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## Arterial Pressure Lowering Effect of Chronic Atenolol Therapy in Hypertension and Vasoconstrictor Sympathetic Drive

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### Abstract

Although the  $\beta_1$ -adrenergic blocking agent atenolol is an established antihypertensive therapy, its effect on peripheral sympathetic vasoconstrictor drive has remained controversial. In patients with hypertension, atenolol therapy has been reported to either increase or have no effect on peripheral vascular resistance, despite other reports showing no change or a decrease in peripheral sympathetic drive. This study was designed, in patients with untreated essential hypertension (EHT), to quantify changes in simultaneously measured peroneal muscle sympathetic nerve activity (MSNA) and calf vascular resistance (CVR) accompanying atenolol therapy. MSNA was quantified as the mean frequency of single units (s-MSNA) and as multiunit bursts (MSNA bursts) using the technique of microneurography, and CVR was measured using a standard plethysmographic technique. Firstly, by comparing two age- and body weight-matched groups, each of 14 patients with hypertension, we found that the group on atenolol therapy (treated-HT) had similar MSNA values counted over the same number of cardiac beats and similar CVR levels (at least  $P > 0.40$ ) to the group without therapy (untreated-HT). Secondly, we examined 10 EHT patients before and after  $8 \pm 0.4$  weeks of oral atenolol therapy (HT-A) in comparison to seven control patients with hypertension and no treatment (HT-C) who were examined over a similar period of time. We found that the measures of MSNA and CVR did not significantly change in both groups. We conclude that the arterial pressure lowering effect of atenolol was not related to significant changes in central vasoconstrictor sympathetic drive to the periphery.

### Keywords

antihypertensive therapy; sympathetic nervous system; hypertension, essential; vascular resistance

Although  $\beta$ -adrenergic blocking agents are widely used to lower arterial pressure in essential hypertension (EHT), the mechanisms underlying this effect are not entirely clear.<sup>1-4</sup> In the case of cardioselective  $\beta_1$ -adrenoceptor antagonists, there has been controversy as to whether or not their arterial pressure lowering effect involves changes to peripheral sympathetic vasoconstrictor drive and hence vascular resistance. For instance, in patients with EHT, atenolol therapy that produced a reduction in arterial pressure and heart rate has been found either to have no effect on forearm and calf vascular resistance or to increase it.<sup>5-9</sup> Similar results have been reported using metoprolol, another  $\beta_1$ -adrenoceptor antagonist.<sup>6,10-12</sup>

Furthermore, in patients with hypertension treated with  $\beta_1$ -adrenoceptor antagonists, reports of an effect on peripheral sympathetic drive mediating the arterial pressure reduction have also been inconsistent. For example, atenolol therapy has been reported to have no effect on biomedical indicators of sympathetic activity such as plasma norepinephrine levels or total body norepinephrine spillover rates.<sup>9,13,14</sup> Even direct measurements of muscle sympathetic nerve activity (MSNA) by peroneal microneurography have been reported to yield equivocal results.<sup>15,16</sup> Although intravenous metoprolol was associated with increased MSNA, either by a direct central or a peripheral reflex effect,<sup>15</sup> chronic therapy did not affect MSNA when the metoprolol-induced heart rate decrease was taken into account.<sup>16</sup>

However, none of those reports has assessed  $\beta_1$ -adrenoceptor antagonist-induced changes in the frequency of MSNA and its effect on vascular resistance, when simultaneously measured in the same patient. This is important because after  $\beta_1$ -adrenoceptor-antagonist therapy, net vascular resistance may reflect the balance between unmasked  $\beta_2$ -adrenoceptor vasodilatory effects and unopposed  $\alpha$ -adrenoceptor vasoconstrictive effects. On the other hand, simultaneous changes in MSNA and vascular resistance, attributed to  $\beta_1$ -adrenoceptor-antagonist therapy, may provide quantitative information as to whether the therapy affects the efferent sympathetic vasoconstrictor drive.

The present study, therefore, was designed in patients with EHT, to quantify any atenolol-induced changes in central sympathetic nerve activity supplying the leg, and to simultaneously measure calf blood flow (CBF) and vascular resistance (CVR). For this purpose, MSNA was obtained by peroneal microneurography and quantified as single unit and multiunit mean frequency, whereas CBF and CVR were simultaneously obtained by standard venous occlusion plethysmography during the steady state. Two investigations were planned. The first was to compare sympathetic activity and CVR in age, body weight, and sex-matched groups with atenolol therapy (treated-HT) and without (untreated-HT). The second was designed in hypertensive patients to quantify changes over 8-weeks of atenolol therapy (HT-A), in comparison to a control group with hypertensive patients who were followed up without therapy for a similar period of time (HT-C).

## Methods

### Subjects

In the first investigation, 28 patients with EHT were examined, comprising two groups, one (14 patients) with atenolol therapy for at least 2 months (treated-HT), and another (14 patients) without (untreated-HT). In the second investigation, 17 patients with EHT were examined twice, 10 patients before and after atenolol (HT-A), and 7 patients without therapy (HT-C). All had similar occupational status and were screened by history, physical, and laboratory examination. None had evidence of secondary hypertension, left ventricular hypertrophy, peripheral vascular disease, arrhythmia, or chronic disease that may influence the autonomic nervous system. Arterial pressure was defined on the basis of the average of at least 3 sphygmomanometer readings, taken on separate occasions, using a standard measurement technique.<sup>4</sup> The presence of hypertension was accepted when systolic blood pressure  $\geq 140$  mm Hg or diastolic  $\geq 90$  mm Hg.<sup>4</sup> In the patients comprising the HT-C group, the clinical decision to start therapy was deferred pending follow-up because of mild and intermittent levels of raised arterial pressure. The details of patients in the cross-sectional investigation and the 2 groups in the longitudinal study are shown in Tables 1 through 3. The investigation was performed with the approval of St. James's University Hospital Ethics Committee, and all subjects provided informed written consent.

## Study Design

In the cross-sectional analysis, differences in sympathetic activity and calf vascular resistance were quantified in the two age- and body weight-matched treated-HT and untreated-HT groups. In the longitudinal investigation, the two study groups, HT-A and HT-C, were examined twice, 8 weeks apart, using an identical protocol. Atenolol was given only to group HT-A, at a dose of 50 to 100 mg per day. This longitudinal design allowed individuals to act as their own control. A placebo group was not included, as a clinical decision had been made before recruitment into the study to start oral antihypertensive therapy, and it was considered unethical to delay treatment.

## General Protocol

Microneurographic and hemodynamic measurements were obtained in an identical manner during each session. A detailed methodological protocol has been published previously.<sup>17-19</sup> Investigations were performed under similar conditions between the hours of 9:00 and 12:00 AM. Patients were asked to have had a light breakfast and to empty their bladder before commencing the study. They were instructed to maintain a normal dietary intake of sodium, and to avoid nicotine and caffeine products for 12 hours, as well as alcohol and strenuous exercise for 24 hours before investigation. During each session, the subjects were studied in the semisupine position when data attained a steady state for at least 30 minutes. Measurements were made in a darkened laboratory in which the temperature was constant between 22 and 24°C. Resting blood pressure was measured from the arm, using a mercury sphygmomanometer. Changes in heart rate and arterial pressure were monitored and recorded, using a standard ECG and a Finometer device (FMS, Arnhem, the Netherlands, TPD Biomedical Instruments).

## Microneurography

Postganglionic muscle sympathetic nerve activity (MSNA) was recorded from the right peroneal nerve, simultaneously with the other data as previously described.<sup>17-19</sup> The neural signal was amplified ( $\times 50\,000$ ), and for the purpose of generating bursts representing multiunit discharge, the signal was filtered (bandwidth of 700 to 2000 Hz), and integrated (time constant 0.1 second). The output of action potentials and bursts from this assembly was passed to a PC-based data-acquisition system (LabView, National Instruments Corp, Austin, Tex), which digitized the acquired data at 12 000 samples/second (16 bits).

MSNA was differentiated from skin sympathetic activity and afferent activity by previously accepted criteria.<sup>20,21</sup> Single units (s-MSNA) in the raw action potential neurogram were obtained by adjusting the electrode position, while using fast monitor sweep, and on-line storage oscilloscope to confirm the presence of consistent action potential morphology, as previously described.<sup>17,21,22</sup> Only vasoconstrictor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial pressure during verification by a preliminary Valsalva maneuver and isometric handgrip exercise. During the Valsalva maneuver, sympathetic activity increased during the latter part of phase-II and/or phase-III and decreased during phase-IV (corresponding to the decrease and increase of arterial pressure). During isometric handgrip exercise, performed using a dynamometer (MIE Medical Research Ltd, Leeds, UK), a delayed increase of sympathetic nerve activity was observed. In addition, simultaneous measurement of calf vascular resistance (CVR) confirmed the vasoconstrictor function of the observed neural activity.

## Other Procedures

CBF was obtained simultaneously with microneurography, using an automated mercury-in-silastic (Whitney) strain gauge venous occlusion plethysmograph (D.E. Hokanson Inc,

Bellevue, Wash). The strain gauge was placed around the widest circumference of the left calf region, and chosen to be 2 to 3 cm smaller than the calf circumference, such that it was applied under slight tension to the calf. Venous occlusion was effected by inflating a contoured thigh cuff (Model CC-22, D.E. Hokanson Inc, Bellevue, Wash), placed around the left thigh, to  $\approx 60$  mm Hg or 20 mm Hg below the predetermined diastolic arterial pressure, whichever was the lesser. The DC output from the plethysmograph was passed to a chart recorder (APC Medical Ltd, Welwyn Garden City, Herts, UK) using heat sensitive paper, so that a graphic record of change in limb volume could be produced. During measurement of CBF, the left foot region was excluded by inflating a pediatric cuff placed around the ankle, to levels greater than the predetermined systolic arterial blood pressure.

## Analysis

Analysis was performed independently off-line, using dedicated software based on the LabView system (National Instruments Corp, Austin, Tex). For sympathetic nerve activity files of recordings acquired over 5 minutes of steady state conditions, an electronic discriminator window was used objectively to count s-MSNA spikes with consistent morphology and a threshold discriminator counted the R-waves of the ECG. The mean frequency of s-MSNA was quantified over one minute and over 100 cardiac beats, to avoid any interference by the length of the cardiac cycle.<sup>23</sup> The bursts of MSNA were identified by inspection when the signal-to-noise ratio was  $>3$ , and were counted and quantified in a similar manner to s-MSNA. The variability of measuring both s-MSNA and MSNA in this laboratory is  $<10\%$ .<sup>17</sup>

For CBF measurements, typically 12 recordings were made over 4 minute periods of steady state conditions. The average of the recordings was expressed in units of  $\text{mL}100 \text{ mL} \cdot \text{min}^{-1} \cdot \text{min}^{-1}$ . The intraobserver reproducibility of CBF measurement in this laboratory, obtained as twice 95% confidence interval of differences between repeated within-session plethysmography amounted to 2.4% of the value of the measurement. Arterial pressure was simultaneously and continuously measured, and its average value was divided by the average CBF, to obtain CVR, which was expressed in arbitrary units.

## Statistics

Unpaired Student *t* tests were used to assess differences between two groups in the cross-sectional investigation, and paired Student *t* tests were used to assess changes within the same group in the longitudinal study. The least square technique was used to assess the linear relationship between variables. Values of  $P < 0.05$  were considered statistically significant. All data are presented as mean  $\pm$  SEM.

## Results

In the cross-sectional investigation, the treated-HT group was matched in respect to sex, age, body weight, and body mass index to the untreated-HT group (Table 1). As expected however, the treated-HT group had significantly lower arterial pressure indices, and a slower heart rate. Although the atenolol-induced bradycardia was associated with a lower mean frequency of sympathetic nerve activity per minute in the treated-HT group, there were no significant differences between the two groups regarding this activity, over the same 100 cardiac beats. Also, there were no significant differences in CVR between the two groups (Table 1).

In the longitudinal investigation, within-patient changes after atenolol therapy for  $8 \pm 0.4$  weeks in the HT-A group (Table 2), were examined and compared with those during follow-up without therapy in the HT-C group (Table 3). Atenolol therapy significantly reduced

heart rate and arterial pressure indices in HT-A, although any changes in these variables were not significant in HT-C. These atenolol-induced effects were significantly greater (at least  $P < 0.02$ ) than any changes observed in the HT-C group, and were accompanied by decreases in sympathetic nerve activity counted over a smaller number of heart beats in the HT-A group (Table 2). No significant changes occurred in any measured variable in the HT-C group (Table 3). When the atenolol-induced decreases in heart rate were accounted for, there were no significant changes in sympathetic nerve activity counted over the same number of 100 cardiac beats in the HT-A group. Also, there were no significant changes in CVR (Table 2). In the HT-C group, the variability in terms of standard deviation of the insignificant changes, expressed in percentage of mean measured data (coefficient of variation) respectively, amounted to 5.5% for MSNA bursts, 6% for s-MSNA impulses, and 16% for CVR. Finally, there were no significant differences in the changes of these variables (at least  $P > 0.40$ ) between HT-A and HT-C groups.

## Discussion

To test mechanisms involving the role of sympathetic vasoconstrictor drive in the atenolol-induced arterial pressure lowering in essential hypertension (EHT), this study has quantified for the first time changes in simultaneously measured central sympathetic nerve activity supplying the leg, CBF, and CVR that can be directly attributed to atenolol therapy. As expected, atenolol therapy decreased the heart rate, and as a consequence, decreased the count of sympathetic nerve activity over the reduced number of heartbeats. When this confounding factor was minimized by measurements made over the same number of heartbeats, atenolol significantly affected neither sympathetic nerve activity nor CVR.

Because it was not possible to conduct a placebo-controlled study in our patients with hypertension, care was taken to avoid potential confounding factors that could affect the change of sympathetic activity to be tested. Therefore, we used cross-sectional and combined longitudinal and cross-sectional investigations in an attempt to examine effects that can be directly attributed to atenolol therapy. Firstly, all patients were examined using the same protocol and under similar laboratory conditions, without interference by changes in dietary intake or body weight, which are known to affect sympathetic activity.<sup>24,25</sup> The two groups in the cross sectional comparisons were matched in respect of these factors, in addition to matching them in respect of age and sex ratio.<sup>17,26</sup> Indeed, the changes in sympathetic nerve activity over the same number of heartbeats and in CVR during follow-up in HT-C and HT-A groups did not exceed the variability between repeated measurements in our laboratory.<sup>17,19</sup>

Other possible confounding factors are related to the fact that atenolol therapy significantly reduced heart rate and arterial pressure indices in every patient. However, although these effects were an integral and unavoidable part of the design of our investigation, they were not likely to have been the sole explanation for our findings. For instance, it is well known in patients with hypertension that arterial pressure levels are neither linearly related to sympathetic nerve activity,<sup>17</sup> nor do they significantly affect the gain of baroreceptor reflex control of this activity.<sup>27</sup> Indeed, we found that despite the lower arterial pressure in the groups given atenolol therapy than those without, there were similar levels of sympathetic nerve activity counted over the same heart rate. Similarly, although a decrease in mean arterial pressure was expected to lead to a lower CBF during the steady state, there were no significant differences in CVR that can be attributed solely to atenolol therapy.

The other  $\beta$ -blocking effect, namely the slowing of heart rate, is known to affect sympathetic nerve activity in a complex fashion.<sup>16,23,28</sup> The bradycardia-induced changes in pulse-to-pulse arterial pressure levels may influence efferent sympathetic nerve activity, and counting

the frequency of this efferent activity over the same number of cardiac cycles (100 cardiac beats) during the steady state has been proposed to provide an index of sympathetic activity that is independent of changes in heart rate.<sup>16,23,28</sup> By lowering the number of cardiac beats occurring over a 1-minute period, atenolol would have indirectly reduced the opportunity for sympathetic outflow, which tends to occur at the nadir of arterial pressure oscillations. The slower heart rate could have indirectly contributed to the atenolol-induced lowering of arterial pressure and, thereafter, absence of atenolol-induced calf vasodilatation. When counted over the same number of cardiac beats to account for these confounding factors, there was no significant change in the mean frequency of efferent sympathetic nerve activity after atenolol therapy. These considerations, and the simultaneous findings of absence of change in efferent vasoconstrictor sympathetic drive and its end organ effect (CVR) indicate that atenolol-induced lowering of arterial pressure was not directly and entirely related to changes in sympathetic vasoconstrictor drive.

Indeed, our findings are consistent with previous reports regarding the effect of atenolol therapy on sympathetic output or CVR in hypertension. Firstly, chronic atenolol therapy was found to have no effect on indirect measures of sympathetic activity, such as plasma norepinephrine levels or total body norepinephrine spillover rates.<sup>9,13,14</sup> As in the present study, chronic metoprolol therapy (another  $\beta_1$ -adrenergic blocking agent) was found to reduce arterial pressure and heart rate without affecting the frequency of multiunit MSNA bursts counted over 100 cardiac beats.<sup>15</sup> The mechanisms of those observations were suggested to involve central effects or adaptations in some baroreflex loops.<sup>15</sup> The present study did not test isolated changes in, or interaction between, the operation of central and reflex control of sympathetic nerve activity as this is not adequately achievable in humans. However, our findings could be argued to infer that the demonstrated efficacy of atenolol in reducing arterial pressure did not involve the sympathetic drive. Secondly, and as we found, neither atenolol nor metoprolol therapy have been reported to affect CVR in several other studies.<sup>5,6,8,12</sup> In this context however, there remains the possibility that the effect of  $\beta_1$ -adrenergic blocking agents on CVR may reflect a balance between emerging unopposed  $\alpha$ -adrenergic vasoconstrictive effects and  $\beta_2$ -adrenergic vasodilating effects. Nevertheless, the present investigations have shown that the absence of demonstrable effect of atenolol therapy on CVR was accompanied by the absence of its effect on the simultaneously measured peripheral vasoconstrictive sympathetic drive. This indicates that the arterial pressure lowering effect of atenolol therapy in the patients with essential hypertension did not directly involve the peripheral sympathetic drive or its vasoconstrictive effect.

## Perspectives

The finding that the mechanism of atenolol-induced arterial pressure lowering did not directly and entirely involve peripheral sympathetic vasoconstrictor mechanisms, can have therapeutic and prognostic implications. Given that hypertension is a state of sympathetic hyperactivity, therapeutic agents that have sympatholytic effects would be expected to lower arterial pressure by reducing the sympathetic drive and hence, result in peripheral vasodilatation. However, for atenolol therapy at least this does not appear to be the case. This could have implications in patients with excessive sympathetic activation, such as that found in young hypertensives, and in those patients in whom excessive sympathetic activation has been associated with increased cardiovascular risk.

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**TABLE 1**  
**Details of the 2 Groups of Patients in the Cross-Sectional Study**

Patients	Treated-HT	Untreated-HT	P
No. (males)	14 (10)	14 (11)	0.50
Age, y	51±2.0	51±3.2	0.43
Body weight, kg	95±4.0	94±4.0	0.43
Body mass index, kg/m <sup>2</sup>	32±1.0	32±1.1	0.43
Heart rate, beats/min	56±2.5	68±2.6	<0.003
MSNA, bursts/min	34±1.8	41±1.8	<0.005
s-MSNA, impulses/min	39±1.9	48±2.8	<0.020
Arterial pressure, mm Hg			
Systolic	128±3.1	162±6.0	<0.0001
Diastolic	79±1.8	97±2.4	<0.0001
Mean	96±2.4	117±3.3	<0.0001
CBF (mL · 100 mL <sup>-1</sup> · min <sup>-1</sup> )	2.4±0.21	2.9±0.24	0.07
MSNA, bursts/100 beats	62±4.8	62±3.8	0.49
s-MSNA, impulses/100 beats	72±5.1	72±5.5	0.47
CVR, units	44±3.8	44±3.6	0.50

Groups shown are those on atenolol therapy (treated-HT) and those who were untreated (untreated-HT).

CBF indicates calf blood flow; CVR, calf vascular resistance; and MSNA, muscle sympathetic nerve activity. Data are mean±SEM. *P* refers to unpaired *t* tests, and Fisher  $\chi^2$  test in the case of gender.

**TABLE 2**  
**Changes of Data in the Longitudinal Study in 10 Patients (HT-A Group) Before and After Atenolol Therapy**

Patients	Before	After	Change	<i>P</i>
Body weight, kg	89±5.1	90±5.3	1.2±0.91	0.11
Body mass index, kg/m <sup>2</sup>	30±1.6	30±1.5	0.36±0.31	0.13
Heart rate, beats/minute	77±3.0	57±2.1	-20±2.6	<0.0001
MSNA, bursts/minute	43±2.0	33±2.0	-10±1.4	<0.0001
s-MSNA, impulses/minute	50±1.8	38±2.1	-12±1.5	<0.0001
Arterial pressure, mm Hg				
Systolic	158±5.5	134±5.0	-24±4.0	<0.0001
Diastolic	95±3.8	82±2.0	-12±3.4	<0.003
Mean	116±3.5	101±3.1	-15±3.1	<0.0005
CBF (mL · 100 mL <sup>-1</sup> · min <sup>-1</sup> )	2.9±0.35	2.5±0.31	-0.40±0.40	0.17
MSNA, bursts/100 beats	58±3.9	59±4.3	2.0±2.9	0.26
s-MSNA, impulses/100 beats	66±3.8	68±4.4	1.9±3.5	0.30
CVR, units	43±6.5	44±5.2	0.7±4.9	0.46

Data are mean±SEM. *P* refers to paired *t* tests.

**TABLE 3**  
**Changes of Data in the 7 Patients (HT-C Group) Followed-Up Without Therapy**

Patients	Baseline	Follow-Up	Change	<i>P</i>
Body Weight, kg	77±4.4	77±4.3	-0.6±0.4	0.47
Body mass index, kg/m <sup>2</sup>	28±0.9	27±0.8	-0.2±0.16	0.43
Heart rate, beats/minute	63±3.1	61±3.2	-2±1.1	0.15
MSNA, bursts/minute	30±4.5	30±4.5	0.1±1.0	0.9
s-MSNA, impulses/minute	34±4.5	34±4.4	0.4±0.5	0.45
Arterial pressure, mm Hg				
Systolic	136±12.6	137±12.4	1±0.8	0.19
Diastolic	85±4.8	83±5.0	-1±1.5	0.36
Mean	102±7.4	102±7.5	-0.3±1.0	0.78
CBF (mL · 100 mL <sup>-1</sup> · min <sup>-1</sup> )	1.9±0.18	1.9±0.19	-0.02±1.6	0.90
MSNA, bursts/100 beats	49±6.8	49±6.2	0.3±1.0	0.79
s-MSNA, impulses/100 beats	54±7.0	55±6.2	1±1.2	0.45
CVR, units	51±3.8	51±3.0	0.2±3.3	0.96

Data are mean±SEM. *P* refers to paired *t* tests.