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SHORT COMMUNICATION

Effect of systemic α1-adrenergic receptor blockade on central blood pressure response during exercise

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Abstract The aortic pulse pressure (PP), which consists mainly of the incident wave and the reflected wave, has emerged as an important property of systemic blood vessels underlying the pathophysiology of cardiovascular disease. To determine the role of sympathetic nerve activity on the aortic PP response during dynamic exercise, we evaluated aortic hemodynamics during the right-leg knee-extension (40 and 60 % of maximal voluntary contraction) in six young adults with and without the systemic α1-adrenergic receptor blockade using prazosin (1 mg/20 kg body weight). The use of prazosin attenuated the exercise-induced increase in aortic PP ($P < 0.05$) but not in radial arterial PP. The amplitude of the reflected waves (via augmentation index) significantly decreased with the exercise and decreased more with the use of prazosin. These results suggest that during dynamic exercise the α1-adrenergic-mediated vasoconstrictor tone of the peripheral resistance vessels is manifestly involved in the magnitude of the reflected wave and the modulation of the aortic PP responses.

Keywords Arterial blood pressure · Wave reflection · Sympathetic activity

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Introduction

The arterial pressure wave within any blood vessel is a part of the summation of a steady-state component, mean arterial pressure (MAP), and a pulsatile component, pulse pressure (PP). The central arterial (e.g., aorta and carotid artery) PP is closely associated with the left ventricular (LV) afterload and potentiates LV hypertrophy [1]. Thus, increased central arterial PP has emerged as an important factor underlying the pathophysiology of cardiovascular disease [2]. Because of such clinical relevance and the notion that the peripheral blood pressure (BP) response to dynamic exercise provides more powerful prognostic information compared with measures taken at rest [3], the response of central arterial BP to exercise and the effect of aging on the exercise response has been examined [4–7]. However, the understanding of the regulatory mechanisms responsible for the central arterial PP response to exercise is incomplete [7].

The pulsatile component of central arteries is determined by a forward traveling wave generated by LV ejection and a reflected wave emanating from the peripheral blood vessels that returns to the aorta [8]. It has been established that the reflected wave arises at sites of impedance mismatch (i.e., aortic bifurcation, branches of

renal arteries, and high resistance arterioles) [8]. We previously reported that the carotid augmentation index (AIx), an index of central wave reflection and LV afterload, is strongly associated with ankle BP independent of brachial BP [9], suggesting that the tone of high-resistance arterioles may be associated with the magnitude and the return timing of the reflection wave. Hence, we reasoned that exercise-related vasodilation in active tissue and vasoconstriction in inactive tissue would influence the wave reflection. However, the influence of basal sympathetic tone on peripheral arteries and its influence on the central arterial wave reflection and BP characteristics are unknown. Accordingly, in the present study, we tested the hypothesis that sympathetic vascular tone affects reflected wave properties and modulates the pulse wave augmentation of central arterial PP during exercise. To test this hypothesis, we used a systemic α1-adrenergic receptor blocker, prazosin, to identify the effects of sympathetic vascular tone on arterial pressure in the arterial tree at rest and during exercise.

Methods

Subjects

Six young healthy adults (2 women; age, 28 ± 2 years; height, 177 ± 4 cm; weight, 77 ± 9 kg; mean ± SEM) participated in the present investigation. All subjects were nonsmokers, free of known cerebral vascular, cardiovascular, and respiratory disease, and were not using prescription or over-the-counter medications. All potential risks and procedures of the study were explained verbally and in writing to the subjects before the experiment. All subjects signed their written informed consent to participate in the study. All experimental procedures were approved by the Institutional Review Board at the University of North Texas Health Science Center and were in accordance with the guidelines of the Declaration of Helsinki.

Experimental protocol

The experimental protocol consisted of 2 separate days with a minimum of 1 day between experiments. Women volunteers were tested on days of availability regardless of the time of their menstrual cycle. All subjects were asked to abstain from drinking alcohol/caffeine and exercise for the 24-h time period before any scheduled experiments. On experimental day 1, using a modified cycle ergometer (Ergomedic 874E; Monark, Vansbro, Sweden) with a semi-recumbent backrest (≈45°) and resistance against knee extension, as we previously described [10], subjects performed a graded dynamic right-leg knee-extension exercise to determine their maximal exercise intensity which were followed by the familiarization of the testing protocols. The subjects began a warm-up period at 6 W for 2 min. During the exercise, the intensity was increased an additional 6 W/min until subjects were no longer able to perform the exercise at a rate of 55–60 kicks/min despite verbal encouragement.

On experimental day 2, all subjects reported to the laboratory in the morning, approximately 2 h after a light breakfast. After the instrumentation (see below), each subject sat quietly on the cycle ergometer for a 15-min rest period. Following this period, each subject performed a graded right-leg knee-extension exercise at intensities equal to 40 and 60 % of each subjects' respective maximal voluntary contraction (MVC) (control condition). After the protocol of the control condition, each subject ingested 1 mg/20 kg body weight of the α1-adrenergic receptor antagonist prazosin (Mylan Pharmaceuticals; Morgantown, WV, USA) followed by a low calorie snack. Two hours after prazosin ingestion, hemodynamic measurements were obtained during rest and the knee-extension exercise test (prazosin condition). The hypertensive response to a bolus injection of phenylephrine immediately prior to the start of the prazosin protocol was compared to the hypertensive response to the same dose of phenylephrine prior to the control condition and was found to be inhibited by 76 ± 2 %.

Measurements

A standard 3-lead electrocardiogram was used for heart rate (HR) monitoring. A catheter (1.1-mm inner diameter, 20-gauge) connected to a pressure transducer (Maxxim Medical, Athens, TX, USA) positioned at the level of the heart was inserted into the radial artery using sterile techniques under local anesthesia with approximately 2 mL of lidocaine and aseptic conditions and remained in place throughout the experiment on day 2. The catheter tube was fixed on the arm to minimize the effect of body movement on blood pressure recording as much as possible. The transducer was connected to a data acquisition system and was used to measure and record beat-to-beat blood pressures throughout each experiment. All data were sampled continuously at 1 kHz using an analog-to-digital converter (Windaq; DATAQ Instrument, Akron, OH, USA) interfaced with a computer. Beat-to-beat systolic, diastolic, and mean arterial pressures (SBP, DBP, MAP) were acquired. The radial arterial pressure waveform was resampled at 128 Hz with data acquisition and analysis software (Acq-Knowledge; BIOPAC Systems). Subsequently, the arterial waveform data were fed into the SphygmoCor software (AtCor Medical, Sydney, Australia), and a generalized

transfer function was applied to estimate aortic BP [11]. Waveform analysis was performed at the stable segment in the last 1 min of each stage. Aortic BP was calibrated by radial arterial MAP and DBP [13]. Peripheral PP amplification was calculated as the ratio of peripheral PP and central PP [6]. The amplitude of the reflected waves was expressed as a percentage of the PP (AIx), as proposed by Murgo et al. [14].

Statistics

Repeated-measure ANOVA using general linear model was performed to determine the effects of exercise and the α1-adrenergic receptor blockade. In addition, ANCOVA was performed on aortic AIx with HR as the covariate. Fisher's LSD test was employed post hoc when main effects were significant. Data are expressed as mean ± SEM. The significance level was set at $P < 0.05$.

Results

With the systemic α1-adrenergic receptor blockade, the exercise-induced increases in HR were significantly augmented, whereas the exercise-induced increases in MAP and DBP were significantly attenuated (Table 1). Aortic SBP and aortic PP were partly but significantly attenuated with the systemic α1-adrenergic receptor blockade, whereas the SBP and PP recorded in the radial artery were not affected by the systemic α1-adrenergic receptor blockade (Fig. 1). The radial arterial PP/aortic PP ratio significantly increased with the exercise and systemic α1-adrenergic receptor blockade ($P < 0.05$ for both; Fig. 2). The aortic AIx was significantly lowered by the exercise and systemic α1-adrenergic receptor blockade ($P < 0.01$ and $P < 0.05$, respectively; Fig. 2). When ANCOVA was performed with HR as the covariate, the effect of exercise on AIx was no longer statistically significant ($P = 0.34$), whereas the effect of the systemic α1-adrenergic receptor blockade on AIx remained significant ($P < 0.05$).

Discussion

To our knowledge, this is the first study to identify that the systemic α1-adrenergic receptor blockade evoked greater attenuation of the exercise-induced increase in aortic PP than obtained in the radial artery. This salient finding may partly explained the fact that: (1) the wave reflection, a determinant of the central PP, decreases during exercise; and (2) the reduction in wave reflection is more pronounced following systemic α1-adrenergic receptor blockade. These results suggest that during dynamic exercise the α1-adrenergic-mediated vasoconstrictor tone of the peripheral resistance vessels is manifestly involved in the wave reflection and modulates the aortic PP.

Table 1 Responses of heart rate, mean arterial pressure, and diastolic blood pressure to the graded right-leg kicking

	Control condition	Prazosin condition
Heart rate, beat/min		
Rest	61 ± 5	66 ± 5
40 % MVC	76 ± 4*	93 ± 3*†
60 % MVC	87 ± 3*	107 ± 4*†
Mean arterial pressure, mmHg		
Rest	86 ± 5	80 ± 4
40 % MVC	97 ± 6*	88 ± 6*†
60 % MVC	101 ± 8*	92 ± 4*†
Diastolic blood pressure, mmHg		
Rest	69 ± 4	64 ± 3
40 % MVC	74 ± 5*	67 ± 5*†
60 % MVC	77 ± 7*	70 ± 4*†

Data are mean ± SEM

MVC maximal voluntary contraction

* $P < 0.05$ vs. baseline

† $P < 0.05$ vs. control condition

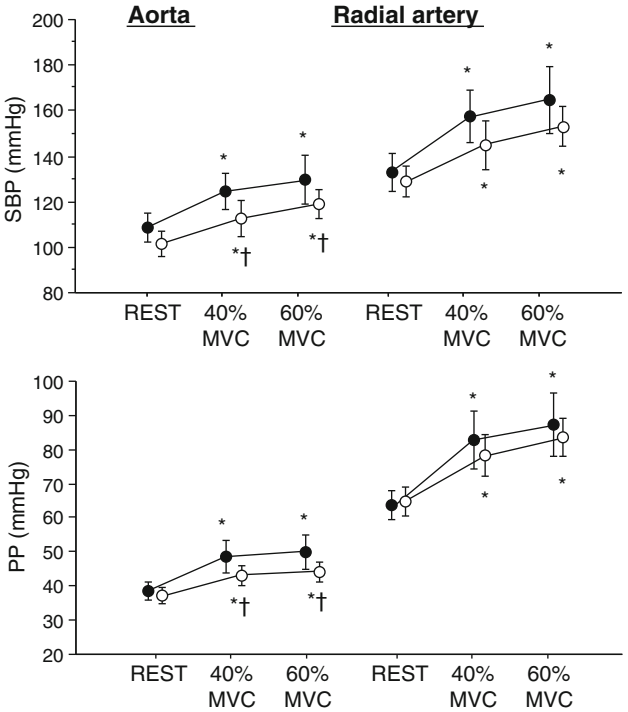

Fig. 1 Aortic and radial arterial systolic blood pressure (*SBP*) and pulse pressure (*PP*) responses to the graded right-leg kicking. *Filled circles* indicate the control condition and *open circles* indicate the systemic α1-adrenergic receptor blockade condition. Data are mean ± SEM. *$P < 0.05$ vs. baseline, †$P < 0.05$ vs. control condition

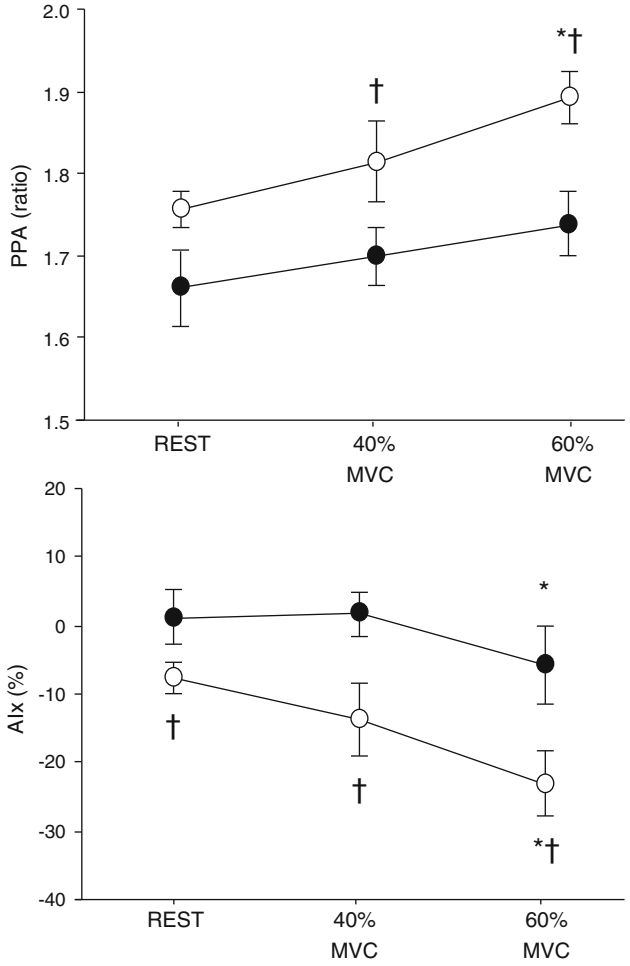

Fig. 2 Responses of the peripheral pulse amplification (*PPA*) and aortic augmentation index (*AIx*) to the graded right-leg kicking. *Filled circles* indicate the control condition and *open circles* indicate the systemic α1-adrenergic receptor blockade condition. Data are mean ± SEM. $^{*}P < 0.05$ vs. baseline, $^{\dagger}P < 0.05$ vs. control condition

Previous studies have reported that the dynamic exercise-induced increase in the central arterial systolic BP was smaller than that in obtained in the peripheral artery [4–7]. However, the regulatory mechanisms responsible for the central arterial systolic BP response to exercise remain in question. Sharman et al. [6] identified that peripheral PP amplification (evaluated by the peripheral PP/central PP ratio) increased during exercise in healthy men primarily because the increase in central PP versus the increase in the peripheral PP was smaller. However, men with hypercholesterolemia exhibited a blunted increase in peripheral PP amplification probably because of endothelial dysfunction. Recently, Sharman et al. [7] examined the contribution of nitric oxide, a potent vasodilator, to the amount of peripheral PP amplification and wave reflection during exercise in healthy men. The investigators reported no significant differences in the ratio of peripheral to central PP during exercise and concluded that the nitric oxide had minimal effect on blood pressure amplification during light exercise.

In the present study, the response of peripheral PP amplification to exercise was significantly increased with systemic α1-adrenergic receptor blockade. This might be due to the greater attenuation of the exercise-related increase in aortic PP by the systemic α1-adrenergic receptor blockade's reduction of the magnitude of the reflected wave as seen in AIx. The contribution of the α1-adrenergic-mediated vasoconstrictor tone to the central arterial PP might be associated with the preferential augmentation of the central arterial PP observed in elderly populations [5] and patients with hypercholesterolemia [6]. In this study, we identified statistical significant effects of the systemic α1-adrenergic receptor blockade on MAP but not on the radial arterial SBP. These results might be partly explained by the disproportional impacts of the systemic α1-adrenergic receptor blockade between central and peripheral arterial PP.

The attenuation of the reflected wave amplitude was identified during exercise and with the presence of systemic α1-adrenergic receptor blockade by the reduction in AIx. In the arterial tree, the high resistance arterioles, as well as arterial branching points (i.e., aortic bifurcation, branches of renal arteries) and areas of alteration in arterial elastance (from elastic artery to muscular artery, i.e., from aorta to femoral artery), are considered to give rise to wave reflection [8]. Therefore, in the present study, the exercise-induced dilation in exercised leg vasculature and the systemic α1-adrenergic receptor blockade-related dilation of inactive tissue vasculature (e.g., non-exercised leg and splanchnic area) appear to depress the wave reflection and the increase in central PP.

The systemic α1-adrenergic receptor blockade evoked a substantial increase in HR during exercise. Although it is well known that HR influences the wave reflection [15], the effect of the systemic α1-adrenergic receptor blockade remained significant even when the influence of HR was accounted for. On the other hand, because the systemic α1-adrenergic receptor blockade-induced tachycardia may influence stroke volume, and, hence, aortic incident wave, further investigation into the influence of HR is warranted.

Several concerns of this study should be emphasized. First, we used the general transfer function to acquire aortic blood pressure. The reliability of this technique has been questioned, i.e., the existence of individual differences [16]. However, a recent study using invasive procedures depicted the accuracy of this technique even during dynamic exercise [17]. Additionally, the frequency response has to be identified if a catheter-tubing-transducer system is to be used to measure peripheral blood pressure wave. A previous study using a similar catheter-tubing-transducer system identified

that the frequency characteristics of the catheter were good enough to generate the pressure waveform precisely [12]. However, because the frequency characteristics of pressure waves could be considerably varied with the diameter and length of the catheter, it was ideal to validate the frequency characteristics (for example, by a step response test) on our blood pressure monitoring system prior to the experiments. Second, we studied a small number of healthy young adults including two women. It is well known that the menstrual cycle influences cardiovascular regulation. Thus, two experiments (i.e., control and prazosin conditions) were conducted on the same day, although we did not standardize for oral contraceptive use and/or menstrual phase in the female subjects. Importantly, intra-individual responses were consistent across all six subjects regardless of gender, though there was a large inter-individual difference (e.g., absolute values of radial BP), and we are confident that our findings identify that during dynamic exercise the α1-adrenergic vasoconstrictor tone affects the reflected wave and modulates the aortic PP. However, the large inter-individual difference in peripheral SBP responses might be partly associated with the non-significant attenuation of prazosin on radial arterial SBP. Third, because of the absence of placebo-treatment and random-order design, the influences of the diurnal variation and carry-over effect of morning exercise could not be completely ruled out.

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Conflict of interest None.

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