Age-Related Changes of Arterial Mechanical Properties in Rats: Analysis Using Exponentially Tapered T-Tube Model

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This study was designed to explore the changes of mechanical properties in the rat's arterial system at different ages by using the exponentially tapered T-tube model. Long-Evans male rats at the ages of 6, 12, and 18 months were anesthetized and thoractomized. Rats at the ages of 6, 12, and 18 months were individually referred to as young, adult, and middle-aged rats. The pulsatile pressure and flow signals in the ascending aorta were measured by a high-fidelity pressure sensor and electromagnetic flow probe, respectively. Model parameters, such as aortic characteristic impedance, vascular tapering index, wave transit time, and arterial load compliance, were inferred from the aortic pressure and flow signals to describe the pulsatile nature of blood flows in the vasculature. The static hemodynamic condition in those animals with different ages was characterized by (i) no change in cardiac output and (ii) a decrease in heart rate, arterial blood pressure, as well as total peripheral resistance. As for the pulsatile nature of the arterial system, the wave transit time remained unaltered, indicating there was no change in the aorta's distensibility of rats at those three different ages. The arterial load compliance, which describes the buffering nature of a hollow vessel, also remained unchanged. On the contrary, there was a significant fall in aortic characteristic impedance in those age-related rats. The decline of aortic characteristic impedance without a significant change in arterial distensibility suggests that lumen growth of the aorta and large arteries may occur in rats up to middle age.

It has been suggested that arterial physical properties, such as elasticity and distensibility, change with age (1-4). Histological alterations of the vasculature, including the degeneration of smooth muscles in the media, the fragmentation and decrease of elastic fibers, and increases of irregularly arranged collagen fibers in the stroma, become obvious in elderly populations (5). In humans, the changes of the mechanical properties occur primarily in large vessels. The stress-strain data of blood vessels show an increase in the elastic modulus or a decrease in the distensibility of aged human vasculature (6-8). The changes in aging dog seem to be similar to those in human (9,10). However, the age-related changes in the rabbit are opposite to those reported in human (11). Contradictory observations were reported in rats, showing no change (12), an increase (13), or a decrease (14) in the elastic modulus with age. These data seem to suggest that the variance may be caused by the difference in species or analytical methods.

Because the mechanical properties of the vasculature can be reflected in the aortic pressure-flow relation, measurements of the aortic input impedance are regarded as essential for the analysis of the arterial mechanics (15-18). Both model-independent and model-based approaches have been adopted to obtain the aortic input impedance. The model-independent approach, such as Fourier series expansion of the aortic pressure and flow signals, involves direct description of the arterial mechanics (15,16). 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 (19,20). However, in the mammalian arterial system, the nature of the vasculature is nonuniformity (16,18,21). In earlier analysis, the changes of vascular diameter and elastic tapering have not been taken into consideration. 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 (22). The method can reflect the physiological behavior of arterial diameter and elastic tapering and is considered as a proper mean to analyze aortic input impedance. The analysis will provide insightful information of the wave transmission in the arterial system.

Earlier studies on the changes of vascular physical properties to rats showed great diversity in response to age. Therefore, the purpose of this study was to reexamine the changes of rat's arterial mechanical properties in relation to age by using the exponentially tapered T-tube model. The aortic characteristic impedance, arterial load compliance, vascular tapering index, and amplitude as well as timing of pulse wave reflection were analyzed to delineate the changes in arterial mechanical properties.

Materials and Methods

Subjects

The specific pathogen-free male Long-Evans rats used in this study were obtained from the colony maintained in the barrier facilities at the Animal Center of Medical College, National Taiwan University. All rats were allowed free access to the Purina chow and water and housed two to three per cage in a 12-h light/dark cycle animal room. Peri-
VASCULAR DYNAMIC CHANGES IN AGE-RELATED RATS

Model Parameters Inferred by the Exponentially Tapered T-Tube Model

All model parameters were estimated and analyzed by the exponentially tapered T-tube model and analyzed by the procedure described previously (22). 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 Figure 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 \( i \)th tube, \( i \) equals \( h \) or \( b \), include a characteristic impedance \( (Z_0) \) at the entrance of the tube and a transmission time \( (\tau) \). \( \tau \) 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 that are high-frequency tube-matching impedance element \( (R_L) \), load compliance \( (C_L) \), and terminal resistance \( (R_L) \). 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 \( (g_{h0}\omega^2\to\infty) \) (22). 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 \( (R_L) \) 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 of 2.33 for normotensive state and 3.17 for hypotensive state (see Appendix, Note 1). With setting \((g_{h0}\omega^2\to\infty)\) equal to \((g_{b0}\omega^2\to\infty)\), the model parameters, such as aortic characteristic impedance \( (Z) \), vascular tapering index \( (g_{h0}\omega^2\to\infty) \), wave transit time \( (\tau,\tau) \), and arterial load compliance \( (C_L,C_B) \), were estimated by using the equations developed for the exponentially tapered T-tube model. The characteristic impedance at the inlet of each tube was calculated by using the upper-to-lower body characteristic impedance ratio of 1.14 for normotensive condition and 1.20 for hypotensive condition (see Appendix, Note 2). The high-frequency tube-matching impedance was determined by the characteristic impedance, tapering index, and terminal resistance (22). The time domain reflection factor was derived as the amplitude ratio of backward-to-forward peak pressure wave according to previously described methods (27). Therefore, the wave reflection phenomenon was characterized by the wave transit time and the wave reflection factor.

In the process of model parameter estimation, the measured aortic pressure was taken as the output variable whereas 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-Mead Simplex algorithm (28). The model parameters leading to the minimum of \( e^* \) were taken as the model estimates of arterial mechanical properties. In one rat, examples of the measured (solid lines) flow wave and pulsatile pressure in the ascending aorta and the mathematically predicted (dashed lines) results were shown in the top of Figure 2. The input impedance spectra of the same rat were shown in the bottom of Figure 2. The solid lines represented the model-generated spectra, and the circles were 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.
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: (i) the coefficient of determination $r^2$, and (ii) the standard error of the estimate $SEE$. We looked for $r^2$ to be close to 1 and for $SEE$ to be of 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 was given in Table 1. Sensitivity analysis on the model parameters was also performed to give insight into these estimators (29). The relative standard error of the parameters over all experimental rats were as follows: $5.4 \pm 1.4\%$ for $\tau_h$, $3.8 \pm 1.6\%$ for $\tau_b$, $5.2 \pm 1.9\%$ for $C_{ch}$, $5.2 \pm 1.5\%$ for $C_{ch}$, $1.8 \pm 0.7\%$ for $Z_c$, and $6.4 \pm 2.1\%$ for $(\rho b_0)_{\omega \to \infty}$. These results indicated that all model parameters were estimated with good accuracy in analyzing the systemic arterial system with the exponentially tapered T-tube model.

Statistics

Results were expressed as means ± SE. When multiple comparisons were made for the age effect on the arterial mechanical properties, statistical significance was determined by analysis of variance (ANOVA). Significant differences were assumed at the level of $p < .05$. If ANOVA for a hemodynamic variable reached the significant level, then the Tukey method was used to determine the groups of rats having different mean values of the variable.

RESULTS

The effect of age on body weight, heart rate, arterial blood pressure, and cardiac output was shown in Table 2. Body weight was similar between 12- and 18-month-old rats and was significantly smaller in 6-month-old rats. A significant decrease in heart rate, systolic, diastolic, and mean arterial blood pressure was observed in 18-month-old rats relative to 12-month-old rats. Cardiac output was not changed in rats at the ages of 6, 12, and 18 months. However, total peripheral resistance was significantly decreased in 18-month-old rats.

Table 3 lists the global vascular parameters that were estimated by the exponentially tapered T-tube model. Rats at 18 months old had a significant fall in aortic characteristic impedance, whereas rats between 6 and 12 months old had no significant change in this parameter. Vascular tapering index, wave reflection factor, and total load compliance were similar among rats at the ages of 6, 12, and 18 months. The pulsatile nature of blood flows in each tube
Figure 2. Example of pulsatile waves and aortic input impedance in one rat. (Top) Pressure and flow signals measured in the ascending aorta (solid lines); pressure predicted by the exponentially tapered T-tube model (dashed line). (Bottom) 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).

Table 1. Indexes of Fitness for the Exponentially Tapered T-Tube Model-Derived Data to 6-, 12-, and 18-Month-Old Rats

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>6 (n = 10)</th>
<th>12 (n = 10)</th>
<th>18 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized root-mean-square error (e*) (×10^-4)</td>
<td>6.16 ± .49</td>
<td>5.86 ± .57</td>
<td>6.19 ± .28</td>
</tr>
<tr>
<td>Standard error of the estimate (%)</td>
<td>.91 ± .24</td>
<td>.95 ± .22</td>
<td>.99 ± .17</td>
</tr>
<tr>
<td>Coefficient of determination</td>
<td>.9902 ± .0017</td>
<td>.9899 ± .0016</td>
<td>.9896 ± .0014</td>
</tr>
</tbody>
</table>

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

and terminal load, represented by wave transit time and arterial load compliance, respectively, were inferred by the exponentially tapered T-tube model; they are summarized in Table 4. There was no significant change in wave transit time in the head and body circulation among rats at those three different ages. Similar was the arterial load compliance in the head and body circulation of those three groups of rats. From Tables 2–4 we drew the results that no significant changes were found in the static and oscillatory components of the ventricular afterload imposed on the heart, when comparison was made only on rats between 6 and 12 months old. These data suggest that the functions of Winkessel and resistance vessels were not modified between rats at the ages of 6 and 12 months.

We also performed a power analysis to discuss the size of the difference that would be theoretically important and to indicate what size of difference could actually be detected with 80% power. We took $C_L$ as an example to delineate this idea. For $C_L$ there was a complete nonsignificant age difference. Because its standard deviation was about .65, we could detect a difference on the order of 2.56, 3.00, and 3.54 across the ages with 80% power. A change any smaller than this would not be of much theoretical importance, so we feel that this result shows that there is no important age change in this variable. For $Z_c$ it exhibited changes with age, but not significantly between 6- and 12-month-old animals. The power analysis pointed out that the smallest true mean difference was about .42 with 80% probability using the $F$ test between 6- and 12-month-old rats. The analysis
reported that if there was a true mean drop of .42 in Z, then the study has a good chance of detecting it. If the true mean change were smaller, the study could more easily miss it.

DISCUSSION

This is the first report of using the exponentially tapered T-tube model to analyze the changes of arterial physical properties in rats at the ages of 6, 12, and 18 months. The impedance is determined by the physical characteristics of the vasculature, including its elastic properties and size, as well as by the viscosity and density of the fluid contained within (15,16). Both model-independent and model-based approaches have been adopted to study arterial input impedance. Because of the arterial distribution, a model-based approach, such as a succinct T-tube model, is more appropriate for the exploration of the pulsatile nature of blood flows in the vasculature. Because the diameter and elastic tapering are of importance in the arterial system (16,18,21), the smooth change of vascular impedance, caused by these tapers, must have substantial impact on the magnitude and/or timing of pulse wave reflection. The diameter and elastic tapering of the vasculature were taken into consideration in the present study to analyze the changes of vascular dynamics in rats at those three different ages.

The static hemodynamic condition in rats at the ages of 6, 12, and 18 months was characterized by (i) no change in cardiac output and (ii) a decline in heart rate, systolic, diastolic, as well as mean arterial blood pressure. There was a

### Table 2. Basic Hemodynamic Data Measured and Calculated in 6-, 12-, and 18-Month-Old Rats

<table>
<thead>
<tr>
<th>Rats</th>
<th>Age (month)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (n = 10)</td>
<td>12 (n = 10)</td>
</tr>
<tr>
<td>BW</td>
<td>419.9 ± 11.1</td>
<td>503.0 ± 15.3</td>
</tr>
<tr>
<td>HR</td>
<td>351.4 ± 7.13</td>
<td>346.7 ± 8.6</td>
</tr>
<tr>
<td>P_a</td>
<td>125.5 ± 2.9</td>
<td>127.2 ± 2.6</td>
</tr>
<tr>
<td>P_s</td>
<td>87.9 ± 2.4</td>
<td>93.7 ± 3.4</td>
</tr>
<tr>
<td>P_L</td>
<td>106.5 ± 2.4</td>
<td>110.7 ± 3.0</td>
</tr>
<tr>
<td>C_O</td>
<td>1.48 ± 0.11</td>
<td>1.50 ± 0.11</td>
</tr>
<tr>
<td>R_p</td>
<td>75.6 ± 5.9</td>
<td>77.7 ± 6.1</td>
</tr>
</tbody>
</table>

Notes: All values are expressed as means ± SE. BW, body weight (g); HR, heart rate (beats/min); P_a, systolic pressure (mmHg); P_s, diastolic pressure (mmHg); P_L, mean pressure (mmHg); C_O, cardiac output (ml/min); R_p, total peripheral resistance (mmHg·min/ml); NS, not significant (p > .05).

### Table 3. Global Parameters Inferred by the Exponentially Tapered T-Tube Model in 6-, 12-, and 18-Month-Old Rats

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (n = 10)</td>
<td>12 (n = 10)</td>
</tr>
<tr>
<td>Z_c</td>
<td>3.09 ± 0.20</td>
</tr>
<tr>
<td>(q_0/w) → ∞</td>
<td>1.967 ± 0.013</td>
</tr>
<tr>
<td>R_t</td>
<td>4.0 ± 0.04</td>
</tr>
<tr>
<td>C_L</td>
<td>2.56 ± 0.24</td>
</tr>
</tbody>
</table>

Notes: All values are expressed as means ± SE. Z_c, aortic characteristic impedance (mmHg·min/ml); (q_0/w) → ∞, tapering index; R_t, wave reflection factor; C_L, peripheral load compliance (μl/mmHg); NS, not significant (p > .05).

### Table 4. Peripheral Load Compliance and Wave Transit Time of the Head and Body Circulation Estimated by the Exponentially Tapered T-Tube Model in 6-, 12-, and 18-Month-Old Rats

<table>
<thead>
<tr>
<th>Age (month)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circulation</td>
<td></td>
</tr>
<tr>
<td>Peripheral load</td>
<td>C_a</td>
</tr>
<tr>
<td>Transmission tube</td>
<td>R_t</td>
</tr>
<tr>
<td>Peripheral load</td>
<td>C_b</td>
</tr>
<tr>
<td>Transmission tube</td>
<td>R_b</td>
</tr>
</tbody>
</table>

Notes: All values are expressed as means ± SE. C_a and C_b, peripheral load compliance in the head and body circulation, respectively (μl/mmHg); R_t and R_b, wave transit time in the head and body circulation respectively (ms); NS, not significant (p > .05).
report that cardiac output is unaffected by age in rats up to 18 months old (30). The decline in heart rate was described in rats with advancing age (31,32). Although the effect of age on arterial blood pressure has been inconclusive, a recent study has noted that arterial blood pressure decreases with age in rats (31). Our results of age-related changes in cardiac output, heart rate, and arterial blood pressure were in accordance with these reports.

A significant fall in total peripheral resistance was observed in 18-month-old rats. 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 (15,16). Because there was no evidence of diseases affecting the viscosity of the blood, the decline in total peripheral resistance suggests that an increase in arteriolar caliber occurred in 18-month-old rats. The maintenance of blood flows for the metabolic needs of bodily organs and tissues indicated that the decrease in total peripheral resistance may be the factor responsible for the decline of arterial blood pressure in middle-aged rats. The decrease in arterial blood pressure in the absence of significant change in cardiac output may contribute to a smaller steady fraction of total ventricular external power in 18-month-old rats.

In a hydraulic vascular system, the ratio of pulsatile pressure to flow is termed the characteristic impedance if only centrifugal waves are present at the origin (16). Characteristic impedance is directly related to the blood density and pulse wave velocity and is inversely related to the lumen radius squared of the tube. For large arteries, pulse wave velocity may be approximately related to the elastic modulus of the vessel; the stiffer the vessel, the higher the pulse wave velocity. Thus, the net result of age on aortic characteristic impedance would be dependent on the relative influence of these counter-balancing factors.

Rats aged 18 months had a significant fall in aortic characteristic impedance. Similarly, Cox (13) calculated the characteristic impedance in rat carotid arteries and found that the characteristic impedance was actually lower in aging rats. As for arterial distensibility, Berry et al. (12) showed no change in the elastic modulus with age in rats. In the present study, the wave transit time in the head and body circulation, which is inversely determined by the pulse wave velocity, remained unchanged in 18-month-old rats. No significant change in wave transit time reflected that the aorta and large arteries in 18-month-old rats were as distensible as those in 6- and 12-month-old rats. The decline of aortic characteristic impedance without significant change in arterial distensibility suggests that lumen growth of the aorta and large arteries occurred in rats up to the middle age.

Just as the elastic modulus is an expression employed 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, for compliance is equal to distensibility times the radius squared of the tube. For large arteries, pulse wave velocity may be approximately related to the elastic modulus of the vessel; the stiffer the vessel, the higher the pulse wave velocity. Thus, the net result of age on aortic characteristic impedance would be dependent on the relative influence of these counter-balancing factors.

The major conclusions arising from this study are as follows: (i) Up to middle age in rats, there is a significant fall in heart rate, arterial blood pressure, total peripheral resistance, and aortic characteristic impedance; (ii) The age-associated increase in arteriolar caliber in rats may be the factor responsible for the decrease of total peripheral resistance and therefore the decrease of mean arterial blood pressure; (iii) The decline of aortic characteristic impedance without significant change in wave transit time suggests that lumen growth of the aorta and large arteries may occur in rats up to the middle age.

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REFERENCES

14. Hume JF. The tensility of the rat's aorta as influenced by age, envi...

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Appendix

Note 1
The upper-to-lower body resistance ratio can be determined when the ratio Kn, between measured descending thoracic aorta mean flow and cardiac output is calculated (20). Under basal condition, approximately 67% of cardiac output in rats consisted of blood flows in kidneys, spleen, small and large intestines, liver, stomach, diaphragm, hindlimb muscles and bones, and skin (34). If blood flow of other tissue and organ in the lower portion of the body was included, it was speculated that Kn in the rat would be similar to that in the dog [70% in Campbell’s report (35)]. From a comparative physiological point of view, the ratio of Kn in rats was then assumed to be 0.7, 0.62, and 0.76 as in dogs under basal, vasocostricted, and vasodilated conditions, respectively (35). Being calculated by the equation of Rn/Rm = Kn/(1-Kn), the upper-to-lower body resistance ratio was 2.33 for normotensive state and 3.17 for hypotensive state.

Note 2
The aortic characteristic impedance Ze can be measured by many different methods. One method is to calculate Zc by averaging high-frequency moduli of impedance data points obtained from the ratio of the corresponding harmonics of pressure and flow. From knowledge of Ze, the ratio of upper-to-lower body characteristic impedance Kn could be inferred by the exponentially tapered T-tube model. In that case, the ratio of upper-to-lower body characteristic impedance rather than the aortic characteristic impedance remained to be estimated. With 10 rats, we have separately determined Kn for basal, vasoconstricted (0.5 mg/kg methoxamine, n = 5), and vasodilated (0.5 mg/kg prazosin, n = 5) conditions. The ratio of upper-to-lower body characteristic impedance was estimated to be 1.142 ± 0.083, 1.375 ± 0.105, and 1.203 ± 0.088 for basal, vasocostricted, and vasodilated states, respectively.