

Does atrial fibrillation affect plasma endothelin level?

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Abstract

Background: Atrial fibrillation (AF) may result in endocardial endothelium dysfunction. The main objective of the study was to evaluate the plasma concentration of endothelin-1 (ET-1) during persistent AF and after sinus rhythm recovery following direct-current cardioversion and to assess the predictive value of ET-1 in AF patients.

Methods: The study group consisted of 43 patients with persistent AF and normal left ventricle systolic function who had undergone successful cardioversion. Blood samples were collected twice: 24 hours before and 24 hours after cardioversion. All patients were also examined in terms of sinus rhythm maintenance on the 30th day after cardioversion.

Results: There were no differences in ET-1 plasma concentration between the persistent AF group and the control group (2.6 ± 2.9 fmol/mL vs 2.3 ± 4.5 fmol/mL, NS). Plasma ET-1 levels did not change within 24 hours after successful cardioversion (2.5 ± 2.8 fmol/mL vs 2.6 ± 2.9 fmol/mL, NS). There was no correlation between the baseline plasma levels of ET-1 in patients with persistent AF and sinus rhythm maintenance 30 days after cardioversion.

Conclusions: Persistent AF does not affect plasma ET-1 concentration in patients with normal left ventricle systolic function and with no symptoms of heart failure. There are no significant changes in plasma ET-1 level during the 24 hours after cardioversion. (Cardiol J 2010; 17, 5: 471–476)

Key words: atrial fibrillation, endothelin, cardioversion

Introduction

The hemodynamic consequences of atrial fibrillation (AF) are related to the loss of atrial contribution to cardiac output, to an increase in heart rate and to irregularity in the diastolic intervals. AF may have a long term deleterious effect on left ventri-

cular function and may precede the development of heart failure. It has been shown that patients with AF and heart failure, but also with preserved left ventricle (LV) function, have a similarly high mortality compared to those patients with decreased left ventricular ejection fraction (LVEF) [1]. AF and chronic heart failure are two common cardiac

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diseases, affecting 1–2% of the population, a proportion that rises with age [2, 3].

A pioneering work by Furchgott and Zawadzki [4], published in 1980, initiated a new understanding of vascular endothelium and its role as the main regulator of vascular homeostasis. Endothelin type 1 (ET-1) is synthesized by the vascular endothelium and is a sensitive biochemical marker of its dysfunction and damage. It exerts in a paracrine fashion pleiotropic effects, including vasoconstriction, direct chronotropism, growth effects on varying cell types, and interactions with other neurohormonal systems. ET-1's influence on the overgrowth, pathological reconstruction and fibrosis of atrial muscle may be significant in AF pathophysiology. The dysfunction and damage of vascular endothelium are the cause of numerous pathologies and constitute the main point of the theory of the *continuum* of the cardiovascular system's disorders. The disorders in the function of vascular endothelium may occur in AF, which then may lead to increased thrombogenesis and finally to the risk of stroke and increased mortality. Elevated plasma concentrations of ET-1, and of its precursor, have been measured in patients with various levels of severity and etiology of chronic heart failure [5, 6]. These observations have led to the hypothesis that pharmacologic blockade of endothelin receptors could improve outcomes for patients with chronic heart failure. However, clinical trials with different endothelin receptor antagonists have not confirmed these speculations [5, 6]. Studies published on the subject do not include data on the possibilities of the practical applications of ET-1 assessment in patients with persistent AF, without symptoms of overt heart failure, undergoing direct-current cardioversion (CV).

The main objective of this study was to evaluate the plasma concentration of ET-1 in patients with persistent AF with preserved LV function and with no symptoms of heart failure, compared to a control group before and after sinus rhythm recovery, and to assess the prognostic importance of these changes.

Methods

The examined group consisted of patients with persistent AF, normal systolic function of LV and no clinical symptoms of heart failure, who underwent successful electrical CV. The main criteria for inclusion were: persistent AF with no-valve etiology, no contraindication for recovering sinus rhythm by means of electrical CV, with preserved

LV function in echocardiography examination (LVEF > 50%), no symptoms of heart failure, properly treated main disease (arterial hypertension, coronary arterial disease, diabetes). The control group consisted of ten people of a similar age, evenly divided as to men and women, treated in hospital for circulatory system disorders (arterial hypertension and coronary artery disease) with sinus rhythm and preserved LV function, with no symptoms of heart failure and no history of AF.

All patients included in the study were examined three times: 24 hours before and 24 hours after CV and on the 30th day after sinus rhythm recovery. Clinical data, echocardiography readings and laboratory determination before and after successful CV were analyzed. In order to recover sinus rhythm, CV was performed with short general anesthesia by means of a Medtronic Physio-Control Lifepak 12 with an electric discharge synchronized with the electrocardiography R wave. The procedure started with an initial 100 J. In cases of persistent AF, we twice attempted to recover sinus rhythm with an impulse of 200 J. The maximum energy delivered within one CV procedure did not exceed 500 J. The CV efficiency was defined as the lack of AF in the 24th hour after the recovery of sinus rhythm.

The transthoracic echocardiography was performed with the use of a digital Siemens device, Acuson Sequoia C 256, with an ultrasonic head with frequency of 2.5–3.5 MHz.

Blood samples for ET-1 concentration were collected into EDTA test tubes in the morning hours by means of venipuncture from fasting patients. The blood was centrifuged at a temperature of 4°C and plasma was frozen at a temperature of –20°C. The ET-1 plasma concentration was marked by means of an ELISA test using an Endothelin ELISA (1-21) Biomedica set no. BI-20052. After successful CV, most patients underwent anti-arrhythmic treatment. The statistical analyses were conducted by means of SYSTAT 7.0 and MedCalc 4.16 software. Permission for conducting the examination was obtained from the National Committee on Bioethics.

Results

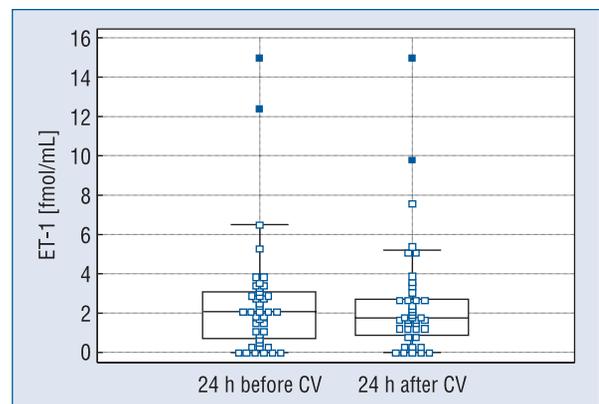
Initially, 45 patients aged 18–75 were qualified for the study. Finally, 43 subjects with successful CV were included. Patients' characteristics are listed in Table 1. The main risk factors of AF occurrence in the study group were arterial hypertension, ischemic heart disease and diabetes. The patients from the control group were compatible in age and

Table 1. The study group's baseline characteristics.

Parameter	Study group (n = 43)	Control group (n = 10)	P
Age (years)	59.0 ± 11.6	57.5 ± 9.2	NS
Gender: women/men	8 (18.6%)/35 (81.4%)	2 (20%)/8 (80%)	NS
Body mass index [kg/m ²]	28.5 ± 3.8	26.7 ± 4.3	NS
Heart rate [beats/min]	85.4 ± 13.0	80.4 ± 16.5	NS
Systolic blood pressure [mm Hg]	130.6 ± 14.9	131.0 ± 17.3	NS
Diastolic blood pressure [mm Hg]	80.3 ± 9.0	81.0 ± 8.7	NS
Hypertension	27 (62.8%)	7 (70%)	NS
Coronary artery disease	8 (18.6%)	3 (30%)	NS
Diabetes	3 (7.0%)	2 (20%)	NS
Lone atrial fibrillation	9 (20.9%)	—	—
Atrial fibrillation duration (weeks)	12.3 ± 15.3	—	—
Left ventricular ejection fraction (%)	57.3 ± 6.1	61.6 ± 6.8	NS
Left atrium dimension [mm]	43.7 ± 5.9	41.0 ± 4.4	NS

gender and did not differ in baseline clinical and echocardiographic data. During the first visit (24 h before CV), the average heart rhythm frequency was 85.4 ± 13.2 bpm, systolic and diastolic blood pressure were normal. The LVEF was of about 57% in the study group. The left atrium diastolic diameter was 43.7 ± 5.9 mm and did not differ significantly when compared to the control group. ET-1 plasma concentration in patients with persistent AF was 2.6 ± 2.9 fmol/mL and did not differ significantly in comparison to the control group (2.3 ± 4.5 fmol/mL). In patients with persistent AF who underwent successful CV, plasma ET-1 concentration evaluated 24 hours after the recovery of sinus rhythm (2.5 ± 2.8 fmol/mL) did not differ significantly from the samples measured 24 hours before CV (2.6 ± 2.9 fmol/mL). Plasma ET-1 concentrations in the group of patients 24 hours before and 24 hours after CV are presented in Figure 1. Within the 24 hours following CV, all 43 patients maintained sinus rhythm. But after 30 days, sinus rhythm without registered episodes of AF was maintained in 24 (56%) patients. Depending on the presence of sinus rhythm on the 30th day after CV, the entire group was divided into two sub-groups: subgroup A, patients with sinus rhythm in a 30-day follow-up from CV; and subgroup B, patients with AF relapse in a 30-day observation period.

Neither subgroup differed in terms of the basic clinical and echocardiographical parameters evaluated by CV. There were no statistically significant differences in the frequency of occurrence of the concomitant circulatory system disorders (coronary heart disease, arterial hypertension or stroke) as well as diabetes in both subgroups. Additionally,

**Figure 1.** Plasma endothelin-1 levels before and after successful cardioversion (CV) in 43 patients with persistent atrial fibrillation.

neither group differed in terms of the anti-arrhythmic treatment after CV. There were also no differences in the frequency of the administration of angiotensin-converting enzyme inhibitors (Table 2). The ET-1 plasma concentration, determined before CV, did not differ significantly between the patients without AF relapse (subgroup A) and the patients with AF recurrence (subgroup B) and was 3.1 ± 3.8 fmol/mL vs 2.0 ± 1.4 fmol/mL respectively, $p = 0.25$). In order to assess the prognostic value of the ET-1 measurement in patients with persistent AF referred to direct-current CV, the logistic regression method was applied. There turned out to be no correlation between the initial ET-1 plasma concentration and the maintenance of sinus rhythm 30 days after CV ($p = 0.24$).

Table 2. The study subgroups' baseline characteristics.

Parameter	Subgroup A (sinus rhythm) n = 24	Subgroup B (atrial fibrillation) n = 19	P
Age (years)	60.1 ± 10.3	57.7 ± 13.6	NS
Heart rate [beats/min]	85.5 ± 13.7	85.3 ± 12.9	NS
Systolic blood pressure [mm Hg]	133.2 ± 14.5	127.4 ± 15.7	NS
Atrial fibrillation duration (weeks)	12.6 ± 18.1	12.0 ± 11.0	NS
Left ventricular ejection fraction (%)	57.8 ± 5.9	56.5 ± 6.5	NS
Left atrium dimension [mm]	43.4 ± 5.9	44.0 ± 6.1	NS

Discussion

This study presents the outcome of the evaluation of ET-1 plasma concentration in patients with persistent AF before CV and after sinus rhythm recovery. The usefulness of the endothelium function evaluation for prognosis of the disease's course, as well as the possible response to treatment, was analyzed. The study included both patients with spontaneous AF and those with AF triggered by hypertension or coronary heart disease, with no symptoms of heart failure, normal LV systolic function, short duration time of arrhythmia (approximately three months) and successful CV with sinus rhythm recovered.

There are few studies on peptides of the endothelin family concerning AF patients. Tuinenburg et al. [7] in 1998 pointed to ET-1 as an important factor responsible for the fibrosis of atrial myocytes in persistent AF. Masson et al. [8] described higher ET-1 plasma concentrations in patients with chronic heart failure and accompanying AF in comparison to the patients with no arrhythmia [8].

So far, no research has been carried out on the influence of AF on ET-1 plasma concentration in patients with normal LV systolic function and no symptoms of heart failure. The mechanisms responsible for the increased release of ET-1 in patients with AF are not well recognized. Atrial volume and pressure overload due to the lack of synchronized contraction of atria and irregular ventricular rhythm may lead to endothelium dysfunction in AF [9, 10]. The mechanism which increases ET-1 plasma concentration may be the increased peptide secretion and release of endothelium from the damaged cells within the cardiac cavities [11]. Brundel et al. [12] state that within the damaged endothelium in patients with AF, there is an increased gene expression for ET-1, increased synthesis and release of active peptide. The increased ET-1 plasma concen-

tration in patients with AF may stimulate the proliferation of smooth muscle cells and fibroblasts, which could lead to overgrowth and fibrosis. ET-1 may also trigger the inflammation process through the stimulation of cytokine production, growth and transformation factors as well as the intensification of leukocyte migration [13, 14]. ET-1 may also influence the electrical remodeling of atrial cardiomyocytes through increased intracellular calcium ions concentration [15, 16]. The influence of ET-1 on the renin-angiotensin-aldosterone system takes place through the stimulation of aldosterone release, which plays an important role in the structural, electrical and neurohormonal remodeling of atriums [17, 18].

In our study, we noticed that ET-1 concentration was not higher in the study group than in the control group, (2.6 ± 2.9 fmol/mL vs 2.3 ± 4.5 fmol/mL, NS respectively). The frequent occurrence of arterial hypertension and type 2 diabetes mellitus in both groups, associated with the dysfunction of the endothelium and increased ET-1 plasma concentration, may have had some impact on the results obtained [19, 20]. However, early-stage atrial disease in the examined group of patients may also have some influence on the results. Our findings are in contrast to the Dézsi et al. [21] study. These authors described a rapid decrease of ET levels after catheter ablation, suggesting that a high ventricular rate could be a trigger of ET production. Patients in our study had well-controlled ventricular rates (average 85 bpm, whereas in the Dézsi study the rates were about 110–170 bpm). A detailed evaluation of the importance of the pathophysiological role of the endothelin system in AF requires further research on a larger group of patients.

In the group examined, there were no important changes in ET-1 plasma concentrations in the first 24 hours after CV. It may be assumed that the recovery of sinus rhythm by treating the hemodynamic disorders which are associated with AF leads

to an improvement in the function of the endothelium. Although successful CV results in heart rhythm stabilization and in a decrease of rhythm frequency, it most probably does not lead to a significant improvement in the endothelium function within 24 hours after the procedure [22]. We observed that the increased ET-1 plasma concentration was maintained from two to seven days after a myocardial infarction or in acute coronary syndrome, which are undoubtedly associated with acute endothelium dysfunction of the coronary vessels [23, 24]. It may also be assumed that the function of the endothelium is not heavily disturbed in patients with arrhythmia (lasting for a short period of time, on average for 12 weeks) and in patients with normal LV systolic function and no symptoms of heart failure. Another reason for such results may be relatively wide ranges of ET levels in both AF and control groups, and inclusion of patients with co-morbidities e.g. diabetes, coronary heart disease, hypertension, obesity.

Predictors most frequently referred to as useful in the prognosis of CV outcome for patients with AF are: patients' age, duration of arrhythmia, arterial hypertension or valvular heart disease [25–27]. The only echocardiographical parameter with a clearly defined negative prognostic value is the significant enlargement of the left atrium, exceeding 60 mm [28, 29]. In patients with congestive heart failure, ET-1 concentration was a better predictor of general mortality than natriuretic peptides [30]. The increased production and release of ET-1 through the damaged endothelium may lead to the intensification of fibrosis processes and unfavorable outcomes of AF direct-current CV. Therefore, it may be assumed that AF recurrence after the recovery of sinus rhythm would be more frequent in patients with high initial ET-1 plasma concentrations. However, in the examined group of patients with persistent AF with normal LV systolic function, there was no association between the basal ET-1 plasma concentration and the maintenance of sinus rhythm in a period of 30 days after CV. This is the first study assessing ET-1 in AF with normal LV systolic function and has come up with controversial results. The issue needs further study.

Limitations of the study

Our cohort represents a non-homogenous group of patients, clinically stable but with histories of hypertension, coronary artery disease or diabetes, and with diverse duration times of AF (seven days to 19 months). No other markers of possible systemic inflammation (CRP-hs, interleu-

kins) with probable relation to ET levels were examined. Furthermore, the present study has the inherent limitation of its relatively small number of patients. However, to our knowledge, the present study is the first to assess ET-1 in AF with normal LV systolic function after CV (not only baseline concentration) as predicting rhythm stability after CV. Therefore the present study offers valuable new insights. We examined patients referred by their primary care physician to CV. The study does not take into account the patients (asymptomatic, undetected or without consent to CV) who were not referred. It would be important to replicate our findings in a larger cohort in order to confirm the data presented.

Conclusions

1. Persistent AF in patients with normal LV systolic function and with no symptoms of heart failure does not lead to an increase in ET-1 plasma concentrations compared to patients with sinus rhythm.
2. The recovery of sinus rhythm following electrical CV in patients with persistent AF does not lead to a significant increase in ET-1 plasma concentration.
3. Plasma ET-1 concentration is not a predictor of the maintenance of sinus rhythm in a period of 30 days after successful CV.

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