Short-Term Effect of Rate Control on Plasma Endothelin Levels of Patients with Tachyarrhythmias

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Radiofrequency catheter ablation or modification of the atrioventricular junction is an effective therapy of drug refractory supraventricular tachyarrhythmias (ST). Higher endothelin (ET) levels were observed during nonsustained STs. We aimed to examine the effect of sustained STs and the applied rate-control therapy on plasma ET levels. Twenty-two patients (12 men; mean age, 64.4 ± 13.2 years; ejection fraction, 41.8 ± 11.2%; New York Heart Association (NYHA) class I: 3 cases, NYHA II: 11 cases, and NYHA III: 8 cases) suffering of atrial fibrillation (n = 11), atrial flutter (n = 7), atrial paroxysmal tachycardia (n = 3), or sinus tachycardia (n = 1) were studied, having coronary artery disease (n = 8), dilative cardiomyopathy (n = 5), or no underlying diseases (n = 9). All groups went under catheter ablation (same protocol, duration: 35 ± 10.3 mins; rate before ablation, 100–170 /min in every case; after ablation, 70–80 /min in Groups I and II and 70–90 /min in Group III). A pacemaker (PM) was implanted 2 months before ablation in Group I (n = 9) and during ablation in Group II (n = 7). No PM was implanted in Group III (n = 6). A control group (n = 13; 7 men; mean age, 66.15 ± 6.7 years) with sinus rhythm got a PM without ST and ablation. Blood samples were collected from the cubital vein immediately before (control), and 5 mins and 24 hrs after ablation. Plasma ET-1 and big ET-1 levels were measured after immunoprecipitation with Western blot analysis. There were no differences between plasma ET-1 levels in the ST groups and the control group (Groups I, II, and III vs. control group: 0.66 ± 0.04 fmol/ml, 0.93 ± 0.12 fmol/ml, and 0.68 ± 0.05 fmol/ml vs. 0.50 ± 0.05 fmol/ml, respectively; $P < 0.05$). Comparing the control, 5-min, and 24-hr samples, ET-1 levels decreased significantly after supraventricular tachycardia ablation in Groups I and III (control vs. Group I, 5 mins and 24 hrs: 0.66 ± 0.04 fmol/ml vs. 0.50 ± 0.04 fmol/ml and 0.29 ± 0.05 fmol/ml; control vs. Group III, 24 hrs: 0.68 ± 0.05 vs. 0.34 ± 0.05 fmol/ml; $P < 0.05$). No plasma big ET-1 changes were measured in any of the groups. The rapid decrease of ET levels after catheter ablation suggests that a high ventricular rate can be a trigger of ET production. PM implantation procedure seems to interfere with the ET decrease in ST patients. Exp Biol Med 231:852–856, 2006

Key words: endothelin; supraventricular arrhythmia; rate control

Introduction

It is well known that sustained supraventricular tachycardias (SVTs) with a high ventricular rate can cause serious complaints and may lead to heart failure. Radiofrequency catheter ablation or modification of the atrioventricular (AV) junction is an effective therapy of drug-refractory supraventricular tachyarrhythmias (STs), or medically untreatable STs because of severe side effects.

Both literature and our previous results showed an elevation of serum endothelin (ET)-1 and big ET-1 levels after spontaneous and triggered nonsustained supraventricular and ventricular tachycardias (1–8). The short-term effect of the restoration of the sinus rhythm (SR) after sustained atrial fibrillation (AF) on brain natriuretic peptide levels is already published (9). A prompt, 24-hr effect of rate control of sustained STs on the ET system has not yet been elucidated.

The aim of this study was to examine the effect of sustained STs and the applied rate-control therapy on plasma ET-1 and big ET-1 levels.

Materials and Methods

AV Node Ablation and Pacemaker (PM) Implantation. Temperature-controlled radiofrequency ablation or modification of the AV node was performed in patients with AF, atrial flutter, or atrial tachycardia with 2:1 conduction and sinus tachycardia. Catheters were inserted *via* the right

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femoral artery into the right atrial, His-node, right ventricular, coronary sinus, and tricuspidal ring positions. The locations of the catheters were controlled by x-rays, and intracardial electrograms were recorded using a Biotronik EP Control system (Biotronik GmbH, Berlin, Germany). AV conduction ceases after ablation of the AV node, whereas only a slowing of the AV node conduction is detectable after AV modification. PM implantation is needed after each AV node ablation procedure, and used only in case of permanent bradycardia after AV modification.

Dual chamber (DDD) PMs (Actros DR, Axios DR; Biotronik GmbH) were implanted either 1 month before or parallel with AV node ablation in patients with AF and atrial flutter. Electrodes were inserted *via* the left cephalic or subclavian vein into the right atrium and ventricle, and devices were placed into an infraclavicular pocket. No patients undergoing AV modification because of atrial flutter, atrial tachycardia, or sinus tachycardia needed PM therapy in our study.

Patient Data. After providing verbal and written consent, 35 patients were enrolled into the study. The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and was approved by the Ethics Committee of Semmelweis University.

Inclusion criteria of patients with SVTs were: presence of SVT with ventricular rate greater than 100/min for more than 3 months but not longer than 6 months, controlled with Holter electrocardiogram monitoring, and a left ventricular ejection fraction between 35% and 50%.

Exclusion criteria of patients having SVTs were presence of valvular diseases, a diastolic left ventricular diameter >60 mm in the long axis parasternal view; existence of renal failure defined as creatinine plasma level >120 μM; presence of known major comorbid conditions; or arrhythmia recurrence during the 24 hrs after ablation.

Patients were divided into three groups (patient data are shown in Table 1):

1. Group I. PM implantation carried out 1 month earlier ($n = 9$). PMs programmed to demand function, operated only after the ablation procedure, when the ventricular rate fell below the basic rate.

2. Group II. PM implantation performed together with the ablation ($n = 7$).

3. Group III. AV node modification, without any PM implantation ($n = 6$).

A control group ($n = 13$) with similar clinical parameters was also examined, undergoing DDD PM implantation because of carotid sinus hypersensitivity ($n = 10$) and third-degree AV block ($n = 3$). These patients in SR had no history of SVTs, thus, no ablation procedure was performed.

Comparison of Patient Groups. There were no significant differences between the studied patient groups in terms of age, ejection fraction, New York Heart Association (NYHA) status, underlying diseases, and ventricular rate of SVTs (Table 1). Group III had more male patients than other groups.

ET Measuring Methods. Blood samples were collected from the cubital vein immediately before the ablation and/or PM implantation procedures, and 5 mins and 24 hrs after the interventions. All blood samples pretreated with EDTA were centrifuged (1500 *g* rpm). After centrifugation, plasma samples were stored below –80°C until use. ET-1 and big ET-1 were prepared by immunoprecipitation and detected by immunoblot using lyophilized rabbit antibodies against human ET and human big ET-1 (Bi-40011 and Bi-40012; BioMedica GmbH, Vienna, Austria) and polyvinylidene difluoride membrane. The membranes were analyzed using Bioscan v.1.01 software (Bioscan, Washington, DC).

Statistics. SPSS 12.0 software (SPSS, Chicago, IL) was used for our calculations. Data were expressed as mean $\pm$ SEM. Student's t test was used for comparison of two groups. Analysis of variance was applied for calculation of changes during the time. Comparison of occurrence of arrhythmias was analyzed by chi-square test. Significance was established at $P < 0.05$.

Results

Comparison of ET-1 and Big ET-1 Levels of the Four Groups. There were no significant differences in plasma ET-1 and big ET-1 levels among the three arrhythmia groups during the examined period (Table 2). No significant differences of control ET-1 and big ET-1 levels were measured between the three arrhythmia groups and the control group. ET-1 levels were significantly lower in Group I and Group III at 24 hrs compared with the control group values.

Changes of ET-1 and Big ET-1 Levels During the Observation Time. Compared with the control period, ET-1 levels decreased significantly at 5 mins and at 24 hrs in Group I, and at 24 hrs in Group III (Table 2). There were no significant changes in big ET-1 levels in any of the arrhythmia groups. ET-1 and big ET-1 levels did not change significantly in the control group during the observation period.

Discussion

Sustained supraventricular arrhythmias cause tachycardiomyopathy in the ventricle (10–13), and electrical and structural remodelling in the atria (14), which may cause depressed contractile function of the heart. The molecular background and pathophysiology of cardiomyopathy that evolves because of SVTs with a high ventricular rate remains an unsolved subject that needs further analysis. AF and atrial tachycardia sustained for 3–4 weeks (AT) led to a marked shortening of the atrial effective refractory period and to an increase in rate, inducibility, and stability of AF (15, 16). A 1–6 month existence of AF and AT caused marked degeneration of the cellular structure of atrial

Table 1. Basic Parameters of Arrhythmia Groups ($n = 22$) and the Control Group ($n = 13$)[a]

	Group I	Group II	Group III	Control group
No. of patients	9	7	6	13
Type of procedure	AV ablation (PM implantation was 2 months ago)	AV ablation and PM implantation	AV modification	PM implantation
Duration of procedures (mins)	35.2 ± 6.7	45.5 ± 11.4	33.7 ± 7.8	30.4 ± 7.7
Men; women	4; 5	3; 4	5; 1	7; 6
Mean age (years)	64.6 ± 2.9	68.4 ± 6.1	59.5 ± 6.2	66.1 ± 6.7
Ejection fraction (%)	40.0 ± 3.5	40.7 ± 2.97	45.8 ± 2.1	45.5 ± 3.9
NYHA stage	2.4 ± 0.1	2.4 ± 0.3	2.0 ± 0.2	2.4 ± 0.2
Underlying diseases	CAD, 3; DCM, 2; none, 4	CAD, 2; DCM, 2; none, 3	CAD, 3; DCM, 1; none, 2	CAD, 8; none, 5
Basic rhythm	AF, 7; FL, 1; AT, 1	AF, 4; FL, 2; AT, 1	FL, 4; AT, 1; ST, 1	SR, 13 (no SVT)
Spontaneous rate before procedure (/min)	110–170 (no PM rhythm)	100–160	110–160	50–90
Rate after procedure (/min)	70–80 (PM rhythm)	70–80 (PM rhythm)	70–90 (spontaneous rhythm)	60–80 (PM rhythm)

[a] NYHA, New York Heart Association Class; CAD, coronary artery disease; DCM, dilatative cardiomyopathy; none, no underlying disease; FL, atrial flutter; AT, atrial tachycardia with 2:1 conduction; ST, sinus tachycardia.

myocytes, and the extracellular matrix and the diameter of the atria increased significantly (16, 17). Impairment of cardiac function in AF has been attributed to the loss of atrial contraction and to rapid ventricular rate. However, some studies suggested that irregularity of the ventricular rhythm can contribute to impairment of cardiac function during AF independently of the ventricular rate (18).

Literature data indicate that the complete ET system is present in the human myocardium (5, 19). Production of the biologically active peptide, ET-1, is supported by the ET-converting enzyme located either in the atrium or in the ventricle, which catalyzes the proteolytic cleavage of the precursor peptide, big ET-1 (20). The diverse biologic activities of ET-1, acting *via* the autocrine/paracrine and endocrine mode, are mediated through the ET_A and ET_B receptors. The vasoconstricting 21-amino acid peptide ET-1 plays a role in the development of coronary artery disease and heart failure (21). Our previous results showed the elevation of serum ET-1 and big ET-1 levels after nonsustained SVTs and ventricular tachycardias (1–5). In the present study, the effect of sustained STs and the short-term, 24-hr effect of rate control of sustained STs on the ET system was investigated.

Comparison of ET-1 and Big ET-1 Levels of the Four Groups. No significant differences of peripheral venous plasma ET-1 and big ET-1 levels were measured between the three arrhythmia groups and the control SR group in the control period, which is in agreement with other observations in the literature (22, 23). Moreover, Brundel *et al*. also presented nonsignificant differences between *ET*-1 mRNA content of atria with AF and SR without any valvular diseases; and ET_A and ET_B receptors of the atria were downregulated (5). However, the *ET*-1 mRNA content of the atria was elevated in patients with sustained AF and valvular diseases.

It is well known that ET-1 and ANP levels increase during heart failure (21). On the contrary, data shown in literature demonstrate decreased ANP levels during sustained AF, either with or without heart failure (24).

In our study, it is conceivable that atrial and ventricular degeneration caused by sustained SVTs generate the depletion of ET-1 production in patients with moderate heart failure, apart from valvular diseases.

Table 2. Changes of Serum ET-1 and Big ET Levels During the Observation Period

	Group I	Group II	Group III	Control group
ET control (fmol/ml)	0.66 ± 0.13	0.93 ± 0.32	0.68 ± 0.12	0.50 ± 0.17
ET 5 mins (fmol/ml)	0.50 ± 0.12*	0.77 ± 0.12	0.61 ± 0.14	0.58 ± 0.24
ET 24 hrs (fmol/ml)	0.29 ± 0.14*,#	0.61 ± 0.15	0.34 ± 0.12*,#	0.68 ± 0.33
Big ET control (fmol/ml)	0.80 ± 0.20	1.34 ± 0.49	1.12 ± 0.64	0.90 ± 0.20
Big ET 5 mins (fmol/ml)	0.78 ± 0.28	1.28 ± 0.60	1.02 ± 0.56	0.93 ± 0.24
Big ET 24 hrs (fmol/ml)	0.67 ± 0.26	0.81 ± 0.49	0.78 ± 0.74	0.95 ± 0.30

*$P < 0.05$ vs. control period; #$P < 0.05$ vs. control group.

Changes of ET-1 and Big ET-1 Levels During the Observation Period. Unchanged plasma ET-1 and big ET-1 levels in the control group show the nonsignificant effect of PM implantation on ET synthesis. Our earlier investigation showed that the ablation procedure *per se* did not affect ET production (4).

The ventricular rate slowed after AV node ablation or modification. Although SR was not restored in these patients, the stress caused by the mechanical-functional disorder, the arrhythmia, and the fast ventricular rate decreased immediately after the procedure (10, 13, 18, 25, 26). In our study, ET-1 levels decreased significantly in the arrhythmia groups but remained unchanged in the control group 24 hrs after the procedures. Because atrial arrhythmias persist after AV ablation or modification, the decrease of ET-1 levels in our study may be caused by the decreasing ET production of the ventricle.

The nonsignificant decrease of ET-1 levels in Group II suggests that the PM implantation procedure might interfere with the ET decrease in ST patients.

Schoonderwoerd *et al.* found only minimal structural changes in atrial myocytes, whereas neither the extracellular matrix nor the diameter of the right atrium increased significantly during rapid atrial pacing. At the same time, degenerations in atria occurred because of rapid AV pacing (16). However, the nature of the ET-1 production of the atria during persistent atrial tachycardia after AV ablation is not known.

There were no significant differences of peripheral venous plasma ET-1 and big ET-1 levels between patients suffering from moderate heart failure with either arrhythmia or SR in the control period. In our study, it is conceivable that atrial and ventricular degeneration caused by sustained SVTs generate the depletion of ET-1 production in patients with moderate heart failure and without valvular diseases.

The unchanged plasma ET-1 and big ET-1 levels of the control group show the nonsignificant effect of PM implantation on ET synthesis. The significant decrease of ET-1 levels after AV ablation or modification may be caused by changes in the ET system of the ventricle. The nature of the ET-1 production of the atria during persistent atrial tachycardia after AV ablation is not known.

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