Original Article

Prevalence of Paroxysmal Atrial Fibrillation Depending on the Regression of Left Ventricular Hypertrophy in Arterial Hypertension

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Arterial hypertension (HTN) represents one of the major causes of atrial fibrillation, a cardiac arrhythmia with high prevalence and comorbidity. The aim of this study was to investigate whether paroxysmal atrial fibrillation can be treated by the regression of left ventricular hypertrophy achieved by antihypertensive therapy. Included in the present study were 104 patients who had had HTN for more than 1 year. None of them suffered from coronary heart disease. All patients were investigated by 24-h Holter ECG and echocardiography at baseline and after a mean of 24 months. Patients were divided into two groups: group A consisted of those (53.8%) who showed a regression of the left ventricular muscle mass index (LVMMI) during the follow-up (154.9±5.1 *vs.* 123.5±2.8 g/m^2), and group B those (45.2%) who showed a progression of LVMMI (122.2±3.2 *vs.* 143.2±3.2 g/m^2). In group A the prevalence of atrial fibrillation decreased from 12.5% to 1.8% ($p<0.05$), while it was increased in group B from 8.5% to 17.0%. The left atrial diameter was reduced following antihypertensive therapy in group A from 39.1±5.3 mm to 37.4±4.6 mm ($p<0.01$) and increased in group B from 37.0±0.7 mm to 39.0±0.9 mm ($p<0.01$). We conclude that a regression of the left ventricular muscle mass leads to a reduction of left atrial diameter and consecutively to a decrease in the prevalence of intermittent atrial fibrillation. This may be explained by a better left ventricular diastolic function following decreased vascular and extravascular resistance of the coronary arteries. This relation shows the benefits of causal antihypertensive therapy for the treatment of paroxysmal atrial fibrillation. (*Hypertens Res* 2007; 30: 535–540)

***Key Words*: atrial fibrillation, left ventricular hypertrophy, arterial hypertension**

Introduction

Atrial fibrillation is an arrhythmia that frequently leads to admission to the hospital (*1*). In 25–62% of cases of atrial fibrillation the arrhythmia occurs as a paroxysmal atrial fibrillation (*2*, *3*). In the majority of cases, the underlying causes of nonrheumatic atrial fibrillation are arterial hypertension and coronary heart disease (*4*). The treatment of this arrhythmia is important because of its high rate of complications. The prevalence of ischemic stroke in patients with nonrheumatic atrial fibrillation and hypertension or coronary heart disease is reported to be up to 2.0–5.6% (*3*, *5*). The therapy consists of either antiarrhythmic therapy or causal therapy of the underlying disease and additional anticoagulation (*6*). Therapy with an angiotensin-converting enzyme (ACE)-inhibitor can lower the incidence of atrial fibrillation in patients with heart failure due to myocardial infarction (*7*). It has been well established that antihypertensive therapy leads to a regression of hypertrophy (*8–10*), as well as an improvement of left ventricular

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diastolic function and coronary reserve (*11–14*). Gottdiener *et al*. showed a decrease of the diameter of the left atrium following antihypertensive therapy (*15*). However, a beneficial effect on the prevalence of atrial fibrillation in hypertensive patients has not been reported yet. Recently, the LIFE study showed that therapy with an angiotensin (AT)-receptor antagonist (losartan) was able to decrease the rate of the phases of atrial fibrillation in hypertensive patients (*16*).

Therefore, the goal of this study was to investigate whether the regression of left ventricular hypertrophy achieved by antihypertensive therapy would result in a reduction in the frequency of intermittent atrial fibrillation in association with a decrease of the left atrial diameter.

Methods

One hundred and four patients who had been suffering from arterial hypertension for more than 1 year were enrolled consecutively into this study (Table 1). All patients were investigated at the time of inclusion into the study and after a mean period of 24 months. All of the patients were investigated by echocardiography and 24-h Holter ECG. Significant coronary artery disease was excluded in all patients by invasive coronary angiography, and the left ventricular ejection fraction was >50%. None of the patients suffered from mitral stenosis or severe mitral regurgitation. No patient showed permanent atrial fibrillation.

After completing the 24 month follow-up patients were divided into two groups: Group A consisted of patients with regression of left ventricular hypertrophy and the control group (group B) of those without regression of hypertrophy.

All patients gave written informed consent. There were no objectives to the study from an ethical point of view.

Echocardiography

Conventional echocardiography was performed using 2D- and M-Mode–echocardiography following the Penn convention (*17*). The analyzed data contained the dimensions of the left atrium and left ventricle (end-diastolic and end-systolic diameter). The thickness of the interventricular septum (IVS) and the posterior wall were also measured. Using the formula of Devereux and Reichek (*17*), the muscle mass and muscle mass indexes were calculated. Left ventricular hypertrophy was defined as a muscle mass index >125 g/m^2 (*18*). Normotensive controls (n=78) of our own clinic showed a mean muscle mass index of 81.66±10.48 g/m^2. Patients in whom exact echocardiographic measures could not be performed were excluded from the study.

The relative wall thickness was determined by the relation of the left ventricular wall thickness (IVS × 2) to the end-diastolic radius. Values of >0.43 represent concentric remodeling, and values of <0.43 represent eccentric remodeling.

Table 1. Baseline Patient Characteristics

Number of patients	104
Age (years)	63.2±11.1
Gender (m/f, %)	58.7/41.3
NYHA (I/II/III, %)	75/23/2
LVEDP (mmHg)	13.8±6.9
LV hypertrophy (%)	67.3
TSH (μIU/mL)	1.2±0.9
Potassium (mmol/L)	4.2±2.4

m, male; f, female; NYHA, New York Heart Association Classification; LVEDP, left ventricular end diastolic pressure; LV, left ventricular; TSH, thyroid-stimulating hormone.

Twenty-Four–Hour Holter Electrocardiogram

For analysis of spontaneous arrhythmia, a 24-h Holter ECG (Reynolds Medical Pathfinder 600) was performed. Using semiautomatic analysis, the Holter tapes were screened for phases of intermittent atrial fibrillation. Paroxysmal atrial fibrillation was defined as intermittently occurring arrhythmic ventricular complexes without visible P-waves, with acute onset, a duration of at least 1 min and spontaneous termination within 7 days, according to the published definitions of the arrhythmia (*19*). Atrial tachycardias were defined as regular tachyarrhythmias with narrow QRS-complexes with visible P-waves and acute onset and termination.

Statistical Analysis

All data are given as the means±SD. For analysis of paired variables, the Wilcoxon rank test was used. Dichotomous variables were analyzed using the McNemar test, and correlations between data were tested using the Spearman test. Values of $p<0.05$ were considered to indicate statistical significance. The SPSS software package (version 11.0) was used for all analyses.

Results

Patient Characteristics

Left ventricular hypertrophy was present in 70 patients (67%) at baseline with a mean muscle mass of 267.4±71.9 g. The geometric pattern of the left ventricle was initially normal in 12 (11.5%) of the patients, concentric remodeling in 26 (25%), concentric left ventricular hypertrophy in 58 (55.8%) and eccentric left ventricular hypertrophy in 8 (7.7%). After therapy the geometric pattern was normal in 14 (13.5%) patients and showed concentric remodeling in 31 (29.8%), concentric left ventricular hypertrophy in 54 (51.9%), and eccentric left ventricular hypertrophy in 5 (4.8%) patients. The mean left atrial size was 38.0±5.4 mm. Paroxysmal atrial fibrillation was documented in 11 patients (10.6%). These

Table 2. Use of Antihypertensive and Antiarrhythmic Drugs in Patients with (Group A) and without (Group B) Regression of Left Ventricular Hypertrophy

Drug	Group A (n=56)	Group B (n=47)
ACE inhibitors	17 (30%)	11 (23%)
AT-1–receptor blockers	11 (20%)	5 (10%)
β-Blockers	10 (17.8%)	11 (23%)
Clonidine	2 (3.5%)	4 (8.5%)
Calcium antagonists	16 (29%)	13 (28%)
Diuretics	11 (20%)	4 (9%)
Class Ic-AD	3 (5%)	2 (4%)
Sotalol	3 (5%)	3 (6%)
Amiodarone	0	0
Verapamil	6 (11%)	8 (17%)
Digitalis	9 (16%)	8 (17%)

ACE, angiotensin-converting enzyme; AT-1, angiotensin type 1; AD, antiarrhythmic drug.

patients felt no symptoms during the arrhythmia and their frequency was in a normal range.

After a mean follow-up period of 24 months, 56 patients (54%) showed a regression of left ventricular hypertrophy (group A). In the remaining patients the left ventricular muscle mass was increased (group B). There was no statistically significant difference concerning the New York Heart Association (NYHA)-classification between the two groups.

The patients of group A showed a significant decrease of the systolic blood pressure (SBP) (146.3±20.1 *vs*. 139.0±17.3 mmHg, $p<0.05$) and a trend towards lower diastolic blood pressure (DBP) values (90.0±12.2 *vs*. 88.2±10.9 mmHg, n.s.). In group B both the SBP and DBP increased (146.3±21.4 *vs*. 149.5±24.1 mmHg and 88.6±12.7 *vs*. 88.7±13.1 mmHg, n.s.).

There were no significant differences between the two groups in regard to the use of antihypertensive drugs (Table 2).

Echocardiographic Data

The left ventricular muscle mass decreased in group A from 299.8±75.3 to 239.3±45.1 g (154.9±37.8 *vs*. 123.5±21.1 g/m^2) ($p<0.001$), whereas in group B the muscle mass increased from 228.6±54.5 to 267.5±42.5 g (122.2±21.6 *vs*. 143.2±22.1 g/m^2) ($p<0.001$). The interventricular wall thickness decreased from 12.9±2.5 to 11.5±1.5 mm in group A ($p<0.001$) and increased from 11.3±1.2 to 12.1±1.6 mm in group B ($p<0.001$).

The left atrial size was reduced in group A from 39.1±5.3 to 37.4±4.8 mm ($p<0.001$) and enlarged in group B from 37.0±5.1 to 39.0±6.1 mm ($p<0.001$) (Fig. 1). The differences of left ventricular mass index and left atrial size were significantly correlated (Fig. 2).

Mild mitral regurgitation was found in 3.6% of patients in group A at baseline and in 12.5% after follow-up (n.s.),

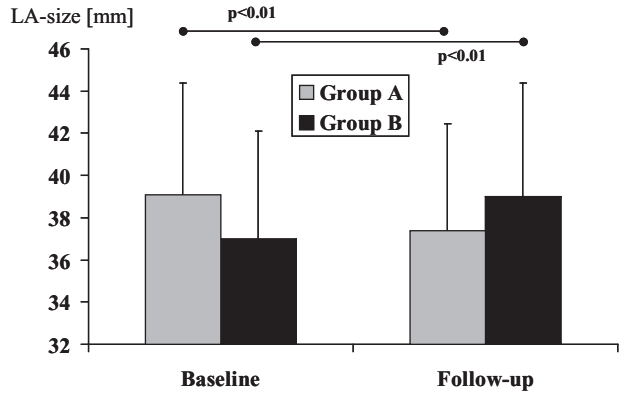

Fig. 1. *Change of atrial size in patients with (group A) and without (group B) regression of left ventricular hypertrophy. LA, left atrium.*

whereas in group B the increase was nearly significant (14.9 *vs*. 25.5%, $p=0.06$).

Arrhythmias

The prevalence of paroxysmal atrial fibrillation decreased from 12.5% to 1.8% ($p<0.05$) in group A and increased in group B from 8.5% to 17.0% (Fig. 3). Supraventricular tachycardias were documented in 14.3% of patients in group A before and in 7.1% of patients after regression of ventricular hypertrophy, n.s. (group B: 14.9 *vs*. 8.5%, n.s.). Ventricular ectopic beats (maximum beats per h) decreased in group A after the follow-up from 287±603 to 80±178 (n.s.). The prevalence of non-sustained ventricular tachycardias was low in both groups (group A: 1.8 *vs*. 1.8%; group B: 0 *vs*. 4.3%; n.s.). Sustained ventricular tachycardias or ventricular fibrillation/flutter were not documented.

The rate of palpitations was comparable between the two groups at baseline and during follow-up. Syncope occurred in 12.7% (7 patients) of group A at baseline. During the follow-up period none of the patients had a relapse of syncope ($p<0.05$). In group B the rate of syncope decreased slightly from 4.3% to 2.1%.

ACE-inhibitors and AT-receptor blockers were the most frequently administered antihypertensive drugs (administered to approximately 42% of patients). Patients with reduction of atrial fibrillation during follow-up were characterized by a higher rate of given ACE-inhibitors/ AT-receptor blockers compared those without (57% *vs*. 41%, n.s.).

Discussion

This is the first study to show an association among the decrease of left ventricular hypertrophy, the reduction of left atrial diameter and the decrease of the prevalence of paroxysmal atrial fibrillation in patients receiving antihypertensive therapy. Patients with a regression of left ventricular hyper-

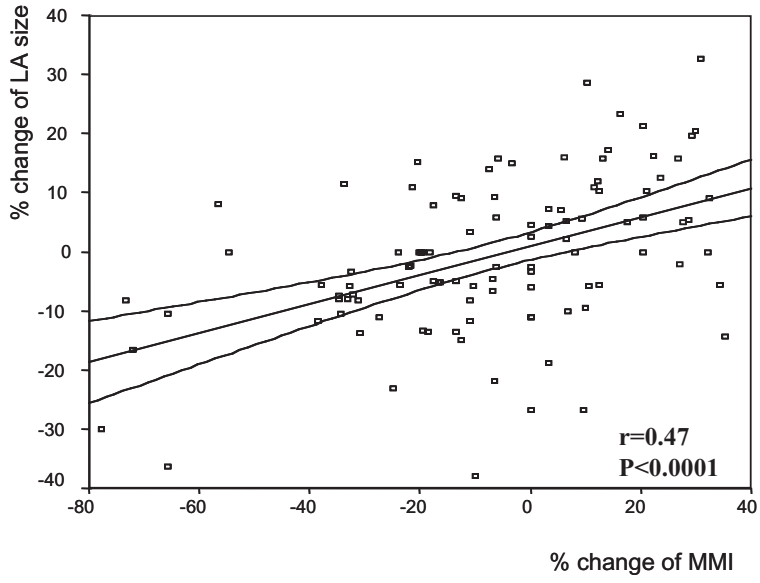

Fig. 2. *Significant correlation between the difference of left atrial size and the difference of left ventricular mass index. LA, left atrium; MMI, muscle mass index.*

trophy developed a reduction of left atrial diameter and a decrease of paroxysmal atrial fibrillation of from 12.5% to 1.8%. On the other hand, patients with an increase of left ventricular hypertrophy, which was associated in our study with higher blood pressure values (despite continued antihypertensive therapy), were characterized by a rise of left atrial diameter and an increase of the prevalence of paroxysmal atrial fibrillation from 8.5% to 17%.

Atrial Arrhythmias and Arterial Hypertension

Atrial arrhythmias occur in 25–50% of patients with arterial hypertension (*20*). The prevalence of atrial arrhythmias is particularly high in patients with left ventricular hypertrophy (*21*). Recently, Verdecchia *et al*. showed that for every 1 SD of left ventricular hypertrophy the risk of atrial fibrillation increases 1.20 times (*22*). The pathophysiologic mechanism is based on diastolic and (later) systolic dysfunction of the left ventricle (*21*). Moreover, in patients with left ventricular hypertrophy, media hypertrophy of the arterioles is seen, resulting in an increased wall thickness-to-radius ratio (*23*, *24*). In consequence, coronary microangiopathy occurs. Furthermore, the coronary flow reserve is reduced by up to 30% due to disturbances of the microcirculation (resistive vessels) and extravascular myocardial alterations (*24–26*). Additionally, interstitial fibrosis and an increased sympathetic tone can participate in the development of cardiac arrhythmias and particularly in the occurrence of atrial fibrillation (*27*, *28*).

Previous studies have shown that atrial fibrillation in arterial hypertension depends on the presence of left ventricular hypertrophy, atrial enlargement and mitral regurgitation (*29*). Left atrial enlargement occurs due to left ventricular hypertrophy, persistent or permanent atrial fibrillation and mitral regurgitation (*30–32*). Moreover, the presence of atrial fibrillation is associated with important complications. Most importantly, the rate of stroke is increased if the left atrium is enlarged and left ventricular hypertrophy persists (*33*).

Regression of Left Ventricular Hypertrophy and Reduction of Left Atrial Size

Several studies have shown that effective antihypertensive therapy leads to a regression of left ventricular hypertrophy (*8*, *10*, *34*). This therapy also lowers the risk of cardiovascular complications (*35*) and results in fewer episodes of simple or complex arrhythmias (*36*). Recent reports have demonstrated that an antihypertensive therapy with regression of left ventricular hypertrophy results in a decrease of atrial diameter. Gottdiener *et al*. (*15*) found that a therapy with hydrochlorothiazide, atenolol, clonidine, and diltiazem led to a regression of left atrial enlargement. However, they did not investigate the effects of this treatment on arrhythmias.

The reasons for the decrease of the prevalence of paroxysmal atrial fibrillation in the present study could be hemodynamic or morphologic changes. The patients of group A showed a decrease of left ventricular mass, but also a better controlled blood pressure. However, it should also be noted that not only the regression of left ventricular muscle mass, but also the effects of the blood pressure itself cause a reduction in paroxysmal atrial fibrillation. Antihypertensive therapy should lead to a better control of arterial hypertension (*35*) and consecutively to a regression of left ventricular hypertrophy (*36*) as well as an improved coronary flow reserve (*14*). These effects in turn cause an improvement of

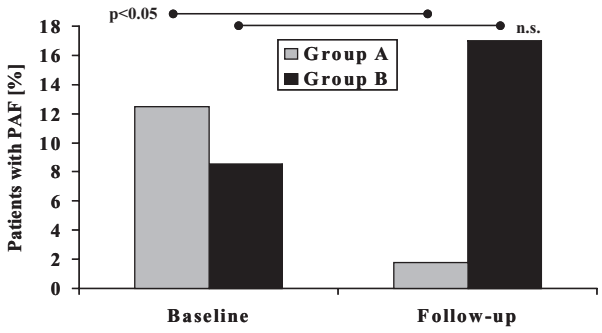

Fig. 3. *Percentage of paroxysmal atrial fibrillation in patients with (group A) and without (group B) regression of left ventricular hypertrophy.*

left ventricular diastolic function (*8*) and a decrease of left atrial dimension (*15*). The decreasing left atrial size, the improvement of hemodynamic disturbances (blood pressure, left atrial pressure due to diastolic dysfunction) and changes in plasma catecholamines that are linked to left ventricular hypertrophy as well as to elevated blood pressure (*37*) could lead to a reduction of episodes of atrial fibrillation. Moreover, it has been shown that in atrial fibrillation the atrial conduction time is shortened by administration of AT II (*38*) and that patients with atrial fibrillation show an ACE-dependent increase in the amount of activated Erk1/Erk2-kinases, a downregulation of the AT-1–receptor protein, and an upregulation of the AT-2–receptor protein (*39*). Asai *et al*. showed the strongest effect on the regression of left ventricular hypertrophy caused by AT-receptor blockers (*40*). Moreover, AT-receptor blockers may inhibit the NO-synthesis and contribute to the regression of atrial fibrillation (*41*). In this regard, two studies showed beneficial effects for the additive therapy of irbesartan or enalapril after electrical cardioversion of atrial fibrillation. The combined therapy of irbesartan or enalapril and amiodarone led to significantly more patients with a stable sinus rhythm after electrical cardioversion than the administration of amiodarone alone (*42*, *43*). In the present study, the higher rate of ACE-inhibitors and AT-blockers in group A could also have influenced the reduction of paroxysmal atrial fibrillation.

Perspectives

This study has important clinical implications. The therapy of paroxysmal atrial fibrillation is one of the great challenges in the treatment of rhythm disturbances. However, treatment of this arrhythmia by drugs, by radiofrequency ablation, or by implantation of antiarrhythmic devices is currently not enough (*3*). The data of this study indicate that antihypertensive treatment and its resultant reduction of left ventricular muscle mass and left atrial diameter could lead to a decrease in the phases of paroxysmal atrial fibrillation. According to these results, causal treatment of the underlying disease would seem to be one of the main goals in treating paroxysmal atrial fibrillation.

Limitations

There are some limitations of this study. The detection of paroxysmal atrial fibrillation would be more accurate if the Holter tape recording could be performed over a longer period than 24 h (*44*) or if event monitoring could be used. These changes might lead to a higher rate of documented paroxysmal atrial fibrillation. Furthermore, the treatment with multiple antihypertensive drugs could have led to a bias. A prospective placebo randomized study should be performed in the future.

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