Gene Expression of Tropoelastin Is Enhanced in the Aorta Proximal to the Coarctation in Rabbits

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INTRODUCTION

Elastin is a major component of larger blood vessels, providing the vessel wall with structural integrity and reversible extensibility or deformability [1]. Synthesis of the elastic protein generally peaks early during arterial growth, decreases rapidly with further development, and essentially ceases in the aortic tissue of adults [2]. During the period of rapid accumulation of aortic elastin, transformation of soluble to insoluble elastin is a rapid and efficient process [3]. Evidence shows that there are marked increases in both elastin and collagen synthesis and steady-state mRNA levels in pulmonary artery tissue and cells from hypertensive neonatal animals [4, 5]. Distribution of tropoelastin mRNA is found in smooth muscle cells in the inner media in normal controls and in the outer media in hypoxic pulmonary hypertension [6]. Tropoelastin gene is also expressed by cells adjacent to the lumen in both small muscular and large elastic pulmonary arteries in a pulmonary hypertension model [7]. The evidence suggests that tropoelastin gene expression is evoked in response to elevated arterial wall tension. However, mechanisms by which elastin biosynthesis is regulated in fully developed aortic tissue in an adult stage are not well known. To further demonstrate tropoelastin gene expression in relation to elevated tensile stress we used thoracic aortic coarctation to create blood pressure gradients and studied the tropoelastin and its mRNA at the proximal region of the aorta to a midthoracic aortic coarctation in rabbits. We characterized the time course of gene expression for tropoelastin and its distribution in response to acute elevation of blood pressure.
MATERIALS AND METHODS

Animal Models

Two animal models in relation to aortic coarctation were used. The first was a simple midthoracic aortic coarctation in rabbits [8]. The second was the aortic coarctation model superimposed by hypercholesterolemia [9]. A blood pressure gradient of 15 to 30 mmHg across the coarctation site was obtained by adjusting the tightness of the band. Mean blood pressures were measured before surgery, during the operation, and at sacrifice. Hypercholesterolemia was induced by feeding the animals with a high-cholesterol diet consisting of 1% cholesterol and 4% corn oil mixed into standard rabbit chow. The blood samples were drawn from the ear vein before starting the cholesterol diet and weekly thereafter for measurement of total serum cholesterol level. Body weights were documented at the beginning and the end of the experiment. Heart weights were measured at sacrifice.

Experimental Design and Specimen Preparation

A time-course study of tropoelastin gene expression was performed for animals with aortic coarctation only. After creation of the midthoracic aortic coarctation, the animals were maintained on regular rabbit chow and water provided ad libitum for 1 day, 3 days, 1 week, 2 weeks, 4 weeks, and 8 weeks (n = 3 for each time point except for n = 5 for 4 weeks). Sham-operated and age-matched animals served as controls (n = 6). Six animals were fed the high-cholesterol diet for 5 weeks without coarctation and named the 5WD group. Six additional animals were fed the high-cholesterol diet for 1 week followed by the midthoracic aortic coarctation. These animals were then kept for 4 more weeks on the high-cholesterol diet and designated as 5WD + 4WC group. Two sets of animals were used for the designed study, one set for obtaining fresh tissue and one for perfusion fixed tissues. At euthanasia, the animals received an overdose of pentobarbital at 120 mg/kg IV. Three samples were taken from the proximal portion as described previously [8]. One cross-sectional ring, 10 mm proximal to the coarctation site, was immediately taken and frozen with OCT compound (Miles Inc., Elkhart, IN) for sectioning. A segment, 20 mm in length proximal to the cross-sectional ring, was divided into two pieces and immediately stored at −80°C for extraction of total RNA and total protein, respectively. Loose connective tissue was removed and care was taken not to strip the adventitia. The aortas for morphometric studies were perfusion fixed with 10% formalin through the left ventricle at a pressure of 100 mmHg for 30 min. Specimens were taken at the same level as the cross-sectional rings for sections.

Molecular Analyses

Molecular Analysis included Northern blotting, in situ hybridization, Western blotting, and immunohistochemistry. All the techniques were the same as used previously [8, 9]. Tropoelastin cDNA was a 0.9-kb REL124D clone from rat aorta [10] carried in plasmid pIBI31 (ATCC, Manassas, VA). It was excised with EcoRI and used as a template to generate a 32P-labeled DNA probe, which was able to cross-hybridize with rabbit 3.5-kb mRNA of tropoelastin in Northern blotting. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA template (from ATCC) was also used in the hybridization for normalization of relative mRNA levels. In situ hybridization was performed on frozen sections with an antisense probe of tropoelastin. Sense probe was used as negative control followed previous procedures [9]. For Western blot analysis, we used mouse antobody tropoelastin monoclonal antibody (Elastin Products Co, Inc) at a dilution of 1:200 and biotinylated antimouse IgG antibody (Sigma) at 1:500 dilution following the ABC method (Vector, Burlingame, CA). The final detection of proteins on blots was performed by enhanced chemiluminescence (ECL) system (Amersham Corporation, Arlington Heights, IL). For immunohistochemistry the same antibodies for Western blot analysis were used and the protocols for the ABC method was followed.

Morphometric Studies

Samples from aortas fixed under in situ pressure perfusion were embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (HE) as well as with the Weigert–Van Gieson’s procedure (WVG) for matrix fibers. Computer-assisted contour tracing was used to determine the following dimensions: outer media diameter, the diameter derived from the circumference of the outermost elastic lamella, the diameter derived from the circumference of the internal elastic lamella (IEL diameter), lumen diameter, average media thickness, and average wall thickness (total thickness of the media and intima). Two-dimensional volume of the aortic wall was measured by calculation of intimal area and media area. The number of media layers was counted on pressure perfusion fixed WVG stained sections. Each section was studied at four points, 90° apart, the mean of these four representing the number of layers for one section. Sections from the proximal and the distal aorta were analyzed.
Wall Stress

Wall tension was calculated as $T = Pr$ and wall stress $S = Pr/d$ [11, 12], where $T$ is wall tension (in dynes per centimeter), $S$ is tensile stress (in dynes per square centimeter), $P$ is the mean blood pressure (in dynes per square centimeter), $r$ is the lumen radius (in centimeters), and $d$ is the wall thickness (in centimeters), including the media and the intima, but not the adventitia for the demarcation of the adventitia is not readily to define. The mean blood pressure used for normal controls was 95 mmHg and for coarcted animals 110 mmHg for the proximal, assuming at least a 15 mmHg increase after coarctation. It was assumed that 1 mmHg $\approx 1333.3$ dynes/cm$^2$.

Statistical Analysis

All data are presented as mean $\pm$ SD. Multiple comparisons were made by ANOVA with Bonferroni’s correction method. Values of $P < 0.05$ were considered significant.

RESULTS

Blood Pressure and Degree of Coarctation

Mean blood pressures for control animals were 94 $\pm$ 10 mmHg at the ear artery and 95 $\pm$ 10 mmHg at the femoral artery. After creation of the midthoracic aortic coarctation, blood pressure gradients across the coarctation ranged from 15 to 31 mmHg ($P < 0.01$ compared to controls). The gradient at sacrifice tended to increase at 2 or 3 weeks compared to that established at surgery. After 4 weeks the gradients seemed to diminish. But they remained greater than 15 mmHg.

Coarctation rate is expressed as the reduction of transverse cross-sectional area encompassed by the internal elastic lamella (IEL area) at the coarctation channel level. The IEL area at the designed coarctation level for normal animals was 9.85 $\pm$ 1.88 mm$^2$. After coarctation, the diameter reduction was over 50% ranging from 57 to 84% for all coarcted animals. Some animals had a coarctation rate as high as 93%, but the blood pressure gradients were not significantly proportional to the coarctation rate.

Body Weight, Heart Weight, and Serum Cholesterol Level

Average body weight of animals was 2.84 $\pm$ 0.30 kg at the starting of experiment. It increased to 2.83 $\pm$ 0.28 kg at 1 week, 3.38 $\pm$ 0.33 kg at 4 weeks, and 3.46 $\pm$ 0.41 kg at 8 weeks. But the increases showed no significant effects on gene expression for tropoelastin. Heart weights increased for the animals with coarctation compared to corresponding controls reflecting the increased resistance due to aortic coarctation. The mean total serum cholesterol level for all animals at the beginning of the experiment was 66 $\pm$ 16 mg/dL. There was no change in serum cholesterol level for all the animals with only aortic coarctation. It was increased rapidly following the initiation of high cholesterol diet. At 1 week it was 15-fold (1009 $\pm$ 205 mg/dL) higher than normal and peaked by 4 weeks for 5WD + 4WC animals (2511 $\pm$ 444 mg/dL) and 5 weeks for 5WD animals (2715 $\pm$ 530 mg/dL) [$P < 0.001$ for all compared to controls (Ctrl)].

Time Course Tropoelastin Expression in the Aorta Proximal to the Coarctation

Northern blot analysis revealed that tropoelastin mRNA increased at the proximal aorta after coarctation. It increased by 1.7-fold at 3 days ($P < 0.01$) and kept increasing. By 4 weeks after coarctation the tropoelastin mRNA level was 3.2-fold higher than that of controls ($P < 0.05$). The mRNA level of tropoelastin returned to the control level at 8 weeks (Fig. 1A).

Western blot analysis showed an increase in tropoelastin 3 days after the aortic coarctation. The protein level peaked at 2 weeks and was 3-fold higher than that of controls ($P < 0.05$). Tropoelastin levels remained 1.8-fold higher than those of controls at 4 weeks and 8 weeks (Fig. 1B).

Intimal Lesion Development and Its Association with Increased Tropoelastin Expression

There was no remarkable intimal lesion in all sham-operated controls and in animals subjected to aortic coarctation only (Figs. 2A and 2B) and mild intimal lesion in animals fed the high-cholesterol diet (5WD)(Fig. 2C). However, a thick intimal lesion, characterized by foam cell accumulation, developed in the 5WD + 4WC animals, which were subjected to a 5-week diet and 4-week coarctation (Fig. 2D). Furthermore, the foam cell lesion development was associated with increased tropoelastin expression. This was attested by in situ hybridization, immunohistochemistry, Northern blot analysis, and Western blot analysis. Northern blot analysis showed a 7.6-fold increase in mRNA of tropoelastin in the 5WD + 4WC group, a 5.7-fold increase in the 5WD group ($P < 0.05$), and 3.8-fold increase in the 4WC group ($P < 0.05$) as compared with controls (Fig. 3A).
Furthermore, the tropoelastin mRNA level of 5WD + 4WC animals was higher than those of 5WD and 4WC animals ($P < 0.05$). Western blot analysis demonstrated a corresponding increase in tropoelastin protein, with the highest level for the 5WD + 4WC animals (Fig. 3B). Although tropoelastin gene expression was observed across the wall, especially in the adventitia, the outer media and the intima, it appeared to be localized more in the intimal lesion with a close association with foal cells (Figs. 2E to 2L).

**Aortic Dimensions**

We previously reported the time-course changes in aortic dimension after coarctation [8]. In brief, lumen diameters
FIG. 2. There was no foam cell lesion in the intima in sham-operated (A) and 4-week coarcted (B, 4WC) animals. After 5 weeks on a high-cholesterol diet, foam cell lesion developed (C, 5WD). But the lesion is much smaller than that of animals subjected to both a 5-week high-cholesterol diet and a 4-week coarctation (D, 5WD + 4WC). (A–D) Paraffin sections were stained with H&E. In situ hybridization revealed increased tropoelastin gene expression, which appears as dark grains. The dark grains distributed mainly in the intima. (E) Sham-operated; (F) 4WC; (G) 5WD; (H) 5WD + 4WC. Immunohistochemistry showed similar distribution pattern of tropoelastin as stained brown. (I) Sham-operated; (J) 4WC; (K) 5WD; (L) 5WD + 4WC. (E–L) Frozen sections counterstained with hematoxylin.

increased significantly by 4 weeks of coarctation. Media thickness and wall thickness appeared to increase but the changes did not reach statistical significance. In the present study, the aortic size, which was represented by the areas and diameters, was similar. Moreover, the aortic size was significantly larger for the 5WD + 4WC and 4WC animals than for the control and 5WD animals ($P < 0.001$). The intimal area (IMA) for 5WD + 4WC and 5WD animals, especially for the former, was greatly increased due to the foam cell lesion ($P < 0.001$ vs Ctrl and 4WC). Media area (MEA), media thickness (MTH), and wall thickness (WTH) for the 4WC and 5WD + 4WC animals were also increased ($P < 0.001$ vs Ctrl and 5WD) (Table 1).

Wall Stress

Wall tension and tensile stress were estimated for the aortic segment proximal to the coarctation by the formula $T = Pr$ and $S = Pr/d$. The results are shown in Table 2. Wall tension for the 5WD + 4WC and 4WC groups was higher than that of Ctrl. The tensile stress for the 5WD and 4WC group was
pressure induced by midthoracic aortic coarctation. The mRNA level of tropoelastin proximal to the coarctation increased gradually and significantly, starting from 3 days and peaked at 4 weeks with a 3.2-fold increase as compared to controls. It declined to baseline level by 8 weeks. Western blotting showed an increase in tropoelastin protein in the proximal aorta to the coarctation, which corresponds well with the mRNA changes except that tropoelastin protein level remained high by 8 weeks. These findings are in general consistent with the gene expression for collagen types I and III under similar hemodynamic conditions [8]. However, gene expression of collagen types I and III returned to baseline level by 4 weeks after coarctation, which was much sooner than that found with tropoelastin. These results suggest that the proximal tropoelastin response is both milder and relatively later than that of collagen types I and III.

The distribution of tropoelastin seemed to localized more in the intima, the adventitia, and the outer media but the intensity was not as remarkable as for type I collagen [8]. Although in situ hybridization did not show a remarkable distribution of tropoelastin mRNA in the adventitia, immunohistochemical staining was able to clearly demonstrate the differential expression for tropoelastin. The distinctive differential distribution of major ECM gene expression has been reported in the aorta hypertension model in rabbits [9, 13]. In a pulmonary hypertension study in rats, tropoelastin gene was expressed by cells adjacent to the lumen and proteoglycans gene expression at the medial–adventitial border in both small muscular and large elastic pulmonary arteries [7].

The elastic properties of many tissues, including large blood vessels, are associated with the presence of elastic fibers in the extracellular space. The basic element of the aortic media is the “lamellar unit,” consisting of two elastic lamellae and intervening tissue [1, 14]. Elastic fibers are important in maintaining the arterial property and function. During systole the energy imparted to the blood is partially absorbed and dampened by expansion of the great vessels, which then recoil during diastole, maintaining the blood pressure and assuring continuous perfusion of the tissues. During development stage, vascular SMCs synthesize a variety of ECMs, including tropoelastin, which, in part, establish the structural integrity of the vessel wall. SMCs in the adult vascular wall, in contrast, are remarkably quiescent and the rates of elastin synthesis in blood vessels fall rapidly after the perinatal period [2, 15, 16]. But the tropoelastin synthesis can be stimulated by injury [16, 17]. This “dedifferentiation” process is thought to play an important role in the pathogeneses of atherosclerosis and hypertension and in restenosis.

**FIG. 3.** (A) mRNA levels of tropoelastin at the proximal were high for all groups as compared to Ctrl (*P < 0.05). And the mRNA for 5WD + 4WC was higher than those of 5WD and 4WC (**P < 0.05). The top panel is an example from multiple Northern blots with GAPDH as an internal control. (B) Protein levels of tropoelastin at the proximal for animals fed with high-cholesterol diet. The top panel is an example from multiple Western blots. Tropoelastin increased for all groups as compared with controls (*P < 0.05). Tropoelastin levels for 5WD + 4WC appeared higher than those of the 4WC and 5WD groups, but the difference did not reach statistical significance.

Numbers of median layers was counted on pressure fixed and WVG-stained paraffin sections. The data are listed in Table 3. The number of layers at the proximal region was not significantly different among groups.

**DISCUSSION**

The present study revealed that tropoelastin gene expression was increased in response to an acute elevation of blood pressure induced by midthoracic aortic coarctation. The mRNA level of tropoelastin proximal to the coarctation increased gradually and significantly, starting from 3 days and peaked at 4 weeks with a 3.2-fold increase as compared to controls. It declined to baseline level by 8 weeks. Western blotting showed an increase in tropoelastin protein in the proximal aorta to the coarctation, which corresponds well with the mRNA changes except that tropoelastin protein level remained high by 8 weeks. These findings are in general consistent with the gene expression for collagen types I and III under similar hemodynamic conditions [8]. However, gene expression of collagen types I and III returned to baseline level by 4 weeks after coarctation, which was much sooner than that found with tropoelastin. These results suggest that the proximal tropoelastin response is both milder and relatively later than that of collagen types I and III.

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after arterial injury [18–20]. Little is known about the synthesis response of tropoelastin to various hemodynamic alterations in the adult aortic wall. The results from this study clearly demonstrated that the arterial wall responded to increased wall tension with synthesis of tropoelastin.

This study also revealed that neointima of foam cell lesions favored the deposition of tropoelastin in animals fed with high cholesterol diet. This local tropoelastin deposition in the intima was more remarkable in the animals with hyperlipidemia superimposed by high blood pressure. This observation agrees somewhat with the findings in human atherosclerotic hypertensive pulmonary arteries [21, 22]. This result confirms again the acceleration effect of hypertension on atherosclerotic lesion development [23, 24]. Mechanisms of the accelerating effect are not very clear. There is a great affinity between lipids and elastin. LDL binding to elastin may foster atherosclerotic lipid deposition [25]. A progressive deposition of lipids in elastic tissues as well as the addition of lipoproteins or lipids to cell and organ cultures was shown to modify matrix biosynthesis [26, 27]. Lipids trapped in the intima attract infiltration of macrophages and smooth muscle cells. Stress may also damage the wall’s function of normal metabolism of the lipids to enhance lipid accumulation in the intima. This is further attested by our observation that the peak of tropoelastin expression at 4 weeks of coarctation was associated with a fully development of the foam cell lesion with a dominant tropoelastin deposition in the intima at that time.

Wall tension is the function of pressure and radius. The elevation of blood pressure after coarctation will result in an increase in the aortic wall tension in the proximal region. Moreover, the increase in the radius also contributes to the increase in the tension as shown in the 4WC and 5WD + 4WC animals (Table 2). An up-regulation of gene expression in collagen [8] and in elastin in the adventitia and the outer media may reflect the response to the higher wall tension in these zones, which situate at the outer site of the wall with greater radius values as compared to inner part of the wall. It is reported that the diameter of collagen fibrils in the outer media and the adventitia of arteries is larger than that of the rest of the media, suggesting an adaptation to greater mechanical stress in these parts of the vessel wall [28–30]. However, the exact correlation between gene up-regulation of these ECM and the possible differential distribution of wall tension across the vessel wall remains to be

### Table 1
Aortic Dimensions at the Proximal Region

<table>
<thead>
<tr>
<th>Groups</th>
<th>OMD (mm)</th>
<th>IELD (mm)</th>
<th>LUD (mm)</th>
<th>MEA (mm²)</th>
<th>IMA (mm²)</th>
<th>MTH (mm)</th>
<th>WTH (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl (n = 6)</td>
<td>3.78 ± 0.28</td>
<td>3.42 ± 0.25</td>
<td>3.41 ± 0.25</td>
<td>2.18 ± 0.60</td>
<td>0.03 ± 0.03</td>
<td>0.18 ± 0.03</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>4WC (n = 5)</td>
<td>5.22 ± 0.45*</td>
<td>4.67 ± 0.41*</td>
<td>4.67 ± 0.41*</td>
<td>4.18 ± 1.19*</td>
<td>0.04 ± 0.06</td>
<td>0.27 ± 0.04*</td>
<td>0.28 ± 0.04*</td>
</tr>
<tr>
<td>5WD + 4WC (n = 6)</td>
<td>4.89 ± 0.41*</td>
<td>4.38 ± 0.39*</td>
<td>4.02 ± 0.37*</td>
<td>3.54 ± 0.57*</td>
<td>2.27 ± 0.40*</td>
<td>0.26 ± 0.02*</td>
<td>0.43 ± 0.03*</td>
</tr>
<tr>
<td>5WD (n = 6)</td>
<td>4.19 ± 0.24</td>
<td>3.82 ± 0.16</td>
<td>3.77 ± 0.14</td>
<td>2.13 ± 0.33</td>
<td>0.17 ± 0.05*</td>
<td>0.18 ± 0.04</td>
<td>0.21 ± 0.06</td>
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</table>

*Note.* OMD, diameter of the circumference of the outermost elastic lamella; IELD, diameter derived from the circumference of the internal elastic lamella; LUD, lumen diameter; MEA, media area; IMA, intimal area; MTH, average media thickness; WTH, average wall thickness. Data are expressed as mean ± SD.

### Table 2
Estimated Wall Tension and Tensile Stress

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>T</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>6</td>
<td>2.64 ± 0.19</td>
<td>12.25 ± 2.80</td>
</tr>
<tr>
<td>4WC</td>
<td>5</td>
<td>3.65 ± 0.32*</td>
<td>12.05 ± 1.64</td>
</tr>
<tr>
<td>5WD + 4WC</td>
<td>6</td>
<td>3.42 ± 0.28*</td>
<td>6.49 ± 0.50*</td>
</tr>
<tr>
<td>5WD</td>
<td>6</td>
<td>2.93 ± 0.16</td>
<td>12.31 ± 2.86</td>
</tr>
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</table>

*Note.* Wall tension (T) and wall tensile stress (S) proximal to coarctation were estimated for the proximal region using the formulas T = Pr and S = Pr²/d. Wall tension for the 4WC and 5WD + 4WC groups was higher than that of Ctrl (*P < 0.05). Tensile stress for the 5WD + 4WC group was reduced (*P < 0.001) compared to all other groups due to perhaps increased wall thicknesses. Unit for wall tension is dynes/cm × 10³ and dynes/cm² × 10³ for tensile stress. Data are expressed as Mean ± SD.

### Table 3
Number of Media Layers

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Proximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>3</td>
<td>24.33 ± 2.52</td>
</tr>
<tr>
<td>4WC</td>
<td>5</td>
<td>26.00 ± 1.00</td>
</tr>
<tr>
<td>5WD + 4WC</td>
<td>3</td>
<td>23.00 ± 1.00</td>
</tr>
<tr>
<td>5WD</td>
<td>3</td>
<td>24.00 ± 2.00</td>
</tr>
</tbody>
</table>

*Note.* The number of media layers (Mean ± SD) was not significantly different proximally among the groups.
further characterized. In contrast, gene up-regulation of these ECM has been also observed in the intima, which is the inner part of the wall. This contrary reminds us that the radius may not be a dominant determinant and there are many other factors contributing to the response of the wall. The tensile stress, expressed as $S = Pr/d$, takes wall thickness $(d)$ into consideration. Thus, the unit wall tension is governed by the wall thickness. Increase in wall thickness, as an adaptation to wall tension, will bring down wall tensile stress. In this study, wall tension was increased after the aortic coarctation due to the elevated blood pressure. However, the tensile stress was not significantly increased (Table 2). Moreover, the estimated tensile stress in the 5WD + 4WC animals declined due to apparently the thick intimal lesions. Whether and to what extent the foam cell lesion in the intima could add tensile strength to the wall is uncertain. Nevertheless, the role of intimal thickening in supporting tangential mural tensile stress has been suggested in a quantitative morphologic study of intimal thickening at the human carotid bifurcation [31].

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