV)			
Mean LA	1.70±0.79	1.17±0.46	0.0016
Anterior LA	1.47±0.61	1.08±0.38	0.0026
Septum	1.41±0.63	1.01±0.48	0.0038
LAA	3.27±1.73	2.03±1.04	0.0009
Venous atrium	1.63±1.36	1.10±0.86	0.0415
Post-inferior LA	1.57±0.84	1.22±0.73	0.0043
Lt lateral isthmus	1.44±1.00	0.95±0.82	0.0189
Serologic biomarkers			
TGF-β (ng/ml)	12.08±8.71	11.58±8.26	0.3467
MMP-1 (ng/ml)	0.22±0.20	0.25±0.31	0.3572
MMP-2 (ng/ml)	91.03±22.82	93.39±8.42	0.4132
MMP-9 (ng/ml)	41.05±27.67	38.03±24.78	0.3559
TIMP-1 (ng/ml)	1.31±0.76	1.30±0.60	0.4490
ACEI (ng/ml)	130.66±46.84	123.48±35.48	0.28981
Angiotensin II (ng/ml)	2.37±2.23	4.13±4.11	0.0300

Abbreviations see in Tables 1–3.

inhibitor (ACEI) or angiotensin-receptor blocker (ARB) was not different, the plasma concentration of angiotensin II was significantly higher in patients with high TGF-β than those with low TGF-β (P=0.0066, Table 1). AF recurrence rates after catheter ablation were 17.6% and 20.0% in patients with TGF-β ≥10.0 ng/ml and those <10.0 ng/ml, respectively (P=0.3446) during follow-up for 21.5±3.2 months.

High Plasma Concentration of TIMP-1 Related to Low LA Voltage

For patients with high plasma concentrations of TIMP-1, LA voltage was generally lower than those with low TIMP-1 (Figure). Table 2 compares clinical findings, LA voltage, and LA volume of the patients with plasma concentrations of TIMP-1 ≥1.1 ng/ml and those with <1.1 ng/ml. For statistical analyses, we decided the cut-off as the median rounded to zero decimal places and validated it by ROC curve analysis. Except for older age of patients with high TIMP-1, other clinical parameters were not significantly different. In the group with TIMP-1 ≥1.1 ng/ml, the mean LA voltage was significantly lower than the group with <1.1 ng/ml (1.26±0.54 mV vs. 1.80±0.83 mV, P=0.0006), and this trend was consistent at the LA anterior wall, septum, LAA, venous atrium, and left lateral isthmus area (Table 2). However, LA volume was not significantly different according to the plasma concentration of TIMP-1. In contrast, the proportion of patients who were taking ACEI/ARB was not different, the plasma concentration of angiotensin II was significantly higher in high TIMP-1 group than in low TIMP-1 group (P=0.0211, Table 2). Plasma concentrations of MMP-1, 2, and 9 were not different depending on LA volume or LA voltage.

Low Ventricular Systolic Function and Electroanatomical Remodeling of LA

As shown in Figure, patients with low EF tended to have an enlarged LA. Patients with EF ≤58% had greater LA size measured by echocardiography (P=0.0420) and LA volume measured by 3D-spiral CT (128.2±47.9 ml vs. 107.2±37.9 ml, P=0.0002) than those with EF >58% (Table 3). Regional volumes of the venous atrium, LAA, and anterior LA were consistently larger in patients with EF ≤58% than those with >58%. In contrast, however, mean LA voltage was higher in low EF group (1.78±0.87 mV) than in high EF group (1.34±0.56 mV, P=0.0038). Plasma concentrations of TGF-β (P=0.0002) and TIMP-1 (P<0.0001) were lower in patients with low EF group than in high EF group. However, plasma concentrations of MMP-1, 2, and 9 were not affected by ventricular systolic function (Table 3). The plasma concentrations of TGF-β (13.5±8.5 ng/ml vs. 9.7±7.8 ng/ml, P=0.0020) and TIMP-1 (1.5±1.2 ng/ml vs. 1.2±0.7 ng/ml, P=0.0034) were higher in patients with LV diastolic dysfunction (E/E' ≥8) than those without it (E/E' <8). However, LA volume or LA voltage was not significantly different. The patients who were taking ACEI/ARB were older (P=0.0003), had lower EF (P=0.0258), greater size of LA (P=0.0001), and lower LA endocardial voltage (P=0.0016) compared with those without ACEI/ARB (Table 4). The plasma concentration of angiotensin II was also lower in patients who were taking

ACEI/ARB than those without it (P=0.0300). Therefore, the patients with more remodeled atrium and lower LV function were taking ACEI/ARB.

Discussion

The current study documented that high plasma concentration of TGF-β indicates low LA endocardial voltage and enlarged LA volume, suggesting electroanatomical remodeling in patients with non-valvular AF. We also found high plasma concentrations of TIMP-1 is related to low LA voltage, and low EF is associated with greater LA volume. Pre-determination of electroanatomical remodeling by these non-invasive parameters might be useful for the understanding of pathophysiology in patients with AF.

Pathophysiology of Structural Remodeling of LA and Maintenance of AF

Wijffels et al[4] reported that the longer the AF lasts, the more persistent it becomes because of atrial remodeling. Prolonged AF induces not only electrical remodeling,[2,4] but also mechanical stretch-related extracellular matrix genes,[19–21] resulting in structural remodeling. Profibrotic signals such as angiotensin II,[22] TGF-β,[11] platelet-derived growth factor,[23] or connective tissue growth factor[24] proceed extracellular matrix remodeling. Those profibrotic signals induce local inflammatory process and proliferation of myofibroblasts,[25] resulting in collagen deposition and barrier to impulse propagation.[26] Dense and disorganized collagen deposition with apoptosis or necrosis of cardiomyocytes[20] reduces the voltage of contact atrial electrogram and enlarges LA volume; electroanatomical remodeling.[15,16] We recently reported that electroanatomically remodeled LA is found with low LA voltage and conduction velocity and high LA volume, especially anterior LA volume.[16] Therefore, slow conduction velocity and large critical mass in electroanatomically remodeled atria perpetuate the maintenance of AF.[27] Electroanatomical remodeling of LA changes AF dynamics and the characteristics or distribution of complex fractionated atrial electrogram.[28] In this study, plasma concentration of TGF-β and EF were found to be related to the enlargement of LA volume. However, TGF-β might not be a sensitive predictor for the structural remodeling process in AF, because it was associated with enlargement of venous atrium or LAA those remodel at the later phase of LA remodeling.[16]

Atrial Fibrosis Associated With Plasma Concentrations of TGF-β and TIMP-1

It has been known that low voltage area in 3D electroanatomical map is related to the fibrotic scar in cardiac magnetic resonance image.[29] We evaluated the association between regional LA voltage and the plasma concentrations of biomarkers in this study. The delicate balance between production and degradation of extracellular matrix is maintained by multiple biophysical and biomolecular signalings that control fibroblast growth and function.[30] Disruption of this balance results in overwhelming fibrosis and structural remodeling with electrical and mechanical dysfunction. TGF-β is central to signaling cascades implicated in the activation of myofibroblasts and the genesis of cardiac fibrosis,[11,25,31] and is associated with an inhomogeneous substrate for electrical propagation.[32] Plasma concentration of TGF-β was reported to be related to the recurrence of AF after maze operation[33] and electrical cardioversion.[10] MMP are involved in the degradation of interstitial architecture[13] and have been found to play a significant role in the development of myocardial remodeling. The balancing of MMP and its antagonist TIMP regulates extracellular matrix turnover.[12–14] Their imbalance, change of MMP type, or elevated turnover of these matrix proteins are associated with atrial extracellular matrix remodeling and atrial dilation in AF.[34] We found that high plasma concentrations of TGF-β or TIMP-1 were associated with low LA voltage. However, MMP-1, 2, and 9 did not indicate the degree of atrial structural remodeling. It might be due to the peripheral blood samples only partially reflecting the remote process in the atria.

Potential Upstream Therapies in Management of AF

In the process of atrial electroanatomical remodeling, neurohormonal factors and hemodynamic factor should be considered. Angiotensin II is one of the important profibrotic molecules.[22] Although 2 recent randomized trials failed to reproduce the benefits of angiotensin II receptor blocker for rhythm control in patients with AF,[35,36] angiotensin II inhibitors might prevent atrial electrical and structural remodeling[37] and recurrence of AF[38] directly or indirectly by improving LV systolic or diastolic functions. In our study, both impaired LV systolic and diastolic functions increased plasma concentrations of TGF-β and TIMP-1, and LA volume was greater in patients with low EF. However, the reason for high LA voltage in patients with low EF remains to be studied. Another potential upstream therapies are statin,[39] ω-3 poly-unsaturated fatty acid,[40] and Perfenidone, a TGF-β1 inhibitor.[41] It has been known that angiotensin II activates GTPase Rac1 and STAT 3, which are the targets of statin and important signaling molecules mediating atrial structural remodeling.[42] ACE activity increases cardiac collagen content by degrading AcSDKP (N-acetyl-Ser-Asp-Lys-Pro), an inhibitor of the phosphorylated TGF-β signaling molecules.[43] Alterations in PDFG or myofibroblast might be another potential targets for upstream therapy that reduces electroanatomical remodeling of AF.[44,45]

Study Limitations

The patients included in this study were a highly selected group referred for AF catheter ablation, and the number of patients was also limited. In this study data, clinical recurrence rate of the patients with LA volume ≥110 ml was significantly higher than those with LA volume <110 ml (25.2% vs. 9.7%, P=0.0018). However, we failed to prove the relationships between TGF-β and TIMP-1; those reflecting atrial remodeling and clinical recurrence of AF. This might be due to a relatively small number of sample size and selection bias excluding the patients with LA size >55 mm. The peripheral blood samples might only partially reflect the remote process in the atria. Because we acquired LA voltage by point-by-point contact mapping, the LA voltage map did not reflect a spatiotemporally homogeneous distribution of endocardial voltage. We analyzed 3D maps using 2 dimensional measurements.

Conclusion

High plasma concentration of TGF-β was related with a low mean LA voltage and enlarged LA volume. The mean LA voltage was lower in patients with high TIMP-1 than those with low TIMP-1. In addition, LA volume was significantly greater in patients with low EF than those with normal LV systolic function. Pre-determination of electroanatomical remodeling by those non-invasive parameters might be useful for clinical decisions on rhythm control strategies and the

understanding of pathophysiology in patients with AF.

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Disclosures

The authors have no conflict of interest disclosures.

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