Serum tenascin-C levels in atrium predict atrial structural remodeling processes in patients with atrial fibrillation

Journal of Interventional Cardiac Electrophysiology (2020) 59:401–406
https://doi.org/10.1007/s10840-019-00670-4

Serum tenascin-C levels in atrium predict atrial structural remodeling processes in patients with atrial fibrillation

Yuichiro Shiomi[1] · Miki Yokokawa[1] · Hiroyasu Uzui[1] · Kaori Hisazaki[1] · Tetsuji Morishita[1] · Kentaro Ishida[1] · Yoshitomo Fukuoka[1] · Kanae Hasegawa[1] · Hiroyuki Ikeda[1] · Naoto Tama[1] · Kenichi Kaseno[1] · Shinsuke Miyazaki[1] · Naoki Amaya[1] · Hiroshi Tada[1]

Received: 25 November 2018 / Accepted: 19 November 2019 / Published online: 9 December 2019

Abstract

Background Fibro-inflammatory processes in the extracellular matrix are closely associated with progressive structural remodeling in atrial fibrillation (AF). Serum concentrations of tenascin-C (TNC), an extracellular matrix glycoprotein, and of high-sensitivity C-reactive protein (CRP) might serve as a marker of remodeling and progressive inflammation of the aorta and in myocardial diseases. This study aimed to clarify relationships between TNC and CRP in patients with AF.

Methods This study included 38 patients with AF and five controls without left ventricular dysfunction who underwent catheter ablation. Blood was collected immediately before ablation from the left atrium (LA), right atrium (RA), and femoral artery (FA), and left and right atrial pressure was measured. Levels of TNC in the LA (TNC-LA), RA (TNC-RA), and FA (TNC-FA) and high-sensitivity C-reactive protein (CRP) were measured. Atrial size was also determined by echocardiography.

Results Levels of TNC corrected by atrial size were maximal in the LA, followed by the RA (3.69 ± 0.32 and 2.87 ± 0.38 ng/mL/cm, respectively). Mean transverse diameter corrected by body surface area was larger and mean atrial pressure was greater in the LA than the RA. A relationship was found between CRP from the femoral vein and TNC-LA and TNC-RA, but not TNC-FA. None of TNC-LA, TNC-RA, or TNC-FA correlated with ANP or BNP in the femoral vein.

Conclusions Intracardiac (atrial) TNC expression plays an important role in the development of remodeling processes in the atrium with AF. Tenascin-C from the LA and RA (but not TNC, ANP, and BNP from FA) might serve as novel markers of these processes.

Keywords Atrial fibrillation · Atrial size · Tenascin-C · Atrial remodeling

1 Introduction

Atrial fibrillation (AF) is a prevalent type of cardiac arrhythmia that can become complicated with thromboembolic events such as stroke and systemic embolism that result in significant morbidity and mortality. Therefore, anticoagulation is an integral part of therapy for all patients with AF [1]. Structural remodeling of the left atrium is a mechanism for thrombus formation, similar to the activation of inflammatory states such as increased circulating concentrations of interleukin-6 or C-reactive protein [2].

Tenascin-C (TNC) is an extracellular matrix glycoprotein that is overexpressed during tissue remodeling, and its concentrations in peripheral veins might serve as markers for cardiac and vascular tissue remodeling in patients with acute myocardial infarction, arterial aneurysms, and dilated cardiomyopathy [3–6]. However, relationships between TNC and atrial remodeling and inflammation in AF remain obscure. The present study aimed to clarify these relationships and determine the role of TNC as a biomarker of these processes.

2 Methods

2.1 Patients and study design

We enrolled 38 patients with AF who underwent catheter ablation at the University of Fukui Hospital, Department of Cardiovascular Medicine between April 2014 and

✉ Hiroyasu Uzui
huzui@u-fukui.ac.jp

[1] Department of Cardiovascular Medicine, University of Fukui, 23-3 Shimoaizuki Matsuoka Eiheiji-cho, Fukui 910-1193, Japan

March 2015. We also included five patients with tachyarrhythmia disease who had no tachycardial symptoms for > 3 months (mean age, 61 years; atrioventricular reentrant tachycardia, $n = 3$; atrial tachycardia, $n = 2$) for comparison. The exclusion criteria comprised coronary artery disease, chronic heart failure, severe renal or hepatic diseases, autoimmune and neoplastic diseases, pregnant or lactating women, perioperative status, and individuals judged unable to participate by their physicians in charge. The purpose and methods of this study were explained to the patients, who provided written informed consent to participate. Serum biomarker levels were measured immediately before ablation. The Ethics Committee at the University of Fukui Hospital approved this study, which proceeded according to the Declaration of Helsinki (2013). A series of patients who underwent various diagnostic procedures served as controls, and follow-up results were registered in the Universal Hospital Medical Information Network Clinical Trials Registry (UMIN000023845).

2.2 Measurements of biomarkers

Blood was collected from the left atrium (LA), right atrium (RA), femoral artery (FA), and femoral vein (FV) immediately before ablation to define TNC levels, and pressure was measured in the left and right atria. Levels of TNC in the LA (TNC-LA), RA (TNC-RA), and FA (TNC-FA) were measured, and high-sensitivity C-reactive protein (CRP), atrial (ANP)- and brain (BNP)-natriuretic peptides were measured in serum separated from blood sampled from femoral veins. All blood samples were placed immediately on ice, separated by centrifugation within 30 min, then stored at − 80 °C. Circulating levels of TNC and CRP were determined using enzyme-linked immunosorbent assays (ELISA), and ANP as well as BNP were also assessed.

2.3 Echocardiography

Transthoracic echocardiograms were acquired from patients in the left lateral decubitus position within 24 h before catheter ablation using a Vivid 7 echocardiograph (GE Vingmed Ultrasound AS, Horten, Norway) with an M3S transducer or a Sonos 7500 (Philips Technology, Andover, MA, USA) with an S3 transducer. Echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography. Images were acquired in parasternal long-axis and apical four-chamber views. Left ventricular end-diastolic and end-systolic dimensions and left ventricular septal and posterior wall thickness were measured using M-mode echocardiography in the parasternal view. The LA diameter was measured during systole along the parasternal long-axis view. Transverse and longitudinal diameters of the LA and RA were acquired in the four-chamber view in the end-systolic frame preceding opening of the mitral valve.

2.4 Statistical analysis

Numeric and categorical variables are expressed as means ± SD and numbers (n, %), respectively. The groups were compared using one-way analyses of variance followed by Scheffé adjustment. Categorical variables were using chi-squared or Fisher exact tests. Correlations between variables were analyzed using Pearson correlation coefficients. The statistical significance of values was defined at $p < 0.05$. All data were statistically analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Patients' characteristics

Table 1 shows the characteristics of the 38 enrolled patients. All patients underwent catheter ablation. One patient each had transient right phrenic nerve injury and gastric hypomotility, and the remaining 36 patients had no complications. Blood was collected and echocardiological examinations proceeded before ablation procedures. Median values were as follows: age, 64 years; male, $n = 26$ (68%); paroxysmal AF for 52 months, $n = 25$ (66%); CHA2DS2VASc score, 2.2; the left atrium size, 38.3 mm; left ventricular ejection fraction, 64%.

3.2 Tenascin-C and atrial size

The mean transverse diameters of the LA and RA and mean pressure in the LA and RA significantly differed (38.5 vs. 32.7 mm; $p < 0.001$ and 14.4 vs. 8.2 mmHg; $p = 0.003$, respectively). We standardized atrial size by calculating an indexed-atrial size determined by dividing the diameter of the right (RADi) and left (LADi) atria by the body surface area (BSA). We compared TNC concentrations adjusted

Table 1 Patients' characteristics

Age (years)	64 ± 12
Male, n (%)	26 (68)
Body mass index	23.8 ± 3.9
Paroxysmal AF, n (%)	25 (66)
AF duration (months)	52 ± 44
CHA2DS2-VASc score	2.2 ± 1.2
Left atrial diameter (mm)	38.3 ± 6.7
Left ventricular ejection fraction (%)	64 ± 9
Left ventricular diameter (mm)	47.9 ± 4.5
Plasma BNP (pg/mL)	79.0 ± 51.2
Serum creatinine (mg/dL)	0.89 ± 0.20

Values are shown as means ± SD or as numbers (%). *AF* atrial fibrillation, *BNP* brain natriuretic peptide

(TNC-index) by the atrial diameter corrected using BSA in each atrial cavity to clarify whether or not TNC concentrations increase depend on the size of the atrium. The TNC-index was higher for the LA than the RA in all 38 patients. The LA and the RA TNC-indices were also higher in all 38 patients than in the control group (Fig. 1). The TNC-index was greater in the order of the LA, RA, and FA (Fig. 1). Figure 2A shows the atrial size indices. The LADi in both the transverse and longitudinal diameters, and the RADi in the longitudinal diameter were higher in the patients with AF than in the controls. Patients with persistent AF had a significantly larger LADi in the transverse and parasternal views than those with paroxysmal AF. The mean pressures of the LA and RA significantly differed between the patients and the controls (Fig. 2B) and between patients with persistent and paroxysmal AF (Fig. 3).

3.3 Correlations between tenascin-C and other variables

Levels of hs-CRP were significantly higher in all patients with AF than in controls (2.21 ± 0.39 vs. 0.44 ± 0.09 mg/L, $p < 0.01$). Furthermore, hs-CRP levels were significantly higher in patients with persistent AF, compared with paroxysmal AF (3.28 ± 0.81 vs. 1.65 ± 0.31 mg/L, $p < 0.05$). Levels of hs-CRP from the femoral vein correlated significantly and positively with TNC-index-LA ($r = 0.56$, $p < 0.001$) and TNC-index-RA ($r = 0.62$, $p < 0.001$) but not with TNC-FA ($r = 0.054$, $p = 0.74$). The LADi and RADi in longitudinal diameter correlated significantly and positively with TNC-index-LA and TNC-index-RA ($r = 0.52$, $p < 0.001$ and, $r = 0.69$, $p < 0.001$, respectively). However, TNC-index-LA, TNC-index-RA, and TNC-FA did not correlate with ANP or BNP in femoral venous blood (Table 2).

4 Discussion

The main findings of the present study were that serum levels of TNC in patients with AF (including paroxysmal AF) were greater in the order of the LA, RA, and FA, and the TNC-index-LA was higher than that in the RA or FA. We also found that the TNC-index in the LA and RA significantly correlated with the transverse diameter of the LA and RA respectively, and with levels of plasma hs-CRP in blood from the femoral vein.

4.1 Serum TNC levels in patients with atrial fibrillation

Serum TNC levels increase after acute myocardial infarction or dilated cardiomyopathy [3–7]. Under these pathological conditions, elevated TNC levels correlated with left ventricular dilation, indicating that they could serve as a surrogate marker of myocardial remodeling. The present study identified elevated serum TNC in patients with AF, and with normal left ventricular function and dimensions. Serum TNC concentrations in the atria were higher among patients with persistent, than paroxysmal AF and correlated with the atrial dimension. Thus, serum TNC levels in the atria might serve as a novel marker of atrial remodeling. Left atrial TNC values did not correlate with LA pressure, serum ANP, or BNP. Thus, serum TNC levels in the atria were not associated with pressure overload in the LA. The finding of elevated TNC in the LA and RA, but not in the FA, indicated an atrial source of TNC. Intestinal fibroblasts, and endothelial and smooth muscle cells produce TNC upon induction in vitro by inflammatory cytokines [8–10], whereas myocytes do not. We speculated that the source of TNC is either atrial myofibroblasts or endothelium. Levels of TNC were also a useful marker of atrial

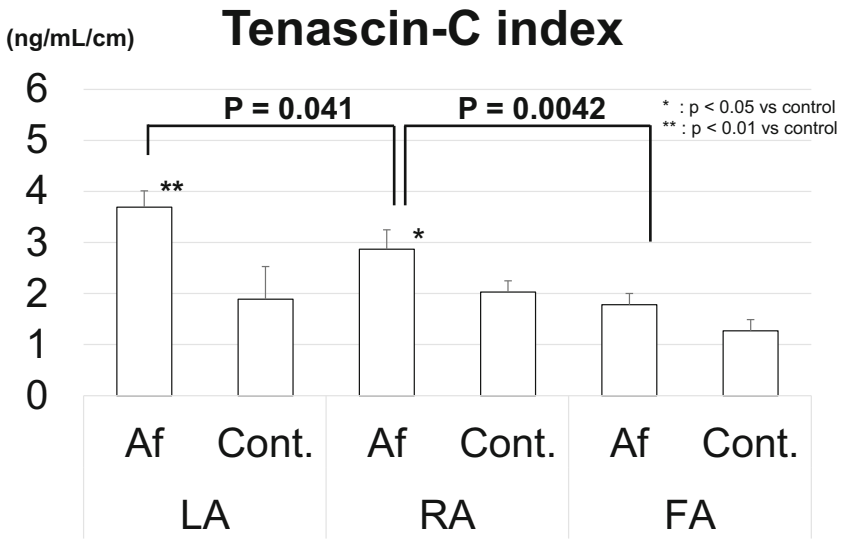

Fig. 1 Serum tenascin-C concentration index. Tenascin-C indices were higher in order of LA, RA and FA. Data are expressed as means ± standard deviation. *p*-values were derived using one-way analysis of variance. AF, atrial fibrillation; Cont, controls; FA, femoral artery; LA, left atrium; RA, right atrium; TNC, tenascin-C

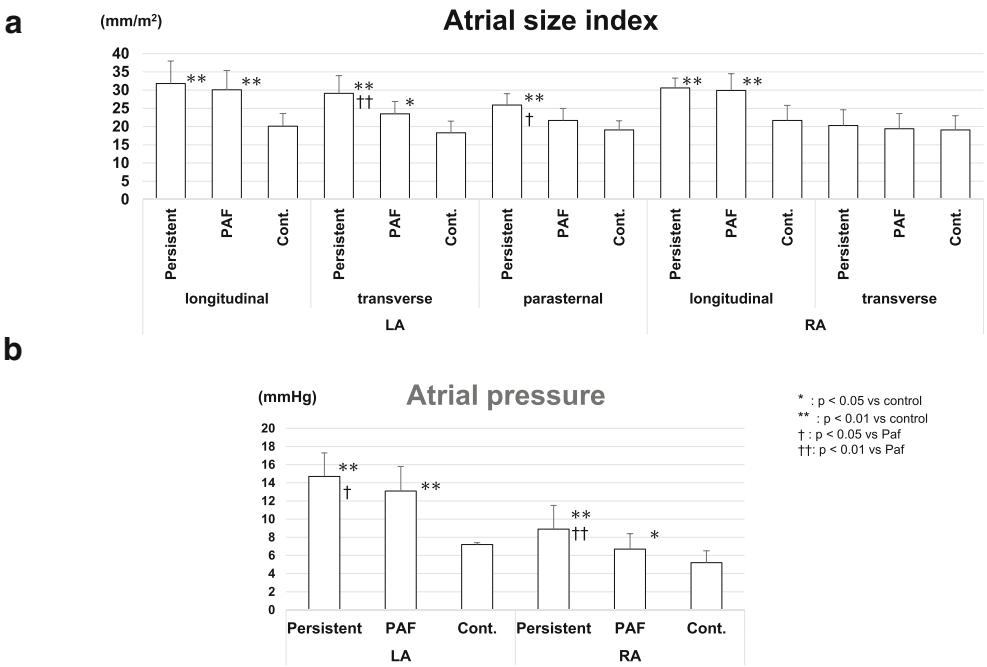

Fig. 2 Atrial Size and Pressure. Bar graphs show left and right atrial size (A), and left and right pressure (B) in patients with persistent, paroxysmal AF and controls. Data are expressed as means ± standard deviation. *p* values were derived using the paired *t* tests. Cont, controls; LA, left atrium; PAF, paroxysmal AF; RA, right atrium

damage. These results indicate that measuring serum TNC in the LA could predict the outcomes of ablation therapy and the likelihood of AF recurrence. From this viewpoint, further prospective studies with larger samples, longer follow-up, serial measurements of TNC from the peripheral vein and more clinical parameters over a longer period are needed to clarify whether TNC can predict the outcomes of ablation therapy and likelihood of AF recurrence.

4.2 Serum TNC levels and inflammation

The present study significantly correlated TNC levels with serum hs-CRP. Thus, we considered that inflammation induces TNC elevation. Although triggered activity can cause AF, even if such a trigger is located in the normal myocardium, the duration of AF would be very short [11]. Inflammation has been associated with AF persistence in

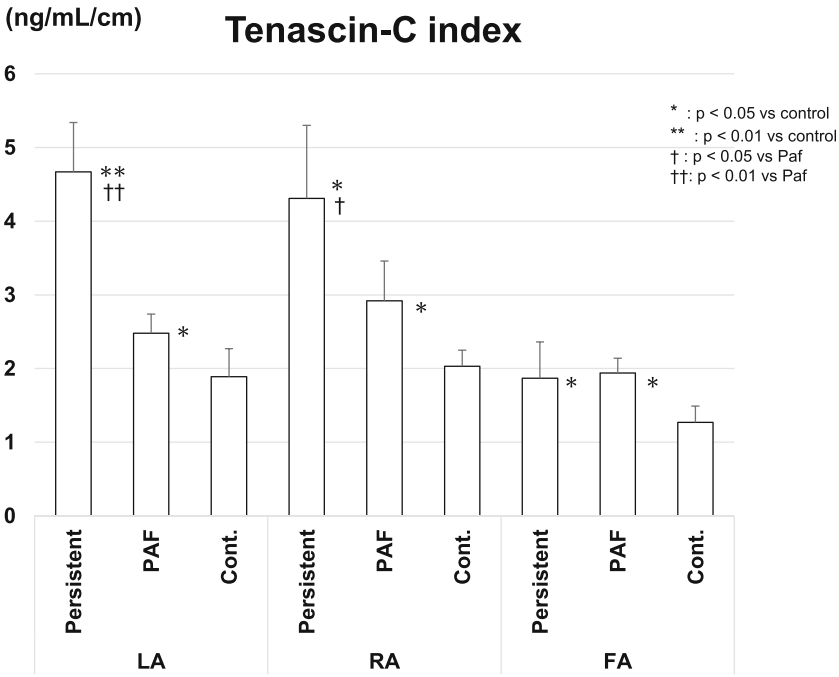

Fig. 3 Tenascin-C in persistent and paroxysmal atrial fibrillation. Serum tenascin-C levels in the RA and the LA significantly differed between patients with paroxysmal and persistent fibrillation. Data are expressed as means ± standard deviation. *p* values were derived using unpaired *t* tests. Cont, controls; FA, femoral artery; LA, left atrium; PAF, paroxysmal atrial fibrillation; RA, right atrium

Table 2 Comparison of tenascin-C from various sites

		TNC-index LA		TNC-index RA		TNC-index FA	
		r	*p*	*r*	*p*	*r*	*p*
Femoral vein	CRP	0.56	< 0.001	0.62	< 0.001	0.085	0.68
	ANP	0.00023	0.92	0.056	0.71	0.12	0.29
	BNP	0.00026	0.91	0.025	0.81	0.18	0.28
LA	Pressure	0.12	0.28				
	Diameter index	0.52	< 0.001				
RA	Pressure			0.19	0.19		
	Diameter index			0.69	< 0.001		

ANP, atrial natriuretic peptide; *BNP*, brain natriuretic peptide; *FA*, femoral artery; *hs-CRP*, high-sensitivity C-reactive protein; *LA*, left atrium; *RA*, right atrium

addition to triggered activity [12]. Concentrations of TNC were higher among our patients with sustained AF, and the values closely correlated with those of hs-CRP. Thus, we inferred that TNC is also involved in AF prolongation. If patients with paroxysmal AF and high TNC levels could be prospectively followed, those who are more likely to progress towards persistent AF could be identified and ablated early.

4.3 Clinical implications

Values of TNC-LA and TNC-RA might become novel markers of atrial inflammation and remodeling. If atrial remodeling could be prevented by controlling TNC, then AF might be suppressed occurrence, and the incidence of recurrent AF after ablation might be reduced.

4.4 Study limitations

Our patient cohort was small, and we could not examine recurrence rates after ablation. The possibility of tissue damage caused by catheterization cannot be ruled out, because the LA was sampled after the Brockenbrough technique, which might have caused damage compared with the RA. Since the TNC concentration was higher in the RA than the FA and correlated with hs-CRP values, we judged that the influence of direct tissue damage was slight.

5 Conclusions

Intracardiac (atrial) TNC expression plays an important role in the development of remodeling processes in the atrium with AF. Both TNC-LA and TNC-RA might serve as novel markers of these processes, whereas TNC-FA, ANP, and BNP cannot.

Acknowledgments The authors thank Ms. Hiromi Nishimura, Ms. Motoko Oku, Ms. Mari Kurata, and Ms. Yoshiko Kurose for providing excellent technical and secretarial assistance.

Funding information This study was partially supported by a Research Grant from the University of Fukui and a JSPS Grant-in-Aid for Scientific Research (C) (Grant number JP16K09426).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
2. Kaireviciute D, Lip GY, Balakrishnan B, Uzdavinys G, Norkunas G, Kalinauskas G, et al. Intracardiac expression of markers of endothelial damage/dysfunction, inflammation, thrombosis, and tissue remodeling, and the development of postoperative atrial fibrillation. J Thromb Haemost. 2011;9:2345–52.
3. Kimura T, Yoshimura K, Aoki H, Imanaka-Yoshida K, Yoshida T, Ikeda Y, et al. Tenascin-C is expressed in abdominal aortic aneurysm tissue with an active degradation process. Pathol Int. 2011;61:559–64.
4. Franz M, Berndt A, Grün K, Kuethe F, Fritzenwanger M, Figulla HR, et al. Serum levels of tenascin-C variants in congestive heart failure patients: comparative analysis of ischemic, dilated, and hypertensive cardiomyopathy. Clin Lab. 2014;60:1007–13.
5. Sato A, Hiroe M, Akiyama D, Hikita H, Nozato T, Hoshi T, et al. Prognostic value of serum tenascin-C levels on long-term outcome after acute myocardial infarction. J Card Fail. 2012;18:480–6.
6. Sakamoto N, Hoshino Y, Misaka T, Mizukami H, Suzuki S, Sugimoto K, et al. Serum tenascin-C level is associated with coronary plaque rupture in patients with acute coronary syndrome. Heart Vessel. 2014;29:165–70.
7. Franz M, Berndt A, Neri D, Galler K, Grün K, Porrmann C, et al. Matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, B+ tenascin-C and ED-A+ fibronectin in dilated cardiomyopathy: Potential impact on disease progression and patients' prognosis. Int J Cardiol. 2013;168:5344–51.

8. Imanaka-Yoshida K, Aoki H. Tenascin-C and mechanotransduction in the development and diseases of cardiovascular system. Front Physiol. 2014;5:283.
9. Imanaka-Yoshida K, Yoshida T, Miyagawa-Tomita S. Tenascin-C in development and disease of blood vessels. Anat Rec (Hoboken). 2014;297:1747–57.
10. Segers VFM, Brutsaert DL, De Keulenaer GW. Cardiac remodeling: endothelial cells have more to say than just NO. Front Physiol. 2018;9:382.
11. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014;63:2335–45.
12. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res. 2014;114:1453–68.