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Hypertensive effects of methoxamine on arterial mechanics in rats: analysis based on exponentially tapered T-tube model

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Abstract

Methoxamine, a specific α_1-selective adrenoceptor agonist, has proven to be useful in the treatment of hypotension, especially hypotension due to failure of the sympathetic nervous system. This study is to explore the vascular dynamic response to methoxamine in Wistar–Kyoto rats, based on the exponentially tapered T-tube model. The pulsatile aortic pressure and flow signals before and after the administration of methoxamine (0.025 mg/kg) were measured by a high-fidelity pressure sensor and electromagnetic flow probe, respectively. Hemodynamic parameters, such as aortic characteristic impedance, wave transit time, and arterial load compliance, were inferred from the aortic pressure and flow signals to describe the pulsatile nature of blood flow in the vasculature. The hypertensive effects of methoxamine on the static components of ventricular afterload were characterized by (1) little change in cardiac output, (2) a decrease in heart rate and (3) an increase in aortic pressure and total peripheral resistance. As for the pulsatile components of ventricular afterload, no significant changes in aortic characteristic impedance and wave transit time were observed, suggesting that the distensibility of the aorta was not altered in rats after the administration of methoxamine. In contrast, there was a significant drop in arterial load compliance mainly due to the elevated arterial blood pressure in methoxamine-treated rats. In conclusion, methoxamine at the dose of 0.025 mg/kg has a greater effect on peripheral resistance vessels than on Winkessel vessels in the rat systemic circulation.

Keywords: Methoxamine; α_1-Adrenoceptor agonist; Aortic input impedance; Arterial pulse wave reflection; T-tube model; Exponentially tapered

1. Introduction

Drugs with predominantly α_1-adrenoceptor-mediated activity can be used to raise blood pressure in patients with decreased peripheral resistance in conditions such as spinal anesthesia or intoxication with antihypertensive medication (Kobinger, 1987). Methoxamine, a specific α_1-selective adrenoceptor agonist, has been used for this purpose, especially for the treatment of hypotension due to failure of the sympathetic nervous system. Furthermore, methoxamine has proven to be useful in resuscitation from asphyxial and fibrillatory arrest because of its potential to maintain a blood pressure that is adequate for perfusion of the central nervous system (Sanders, 1984; Bleske et al., 1989). With regard to the hypertensive effects of methoxamine, many studies have focused on changes in the static components of ventricular afterload such as arterial blood pressure, cardiac output, peripheral vascular resistance and heart rate (Sanders, 1984; Curtis et al., 1989; Bleske et al., 1989). Little attention has been given to the pulsatile hemodynamic response to methoxamine in causing the vascular smooth muscle cells to contract. There is evidence to show that changes in the physical properties of Winkessel vessels, such as aorta distensibility, may have a drastic impact on ventricular structure and performance (Levy et al., 1987, 1988a,b). As such, more comprehensive hemodynamic features should be examined to give insight into the mechanism of action of methoxamine.

Since the mechanical properties of the vasculature can be reflected in the aortic pressure-flow relation, measurement of the aortic input impedance is regarded as essential for the analysis of vascular dynamics (Taylor, 1964; McDonald, 1974; O'Rourke, 1982; Milnor, 1989). Both model-independent and model-based approaches have been adopted to study aortic input impedance. The model-independent approach, such as Fourier series expansion of the aortic pressure and flow signals, involves direct description

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of the arterial mechanics (McDonald, 1974; Milnor, 1989). This approach tends to be purely observational and may overlook the complexity of the distributed vasculature. The model-based approach, such as wave transmission model based on T-tube topology, has been used to explain the arterial wave propagation and reflection phenomena (Burattini and Campbell, 1989; Berger et al., 1994). In the mammalian arterial system, the vasculature is nonuniform (Taylor, 1964; Milnor, 1989; Chang, 1996) and the changes in vascular diameter and elastic tapering should be taken into consideration in impedance analysis. A new approach with the exponentially tapered T-tube model was developed recently to relate the pulsatile pressure and flow waves measured in the ascending aorta (Chang and Kuo, 1996). Such an approach can reflect the physiological behavior of artery diameter and elastic tapering and is considered an appropriate way to analyze the aortic input impedance.

The purpose of this study is to evaluate the vascular dynamic response to methoxamine in rats, by making use of the exponentially tapered T-tube model. The aortic characteristic impedance, arterial load compliance, and amplitude as well as timing of pulse wave reflection were analyzed to delineate the hypertensive influence of methoxamine on the mechanical properties of the vasculature in rats.

2. Materials and methods

2.1. Animals and catheterization

Ten male Wistar–Kyoto rats weighing 320 ± 47 g were studied. Each rat was anesthetized with sodium pentobarbital (35 mg/kg, i.p.). The femoral artery was cannulated for the recording of femoral arterial pressure. The femoral vein was cannulated for the administration of supplemental pentobarbital (30 mg/kg every 2 h) and for the administration of methoxamine at the dose of 0.025 mg/kg, which was used to determine the peripheral action of methoxamine in vivo rat preparations (King et al., 1987). Tracheotomy was performed to provide artificial ventilation with a tidal volume of 6–8 ml/kg and respiratory rate of 50–70 breaths/min (Cilley et al., 1993). The chest was opened through the right second intercostal space. An electromagnetic flow probe (Carolina Medical Electronics, Model 100 series, internal circumference 8 mm) was placed around the ascending aorta to measure the

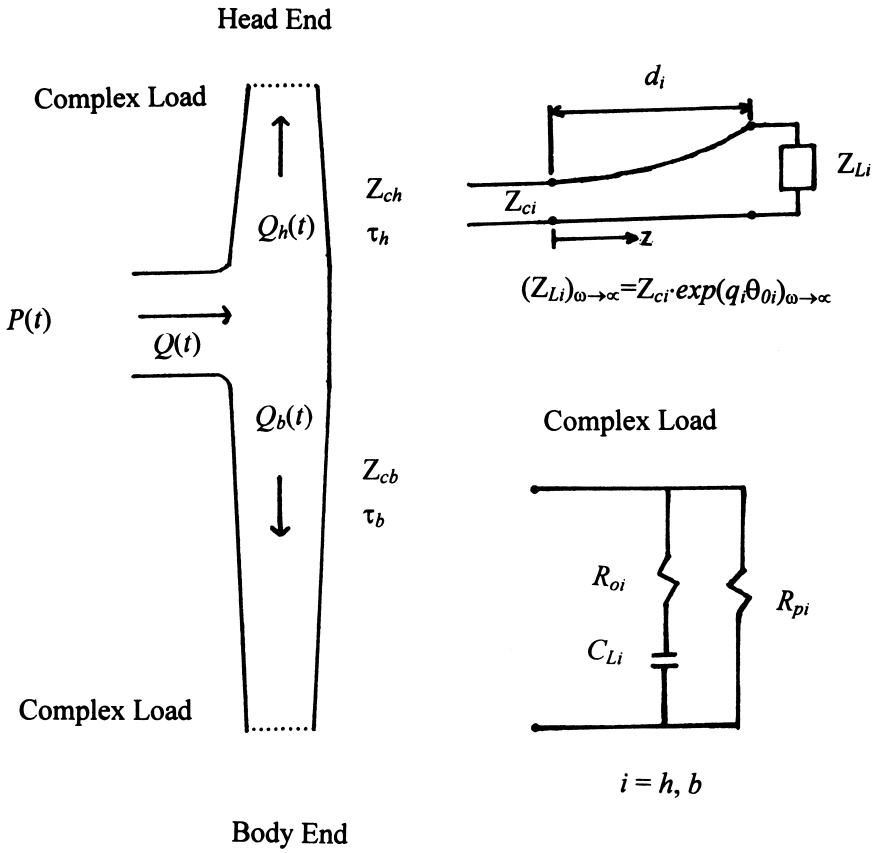

Fig. 1. T-tube arterial system model with asymmetric head and body circulation paths. Each path consists of a nonuniform transmission tube and a complex terminal load. Properties of each tube include an input characteristic impedance Z_{ci} and a characteristic delay time τ_i. The quantity $e^{(q\theta_0)_{\omega\to\infty}}$ is used to relate the characteristic impedance at the distal end of the tube to that at the inlet of the tube. Complex loads possess R_{oi}, C_{Li} and R_{pi} as described in text (Chang and Kuo, 1996).

Table 1
Data derived from the exponentially tapered T-tube model in rats ($n = 10$) before and after methoxamine administration

	Before methoxamine	After methoxamine
Normalized root-mean-square error ($e*$), $\times 10^{-4}$	5.47 ± 0.31	4.92 ± 0.29
Standard error of the estimate (%)	0.95 ± 0.17	0.93 ± 0.15
Coefficient of determination	0.9932 ± 0.0013	0.9924 ± 0.0012

All values are expressed as means ± S.E. These indexes are the linear regression parameters of the model output pressure over the measured pressure.

pulsatile aortic flow. A Millar catheter with a high-fidelity pressure sensor (Millar Instruments, Model SPC 320, Size 2F) was used to measure the pulsatile aortic pressure. Before insertion of the catheter, the pressure sensor was prewarmed in 37°C saline for at least 1 h. The catheter was inserted via the isolated right carotid artery into the ascending aorta. The catheter tip of the pressure transducer was positioned 1–2 mm distal to the downstream edge of the electromagnetic flow probe to avoid interference with the flow measurements. After being withdrawn from each rat, the catheter was reimmersed in the bath to check for baseline drift. At the end of the experiment, the pressure reading from the sensor barely submerged in saline at atmospheric pressure and room temperature was used as the zero pressure reference (Zuckerman and Yin, 1989). The electrocardiogram (ECG) of lead II was recorded with a Gould ECG/Biotach amplifier. The analogue waveforms were sampled at 500 Hz, using a 12-bit simultaneously sampling analog-to-digital (A/D) converter interfaced to a personal computer. Selection of signals of 5–10 beats at steady state was made on the basis of the following criteria: (1) recorded beats had an optimal velocity profile that was characterized by a steady diastolic level, maximal systolic amplitude, and minimal late systolic negative flow; (2) beats with an RR interval less than 5% different from the average value for all recorded beats; (3) exclusion of ectopic and postectopic beats. The selective beats were averaged in the time domain, using the peak R wave of ECG as a fiducial point. Timing between the pulsatile pressure and flow signals, due to spatial distance between the flow probe and proximal aortic pressure transducer, was corrected by a time-domain approach, in which the foot of the pressure waveform was realigned with that of the flow (Mitchell et al., 1994). The resulting pressure and flow signals were subjected to further analysis.

2.2. Model parameters inferred by the exponentially tapered T-tube model

All model parameters were estimated and analyzed by using the exponentially tapered T-tube model according to the procedure previously described (Chang and Kuo, 1996). In brief, an asymmetric T-tube model with vascular nonuniformity was used to relate the pulsatile pressure and flow waves in the ascending aorta. The nonuniform T-tube model and its terminal complex load are shown in Fig. 1. This model consists of two sections of different lengths. The shorter section represents the circulation of head, neck, and upper limbs (head or upper body circulation), and the longer section represents the circulation of trunk and lower limbs (body or lower body circulation). The subscripts h and b represent the head and body circulation, respectively. Properties of the ith tube, i equals h or b, include a characteristic impedance (Z_{ci}) at the entrance of the tube and a transmission time (τ_i). τ_i is the time for a wave to propagate from one end of the tube to the other. Properties of the load are given by the load elements which are the high-frequency tube-matching impedance element (R_{oi}), load compliance (C_{Li}), and terminal resistance (R_{pi}). The relation between the characteristic impedance at the distal end of the tube and that at the entrance of the tube is quantified by the tapering index $(q_i \theta_{0i})_{\omega \to \infty}$ (Chang and Kuo, 1996). In this system, the parallel combination of the head circulation and body circulation is defined as the global circulation. Peripheral resistance of the global circulation (R_p) was calculated as mean pressure divided by mean flow. The terminal resistance of each tube was computed by using the upper-to-lower body resistance ratio. The upper-to-lower body resistance ratio can be determined when the ratio K_{dta} between measured descending thoracic aorta mean flow and cardiac output is calculated (Burattini and Campbell, 1989). Under basal conditions, approximately 67% of cardiac output in

Table 2
Basic hemodynamic data and global parameters calculated by using the exponentially tapered T-tube model in rats ($n = 10$) before and after methoxamine administration

	Before methoxamine	After methoxamine	P-value
P_m	121.5 ± 3.25	135.3 ± 3.57	< 0.05
Q_m	0.87 ± 0.10	0.80 ± 0.08	NS
HR	401 ± 6	352 ± 7	< 0.05
R_p	139.66 ± 8.81	171.96 ± 6.89	< 0.01
Z_c	3.04 ± 0.27	3.31 ± 0.33	NS
Z_{ch}/Z_{cb}	1.10 ± 0.03	1.35 ± 0.04	< 0.01
$(q\theta_0)_{\omega \to \infty}$	0.1315 ± 0.0076	0.1836 ± 0.0048	< 0.01
R_f	0.45 ± 0.02	0.67 ± 0.02	< 0.01
C_L	1.35 ± 0.07	0.94 ± 0.06	< 0.01

All values are expressed as means ± S.E. P_m, mean aortic pressure (mmHg); Q_m, mean aortic flow (ml/min); HR, heart rate (beats/min); R_p, total peripheral resistance ((mmHg min)/ml); Z_c, aortic characteristic impedance ((mmHg min)/ml); Z_{ch}/Z_{cb}, ratio of upper-to-lower body characteristic impedance; $(q\theta_0)_{\omega \to \infty}$, tapering index; R_f, wave reflection factor, C_L, peripheral load compliance (μl/mmHg).
NS, not significant ($P > 0.05$).

rats is accounted for by blood flow to the kidneys, spleen, small and large intestines, liver, stomach, diaphragm, hindlimb muscles and bones, and skin (Kuwahira et al., 1993). If blood flow to other tissues and organs in the lower portion of the body is included, then K_{dta} in the rat would be similar to that in the dog, that is 70% in the report of Campbell et al. (1990). From a comparative physiological point of view, the ratio of K_{dta} in rats was assumed to be 0.7 and 0.62 as in dogs under basal and vasoconstricted conditions, respectively (Campbell et al., 1990). The equation of $R_{ph}/R_{pb} = K_{dta}/(1 - K_{dta})$ was used to calculate the upper-to-lower body resistance ratio as being 2.33 for a normotensive state and 1.63 for a hypertensive state. Aortic characteristic impedance of the global circulation (Z_c) was computed by averaging high-frequency moduli of impedance data points obtained from the ratio of the corresponding harmonics of pressure and flow. The first impedance minimum was included in the average in order to prevent overestimation of the characteristic impedance in rats (Mitchell et al., 1994). With setting $(q_h\theta_{0h})_{\omega\to\infty}$ equal to $(q_b\theta_{0b})_{\omega\to\infty}$, the model parameters, such as the upper-to-lower body characteristic impedance

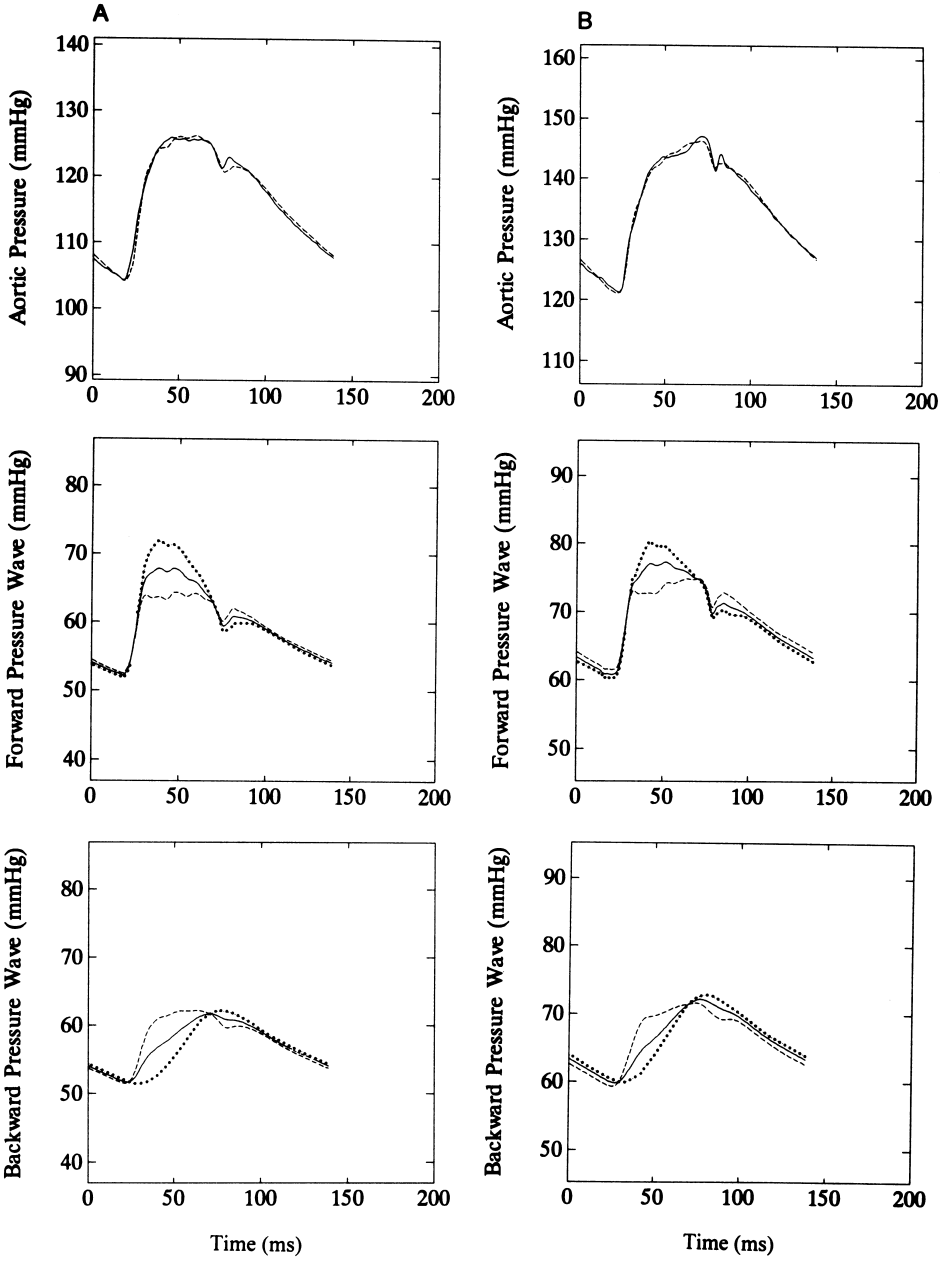

Fig. 2. Example of pulsatile pressure waves before and after methoxamine administration, depicted in (A) and (B), respectively. Top: Pressure signals measured in the ascending aorta (solid line) and predicted by the exponentially tapered T-tube model (dashed line). Middle and bottom panels show the forward and backward pressure components, respectively, as described by the exponentially tapered T-tube model at the entrance of the head circulation (dashed lines), body circulation (dotted lines) and in the ascending aorta (solid lines).

ratio (Z_{ch}/Z_{cb}), vascular tapering index $(q\theta_0)_{\omega\to\infty}$, wave transit time ($\tau_h$,$\tau_b$) and arterial load compliance (C_{Lh},C_{Lb}), were estimated by using the equations developed for the exponentially tapered T-tube model. The high-frequency tube-matching impedance is determined by the characteristic impedance, tapering index, and terminal resistance (Chang and Kuo, 1996). The time domain reflection factor was derived as the amplitude ratio of backward-to-forward peak pressure wave according to the methods previously described (Westerhof et al., 1972). Therefore, the wave reflection phenomenon was characterized by the wave transit time and wave reflection factor.

In the process of model parameter estimation, the measured aortic pressure was taken as the output variable while the measured aortic flow was the model input variable. Parameters of the model were adjusted to minimize the normalized root-mean-square error ($e*$), using the Nelder–Meade simplex algorithm (Dennis and Woods, 1987). The model parameters leading to the minimum of $e*$ were taken as the model estimates of arterial mechanical properties. Fitness of the data generated by the model was judged by the magnitude of $e*$ and by indices from a linear regression of the model-generated pressure on the measured pressure. Two indices were used to evaluate the goodness of fit: (1) the coefficient of determination r^2; (2) the standard error of the estimate S.E.E. We looked for r^2 to be close to 1, so that S.E.E. would be in the order of 1% when expressed relative to the mean of all pressure observations. A summary of the measures indicating goodness of the exponentially tapered T-tube model fits is given in Table 1. Sensitivity analysis with the model parameters was also performed to gain insight into these estimators (Bard, 1974). The relative standard errors of the parameters over all experimental rats were as follows (means ± S.E.): $5.3 \pm 0.4\%$ for τ_h, $2.5 \pm 0.3\%$ for τ_b, $6.4 \pm 0.5\%$ for C_{Lh}, $3.8 \pm 0.4\%$ for C_{Lb}, $3.3 \pm 0.3\%$ for Z_{ch}/Z_{cb}, and $3.9 \pm 0.4\%$ for $(q\theta_0)_{\omega\to\infty}$. This indicated that all model parameters were estimated with good accuracy in analyzing the systemic arterial system with the exponentially tapered T-tube model.

2.3. Statistics

Results are expressed as means ± S.E. Since drug intervention was preceded by a control state, the effect of methoxamine in experimental rats was analyzed by paired *t*-tests. Significant differences were assumed to be at the level of $P < 0.05$.

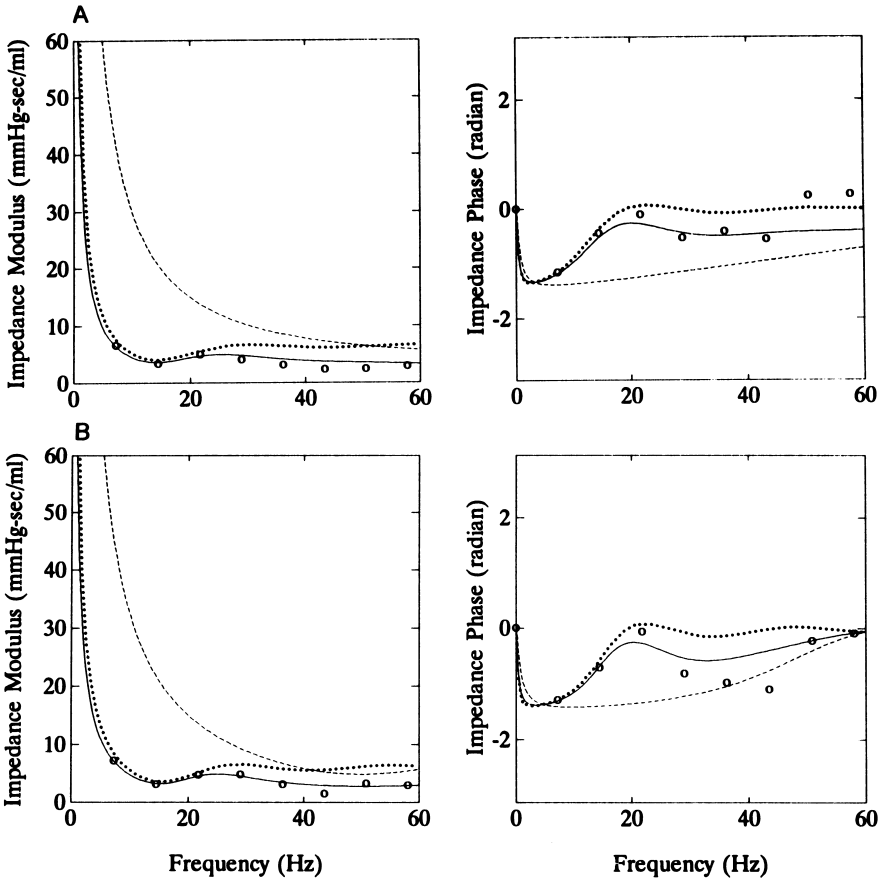

Fig. 3. Example of input impedance spectra in the same rat before and after methoxamine administration, depicted in (A) and (B), respectively. Input impedance spectra of head circulation (dashed lines), body circulation (dotted lines), and global circulation (solid lines), as represented by the exponentially tapered T-tube model. Data points obtained from the ratio of ascending aortic pressure harmonics to the corresponding flow harmonics (circles).

3. Results

The basic hemodynamic data and global parameters, estimated by making use of the exponentially tapered T-tube model, are shown in Table 2. In one rat, examples showing the similarity between computed and measured pressure waveforms under basal and vasoconstricted states are shown in Fig. 2. The input impedance spectra of the same rat are shown in Fig. 3. The solid lines represent the model-generated spectra and the circles are data points obtained from the ratio of the ascending aortic pressure harmonics to the corresponding flow harmonics. The aortic impedance spectra of the measured and mathematically deduced results were similar. As expected, after the administration of methoxamine, this specific α_1-selective adrenoceptor agonist contributed to a significant rise in arterial blood pressure and total peripheral resistance, by 11.4% and 23.1%, respectively. In contrast, heart rate was reduced by about 12.2%. Cardiac output remained unchanged. As for the impedance measurements on rats, there was no significant change in aortic characteristic impedance after methoxamine intervention. Conversely, the arterial load compliance was decreased and the wave reflection factor was increased by the hypertensive influence of methoxamine. Furthermore, an increase of 23% in the ratio of upper-to-lower body characteristic impedance was observed in rats treated with methoxamine. Under basal conditions, the estimated value in $(q\theta_0)_{\omega\to\infty}$ showed that the distal characteristic impedance was 14% higher than the input characteristic impedance. In the vasoconstricted state, the distal characteristic impedance was 21% higher than the input characteristic impedance.

The mechanical properties of the tube and terminal load, represented by the wave transit time and load compliance respectively, in the head and body circulation were estimated by using the exponentially tapered T-tube model and are summarized in Table 3. There was no alteration in the wave transit time in the head and body circulation in rats after the administration of methoxamine. There were no significant changes in either the aortic characteristic impedance or wave transit time, which suggests that the distensibility of the aorta in rats is not influenced by methoxamine. However, a significant decrease in the arterial load compliance of the head and body circulation was observed in rats after the administration of methoxamine.

Table 3
Peripheral load compliance and wave transit time of the head and body circulation estimated by using the exponentially tapered T-tube model in rats ($n = 10$) before and after methoxamine administration

	Before methoxamine	After methoxamine	*P*-value
Head circulation			
Peripheral load, C_{Lh}	0.30 ± 0.02	0.20 ± 0.02	< 0.01
Transmission tube, τ_h	4.05 ± 0.27	3.42 ± 0.38	NS
Body circulation			
Peripheral load, C_{Lb}	1.05 ± 0.07	0.74 ± 0.05	< 0.01
Transmission tube, τ_b	17.33 ± 1.03	16.89 ± 1.11	NS

All values are expressed as means ± S.E. C_{Lh} and C_{Lb}, peripheral load compliance in the head and body circulation, respectively (μl/mmHg); τ_h and τ_b, wave transit time in the head and body circulation, respectively (ms).
NS, not significant ($P > 0.05$).

4. Discussion

The hypertensive effects of methoxamine on the vascular mechanics in rats were analyzed by making use of the nonuniform, exponentially tapered T-tube model. The impedance is determined by the mechanical characteristics of the vasculature, including its elastic properties and size, as well as by the viscosity and density of the fluid within (McDonald, 1974; Milnor, 1989). Both model-independent and model-based approaches have been adopted to characterize the aortic input impedance. Because of the arterial distribution, a model-based approach, such as a T-tube model, is more appropriate for the exploration of the pulsatile nature of blood flows in the vasculature. Since vessel diameter and elastic tapering are of importance in the arterial system (Taylor, 1964; Milnor, 1989; Chang, 1996), the smooth change of vascular impedance, caused by these tapers, must have a substantial impact on the magnitude and/or timing of pulse wave reflection. Vessel diameter and elastic tapering of the vasculature were taken into consideration in the present study to analyze the changes in vascular dynamics in rats before and after the administration of methoxamine.

According to the report of King et al. (1987), methoxamine at the dose of 0.025 mg/kg can be used to increase arterial blood pressure. In our laboratory, there is evidence that the contractile state of the left ventricle in rats is not affected by methoxamine at this dose. The purpose of this study was to determine the hypertensive effects of methoxamine on vascular dynamics without affecting the contractile state of the left ventricle. Therefore, methoxamine at the dose of 0.025 mg/kg was used to evaluate its hypertensive effects on arterial mechanics.

The effects of methoxamine on the static components of ventricular afterload were characterized by (1) little change in cardiac output, (2) a fall in heart rate, and (3) a rise in arterial blood pressure as well as total peripheral resistance. These data were in accordance with many other reports in the literature (King et al., 1987; Leenen et al., 1994). Hydraulic vascular resistance, a parameter defined as the ratio of driving pressure to flow, is directly proportional to the viscosity of the blood and inversely proportional to the fourth power of the tube radius (McDonald, 1974; Milnor, 1989). Because the viscosity of the blood did not have an effect, the rise in total peripheral resistance

suggests that a decrease in arteriolar caliber occurs in rats after the administration of methoxamine. The maintenance of blood flow, for the metabolic needs of organs and tissues, indicates that the increase in total peripheral resistance may be responsible for the elevation of aortic pressure in rats after methoxamine intervention. This moderate increase in arterial blood pressure in the absence of a significant change in cardiac output may be advantageous in the treatment of hypotension, especially in hypotension due to failure of the sympathetic nervous system.

The activation of vascular smooth muscle with a significant rise in aortic pressure will increase the elasticity of the blood vessel wall and cause a decline in the distensibility of the aorta (Milnor, 1989). Characteristic impedance, defined as the ratio of pulsatile pressure to flow if only centrifugal waves are present at the origin, is directly related to the pulse wave velocity (McDonald, 1974; Milnor, 1989). For large arteries, the pulse wave velocity may be proportional to the elasticity of the blood vessel wall: the stiffer the blood vessel wall, the higher the pulse wave velocity. Thus, a decline in aorta distensibility may contribute to an elevation in aortic characteristic impedance. Concurrently, the decline in aorta distensibility can be reflected by the short time taken for a wave to travel along the arterial system (McDonald, 1974; Milnor, 1989). In the current study, a slight but not statistically significant increase of 8.9% in the aortic characteristic impedance was observed in rats after methoxamine. Incidentally, there was no significant change in wave transit time in both the head and body circulation after methoxamine administration. This lack of significant changes in both the aortic characteristic impedance and wave transit time suggests that aorta distensibility in rats is not influenced by methoxamine. Thus, methoxamine may have a beneficial effect by not affecting the physical properties of Winkessel vessels and thus does not interfere with ventricular performance.

Just as the elasticity is an expression used to characterize material properties, so distensibility is a term used to describe the elastic behavior of a hollow vessel or chamber. However, compliance and distensibility are quite different, because compliance is determined by the stroke volume, arterial blood pressure and characteristic impedance (Liu et al., 1986). The arterial compliance is directly proportional to the stroke volume and is inversely proportional to the characteristic impedance as well as the arterial blood pressure. The stroke volume is strongly determined by the vascular resistance, venous return and ventricular contractility, when the ventricle is coupled to the circulation system (Sunagawa et al., 1987). Data from our laboratory showed that the contractile state of the rat left ventricle was not affected by methoxamine at the dose of 0.025 mg/kg due to no significant alteration in maximal systolic elastance (unpublished results). The stroke volume remained unchanged in rats after the administration of methoxamine because of the increases in both the vascular resistance (vasoconstriction) and venous return (venoconstriction). Thus, the significant fall in the arterial load compliance may be mainly due to the increase in arterial blood pressure in methoxamine-treated rats while the characteristic impedance and stroke volume remained unaltered.

Some limitations of the current study deserve consideration. Since aortic input impedance can not be measured in conscious animals, it is difficult to evaluate the effect of pentobarbital anesthesia on the pressor response of methoxamine. In this report, the results pertained only to measurements made in the anesthetized open-chest rat. This setting induced a fall in blood pressure and may introduce reflex effects not found in the close-chest setting (Zuckerman and Yin, 1989). It is uncertain how great the effects of anesthesia and thoracotomy are on pulsatile hemodynamics in rats. However, studies with other animal models suggest that the effects are small relative to the biological and experimental variability between animals (Cox, 1974).

In conclusion, methoxamine at the dose of 0.025 mg/kg has a greater effect on the peripheral resistance vessels than on the Winkessel vessels in the rat systemic circulation. Methoxamine has a beneficial effect by not affecting the physical properties of Winkessel vessels and thus does not interfere with ventricular performance. Under such conditions, the moderate increase in arterial blood pressure in the absence of a significant change in cardiac output may be advantageous in the treatment of hypotension, especially when hypotension is due to failure of the sympathetic nervous system.

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