Cardiotrophin-1: A new predictor of atrial fibrillation relapses after successful cardioversion

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ABSTRACT

We aimed to investigate whether or not cardiotrophin-1 (CT-1) can be used as a predictor of sinus rhythm constancy in patients with atrial fibrillation (AF) converted to sinus rhythm. Thirty two patients with AF (48-78 years), without any structural heart disease were enrolled for the study. The control group consisted of 32, age and gender matched healthy persons. Measurements of CT-1 were made after transthoracic and transesophageal echocardiography prior to cardioversion (CV). Relapses of AF were investigated by monthly electrocardiograms (ECGs) and ambulatory ECGs at 1st, 3rd, and 6th month. At the end of 6th month, measurements of CT-1 were repeated. At the beginning patients with AF had increased CT-1 levels when compared to controls (0.94 ± 0.32 pg/mL vs. 0.30 ± 0.12 pg/mL, [$p < 0.001$]). At the end of follow-up of the 32 patients, 17 (53%) had AF relapse. Age, initial duration of AF, left ventricle diameters, ejection fraction, left atrium appendix flow rates were similar among patients with and without AF relapse. However, basal left atrium diameter (4.24 ± 0.14 cm vs. 4.04 ± 0.22 cm, $p = 0.005$), pulmonary artery pressure (32.82 ± 5 vs. 28.60 ± 6.23 mmHg, $p = 0.004$) and CT-1 values (1.08 ± 0.37 vs. 0.82 ± 0.16 pg/mL, $p = 0.02$) were significantly increased in patients with AF relapse. Furthermore, patients with relapsed AF had higher CT-1 levels at 6th month when compared to those in sinus rhythm (1.00 ± 0.40 vs. 0.71 ± 0.23 pg/mL). We conclude that post-CV, AF relapses are more frequent among patients with increased baseline CT-1 levels, and CT-1 may be a potential predictor of AF relapse.

KEYWORDS: Atrial fibrillation; cardioversion; cardiotrophin-1
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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1]. The prevalence of AF doubles with each advancing decade of age, from 0.5% at age 50-59 years to almost 9% at age 80-89 years [2]. The annual risk for ischemic stroke is estimated around 5% in patients with AF without anti-thrombotic therapy. Ageing, history of diabetes mellitus, hypertension, cardiac failure, prior stroke or transient ischemic attack, female gender, and vascular diseases are risk factors for stroke in AF while some of these factors are also involved in the development and persistence of AF [3-5].

Electrical remodeling that can be defined as shortening of atrial refractoriness develops within the first days of AF, stabilizes AF and contributes to its persistence. Atrial contractile remodeling, that can be defined as the loss of atrial contractility, leads to a reduced atrial transport function after cardioversion (CV) of AF. Reduced atrial contractility may also enhance atrial dilatation and contribute to the persistence of AF. In the long-term, persistent tachycardia causes myolysis and loss of atrial contractile force. Fibrosis of the atrial tissue leads intra-atrial conduction disturbances. Other underlying cardiovascular diseases also contribute to remodeling [6]. Thus, recurrent fibrillatory activity promotes progressive electrical and tissue structural remodeling, [6-8] and reduction of left atrial (LA) endocardial voltage through fibrosis [9]. These remodeling mechanisms affect LA volumes, endocardial voltages and conduction velocities [10].

Cardiotrophin-1 (CT-1) is a cytokine belonging to interleukin-6 (IL-6) family that plays pivotal roles including maturation of cardiac myocytes, promotion of cell survival in cardiomyocytes via anti-apoptotic pathways mediated by mitogen-activated protein kinase, extracellular signal-regulated protein kinases 1 and 2, and induction of hypertrophy in neonatal

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ventricular cardiomyocytes [11,12]. Recent studies established that CT-1 acts via transmembrane signaling protein glycoprotein 130 (gp130), and mice lacking gp130 exhibit severe ventricular hypoplasia [13]. Of note, experimental studies indicated that CT-1 can limit myocardial injury even when administered at the onset of reperfusion [14]. Increased levels of CT-1 has been determined in patients with stable or unstable angina, acute myocardial infarction, aortic stenosis, mitral regurgitation, left ventricular (LV) hypertrophy, and LV systolic dysfunction [15]. A recent study investigated the role of CT-1 on atrial myocardial fibrosis in a canine model, and established that expression of CT-1 significantly increased in atrial fibrosis and irbesartan could decrease its expression [16]. The association between the arrhythmogenic potential of CT-1 has been established in another rat ventricle model in which cardiomyocytes treated with CT-1 have presented high spontaneous calcium release during diastole, a proposed mechanism that links to arrhythmogenicity in the pathologic heart [17].

In this study, we aimed to investigate the role of CT-1 in AF remodeling and whether CT-1 can be used as a predictor of sinus rhythm maintenance among persistent AF patients converted to sinus rhythm via electrical CV.

MATERIALS AND METHODS

Patient selection

The study was approved by Institutional Ethics Committee, and all the patients gave written informed consent prior enrolment. Thirty two consecutive persistent AF patients (18 women (56.25%), mean age 56.47 ± 9.02 years) without any structural heart and valve disease were enrolled to the study from the outpatient clinic. The mean duration of AF was 6.3 ± 3.42 months.

Patients with severe LV hypertrophy, chronic liver disease (or over 3-fold increased serum transaminases), renal disease (serum creatinine levels of >132.6 μmol/L), hypotension, pregnancy, prominent heart valve disease (stenosis or regurgitation), hypothyroidism or hyperthyroidism, pulmonary embolism, hypoxemia, anemia, a prior history of hypersensitivity to either angiotensin converting enzyme inhibitors or angiotensin receptor blockers, an ejection fraction (EF) of <50%, a left atrium of >4.5 cm, and contraindication for oral anticoagulation were excluded. The control group consisted of 32, age and sex matched healthy people (mean age 56.66 ± 8.92 years, 55.4% women). These healthy controls enrolled to the study were randomLy chosen among both staff and patients' families. A total of 45 patients have been excluded according to the exclusion criteria.

Study protocol

Baseline medical history and complete physical examination including weight and height measurements of the participants were recorded at the beginning. Standard echocardiographic examinations were also performed. Patients on oral anticoagulation therapy underwent direct transesophageal echocardiographic (TOE) study while patients who were not taking anticoagulants were prescribed warfarin for 3 weeks with a target international normalized ratio 2.0-3.0. These patients underwent TOE study after successful oral anticoagulation therapy. All the patients were hospitalized for electrical direct current CV (DC-CV). After 12 hours fasting propafenone infusion was started intravenously, and electrical CV was performed under anesthesia in the coronary intensive care unit. Oral propafenone and warfarin therapies were continued after successful conversion to sinus rhythm. Patients were discharged 48 hours after DC-CV. Patients were followed up with monthly physical examinations and electrocardiograms (ECGs) for 6 months (in the first month, once every week). Patients were advised to come immediately whenever they had palpitations. At the end of 1st, 3rd and 6th month 24 hours ambulatory ECGs were recorded. At 6th month, echocardiographic studies were repeated.

Blood samples were collected via superficial veins of the right arm in 10 mL ethylenediamine tetra acetic acid (EDTA) containing tubes before CV and at 6th month.

Echocardiography

All echocardiographic studies were performed by an experienced cardiologist with commercially available "Vivid 7 dimension" system (Vingmed Ultrasound, GE Healthcare, USA) using a 2.5-3.5 Mhz probe. Two-dimensional echocardiographic measurements were recorded in parasternal long axis, apical 2, 4, and 5 chambers windows according to the principles defined by the "American Society of Echocardiography." LV septal and posterior wall thicknesses, LV diastolic and systolic dimensions were measured via M-mode echocardiography on parasternal long axis windows. LVEF was calculated via "Teichholz" method. LA diameters were measured from parasternal and apical windows. Color Doppler echocardiography was used to determine valve function. TOEs were performed by an experienced cardiologist in the echocardiography laboratory under local anesthesia with 10% xylocain solution and sedation with 1-5 mg intravenous midazolam. Upper transesophageal, mid transesophageal and transgastric images were recorded. Left atrium appendage (LAA) was examined for potential thrombi and LAA flows were recorded.

Ambulatory ECGs

Ambulatory ECG monitorization was performed during the follow-up period at 1st, 3rd, and 6th month of the study. We have used the "Cardio Navigator 8.407" system (Del Mar Reynolds Medical, Edinburg and Hertford, UK). The results

were evaluated by the investigators who are experienced in the field.

Measurement of CT-1 levels

Blood samples collected in EDTA-containing tubes were stored at –80°C. Levels of CT-1 were determined with a commercially available CT-1 "enzyme-linked immunosorbent assay" (ELISA) kit (Human CT-1 ELISA, RayBiotech, Norcross, GA) on a manual "DNM-9602 MicroPlate Reader." The automatic washing procedure was performed with a "DNX-9620 MicroPlate Washer" (Nanjing Perlove Medical Equipment, Jiangsu, China) device. The linearity was 106% (97-113). The intra-assay and interassay variability were 6 and 8%, respectively.

Statistics

Descriptive statistics were expressed as mean ± standard deviation. Median and percentage distribution have been used to determine deviation from normality. Continuous variables having normal distribution were evaluated by Student *t* test. Categorical data were evaluated by Chi-square test. Mann-Whitney U test was used to evaluate continuous variables having abnormal distribution. Receiver operating characteristic (ROC) curves were used to calculate cut-off values for AF relapse in AF patients and healthy controls. Pearson's linear regression test was used to determine the relationship between CT-1 and relapse of AF. Furthermore, logistic regression analysis was used to evaluate potential confounders to the relapse of AF. A $p < 0.05$ was accepted as statistically significant. All statistical analyses were prepared with commercially available SPSS V 15.0 software (Statistical Package for the Social Sciences INC., Chicago, Illinois, USA).

RESULTS

The mean basal CT-1 level was 0.30 ± 0.12 pg/mL and 0.94 ± 0.32 pg/mL among healthy controls and AF patients, respectively ($p < 0.001$). The ROC curve analysis indicated a cut-off of 0.47 pg/mL with 94% sensitivity and 93% specificity (Figure 1). At the end of 6 months, follow-up, of the 32 patients, 17 (53%) had AF relapse. The mean time between DC-CV and AF relapse was 25.29 ± 32.30 (2-120) days.

Age, initial duration of AF, LV diameters, right ventricle diameters, EF, left atrium appendix flow rates were similar among patients with and without AF relapse. However, basal left atrium diameter (4.24 ± 0.14 cm vs. 4.04 ± 0.22 cm, $p = 0.005$), pulmonary artery pressure (32.82 ± 5 vs. 28.60 ± 6.23 mmHg, $p = 0.004$) and CT-1 values (1.08 ± 0.37 vs. 0.82 ± 0.16 pg/mL, $p = 0.02$) were found significantly increased in patients with AF relapse. Furthermore, patients with relapsed AF had higher CT-1 levels at 6th month when compared to those in sinus rhythm (1.00 ± 0.40 vs. 0.71 ± 0.23 pg/mL). We did not determine a significant correlation between the LA diameter and CT-1 levels (r = 0.17, p = not significant). The ROC curve analysis indicated CT-1 level of 0.89 pg/mL as the cut-off value for the prediction of AF relapse (76% sensitivity and 74% specificity, $p < 0.001$) (Figure 2). Of note, we determined that LA diameter over 4 cm can predict AF relapse with 88% sensitivity, but only 40% specificity (Figure 3).

The relationship between the echocardiographic parameters and relapse of AF are shown in Table 1. The relationship between CT-1 levels and AF relapse after CV are shown in Table 2. Patients with relapsed AF had higher CT-1 levels at 6th month when compared to those in sinus rhythm (1.00 ± 0.40 vs. 0.71 ± 0.23 pg/mL, $p = 0.009$). Patients without relapsed AF had higher CT-1 levels at 6th month when compared to those in sinus rhythm (1.08 ± 0.37 vs. 0.82 ± 0.16, $p = 0.008$).

The logistic regression analysis indicated that a CT-1 levels were independent predictor of AF relapse and

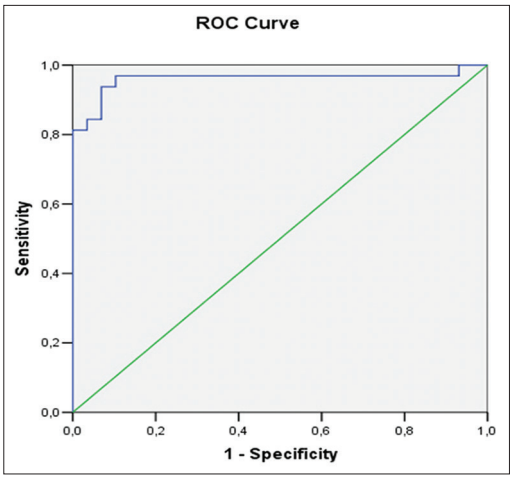

FIGURE 1. The receiver operating characteristic curve for cardiotrophin-1, as a predictor of atrial fibrillation.

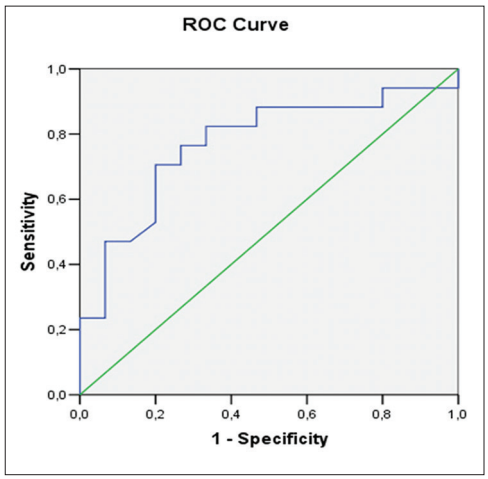

FIGURE 2. The receiver operating characteristic curve for cut-off value of cardiotrophin-1 for the prediction of atrial fibrillation relapse.

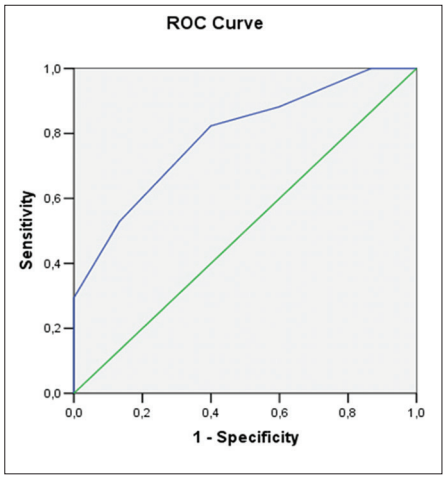

FIGURE 3. The receiver operating characteristic curve used for the cut-off value of left atrium diameter for the prediction of atrial fibrillation relapse.

TABLE 1. Relationship between the echocardiographic parameters and AF relapse after CV

Echocardiographic parameters	AF relapse (n=17)	Sinus rhythm (n=15)	*p*
Left atrium diameter (cm)	4.24±0.14	4.04±0.22	0.004
LVDD (cm)	4.74±0.41	4.80±0.41	NS
LVSD (cm)	3.14±0.35	2.97±0.42	NS
EF (%)	62.12±3.87	65±5	0.05
PAP (mmHg)	32.82±5	28.60±6.23	0.01
Right ventricle diameter (cm)	2.57±0.23	2.52±0.13	NS
LAAFV (m/sn)	0.36±0.11	0.35±0.10	NS

LVDD: Left ventricle end diastolic diameter; LVSD: Left ventricle end systolic diameter; EF: Ejection fraction; PAP: Pulmonary artery systolic pressure; LAAFV: Left atrial appendage flow velocity; AF: Atrial fibrillation; CV: Cardioversion; NS: Not significance

TABLE 2. Relationship between CT-1 levels and AF relapse after CV

CT-1 levels	AF relapse (n=17)	Sinus rhythm (n=15)	*p*
Basal CT-1 (pg/mL)	1.08±0.37	0.82±0.16	0.008
6th month CT-1 (pg/mL)	1.00±0.40	0.71±0.23	0.009

AF: Atrial fibrillation; CT-1: Cardiotrophin-1; CV: Cardioversion

values ≥0.89 pg/mL increased ~9-fold the risk of AF relapse (Odds ratio [OR]: 8.93; 95% confidence interval [CI] 1.80-44.3).

DISCUSSION

In our study CT-1 levels over 0.47 pg/mL reflected the pathologic limit for healthy controls and CT-1 > 0.89 pg/mL was associated with approximately 9-fold increased AF relapse risk in patients converted to sinus rhythm. Although several parameters including low EF, pulmonary hypertension, increased LA diameter, duration of AF and CT-1 level were found associated with AF relapse after successful CV, our multivariate analysis indicated CT-1 level as the prominent predictor of AF relapse. We think that atrial remodeling in patients with persistent AF is associated with increased CT-1 levels, and the increase of this mediator contributes to AF relapses after successful CV.

This is the first human study indicating that CT-1 levels are increased in patients with persistent AF and increased CT-1 levels over a cut-off value can be used for the prediction of AF relapse after successful CV. Recently, a single experimental study based on pacing-induced sustained AF model on pigs, has indicated no increase in tissue levels of IL-6, leukemia inhibitory factor (LIF) and CT-1, which are known to activate signal transducers and activators of transcriptions through membrane gp130 and Janus kinase [18].

Recent studies determined that CT-1 plays an active role in promoting structural changes (hypertrophy of myocytes, collagen synthesis, and progression of remodeling) in cardiovascular diseases including hypertension, valve diseases, congestive heart failure, and coronary artery disease [19]. Two experimental studies revealed the importance of CT-1 in the pathogenesis of atrial myocardial fibrosis and developing arrhythmias over the release of high concentrations of calcium during diastole [16,17]. There are evidence that CT-1 plasma levels can be elevated in patients with hypertension [20], coronary artery disease [21,22], and heart failure [23]. A recent experimental study indicated that CT-1 accelerates the development of atherosclerotic lesions by stimulating the inflammasome, foam cell formation associated with CD36 and acyl-CoA: cholesterol acyltransferase-1 upregulation in macrophages, and migration, proliferation, and collagen-1 production in vascular smooth muscle cells [24]. Our study provided new information on increased CT-1 among persistent AF patients without structural heart disease.

The success of CV depends on several factors including, the duration of AF, LA diameter, LA appendage flow velocities, underlying organic heart disease, local factors (e.g. chest wall impedance) and technique. In general, successful conversion to sinus rhythm is achieved in about 79% (monophasic) to 94% (biphasic) of patients after CV, however, 50-60% of the patients return to AF in a few months [25,26]. A recent study indicated that sinus rhythm was restored in 89% by DC-CV but maintained only in 34% of the AF patients at a median follow-up of 930 days [27]. In our study, all the patients returned to sinus rhythm with CV, but during the follow-up (6 months) relapsed AF was determined in 17 patients (53%). It is conceivable that structural remodeling comprising progressive LA enlargement, atrial fibrosis, and loss of rate concordance might have a pivotal contribution to the relapse of AF.

CT-1 is reported to exhibit cytoprotective, pro-proliferative and profibrotic effects on the heart via a unique receptor system comprising LIF receptor (LIFRβ) and a common signal transducer, the gp130 [28]. CT-1 was also proposed as a prognostic biomarker for death and heart failure in patients with acute myocardial infarction [29] as well as increased levels of

CT-1 were reported to be associated with fibrosis, remodeling and depression of myocardial contractility in patients with heart failure [23]. We think that inflammation leads structural and electrical remodeling that consequently induces AF relapse and investigation of this vicious circle may provide pivotal information for the prevention of AF.

In our study, we excluded patients with severe structural heart disease in order to decrease the effect of potential contributors to AF relapse. We also aimed to investigate more accurately the relationship between CT-1 levels and cardiac remodeling seen in AF patients. Our study has limitations including the sample size, and the duration of follow-up.

CONCLUSION

The increased CT-1 levels were associated with increased AF relapses after successful CV in persistent AF patients. We conclude that CT-1 can be a potential predictor for AF relapse among persistent AF patients who are candidates for CV.

DECLARATION OF INTERESTS

The authors declare no conflicts of interests.

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