Original Article

Add-On Therapy with a Nighttime Dose of Doxazosin in Patients with Uncontrolled Hypertension: Effects on Autonomic Modulation of the Cardiovascular System

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This study was designed to determine whether or not the addition of a single nighttime dose of doxazosin in extended-release form (GITS; gastrointestinal therapeutic system) would affect the autonomic modulation of the cardiovascular system in patients with uncontrolled hypertension treated with a multi-drug regimen. Resting 5-min noninvasive finger blood pressure and ECG signals, as well as 24-h Holter ECGs, were recorded in 30 patients with uncontrolled hypertension on multi-drug treatment before and after 16-week add-on therapy with doxazosin GITS. Cardiovascular autonomic modulation was evaluated by spectral analysis of heart rate variability (HRV) and a cross-correlation method for spontaneous baroreflex sensitivity (BRS) in 5-min resting recordings, and by the analysis of Poincaré plots and phase-rectified signal averaging of the duration of cardiac cycles in 24-h ECG recordings. This combined therapy significantly reduced systolic pressure (19.4±3.5 mmHg; $p<0.0001$), diastolic blood pressure (9.4±2.0 mmHg; $p=0.0003$), and pulse pressure (10.0±2.8 mmHg; $p=0.0021$). Concomitantly, there was a significant increase in resting spontaneous BRS ($p=0.0191$) and increases in 24-h short-term ($p=0.0129$) and total ($p=0.0153$) HRV, but with no significant change in heart rate or other measures of HRV. The improvements in HRV and BRS were observed mainly in patients already treated with thiazide diuretics. There was a significant association ($r=0.49$; $p=0.0065$) between the degree of change in diastolic blood pressure and short-term HRV caused by the combined treatment. The addition of 4 mg doxazosin GITS to multi-drug antihypertensive therapy is associated with an improvement in cardiovascular autonomic control. (*Hypertens Res* 2008; 31: 443–453)

***Key Words*: doxazosin, heart rate variability, baroreflex sensitivity, phase-rectified signal averaging, Poincaré plots of RR intervals**

Introduction

There is no doubt that autonomic dysregulation plays an important role in the development of various complications and events in the cardiovascular system (*1*, *2*). Heart rate variability (HRV) has emerged as a practical, noninvasive tool to investigate parasympathetic tone and sympathetic-parasympathetic balance (*3*, *4*). Baroreflex sensitivity (BRS) is another measure of autonomic modulation of the cardiovas-

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cular system (*5*). Survivors of myocardial infarction with reduced HRV and/or BRS are at increased risk of mortality.

Sympathetic overdrive and/or reduction in parasympathetic tone are quite common in patients with hypertension and are related to further progression and the development of end-organ damage in the course of disease (*6*, *7*). Moreover, hypertension may be preceded by the presence of autonomic dysregulation. Baroreflex abnormalities have also been described early in the course of hypertension as contributing to the maintenance of blood pressure elevation. It has even been postulated that reducing blood pressure in hypertensive patients should be accompanied by normalization of their sympathetic-parasympathetic balance (*7*, *8*).

Blood pressure control can be achieved by dose titration and the use of various combinations of pharmacologic agents. Nevertheless, various prescribed therapies have different effects on autonomic modulation, and these differences are not always explicable (*8*). Most of the drugs commonly used in the treatment of hypertension influence the activity of the autonomic nervous system. β-Adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, and diuretics affect the autonomic control of the heart and circulation by different mechanisms (*8*, *9*).

Doxazosin is an antihypertensive agent influencing the autonomic nervous system directly by blocking peripheral α1-adrenergic receptors (*9*, *10*). It lowers the blood pressure *via* arterial vasodilation and is currently used in the treatment of hypertension and benign prostatic hyperplasia. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that the short-acting form of doxazosin, when used as a monotherapy, was less effective than chlorthalidone in preventing cardiovascular disease and events in patients with hypertension, and was associated with an increased risk of heart failure (*11*, *12*). The short-acting form of doxazosin produces hypotension with reflex tachycardia, suggesting a sympathetic stimulation (*12*, *13*). In contrast, the extended-release form (GITS; gastrointestinal therapeutic system) of doxazosin is effective in reducing blood pressure with no evident acceleration of the heart rate, which may suggest that it does not produce any significant sympathetic stimulation (*14*, *15*). Moreover, de Alvaro *et al*. showed, in the ASOCIA study, that heart rate was in fact reduced after 16-week add-on therapy with doxazosin GITS in a group of over 3,500 hypertensive patients (*15*). However, there are no data concerning the influence of doxazosin GITS on autonomic activity. In this study, we aimed to analyze whether the addition of doxazosin GITS would affect autonomic modulation of the cardiovascular system in patients with uncontrolled hypertension who were already being treated with a multi-drug regimen.

Methods

Study Population

Thirty adult (>18 years old) patients with inadequately controlled mild-to-moderate essential hypertension, as measured by the criteria of the Seventh Report of the Joint National Committee, were recruited. Inadequately controlled hypertension was defined as an average arterial blood pressure ≥140/90 mmHg from three different measurements performed on three separate days 1 h after morning medications consisting of at least two drugs (diuretic, β-blocker, calcium channel antagonist, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers). Blood pressure was measured in a sitting position after 10 min of rest, with an oscillometric method (Omron M-5, Omron Healthcare UK, West Sussex, UK) on the patient's arm; this revealed higher blood pressure during the first visit. Measurements were obtained from each patient using the same sphygmomanometer, and the following values were used in the analysis: systolic blood pressure, diastolic blood pressure and pulse pressure. Exclusion criteria consisted of a lack of agreement to participate in the study, renal insufficiency, pregnancy, any known malignancy, aortic aneurysm, type 1 diabetes mellitus, or heart failure. The use of long-acting nitrates and the introduction of statins during the study were not allowed. All patients gave written, informed consent before entering the study, and the institutional ethics committee approved the study protocol. All subjects were evaluated by routine physical examination and standard resting 12-lead ECG.

Study Design

This was an open, noncomparative, proof-of-concept study lasting 16 weeks. Doxazosin, 4 mg, was given once a day at bedtime to patients in an extended-release GITS form (Cardura XL, Pfizer, New York, USA) as an adjunct to their ongoing antihypertensive treatment (*9*). This regimen remained unchanged for 16 weeks. No changes in the antihypertensive treatment were allowed after enrollment into the study and during the follow-up. All measurements of autonomic control of the cardiovascular system, *i.e.*, 24-h ECG Holter recordings and 5-min ECG and continuous blood pressure recordings, were performed before the initiation of doxazosin GITS treatment and after 16 weeks of continuous treatment.

Long-Term ECG Recordings

Prolonged (up to 24 h), digital 12-channel ECG (sampling frequency 200 Hz) was recorded with DigiTrak-Plus Recorders (Philips Medical Systems, Bothell, USA). The recorded Holter ECGs were downloaded to a personal computer, then edited and analyzed with the use of commercially available software (Zymed 1810, Philips Medical Systems). After a careful and detailed analysis, all RR intervals (defined as the distances between R waves of consecutive QRS complexes) with a proper annotation indicating the beat type (normal, supraventricular, ventricular, or artifact) were exported to text files for further analysis.

Determination of HRV by Poincaré Plot Analysis in 24-h ECG Recordings

The mean RR interval and HRV obtained by analysis of the Poincaré plots were measured in 24-h ECG recordings. Poincaré plotting of RR intervals is a method of HRV analysis. It has also been used to measure the autonomic modulation of heart rate (*3*, *4*). This analysis was performed with the use of in-house software written in Python (Python Foundation, Ipswich, USA), according to published references (*4*, *16*, *17*).

The Poincaré plot is a graphical representation of temporal correlations within the RR intervals derived from an ECG (*16*). In this plot, each RR interval is a function of the preceding RR interval, *i.e.*, the duration of the current cardiac beat (RR_n) is represented on the *x* axis, and the duration of the following beat (RR_{n+1}) on the *y* axis, so each point (RR_n, RR_{n+1}) in the plot corresponds to two successive heart beats. We have used four different descriptors associated with this plot:

1) SD1: the standard deviation measuring the dispersion of points in the plot across the identity line. This parameter is interpreted as a measure of short-term HRV caused by the fastest oscillations of the cardiovascular system, usually caused by respiration. SD1 is believed to reflect vagal influences on sinus node (*4*).

2) SD2: the standard deviation measuring the dispersion of points along the identity line. This variable is interpreted as a measure of both short- and long-term HRV, which means that fast and slow cardiovascular oscillations are responsible for SD2 generation. Various phenomena contribute to short- and long-term variability, starting from respiratory effects (the fastest oscillations) to fluctuations from arterial blood pressure control, peripheral vasomotor regulation, and many other contributing factors. SD2, therefore, shows variability in RR intervals caused by changes in both parasympathetic and sympathetic tones (*4*).

3) *S*: corresponds to the area of an imaginary ellipse ($S = \pi \times SD1 \times SD2$) with axes of lengths SD2 and SD1. This variable is interpreted as a measure of total HRV, which is caused by all fluctuations affecting sinus node activity. Usually, reduced values of total HRV correspond to worse cardiovascular autonomic regulation (*2*, *4*).

4) SD2/SD1: is the ratio of SD2 to SD1. This variable is interpreted as a measure of balance between long- and short-term HRV and the sympathetic-parasympathetic drives (*4*).

A more detailed description of Poincaré plot analysis including its mathematical background may be found elsewhere (*4*, *16*, *17*).

Determination of Deceleration Capacity by Phase-Rectified Signal Averaging in 24-h ECG Recordings

Phase-rectified signal averaging (PRSA) is a novel approach to HRV analysis characterizing rhythm modulations associated separately with heart rate deceleration and acceleration (*18*). The PRSA technique provides separate characterizations of deceleration- and acceleration-related modulations, quantified by deceleration capacity (DC) and acceleration capacity, respectively. It has been shown that diminished deceleration-related modulation of heart rate, *i.e.*, a reduced DC, is a powerful predictor of total mortality after myocardial infarction (*18*). Therefore, only DC was analyzed in this study. DC was calculated with the use of in-house software written in Python.

Table 1. Baseline Clinical Characteristics of the Patients Studied

Continuous variables	Mean
Age (years)	57.0±2.2
BMI (kg/m^2)	30.8±0.8
Cholesterol (mg/dL)	217.4±6.8
LDL cholesterol (mg/dL)	133.8±6.8
HDL cholesterol (mg/dL)	47.2±2.9
Triglycerides (mg/dL)	163±98
Creatinine (mg/dL)	0.9±0.1
Glucose (mg/dL)	99.7±5.4
AST (IU/dL)	25.8±2.3
ALT (IU/dL)	34.6±4.7
Dichotomized variables	***n* (%)**
Women	14 (47.7)
Previous myocardial infarction	2 (6.7)
Stable angina pectoris	15 (50.0)
Diabetes type 2	5 (16.7)
PCI	5 (16.7)
Smokers	8 (26.7)
ACE inhibitors	26 (86.7)
Angiotensin II blockers	4 (13.3)
β-Blockers	21 (70.0)
Calcium-channel antagonists	10 (33.3)
Diuretics	21 (70.0)
Statins	15 (50.0)

ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention.

Short-Term ECG and Blood Pressure Recording

Three channels of a bipolar ECG chest lead with finger blood pressure waves were simultaneously recorded, with a sampling frequency of 1,600 Hz, by an analogue/digital (A/D) converter (Porti 5, TMSI, Enschede, the Netherlands) for 5 min at rest in a supine posture. The recording period was preceded by a 10-min rest period for cardiovascular adaptation. The recordings obtained from the A/D converter were transferred to a PC for on-screen monitoring and data storage. For BRS measurement, noninvasive beat-to-beat finger arterial

Table 2. Blood Pressure at Baseline and after 16 Weeks of Add-On Therapy with Doxazosin GITS

	Baseline values	After therapy with doxazosin GITS	*p*
Systolic blood pressure (mmHg)	158.8±2.7	139.4±3.1	<0.0001
Diastolic blood pressure (mmHg)	91.9±2.1	82.5±2.0	0.0003
Pulse pressure (mmHg)	66.8±2.7	56.8±2.6	0.0021

End point: after 16 weeks of 4 mg of doxazosin GITS as adjunct to on-going antihypertensive therapy. GITS, gastrointestinal therapeutic system.

blood pressure was recorded continuously with the use of a volume-clamp photoplethysmographic method (Portapres 2, FMS, Amsterdam, the Netherlands) and transferred to the A/D converter (*19*). The preliminary automatic evaluation of the recordings was performed with the use of libRASCH/RASCHlab software from the libRASCH project (v. 0.6.1; http://www.librasch.org, Germany). This was followed by a visual inspection of all signals, and any necessary corrections of the obtained values were made. The values of the RR intervals and systolic blood pressure were retrieved from the stored recordings and used in further analysis.

Determination of HRV by Spectral Analysis in 5-min ECG Recordings

HRV frequency domain analysis was made by calculating the following parameters (*3*): 1) low-frequency power (LF) (from 0.04 to 0.15 Hz). LF describes the low-frequency oscillations that depend on both sympathetic and parasympathetic activities and are responsible for long-term HRV. 2) high-frequency power (HF) (from 0.15 to 0.4 Hz). HF is usually interpreted as reflecting the high-frequency oscillations caused mainly by changes in vagal tone, which are responsible for short-term HRV. 3) the ratio LF/HF. This variable reflects the balance between low- and high-frequency oscillations.

Calculation of spectral HRV was performed with the use of in-house software written in Python. The parameters of spectral HRV analysis were calculated with an equidistant tachogram of normal-to-normal RR intervals (at least 300 ms and no more than 2,000), its linear interpolation, smoothing with a boxcar filter with a width of two samples, and the application of Hanning's window. Finally, the Fast Fourier Transform was performed with the calculation of power in the frequency bands as recommended.

Baroreflex Sensitivity

BRS was measured in all 5-min segments with the use of the cross-correlation method, which computes a time-domain sequential BRS on spontaneous systolic blood pressure and RR interval variability (*5*). This method observes a window of fixed 10-s lengths of blood pressure and heart rate. It computes the running cross-correlation and regression between systolic blood pressure and RR intervals for positive time shifts in RR intervals of 0 to 5 s to obtain BRS at the shift with the highest cross-correlation, significant at $p<0.05$, and with a positive regression slope. The regression slope of RR intervals on systolic blood pressure is divided by the correlation coefficient and used as the BRS estimate. The procedure is repeated several times by shifting the window over the whole recording every 1 s, yielding a series of BRS values along time. The geometric mean of the obtained series of BRS estimates from each 5-min segment was included in further analysis.

Statistical Analysis

The results of continuous variables are expressed as the mean±SEM. Comparisons of continuous data before and after the treatment were made using the Wilcoxon matched-pairs signed-rank test. With the use of univariate logistic regression models, the association between improvements in the studied indices of autonomic modulation of the cardiovascular system and the clinical characteristics were analyzed. For the significant associations found in univariate analyses (SD1, *S*, and BRS with the use of thiazide diuretics), see the Results section. The odds ratio for the improvements of these indices was calculated with multivariate logistic regression models adjusted for age and gender. In addition, the Wilcoxon test was used for the comparison of SD1, *S*, and BRS before and after the add-on of doxazosin GITS within the groups that had been off or on earlier thiazide therapy. For the comparison of the changes of SD1, *S*, and BRS between patients off and those on thiazides, the Mann-Wilcoxon test for unpaired data was applied. Finally, the nonparametric Spearman test was used to analyze any correlation between blood pressure, or pulse pressure, changes and the changes in autonomic indices caused by the treatment. All tests were two-sided. The statistical analyses were performed using Instat version 4.3 for Windows (GraphPad Software, San Diego, USA) or SPSS for Windows v. 7.0 (SPSS, Chicago, USA). Statistical significance was set at $p<0.05$.

Results

The baseline clinical characteristics of the 30 patients, of whom 14 were women, are shown in Table 1. The mean age

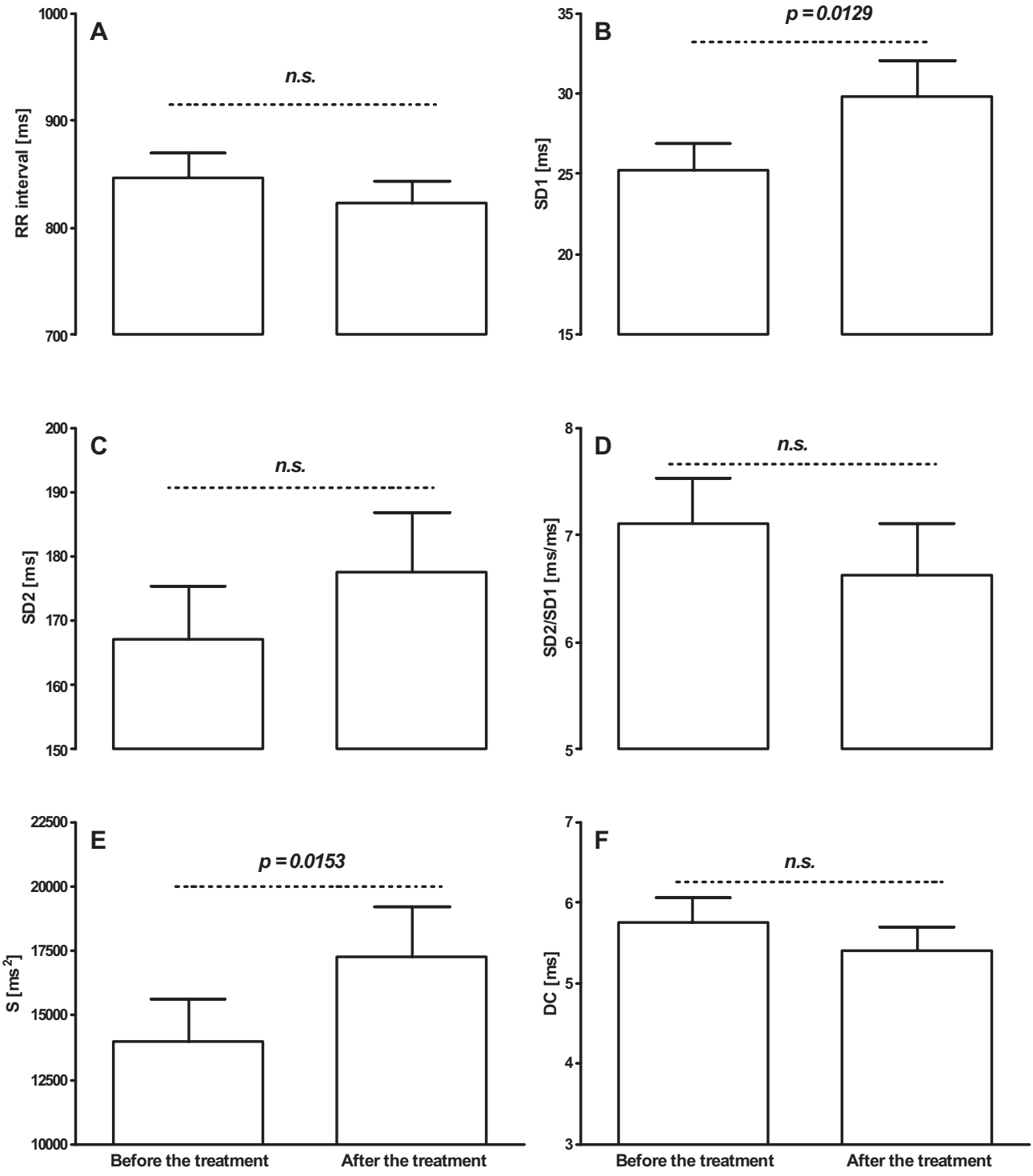

Fig. 1. *The mean (±SEM) values of mean RR intervals (A), SD1 (B), SD2 (C), SD2/SD1 (D), S (E), and DC (F) derived from 24-h ECG recordings made before and after 16-week treatment with doxazosin GITS. Further explanations are in the main text. n.s., not significant; SD1, the standard deviation of points across the identity line of Poincaré plot of RR intervals; SD2, the standard deviation of points along the identity line of Poincaré plot of RR intervals; SD2/SD1, the ratio of SD2 to SD1; S, the area of an imaginary ellipse of Poincaré plots of RR intervals; DC, deceleration capacity.*

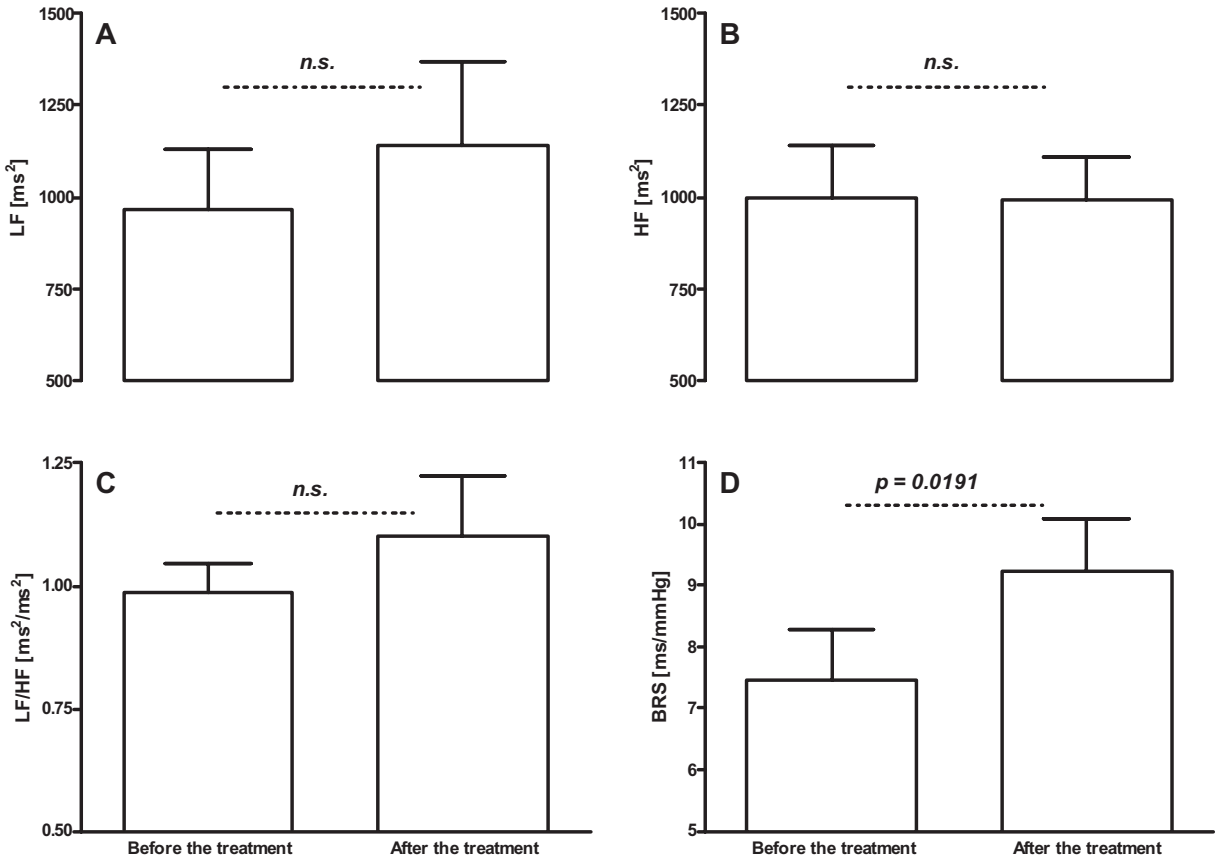

Fig. 2. *The mean (±SEM) values of the power of LF (A), HF (B), the ratio of LF/HF (C), and spontaneous BRS (D) measured in resting 5-min recordings made before and after 16-week treatment with doxazosin GITS. Further explanations are in the main text. n.s., not significant; LF, low-frequency power; HF, high-frequency power; LF/HF, the ratio of LF to HF; BRS, baroreflex sensitivity.*

was 57.0±2.2 years. The studied population was obese, with increased total cholesterol and low-density lipoprotein (LDL) cholesterol fraction. The presence of stable angina pectoris was observed in half of the group, nearly one-third of whom were current smokers. There were 2 survivors of a previous myocardial infarction, 5 patients who had undergone percutaneous transluminal coronary angioplasty, and 5 with diabetese. All patients were receiving either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker combined with at least one additional antihypertensive agent from a group consisting of diuretics (70%), β-blockers (70%), or calcium-channel antagonists (33.3%). Half the patients were on statin therapy before inclusion in the study. There were no serious adverse effects during the study period.

Hemodynamic Variables

The mean values of blood pressure and pulse pressure at baseline and at the end of the study are shown in Table 2. There were significant reductions in systolic (of 19.4±3.5 mmHg) and diastolic (of 9.4±2.0 mmHg) blood pressure, accompanied by a significant drop in pulse pressure (of 10.0±2.8 mmHg) after 16 weeks of add-on treatment with doxazosin GITS.

Indices of Autonomic Control of the Cardiovascular System

The addition of doxazosin GITS to the treatment regimen of patients with inadequately controlled hypertension for 16 weeks caused a significant increase in SD1 ($p=0.0129$) and S ($p=0.0153$) with no significant change in the values of mean RR intervals, other measures of HRV, or deceleration capacity by PRSA derived from 24-h ECG recordings (Fig. 1). Additionally, after the treatment with doxazosin GITS, there was a significant increase in BRS ($p=0.0191$) but no significant change in spectral HRV (Fig. 2).

Table 3. The Results of Univariate (on the Left) and Multivariate (Adjusted for Age and Gender) (on the Right) Logistic Regression for the Improvement of SD1, *S* or BRS after the Treatment with Doxazosin GITS

	Univariate LR			Multivariate LR		
	OR	95% CI	*p*	OR	95% CI	*p*
Improvement of SD1						
Age (for each 1 year)	1.0	0.9–1.0	n.s.	—	—	—
Gender (1 for male)	0.6	0.1–3.1	n.s.	—	—	—
Concomitant use of thiazides	7.5	1.2–45.1	0.0278	10.7	1.3–86.1	0.0258
Improvement of *S*						
Age (for each 1 year)	1.0	0.9–1.1	n.s.	—	—	—
Gender (1 for male)	0.4	0.1–1.8	n.s.	—	—	—
Concomitant use of thiazides	21.0	2.9–153.8	0.0027	19.7	2.6–150.6	0.0041
Improvement of BRS						
Age (for each 1 year)	1.0	0.9–1.1	n.s.	—	—	—
Gender (1 for male)	0.2	0.1–1.3	n.s.	—	—	—
Concomitant use of thiazides	12.0	1.9–76.2	0.0084	12.1	1.6–90.9	0.0151

GITS, gastrointestinal therapeutic system; LR, logistic regression; OR, odds ratio; CI, confidence interval; BRS, baroreflex sensitivity; for other abbreviations see text.

Association between the Improvement of Autonomic Indices and Clinical Characteristics

Univariate logistic regression showed that out of all clinical variables, only the concomitant use of thiazide diuretics was significantly related to the improvement of the autonomic indices after doxazosin GITS. More precisely, there was a significant association between the use of thiazides and the improvement of SD1, *S*, and BRS (Table 3). Therefore, in multivariate logistic regression models, adjusted for age and gender, only the use of thiazide diuretics was further analyzed. This analysis showed that the use of thiazides was associated with a significantly higher odds ratio for the improvement of SD1 (nearly 11), *S* (nearly 20), and BRS (approximately 12) (Table 3).

Figure 3 shows the values of SD1, *S*, and BRS before and after the add-on therapy with doxazosin GITS for patients with and without the concurrent use of thiazides. Significant increases of SD1, *S*, and BRS were found in a subgroup of patients who had been on thiazide therapy. By contrast, no significant changes in these autonomic indices were found in the subgroup of patients who were not receiving thiazide diuretics. There was no statistical difference in the values of SD1, *S*, and BRS between the subgroups treated with and without thiazides before entering the study, as revealed by the Mann-Whitney test. Similarly, there were no significant differences in mean RR interval, blood pressure, pulse pressure, and other HRV parameters between patients on or off thiazides before entering the study.

There were significant differences between the mean values of changes (after *vs*. before the treatment with doxazosin GITS) of SD1 (-2.3 ± 10.0 *vs*. 7.6 ± 9.0 ms; $p=0.0335$), *S* ($-3{,}204\pm7{,}464$ *vs*. $6{,}048\pm7{,}518$ ms^2; $p=0.0028$), and BRS (-1.3 ± 3.9 *vs*. 3.1 ± 3.3 ms; $p=0.0028$) between the patients on thiazide therapy *vs*. those off.

Finally, there was a significant association ($r=0.49$; $p=0.0065$) between the extent of changes in diastolic blood pressure and SD1 caused by the treatment (Fig. 4). The magnitude of changes to the systolic blood pressure and pulse pressure were not significantly related to the changes in SD1, *S*, and BRS.

Discussion

In this study, we found that the 16-week add-on therapy with 4 mg of doxazosin GITS taken at bedtime by patients with previously inadequately controlled hypertension was associated with an improvement in short-term (SD1) and total HRV (*S*) as well as in resting, spontaneous BRS. Moreover, the improvement in these autonomic indices of the control of heart rate was associated with a concomitant use of thiazide diuretics, independent of patients' age and gender. These findings were accompanied by a significant reduction in blood pressure and pulse pressure and no significant change in diurnal heart rate. Moreover, the extent of the change in diastolic blood pressure was positively related to the value of the change of SD1.

The extended-release form of doxazosin has been shown to be efficacious, safe, and well tolerated by hypertensive patients treated with a combined therapy (*9*, *14*, *15*). As reported by de Alvaro *et al*., blood pressure and heart rate were significantly reduced by a combined treatment with doxazosin GITS (*15*). In their study, the mean reduction in systolic blood pressure was approximately 25 mmHg, that in diastolic blood pressure was >14 mmHg, and that in heart rate 3 beats/min. In another study, Campo *et al*. showed that in patients with hypertension not controlled with monotherapy, the use of the doxazosin GITS for 4 months was simi-

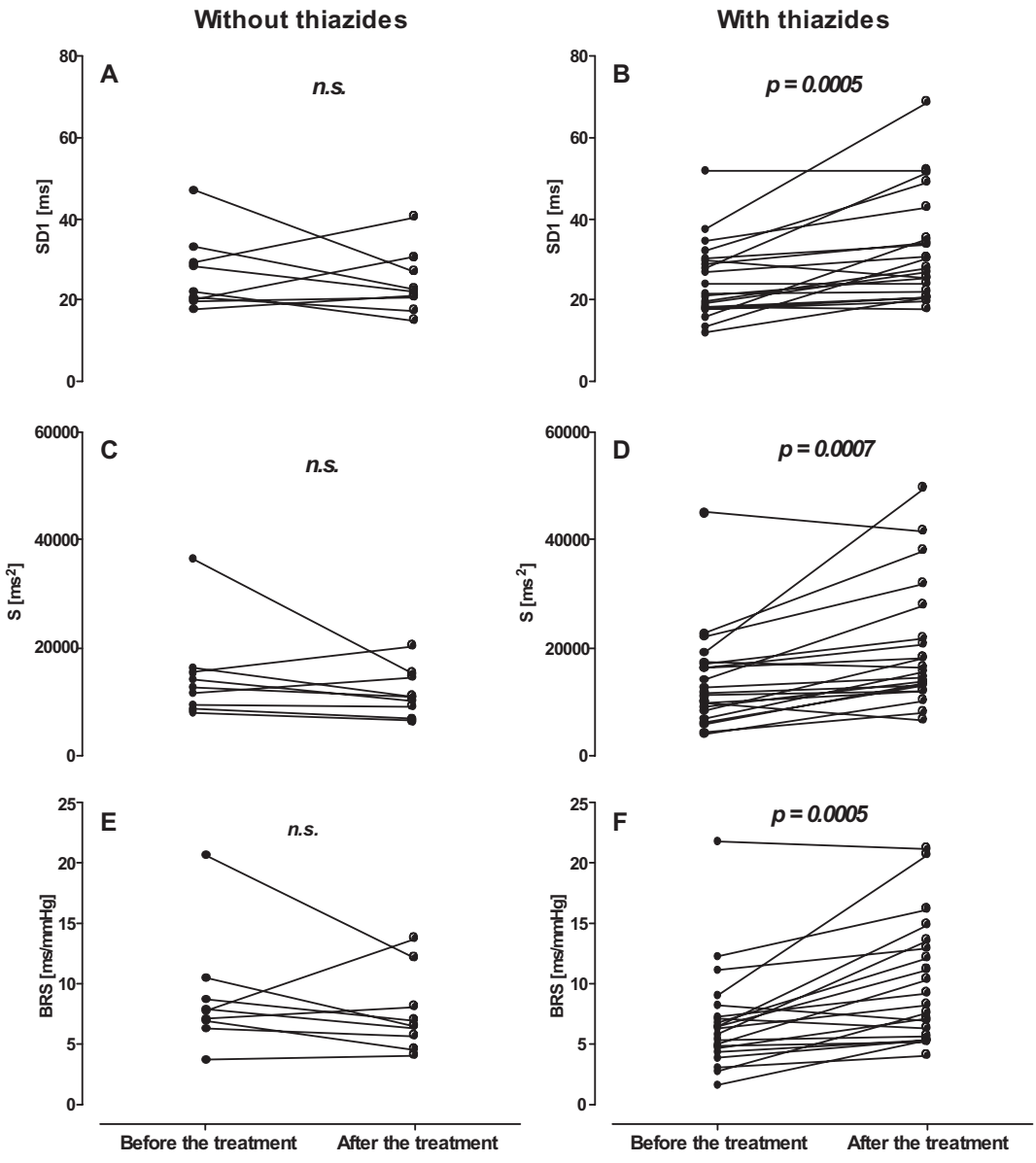

Fig. 3. *The individual values of SD1 (A and B), S (C and D), and BRS (E and F) observed in patients off (A, C and E, respectively) or on (B, D and F, respectively) concurrent use of thiazide diuretics before and after 16-week treatment with doxazosin GITS. Further explanations are in the main text. n.s., not significant; abbreviations SD1, S and BRS as in text and Figs. 1 and 2.*

larly effective when used in addition to thiazide diuretics (*20*). However, the use of doxazosin was associated with more beneficial metabolic effects such as lower levels of total cholesterol, LDL cholesterol, and uric acid, and higher levels of high-density lipoprotein (HDL) cholesterol and serum potassium when compared to thiazide diuretics (*20*). These, and some other studies, have shown that doxazosin is a valuable antihypertensive agent, although more recent studies and recommendations suggest that it should be used only as a second- or third-line treatment for hypertension (*9*, *12*, *20*, *21*). In our study, we noticed similar results with regard to a reduction in blood pressure, although our primary aim was to evaluate the influence of combined treatment with doxazosin GITS on the autonomic control of the cardiovascular system.

Hypertension has been associated with some disturbances in the activity of both the sympathetic and parasympathetic nervous systems, most notably impairment of baroreceptor function (*6*–*8*). Patients with hypertension show elevated plasma catecholamine concentration and renin activity, total body, renal, and cardiac spillover of norepinephrine, and muscle sympathetic nerve activity (*7*, *22*). Moreover, noninvasive markers of cardiovascular autonomic control, *i.e.*, HRV and BRS, are also reduced in patients with essential and/or secondary hypertension accompanying renal diseases

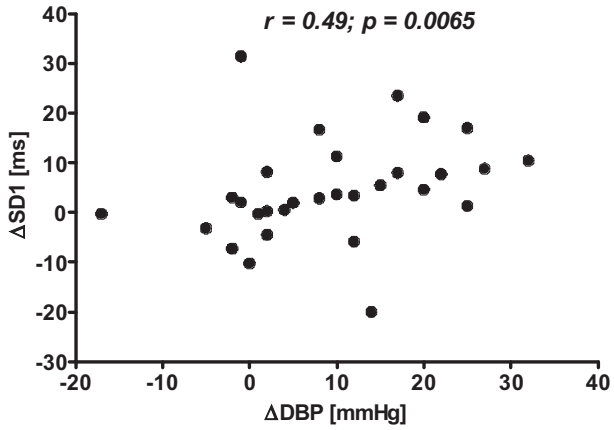

Fig. 4. *Correlation between the changes in diastolic blood pressure and changes in SD1 caused by treatment with doxazosin. The r value represents the coefficient of Spearman correlation.*

or diabetes (*22*). Most antihypertensive medications directly affect autonomic function. However, the indirect effect of such agents cannot be ruled out, as the resulting fall in blood pressure *per se* influences the sympathetic-parasympathetic balance by, for example, improving the function of arterial and/or cardiopulmonary baroreceptors (*23*). Previous studies on the use of short-acting doxazosin in hypertensive patients have shown sympathetic activation by the drug (*9*, *10*, *12*, *13*). By antagonizing peripheral α1-adrenergic receptors, this agent reduces sympathetic effects on the cardiovascular system but not the adrenergic drive. As previously reported, short-acting doxazosin causes reflex tachycardia after a sudden drop in blood pressure (*12*, *13*). In addition, the plasma norepinephrine concentration and plasma renin activity were increased by doxazosin treatment and declined after discontinuation of the drug (*24*). Similar effects were observed in normotensive volunteers. After a 4-week doxazosin regime, the plasma norepinephrine concentration fell and plasma renin activity trended lower (*25*). Although heart rate, being a sensitive index of sympathetic-parasympathetic balance, declines after the antihypertensive treatment with doxazosin GITS (*15*), there are, unfortunately, no reported studies on the influence of this form of the drug on catecholamines and other autonomic measures.

In this study, we measured neither biochemical markers of autonomic activity nor muscle sympathetic activity, both of which more directly reflect sympathetic tone (*7*, *22*). Instead, we evaluated various noninvasive indices of HRV and BRS. Although the resting HRV by spectral analysis (LF, HF, LF/HF) was unaffected by doxazosin GITS, the value of resting BRS, together with SD1 and *S* in 24-h ECG recordings, was significantly increased after the 16-week treatment, mainly in patients who were on concomitant thiazide therapy. It is relevant that the baseline SD1, *S*, and BRS values, measured before starting the add-on therapy with doxazosin GITS, were no different in patients with or without concomitant use of thiazide. It seems, therefore, that the improvement in autonomic indices found in patients on thiazides is secondary to the action of doxazosin. This improvement might be caused by a direct effect of the drug on the sympathetic-parasympathetic balance or by a doxazosin-induced reduction in blood pressure, or it may be that both mechanisms are responsible for the results. Another important property of doxazosin, which could be responsible for our findings, is an improvement in insulin sensitivity and a reduction in its resistance (*26*). This mechanism should also be taken into consideration because the interaction between insulin and sympathetic activity has been recognized (*27*). Considering that thiazides are able to impair glucose metabolism and insulin sensitivity (*28*) while doxazosin, working in an opposite direction, can improve them, it is plausible that the increased HRV and BRS result from some interaction of both antihypertensives. Finally, the short-acting form of doxazosin raises the norepinephrine level, thus causing the retention of sodium and water (*11*, *13*, *24*). Even if we assume that doxazosin GITS could also cause such retention, the simultaneous use of thiazide diuretics attenuated or prevented this effect so efficiently that autonomic control of heart rate improved. Whatever the mechanism is, it appears that the addition of doxazosin GITS to multi-drug antihypertensive treatment brings some benefits for the autonomic regulation of heart rate, at least when taken before bedtime, which was done to prevent an early morning increase in blood pressure (*9*). Doxazosin GITS, in contrast to the short-acting form of doxazosin, does not appear to stimulate the sympathetic nervous system, at least in patients concurrently taking thiazide diuretics. It seems that this medication to some extent helps recover parasympathetic control of heart rate, which is indirectly shown by significant increases in SD1, *S*, and BRS after the treatment with doxazosin GITS.

As found in this study, pulse pressure was significantly reduced, by approximately 10 mmHg, after the applied treatment with doxazosin GITS. Pulse pressure is a function of systolic ejection and increases with stroke volume, amount of circulating blood, and myocardial contractility. It is also related to afterload (dependent on arterial resistance) and the mechanical properties of arteries (pulse pressure is higher in patients with stiffer arteries) (*9*, *29*). It is reasonable to assume that the observed reduction in pulse pressure might be secondary to the decrease in stroke volume and/or afterload, and/or to the decrease in arterial stiffness. Stroke volume, venous return, and cardiac output (both representing the amount of circulating blood), and the function of resisting arteries are regulated by autonomic activity, which, as shown by this study and others (*9*, *12*, *13*, *24*), doxazosin changes. On the other hand, as reported by Komai *et al*. and our group, treatment of hypertension with doxazosin improves endothelial function and decreases arterial stiffness (*30*, *31*). Therefore, the reduction in pulse pressure, along with decreases in

systolic and diastolic pressures, is not surprising.

Study Limitations

One important limitation of this proof-of-concept study is the open-label aspect, *i.e.*, neither the patients nor the physicians were blinded to the add-on treatment. Other limitations include the small number of patients (n=30) and the quite short duration of treatment (16 weeks). However, we used consecutive patients with hypertension inadequately controlled by various antihypertensives but none on any α-blocker treatment. As for the autonomic indices employed, we used the Poincaré plot analysis of RR intervals from Holter ECG recordings, since this method has been shown to express the autonomic regulation of heart rate (*4*). Deceleration capacity, on the other hand, is a brand new HRV method describing the information derived from decelerations of heart rate and is believed to be related to vagal regulation of heart rate (*18*). Following published recommendations, spectral analysis of HRV has been applied only to short resting recordings of 5-min duration. Working with these recordings and using the cross-correlation method to assess spontaneous BRS, insight into autonomic and cardiovascular interactions has been widened. This relatively new method for BRS has been applied in different studies and has been shown to be reliable (*5*).

In summary, 16-week treatment of add-on therapy with doxazosin GITS in patients with hypertension reduced their blood pressure and also improved autonomic control of the cardiovascular system. This effect was seen most clearly in patients already on thiazide therapy. This suggests that the combination of thiazides with doxazosin GITS is not only an effective method of treating hypertension but may also improve autonomic control of the cardiovascular system. However, as the finding of a beneficial autonomic effect of doxazosin GITS in patients already on thiazides was rather accidental, other potentially valuable consequences of such a combination should be elucidated in future studies. As mentioned above, the comparative ALLHAT study showed the superiority of chlorthalidon over doxazosin in the treatment of hypertension. However, it seems that no studies have evaluated the effects of a combination of both agents.

Conclusions

What Is Known about the Topic

1) The increased sympathetic activity and/or reduced parasympathetic drive are associated with the development of hypertension, its further progression, and clinical complications.

2) Clinical studies indicate that short-acting doxazosin is not the first-line therapy of hypertension because it may be associated with increased risk of heart failure, probably because it stimulates the sympathetic nervous system.

3) The extended-release form of doxazosin, *i.e.*, doxazosin GITS, is commonly used in the treatment of prostate hyperplasia and is suggested as an additional agent in a combined therapy for hypertension.

4) Doxazosin GITS is a well-tolerated antihypertensive agent of unknown influence on autonomic control of the cardiovascular system.

What This Study Adds

1) The 16-week add-on therapy with 4 mg of doxazosin GITS of uncontrolled hypertension is associated with an increase of short-term and total HRV as well as improved baroreflex sensitivity, which might suggest a reduction in sympathetic tone and/or an increase of parasympathetic activity.

2) The improvement of the autonomic modulation of the cardiovascular system appears to be mainly observed in patients who have been concurrently using thiazide diuretics.

3) The degree of improvement of short-term HRV caused by doxazosin GITS is related to the extent of reduction in diastolic blood pressure produced by this medication.

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