Catalase overexpression in aortic smooth muscle prevents pathological mechanical changes underlying abdominal aortic aneurysm formation

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Maiellaro-Rafferty K, Weiss D, Joseph G, Wan W, Gleason R L, Taylor WR. Catalase overexpression in aortic smooth muscle prevents pathological mechanical changes underlying abdominal aortic aneurysm formation. Am J Physiol Heart Circ Physiol 301: H355–H362, 2011. First published May 6, 2011; doi:10.1152/ajpheart.00040.2011.—The causality of the associations between cellular and mechanical mechanisms of abdominal aortic aneurysm (AAA) formation has not been completely defined. Because reactive oxygen species are established mediators of AAA growth and remodeling, our objective was to investigate oxidative stress-induced alterations in aortic biomechanics and microstructure during subclinical AAA development. We investigated the mechanisms of AAA in an angiotensin II (ANG II) infusion model of AAA in apolipoprotein E-deficient (apoE−/−) mice that overexpress catalase in vascular smooth muscle cells (apoE−/−xTgSMC-Cat). At baseline, aortas from apoE−/−xTgSMC-Cat exhibited increased stiffness and the microstructure was characterized by 50% more collagen content and less elastin fragmentation. ANG II treatment for 7 days in apoE−/− mice altered the transmural distribution of suprarenal aortic circumferential strain (quantified by opening angle, which increased from 130 ± 1° at baseline to 198 ± 8° after 7 days of ANG II treatment) without obvious changes in the aortic microstructure. No differences in aortic mechanical behavior or suprarenal opening angle were observed in apoE−/−xTgSMC-Cat after 7 days of ANG II treatment. These data suggest that at the earliest stages of AAA development H2O2 is functionally important and is involved in the control of local variations in remodeling across the vessel wall. They further suggest that reduced elastin integrity at baseline may predispose the abdominal aorta to aneurysmal mechanical remodeling.

hydrogen peroxide; reactive oxygen species; opening angle; arterial mechanics; extracellular matrix

DESPITE A CLEAR ROLE FOR OXIDATIVE stress in the development of abdominal aortic aneurysms (AAA; Refs. 27, 44), the link between changes in oxidative stress and the local biomechanical response is not well understood. Animal models deficient in enzymatic sources of reactive oxygen species (ROS), such as inducible nitric oxide synthase, NOX1, and p47phox, clearly demonstrate preservation of aortic wall morphology and attenuated AAA development (12, 39, 44). A functional link between ROS and vascular mechanics has been previously demonstrated in nonaneurysmal human vascular tissues, which exhibit decreased aortic compliance in the presence of increased vascular superoxide (9). These studies illustrate that oxidative stress plays an important role in both the molecular and mechanical events associated with AAA. However, there is little evidence that links ROS directly to the biomechanical changes involved in AAA development.

ROS have been detected at all stages of aneurysm development (13, 29, 30) and are established mediators of extracellular matrix (ECM) degradation and remodeling (16, 34). AAA formation proceeds from localized remodeling and vessel dilation attributable to degeneration of elastin and alterations in collagen proteins within the aortic wall. Both events potentially reduce the compliance and tensile strength of aneurysmal aortas (19, 32, 41). Aneurysm formation is limited by inhibition of proteolytic enzymes, such as matrix metalloproteinases (MMPs; Ref. 26), and in animal models deficient in MMPs (Refs. 2, 20, 23, 37). These data suggest that proteolytic activity is necessary for AAA formation and that synergistic factors, such as spatial vulnerability to mechanical changes, are also relevant in the early stages of AAA formation.

We were motivated by the observation in a previous study from our group that transgenic apolipoprotein E-deficient (apoE−/−) mice with vascular smooth muscle cell (SMC)-specific overexpression of the human catalase gene (apoE−/−xTgSMC-Cat) were completely protected from AAA formation when treated with angiotensin II (ANG II; Ref. 28). ANG II infusion into apoE−/− mice has been shown by several groups to promote AAA formation (7, 8). We utilized this model to investigate H2O2-mediated alteration of aortic mechanics in the earliest stages of AAA formation, because previous studies in this model (45) demonstrated that aorta from WT mice showed significant ANG II-mediated aortic ROS production after 14 days, an event that was blunted in the TgSMC-Cat mice. The working hypothesis was that H2O2 is mechanistically and spatially linked to the biomechanical remodeling that promotes AAA. The data obtained in this study are the first to measure early changes in mechanical behavior in a mouse model of ANG II-induced AAA and demonstrate that local H2O2 is associated with the development of early alterations in local circumferential strain across the aortic wall.

METHODS

Animals. Transgenic mice with smooth muscle-specific overexpression of catalase (apoE−/−xTgSMC-Cat) and littermate control (apoE−/−) were used in this study. ANG II (0.75 mg·kg−1·day−1) was dissolved in sterile saline and delivered subcutaneously via osmotic minipumps (Alzet, Cupertino, CA) for 7 days. Mice were fed either a standard chow diet (Certified Rodent Chow 5001; Purina) or a high-fat diet (atherogenic diet; Research Diets, New Brunswick, NJ). The generation and phenotypic characterization of the apoE−/−xTgSMC-Cat mice have been preformed previously (45). All procedures were approved by the Emory University Institutional Animal Care and Use Commit-
CATA LASE OVEREXPRESSION PREVENTS MECHANICAL CHANGES IN AAA

\[ r = \sqrt{\frac{\pi}{\pi - \Phi}} \left( R^2 - R^2 \right) + a^2 \]  

Following Rachev (33), changes in axial length and wall thickness between the unloaded configuration and the radially cut, stress-free configuration are typically small and may be neglected. For this case, for a given opening angle measurement, \( R_1 \) and \( R_2 \) may be calculated as

\[
R_1 = \frac{\pi(B + A)}{2(\pi - \Phi)} - \frac{H}{2} \quad \text{and} \quad R_2 = \frac{\pi(B + A)}{2(\pi - \Phi)} - \frac{H}{2}.
\]

Thus, given the unloaded radius and thickness, the opening angle, and loaded outer diameter, the stress free inner and outer radius can be approximated. For all locations across the vessel wall (\( R \) in the stress-free location), from the inner wall location \( R_i \) to the outer wall location \( R_o \), the radial location in the loaded configuration (\( r \)) may be calculated via Eq. 2 and the circumferential Green strain may be calculated via Eq. 1. The distribution of \( E_a \) vs. radius can then be plotted.

Total aortic collagen content. To quantify aortic collagen content, total aortic collagen per dry weight was measured by hydroxyproline assay as described by Woessner (43). Briefly, aortic tissue freed from fat was weighed and dehydrated in a speed vacuum for 2.5 h, and the dry weight was recorded. The dry tissue was digested in 500 µl 0.25 M sodium phosphate buffer with 0.0125 g protease K/g wet weight and then hydrolyzed into amino acid components in 6 N HCl at 120°C for 14 h. Fifty microliters of each sample and hydroxyproline standards were oxidized with Chloramine-T (Sigma). Oxidation was terminated with perchloric acid solution. A colormetric reaction was performed with p-dimethylaminobenzaldehyde at 60°C, and the plate was read at 540 nm. Total collagen content per dry weight was calculated on the assumption that collagen is 13% hydroxyproline.

Histological analysis. Histological analysis was performed on the bisected aortic rings used for opening angle measurement, which were snap frozen in optimal cutting temperature medium after each experiment. Five-micrometer sections from each sample were stained with Verhoff van Geison Elastic stain (Sigma-Aldrich) for thickness measurement and quantification of elastin fragmentation or with picrosirius red (staining performed on intact aortic rings) to analyze collagen (3). Dimension analysis was performed using Image J software (NIH, Bethesda, MD). Elastin fragmentation was expressed as the number of elastin breaks per medial area, which was measured as the area between the inner and outer elastic laminae.

Statistical analysis. Data are presented as means ± SE. Statistical analyses were performed using GraphPad Prism software. The pressure-diameter data were analyzed by ANOVA to examine the effect of mouse background on aortic compliance, and Bonferroni post tests were used for post hoc analyses. All other analysis between groups was performed with Mann-Whitney test. Analysis of covariance and an F-test to compare slopes were performed on the mean circumferential strain vs. radius data. \( P < 0.05 \) was considered significant.

RESULTS

Overexpression of catalase alters aortic mechanical behavior. To determine whether AAA protection may derive from endogenous differences in mean systolic blood pressure and descending aortic mechanical behavior, unloaded and loaded dimensions (Table 1) and \( P-d \) response were measured in apoE\(^{-/-}\) and apoE\(^{-/-}\)xTg\(^{SMC-Cat}\) mice. Mean systolic blood pressure for each group was the same (96 ± 9.3 vs. 102 ± 10 mmHg; \( P = \text{NS} \)). At baseline, descending aortas from apoE\(^{-/-}\)xTg\(^{SMC-Cat}\) mice demonstrated reduced in vivo axial stretch, \( \lambda_c \), compared with aortas from apoE\(^{-/-}\) mice (Table 1; 1.26 ± 0.008 vs. 1.48 ± 0.005, respectively), indicating altered axial...
loading. The P-d data (Fig. 1A) of both groups exhibited biphasic behavior. The apoE⁻/⁻×TgSMC-Cat P-d curve was shifted downward from apoE⁻/⁻, indicating that apoE⁻/⁻×TgSMC-Cat aortas had smaller diameters and were less distensible. Pressure-dependent compliance (Cₚ) curves (Fig. 1B) further demonstrated that apoE⁻/⁻×TgSMC-Cat aortas were stiffer than apoE⁻/⁻ aortas at mid-range pressure. Mean circumferential stress-strain (δ₀ − E₀) curves (Fig. 1C) of each group were nonlinear and exhibited increased stiffening at high strain. The δ₀ − E₀ curves indicate that apoE⁻/⁻×TgSMC-Cat aortas had higher material stiffness compared with apoE⁻/⁻ aortas at baseline.

Opening angles were measured to quantify variations in strain across the wall of the suprarenal aorta at the site of AAA formation. At baseline, apoE⁻/⁻ and apoE⁻/⁻×TgSMC-Cat aortic rings exhibited comparable opening angles (Table 1), with magnitudes in agreement with published values from apoE⁻/⁻ mice (18). Mean circumferential strain E₀ across the wall was nearly uniform for both groups (Fig. 1D), although the strain magnitude of apoE⁻/⁻ aortas was higher than apoE⁻/⁻×TgSMC-Cat aortas. Thus, at baseline, the apoE⁻/⁻×TgSMC-Cat abdominal aortas had different axial strain, diameter-pressure behavior, mean circumferential strain magnitude, and material properties compared with the apoE⁻/⁻ aortas. Furthermore, both groups exhibited comparable opening angle and nearly uniform distribution of circumferential strain across the vascular wall.

Overexpression of catalase alters aortic microstructure. To investigate the structural basis for the mechanical differences between the two groups, matrix composition of the aortic walls was examined. At baseline, collagen content in the apoE⁻/⁻ group was 50% lower than the apoE⁻/⁻×TgSMC-Cat group (Fig. 2A). Measurement of unloaded wall thickness (Table 1), adventitial thickness (Fig. 2B), and picrosirius red staining of untreated aortic cross sections imaged under polarized light (Fig. 2, C and D) confirmed that apoE⁻/⁻ aortas were thinner and had less adventitial collagen than apoE⁻/⁻×TgSMC-Cat aortas. Elastin fragmentation was significantly greater in

Table 1. Mechanical and geometry results of aortas from apoE⁻/⁻ and apoE⁻/⁻×TgSMC-Cat mice with and without ANG II treatment

<table>
<thead>
<tr>
<th>ANG II</th>
<th>λ₀</th>
<th>d, mm</th>
<th>B, mm</th>
<th>H, μm</th>
<th>O.A., °</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoE⁻/⁻</td>
<td>−</td>
<td>1.48 ± 0.005</td>
<td>1.37 ± 0.03</td>
<td>0.343 ± 0.02</td>
<td>89 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1.38 ± 0.004</td>
<td>1.39 ± 0.08</td>
<td>0.342 ± 0.06</td>
<td>89 ± 1.9</td>
</tr>
<tr>
<td>apoE⁻/⁻×TgSMC-Cat</td>
<td>−</td>
<td>1.26 ± 0.008*</td>
<td>1.16 ± 0.01*†</td>
<td>0.347 ± 0.005</td>
<td>98 ± 2.1*†</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>1.23 ± 0.05*</td>
<td>−</td>
<td>−</td>
<td>88 ± 1.62</td>
</tr>
</tbody>
</table>

Values are means ± SE. Stretch ratio and loaded diameter data were acquired during isolated aortic inflation. Unloaded morphology was acquired from histological analysis of bisected aortic rings used in opening angle (O.A.) measurement. apoE⁻/⁻, apolipoprotein E-deficient mice; apoE⁻/⁻×TgSMC-Cat, apoE⁻/⁻ mice that overexpress catalase in vascular smooth muscle cells; λ₀, axial stretch ratio (L/L₀), where L is loaded length and L₀ is unloaded length; d, ex vivo loaded diameter; B, unloaded outer radius; H, unloaded thickness. *P < 0.05 vs. apoE⁻/⁻. †P < 0.05 vs. apoE⁻/⁻ + ANG II. ‡P < 0.05 vs. apoE⁻/⁻×TgSMC-Cat.
ANG II infusion alters the circumferential strain distribution of aortas from apoE<sup>−/−</sup> mice but does not affect aortic microstructure. To determine if H<sub>2</sub>O<sub>2</sub> is causally associated with the modulation of aortic mechanics during AAA progression, apoE<sup>−/−</sup> mice were treated with ANG II and an atherogenic diet for 7 days. This time point captured the earliest stage of ANG II-mediated AAA formation. The P-d behavior and compliance were unchanged in aortas from ANG II-treated apoE<sup>−/−</sup> mice compared with untreated apoE<sup>−/−</sup> mice (Fig. 3, A and B), and axial stretch was reduced (Table 1). The aortic mean circumferential stress-strain (E<sub>0</sub>) behavior (Fig. 3C) in both groups was comparable at low and mid-range strain, but ANG II-treated aortas reached greater strain values. Abdominal aortic opening angle increased significantly with ANG II treatment (Table 1 and Fig. 4A). In addition, after a 7-day ANG II treatment, mean circumferential wall strain change with radius E<sub>cr</sub>(r), which was fairly uniform across the vessel wall at baseline, was higher at the outer vessel wall compared with the inner wall (Fig. 3D). Note also that the circumferential strain at the inner wall was similar before and after ANG II treatment. These data indicate that short-term ANG II treatment alters the opening angle and circumferential strain distribution in the apoE<sup>−/−</sup> abdominal aorta.

To determine if catalase overexpression in apoE<sup>−/−</sup>xTg<sub>S</sub><sup>SMC-CAT</sup> aortas protected against ANG II-induced changes in wall strain, blood pressure and opening angle were measured after treatment with ANG II for 7 days. ANG II infusion elevated mean systolic blood pressure equally in both apoE<sup>−/−</sup> and apoE<sup>−/−</sup>xTg<sub>S</sub><sup>SMC-CAT</sup> mice (150 ± 13 vs. 147 ± 10 mmHg; P = NS). Importantly, catalase overexpression blunted the ANG II-induced changes in opening angle (Table 1) and in mean circumferential strain distribution (Fig. 3D).

To determine if ANG II promoted matrix changes that altered opening angle and circumferential strain in aortas from apoE<sup>−/−</sup> mice, total collagen protein and elastin fragmentation were measured in aortas from ANG II-treated apoE<sup>−/−</sup> and apoE<sup>−/−</sup>xTg<sub>S</sub><sup>SMC-CAT</sup> mice. Total collagen content (Fig. 4B) and adventitial thickness (Fig. 4C) in the ANG II-treated apoE<sup>−/−</sup>xTg<sub>S</sub><sup>SMC-CAT</sup> group decreased to the same level as aortas from apoE<sup>−/−</sup> mice. ANG II treatment had no effect on elastin fragmentation, which remained higher in apoE<sup>−/−</sup> aortas compared with apoE<sup>−/−</sup>xTg<sub>S</sub><sup>SMC-CAT</sup> aortas (Fig. 4D). Thus the data suggest that ANG II-induced decreases in apoE<sup>−/−</sup> mean circumferential wall strain and opening angle were not attributed to changes in collagen content or elastin fragmentation measured in the aortic ECM.
DISCUSSION

In this study, we examined the contribution of \( \mathrm{H}_2\mathrm{O}_2 \) to baseline vascular mechanics and to associated biomechanical changes in the setting of AAA formation in apoE\(^{-/-}\) mice. The data show, that early in ANG II-induced AAA formation, mean circumferential strain is increased in the outer abdominal aortic wall, while global aortic pressure-diameter mechanics are conserved. We further showed that SMC-specific catalase overexpression in the aortas of these mice prevented ANG II-induced mechanical alterations. Thus these data support an association between ROS production and early aneurysmal remodeling and mechanical adaptation.

AAA formation results from local aortic mechanical failure, but whether the spatial vulnerability of aneurysmal dilation is dominated by external hemodynamic forces or by local aortic weakness is not fully understood. Our study suggests that aortic microstructure in apoE\(^{-/-}\) mice may confer mechanical vulnerability to AAA formation. At baseline, the mechanical and material properties of apoE\(^{-/-}\) aortas were different from apoE\(^{-/-}\) \( \times \) Tg\( \text{SMC-Cat} \) aortas, in that apoE\(^{-/-}\) aortas had greater circumferential strain magnitude, i.e., had reduced circumferential stiffness, contained less adventitial collagen, and had less functional elastin. As elastic laminae rupture has been shown to reduce the stiffness of the rat abdominal aorta (31), elastin fragmentation in apoE\(^{-/-}\) aortas likely contributes to low stiffness compared with apoE\(^{-/-}\) \( \times \) Tg\( \text{SMC-Cat} \). The critical role of elastin to vessel stability is well established in AAA, as emphasized by other models of AAA development that directly degrade elastin fibers to cause aortic dilation (1). In this case, the basal increase in elastin fragmentation in apoE\(^{-/-}\) aortas may be due to the advanced age (16–18 wk) of the mice, as loss of elastin fiber structural integrity with aging is well established (35). Thus, given the baseline differences in elastin fragmentation between aortas from apoE\(^{-/-}\) and apoE\(^{-/-}\) \( \times \) Tg\( \text{SMC-Cat} \) mice, reduced elastin integrity may be a predisposing factor in the ANG II-infusion model of AAA.

ANG II infusion stimulates the progression of AAA in apoE\(^{-/-}\) mice, and short-term infusion allowed examination of early aneurysmal changes in the descending aorta and in the local abdominal aorta where AAA develop. Acute ANG II treatment promoted increased aortic opening angle and redistribution of mean circumferential stress across the abdominal aortic wall, despite conservation of global pressure-diameter behavior. Opening angle is a manifestation of residual stresses in an unloaded aortic ring. Residual stress is thought to be a consequence of achieving uniform stress distribution across the adventitial thickness under physiologic loading. Opening angle is affected by multiple factors, including changes in geometry (e.g., radius-to-thickness ratio) and changes in material properties, which arise through changes in the content and organization of cells and ECM. Evidence that opening angles are larger in aortic rings containing intimal atheromas compared with autologous nonatherosclerotic regions (40) suggests that opening angle enlargement is indicative of preferential growth and/or increased compressive forces in the vessel interior (11). The converse, however, has been demonstrated by Greenwald et al. (14), wherein enzymatic degradation of medial elastin and collagen affected an opening angle decrease. ANG II-treated apoE\(^{-/-}\) aortas in our study, however, did not have atheromas or significant changes in elastin integrity or collagen content. A possible difference...
between the characterization by Greenwald et al. and our study is that, in our model, degraded elastin fibers remained embedded within an intact medial collagen. Because other factors not measured here, such as collagen undulation and recruitment or ECM cross-linking, may underlie the microstructural basis for opening angle changes, a mechanical evaluation of strain distribution across the abdominal vessel was performed.

After ANG II treatment, mean circumferential strain distribution in the apoE<sup>−/−</sup> aorta outer wall adjusted to higher strain. Physiologic strain redistribution toward the adventitia has been explored as a protective mechanism to offload stress from the intima during hypertension (42) and may underlie the changes in mean strain observed here, especially given that ANG II infusion induced hypertensive blood pressure in apoE<sup>−/−</sup> mice. However, ANG II treatment raised blood pressure in apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> mice, with no change from baseline in either group.<sup>∗</sup><sup>P</sup> < 0.05; n = 3 for apoE<sup>−/−</sup>; n = 5–8 for apoE<sup>−/−</sup> + ANG II; n = 4 for apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub>; n = 5 for apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> + ANG II.

Fig. 4. Opening angle of apoE<sup>−/−</sup> and apoE<sup>−/−</sup> + ANG II aortas and morphology of apoE<sup>−/−</sup> and apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> aortas after ANG II treatment for 7 days. (A) apoE<sup>−/−</sup> abdominal aortic opening angle (α) increased after ANG II treatment. (B) Collagen content decreased in the apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> group and was unchanged in the apoE<sup>−/−</sup> after ANG II treatment. (C) Adventitial thickness in apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> aortas decreased to the same level as apoE<sup>−/−</sup>. (D) Elastin fragmentation in the abdominal aortic wall of apoE<sup>−/−</sup> mice remained higher than in aortas from apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> mice, with no change from baseline in either group. <sup>∗</sup><sup>P</sup> < 0.05; n = 3 for apoE<sup>−/−</sup>; n = 5–8 for apoE<sup>−/−</sup> + ANG II; n = 4 for apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub>; n = 5 for apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> + ANG II.

Changes in mice with overexpression of catalase before the development of AAA, the current data suggest that there are additional ROS-associated changes in the vessel wall that remain to be elucidated.

SMC-specific overexpression of catalase in apoE<sup>−/−</sup> mice allowed us to determine if H<sub>2</sub>O<sub>2</sub> is a critical molecular mediator in the subclinical mechanism of AAA pathogenesis. Aortas from these mice had thicker walls, greater functional elastin, and increased collagen content, which clearly accounted for the increases in mechanical stiffness detected at baseline compared with the apoE<sup>−/−</sup> group. However, after ANG II treatment, the collagen content and adventitial thickness of both apoE<sup>−/−</sup> and apoE<sup>−/−</sup>xTg<sub>SMC-Cat</sub> aortas were equivalent. Thus, given that overexpression of catalase-blunted ANG II-mediated changes in opening angle and mean circumferential strain distribution across the aorta, our data suggest that H<sub>2</sub>O<sub>2</sub> is functionally important and is involved in the control of local variations in remodeling across the vessel wall. ROS are shown to be significantly upregulated in established AAA (13, 29, 30), promoting ECM degradation by upregulating MMP activity via the NAD(P)H oxidase (16, 34). Our data establish H<sub>2</sub>O<sub>2</sub> as a mediator of subclinical AAA and support the pivotal role of ROS at all stages of AAA pathogenesis. Antioxidant studies in animal models also support the link between H<sub>2</sub>O<sub>2</sub> and AAA. Catalase deficiency was associated with AAA formation in a study utilizing the elastase infusion model (15), supporting our finding that catalase participates in mitigating AAA formation. It is plausible that hydrogen peroxide-scavenging by catalase blunted AAA formation by activating the subclinical mechanism to compensate for ANG II-induced collagen degradation. Indeed, our investigation showed a trend for increased procollagen type I
mRNA expression in apoE−/−xTgSMC-Cat aortas. We note that in the transgenic model of SMC-specific catalase overexpression studied here, we cannot exclude the possibility that catalase was a “sink” for freely diffusible H2O2 secreted by other cell types within the vessel wall.

In conclusion, the present study suggests that the earliest local mechanical changes in ANG II-mediated AAA development are associated with the local production of ROS. The ANG II-mediated increase in abdominal aorta opening angle was blunted by overexpression of catalase, suggesting that H2O2 is a pivotal molecular signal in the pathogenesis of AAA. Furthermore, our data suggest that H2O2 initially impacts arterial wall biomechanics via a mechanism independent of overt changes in the aortic microstructure metrics that we examined. Thus the data provide a critical links between oxidative stress, matrix composition, and biomechanical behavior.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).


