HEART FAILURE’S STRONG ASSOCIATION with old age (9, 28, 54) and exercise training

Mina A. Hanna, Curtis R. Taylor, Bei Chen, Hae-Sun La, Joshua J. Maraj, Cody R. Kilar, Bradley J. Behnke, Michael D. Delp, and Judy M. Muller-Delp

Structural remodeling of coronary resistance arteries: effects of age and exercise training

Young (4 mo old) and old (21 mo old) male Fischer 344 rats were acquired from the National Institute on Aging. The strain was sedentary or underwent 10 wk of treadmill exercise training. Coronary resistance arteries were isolated for determination of wall-to-lumen ratio, effective elastic modulus, and active and passive responses to changes in intraluminal pressure. Elastin and collagen content of the vascular wall were assessed histologically. Wall-to-lumen ratio increased with age, but this increase was reversed by exercise training. In contrast, age reduced stiffness, and exercise training increased stiffness in coronary resistance arteries from old rats. Myogenic responsiveness was reduced with age and restored by exercise training. Collagen-to-elastin ratio (C/E) of the wall did not change with age and was reduced with exercise training in arteries from old rats. Thus age induces hypertrophic remodeling of the vessel wall and reduces the stiffness and myogenic function of coronary resistance arteries. Exercise training reduces wall-to-lumen ratio, increases wall stiffness, and restores myogenic function in aged coronary resistance arteries. The restorative effect of exercise training on myogenic function of coronary resistance arteries may be due to both changes in vascular smooth muscle phenotype and expression of extracellular matrix proteins.

Verhoeff; van Geison; nanindentation; elastic modulus; hypertrophy

Address for reprint requests and other correspondences: J. Muller-Delp, Department of Biomedical Sciences, Florida State University, College of Medicine, 1115 West Call St., Tallahassee, FL 32306-4300 (e-mail: judy.delp@med.fsu.edu).

Heart failure’s strong association with old age (9, 28, 54) presents itself as the foremost cause of hospitalizations for patients over 65 yr of age (15), a population (13%) that will double in the next 30 yr (3, 26). Heart failure, a clinical diagnosis that is multifactorial in etiology, but nonetheless broadly characterized as being systolic or diastolic in nature, is often accompanied by an increase in left ventricular stiffness (1, 2, 7, 12, 27, 30, 46, 60, 61) and large-artery stiffening and correlates with the presence of ischemic disease (1, 8, 32). Structural remodeling of resistance arteries is an important determinant of microvascular dysfunction in both age- and diabetes-related heart failure (21, 40). Given the significance of coronary resistance arteries (50–150 μm) in distribution of oxygen and nutrient delivery to the heart (>50% of coronary vascular resistance is present in vessels of this size vs. 7% of coronary vascular resistance that resides in large-conduit arteries) (10, 20) and the association between ventricular and vascular stiffening, it is reasonable to conclude that coronary microvascular restructuring and dysfunction may accompany age-related heart failure. Although there are consistent reports of age-related reduction of elastic properties and medial degeneration in large-conduit arteries, e.g., aorta and carotid arteries (35, 43), age-induced alterations of the structure of resistance arteries do not follow the same pattern (43, 44), and little is known of the effects of age on remodeling of coronary resistance arteries. Similar to findings in age-induced vascular stiffening, individuals with diabetes mellitus demonstrate an increase in the stiffness in large-conduit arteries (1); however, Katz and colleagues (31) have recently shown that the stiffness of coronary resistance arterioles (<150 μm) declines with type 2 diabetes mellitus. Thus it cannot be assumed that the stiffness of coronary resistance arteries will increase with age, as does the stiffness of larger conduit arteries.

Exercise training has been shown to reduce stiffening of peripheral conduit arteries with age (52); however, the effects of exercise training on coronary arteriolar structure and stiffness have not been investigated. Similarly, although our laboratory has previously reported that age impairs both contractile and vasodilatory function of coronary resistance arteries (28, 37, 38), the interactive effects of age and exercise training on remodeling of coronary resistance arteries and related vasomotor function remain relatively unexplored. Therefore, the purpose of this study was to determine 1) whether aging increases the stiffness and impairs myogenic function of coronary resistance arteries, and 2) whether exercise training initiated at an advanced age reverses age-related changes in the stiffness and myogenic function of coronary resistance arteries.

MATERIALS AND METHODS

All procedures performed in this study were approved by the University of Florida Laboratory Animal Care and Use Committee. All methods employed complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (updated, 2011).

Animals. Young (4 mo old) and old (21 mo old) male Fischer 344 rats were acquired from the National Institute on Aging. The strain...
was chosen because cardiovascular function decreases with age without the development of hypertension (33). The animals were housed in a temperature-controlled room (23 ± 2°C) and kept on a 12:12-h light-dark cycle with water and rat chow provided ad libitum.

**Endurance exercise training.** Young and old rats were randomly assigned to a sedentary control group (YMS and OMS for young and old male sedentary, respectively) and exercise-trained group (YME and OME). Exercise-trained rats underwent exercise habituation, during which each rat walked on a motor-driven treadmill at 15 m/min (0° incline) and 5 min/day for 3 days. Posthabituation, the incline was raised to 15° for the duration of the training period, while the 15 m/min speed was maintained. In the first 5 wk of training, the time of exercise was increased by 10 min/wk until 60-min duration was reached by week 6. The exercise-trained rats continued to exercise 5 days/wk for 60 min/day for the remainder of the 10- to 12-wk training period (5). Vascular responses were determined no less than 48 h after the last exercise bout in exercise-trained rats. To determine the efficacy of the training protocol, skeletal muscle (soleus and gastrocnemius) was stored at −80°C for determination of citrate synthase activity, a measure of muscle oxidative capacity.

**Microvessel preparation.** Animals were anesthetized through isoflurane inhalation (3%/O2 balance) and euthanized via excision of the heart, followed by rapid placement of the heart into 4°C physiological saline buffer solution (PSS). Resistance arteries (<150 μm) branching from the left anterior descending artery were dissected using a stereomicroscope (Olympus SZX12). In vitro experimentation was conducted on the artery to determine myogenic vasoconstrictor responses, passive pressure-diameter characteristics, and gross vascular structure. Second-order distal septal resistance arteries (<180 μm) were used to determine vascular tissue mechanics via nanoindentation methodology (53).

**In vitro experimentation.** Resistance arteries were transferred to a Lucite container containing PSS, cannulated at each end with glass micropipettes, and secured via 11-0 ophthalmic suture (Alcon Laboratories, Fort Worth, TX). The isolated vessel chamber was transferred to the stage of an inverted microscope (Olympus IX71) interfaced in series with a video camera (Panasonic BG310), a horizontal video caliper (307A, Colorado Video, Boulder, CO), a data-acquisition system (Powerlab, AD Instruments, Colorado Springs, CO), and a video monitor (Panasonic WV-BM1410). Intraluminal pressure was maintained through isoflurane inhalation (3%/O2 balance) and euthanized via excision of the heart, followed by rapid placement of the heart into 4°C physiological saline buffer solution (PSS). Resistance arteries (<150 μm) branching from the left anterior descending artery were dissected using a stereomicroscope (Olympus SZX12). In vitro experimentation was conducted on the artery to determine myogenic vasoconstrictor responses, passive pressure-diameter characteristics, and gross vascular structure. Second-order distal septal resistance arteries (<180 μm) were used to determine vascular tissue mechanics via nanoindentation methodology (53).

**Nanoindentation.** Nanoindentation of all distal septal resistance arteries occurred within 1 h of vessel dissection. Following dissection, the distal septal resistance arteries were opened longitudinally using microscissors and placed onto the functionalized surface of a microscope slide (Fisherbrand Superfrost Plus), creating an “en face” endothelial protocol. The microscope slides were chosen since they promote adhesion by providing enough intermolecular forces to minimize sample movement during probe loading (53). To ensure proper adhesion of the vessel to the microscope slide, a modification to a previously established protocol used to adhere hydrogels to glass slides (57) allows for the deposition of a thin layer of glutaraldehyde. To do so, the microscope slides were first etched with a diamond tip scriber, such that identification of the treated area can be established postprotocol. To wash off particulates and ensure a clean surface, slides were washed with 100% EtOH and milipore H2O and placed in a 65°C oven until dry. Subsequently, 0.1 M NaOH was applied to sufficiently cover the region identified by the etched perimeter. The slides were then placed in the 65°C oven until dry (~30 min). Then 97% 3-aminopropyltrimethoxy silane (Sigma-Aldrich 440140) was pipetted onto the surface, completely covering the established region for 5 min. Slides were then rinsed and submerged in distilled water for 15 min. Postsubmerging, slides were rinsed again and placed in the 65°C oven to dry (5–10 min). Glutaraldehyde 0.5% (vol/vol) in phosphate-buffered saline (PBS; Cellagro 46-013-CM) was pipetted onto the slides for 30 min, followed by rinse/submerging for 10 min, and rinse/dry in oven for 5–10 min. Preparation of the slide preceded vessel dissection so that the excised vessel could immediately be placed on the slide. Approximately 40 μl of PBS was placed onto the surface of the slide, ensuring sample hydration during nanoindentation. To determine vessel location via the in situ optical microscope in the nanoindenter, a paper grid with black concentric circles and a center cross hair was attached using cyanoacrylate (superglue) to the bottom of the glass slide (53).

**Nanoindentation.** Nanoindentation was performed via a Tribolindenter (Hysitron, Minneapolis, MN), as previously described (53), using a nominal 100-μm-radius diamond cono-spherical fluid cell tip (Hysiti,

**Nanoindentation.** Nanoindentation was performed via a Tribolindenter (Hysitron, Minneapolis, MN), as previously described (53), using a nominal 100-μm-radius diamond cono-spherical fluid cell tip (Hysitron, AA03171104), as its radius acts to minimize stress concentrations for soft samples (~kPa range). This enables measurement within the linear stress-stain limit (elastic region) of the material (19).

The treated microscope slide with sample was attached to an iron block (~1 × 2 × 3 cm) via cyanoacrylate and loaded into the nanoindentation system. The sample was located using an in situ optical microscope, calibrated to allow indentation at identified position (6). Indents were made in the displacement-control mode of the instrument with a maximum displacement of 4,000 nm. A trapezoidal displacement cycle was used with a loading rate of 400 nm/s to maximum displacement, followed by a 5-s hold, followed by an unloading rate of 400 nm/s. All indents were performed at 25°C with the sample submerged in PBS. Surface detection was determined at 2 μN following calibration in the fluid reservoir to account for the forces the fluid exerted onto the tip. A minimum of five indents were done on the vessel within 1 h of excision. Indents spanned the length of the sample (spacing ≥ 60 μm). A total of 33 samples were tested (OME, n = 9; OMS, n = 8; YME, n = 9; YMS, n = 7). Methanol-soaked (99.8%) cotton swabs were used to clean the tip. Cleaning of the tip and the addition of PBS to the sample was done ad libitum.
Immunohistochemical analysis of elastin and collagen content.

Arteries were cannulated, pressurized, and fixed in Bouin’s solution. Fixed arteries were placed in optimal cutting temperature compound and stored at −80°C. Five-micrometer-thick cryosections were cut for analysis of collagen and elastin. Sections were stained with Verhoef-van Gieson (SycyteK Laboratories, ETS-1) for elastin (Verhoeff) and collagen (van Gieson) (25). Collagen and elastin measurements were determined via a color threshold in MATLAB (Mathworks, Natick, MA). A total pixel measurement for each vessel was done via Image J using a set threshold for all images. To accommodate for cross staining of both elastin and vessel nuclei by the Verhoef stain, an analysis of nuclei per cross-sectional area was done via 4,6-diamidino-2-phenylindole and green fluorescent protein using an overlap identification with color threshold in MATLAB. The analysis concluded no significant difference among groups; as such, the data presented herein also includes the nuclei cross-sectional area.

Solutions. PSS contained (in mM) 145 NaCl, 4.7 KCl, 1.2 NaH2PO4, 1.17 MgSO4, 2.0 CaCl2, 5.0 glucose, 2.0 pyruvate, 0.025 EDTA, and 3.0 MOPS with a pH of 7.4. PSS was supplemented with bovine serum albumin (1 g/100 ml; USB, Cleveland, OH) and passed through a 0.22-μm cellulose acetate filter (430015, Corning). Ca2+ -free PSS buffer preparation was identical except for the addition of 2 mM EDTA, the replacement of CaCl2 with 2.0 mM NaCl, and the exclusion of bovine serum albumin (53).

Statistical and data analysis. The development of spontaneous tone was expressed as the percent constriction relative to maximal diameter, and was calculated as:

\[
\text{Spontaneous Tone (\%)} = \left( \frac{\text{IDS} - \text{IDb}}{\text{IDS}} \right) \times 100
\]

where IDS is the steady-state inner diameter recorded in Ca2+-free PSS at a pressure of 60 cmH2O, and IDb is the starting baseline diameter.

Active and passive responses to pressure changes were normalized to the maximal diameter according to the formula:

\[
\text{Normalized Diameter} = \left( \frac{\text{ID}}{\text{IDS}} \right)
\]

where ID is the contact area at maximum force.

RESULTS

Animals. Body mass increased with age (Table 1). Exercise training reduced body mass in old rats. A significant difference in body mass was not observed for young rats with exercise training (Table 1). Heart-to-body weight ratio increased with exercise training in young and old rats. No difference in the left ventricle-to-heart weight ratio was determined between groups (Table 1). Exercise training increased citrate synthase activity by 46.5% in the young rats, and 82.2% in the old rats (Table 1), confirming the efficacy of the exercise training regimen, as previously demonstrated (51).

Characteristics of isolated vessels. Maximal diameter of resistance arteries was not altered by age or exercise training status (Table 1). Initial development of spontaneous tone during equilibration at a pressure of 60 cmH2O was greater in arteries from YME rats compared with all other groups (Table 1). Medial wall thickness was greater in arteries from old rats, regardless of training status (Table 1). Aging increased the wall-to-lumen ratio; exercise training reduced wall-to-lumen ratio in arteries from old rats to a level comparable to that of arteries from YME rats (Fig. 1). Exercise training also decreased wall-to-lumen ratio in arteries from young rats.

Myogenic responses. Myogenic constriction to increasing intraluminal pressure was reduced in coronary resistance arteries from old rats (Fig. 2A). Age did not alter passive responses to increasing pressure (Fig. 2B). Exercise training increased active myogenic responsiveness in coronary resistance arteries from both young and old rats (Fig. 2A). Following exercise training, myogenic responses in coronary resistance arteries from old rats no longer differed from the responses of arteries from YME rats. Passive pressure-diameter responses were not altered by exercise training (Fig. 2B).

Mechanical properties. \(E_{\text{eff}}\) and \(S\) declined with age in arteries from sedentary rats. In arteries from old rats, \(E_{\text{eff}}\) and
$S$ increased with exercise training. Load-displacement curves demonstrate a linear loading segment, indicative of an elastic response (Fig. 3C). A lower slope indicates a lower stiffness. A higher curvature of the upper 20% of the unloading segment is often observed and is indicative of sample-tip adhesion, commonly observed in the nanoindentation of soft biological tissue (39). This tip-sample adhesion is also the cause of the loading curve to return to a negative force rather than 0. Exercise training reduced the $E_{\text{eff}}$ (Fig. 3A) and $S$ (Fig. 3B) in the young rats to a level comparable to OMS, whereas an increase in $E_{\text{eff}}$ and $S$ was observed with exercise training in arteries from old rats.

**Elastin and collagen content.** Representative cross sections demonstrating collagen and elastin staining in 1) YMS, 2) OMS, 3) YME, and 4) OME are shown in Fig. 4A. The C/E was highest in arteries from OMS rats; however, there was not a significant increase above the C/E in arteries from YMS rats (Fig. 4B). Exercise training reduced the C/E in arteries from old, but not young, rats. The percent elastin, as a function of cross-sectional area, was higher in OME compared with all other groups (Fig. 4C). No significant difference in percent collagen as a function of cross-sectional area was detected among groups (Fig. 4D). Figure 4E, ii and iii, shows a representative figure for cross-sectional area, as done via Image J, and elastin and collagen in a given cross section as done via a color threshold in MATLAB, respectively. Figure 4F is a representative figure showing the background subtraction process.

**DISCUSSION**

In large peripheral conduit arteries, aging induces intimal-medial thickening and an increase in stiffness (34, 45). Arterial stiffness depends on intrinsic stress-strain relationships that are determined by structural properties of the blood vessel wall and by smooth muscle tone. In resistance arteries, structural changes and alterations in vascular smooth muscle function could lead to changes in both stiffness and intrinsic pressure-induced tone development, i.e., myogenic responsiveness. We tested the hypothesis that age would increase the stiffness of coronary resistance arteries, contributing to greater myogenic constriction in response to transmural pressure. In contrast to our hypothesis, the results demonstrate that age induced hypertrophic remodeling of the medial wall, but reduced the stiffness of coronary resistance arteries. Myogenic responses to increasing transmural pressure were impaired in the less stiff
coronary resistance arteries from old rats. Ten weeks of treadmill exercise training induced hypertrophic remodeling of the medial wall in coronary resistance arteries from both young and old rats; this remodeling was accompanied by an increase in stiffness of coronary resistance arteries from old rats, and a decrease in stiffness in arteries from young rats. Exercise training restored myogenic responsiveness in coronary resistance arteries of old rats to a level not different than that of YMS rats, and exercise training also enhanced myogenic responsiveness of coronary resistance arteries from young rats. C/E did not change in coronary resistance arteries with age, but decreased in aged arteries with exercise training. These data suggest that age-induced hypertrophic remodeling of coronary resistance arteries may result from smooth muscle hypertrophy, with concomitant loss of smooth muscle contractile function. Exercise training appears to restore vascular smooth muscle contractile function and increase elastin content in aged coronary resistance arteries; however, the increase in elastin content does not prevent stiffening of the aged vascular wall with exercise training.

Our laboratory (50) has previously reported an impairment of contractile responses in intact coronary resistance arteries of aged Fischer 344 rats and found evidence that endothelial mechanisms, potentially both endothelium-dependent constrict-

Fig. 3. Effective elastic modulus ($E_{\text{eff}}$, KPa; A), calculated stiffness ($S$, N/m; B), and representative load-displacement curves for second degree septal arteries (<180 μm; C). Exercise training reduced the $E_{\text{eff}}$ and $S$ in the young group to a level comparable to OMS, whereas an increase in $E_{\text{eff}}$ and $S$ was observed with exercise training in the old group. Values are means ± SE; n, no. of rats. *$P < 0.05$ vs. corresponding old group. ^$P < 0.05$ vs. age-matched sedentary group.

Fig. 4. A: representative 5-μm-thick cross sections for YMS (i), OMS (ii), YME (iii), and OME (iv) rats. B: collagen-to-elastin ratio (C/E) for YMS, OMS, YME, and OME rats, measured in pixels/total pixels. The C/E is most uniform (approaches 1) for OME, which is significantly different from its age-matched sedentary group (OMS) and corresponding young group (YME). C: percent elastin (%E) as a function of cross-sectional area, measured in pixels/total pixels. %E demonstrates the highest concentration of elastin in the OME group, significantly different from OMS and YME. D: percent collagen (%C) as a function of cross-sectional area, measured in pixels/total pixels. No differences in %C were detected between groups. E: representative cross section (i) demonstrating which pixels were counted for cross-sectional area (ii), and which pixels were counted for collagen and elastin (iii). With respect to iii, red pixels indicate collagen, green pixels elastin, and the yellow pixels are the regions where the two overlap. F: representative cross section demonstrating background subtraction: $i \rightarrow ii$. Values are means ± SE; n, no. of rats. *$P < 0.05$ vs. corresponding old group. ^$P < 0.05$ vs. age-matched sedentary group.
tors and/or dilators, contributed to the reduction of myogenic tone development. In the present work, we evaluated myogenic responsiveness in the absence of the endothelium; consistent with our previous work, we found myogenic responses to be impaired in denuded coronary resistance arteries from old rats, indicating that age-induced changes in the vascular smooth muscle also contribute to the blunting of myogenic responses. Indeed, we found that this impairment of myogenic responsiveness manifested as a loss of myogenic gain over the range of pressures that constitute the autoregulatory range (70–140 cmH$_2$O).

Our application of nanoindentation technology indicates that the mechanical properties of the arteriolar wall change with age and exercise training, independent of geometric remodeling. It is important to note that our purpose was to compare the stiffness of the arteriolar wall between young and old groups, and between age-matched sedentary and exercise-trained groups. Our approach, previously used to document reduced stiffness in cerebral vessels of space-flown mice (53), was uniformly applied to vessel segments adhered to glass slides in an en face presentation to avoid substrate variability; however, our results do not allow us to determine whether these material changes are paralleled by changes in arteriolar compliance at physiological blood pressure levels. The reported differences in stiffness could be due to changes in the endothelium, smooth muscle, or extracellular matrix components, and further study will be required to determine how specific changes in the material components of the arteriolar wall contribute to alterations in myogenic behavior.

Surprisingly, wall stiffness was reduced in the resistance arteries from old rats, a finding that is directionally opposite from reports in large-conduit arteries (34, 45). With advancing age, vascular smooth muscle has been reported to transform to a more secretory phenotype in large arteries, contributing to changes in the extracellular matrix and a proinflammatory environment in the vascular wall (13, 58). In coronary resistance arteries, switching of the phenotype of vascular smooth muscle could contribute to the change in C/E observed in the present study. In addition, a transition away from a contractile smooth muscle phenotype could contribute to the loss of myogenic contractile function in these resistance arteries (Fig. 2A).

The composition of the extracellular matrix is regulated by the vascular smooth muscle and fibroblasts, and, in turn, the function of both the endothelium and the vascular smooth muscle are regulated by interactions with extracellular matrix proteins. In coronary resistance arteries from old rats, wall-to-lumen ratio and the C/E increased; however, the stiffness of resistance arteries from OMS rats decreased, consistent with the idea that this reduction was related to decreased stiffness of the vascular smooth muscle, as opposed to changes in extracellular matrix components. Our previous data (36, 50) and the current assessment of myogenic responsiveness in aged coronary resistance arteries indicate a loss of contractile function in the smooth muscle, suggesting that aging may promote a transition from a contractile vascular smooth muscle to a less stiff smooth muscle. In contrast, the stiffness of aortic smooth muscle cells from monkeys increased with age, as assessed by atomic force microscopy of isolated cells (49); however, it should also be considered that reports of enhanced, unchanged, and diminished contractile function have been reported in the aged aorta (16, 23, 41, 47).

Exercise training reduced the C/E in arteries from aged rats, primarily due to an increase in the elastin content of the vessel wall. Interestingly, this increase in elastin was accompanied by increased wall stiffness, possibly due to stiffer vascular smooth muscle cells. Although total collagen content did not change with exercise training, collagen cross-linking may have altered the mechanical properties of the vascular wall in a manner that could not be reversed by the increase in elastin content that occurred with exercise training. Collagen cross-linking has been reported to be a major determinant of increasing ventricular stiffness and a key contributor to age-related diastolic dysfunction (3, 4, 9). The possibility of an exercise training-induced transition to a contractile (and possibly stiffer) smooth muscle phenotype is supported by the increase in myogenic responsiveness that we found in aged coronary resistance arteries post-exercise training. Further study will need to be performed to evaluate the effects of age and exercise training on vascular smooth muscle phenotype and collagen cross-linking in coronary resistance arteries.

Exercise training induced a reduction of wall-to-lumen ratio in coronary resistance arteries from both young and old rats. This finding is consistent with reports of exercise training-induced outward remodeling in the aorta and in coronary and skeletal muscle resistance arteries (22, 55). This remodeling effect, which may be mediated through long-term exercise-induced increases in flow (21), appears to be preserved with age. These results further suggest that the hypertrophic remodeling of the medial wall that occurred in arteries from OMS rats may be related to decreases in physical activity (4) and a subsequent reduction in the shear stimulus on the vascular wall.

The physiological mechanisms that underlie age-induced adaptations of the vascular wall were not investigated in this study; however, our results demonstrate some similarity with models of obesity and diabetes, suggesting potential common mechanisms. Coronary arterioles from type 2 diabetic mice undergo hypertrophic remodeling and demonstrate decreased stiffness (31). Similarly, hypertrophic remodeling is accompanied by reduced stiffness in coronary microvessels from pigs with metabolic syndrome (56). Microvascular remodeling in these models and in our model of aging may be driven by increased blood pressure, oxidant stress, or alterations in neurohumoral or inflammatory factors. Elevation of blood pressure often occurs in both type 2 diabetes and the metabolic syndrome; however, blood pressure does not increase with age in Fischer 344 rats (14, 18), suggesting that age-induced hypertrophic remodeling of coronary arterioles is blood pressure independent. In contrast, age-related endothelial dysfunction is accompanied by reduction of antioxidant protein levels in coronary arterioles (28), and endothelial dysfunction may exacerbate remodeling related to vascular smooth muscle hypertrophy. In the aged heart (24), as in the hearts of pigs with metabolic syndrome (56), inadequate coronary flow reserve may lead to ischemic conditions and increase the expression or cross-linking of collagen in coronary microvessels as well as in the myocardium. The physiological contributors to age-induced coronary microvascular remodeling remain to be identified. Similarly, the ability of exercise training to mitigate the effects of these signals will require further study.

J Appl Physiol • doi:10.1152/japplphysiol.01296.2013 • www.jappl.org
In summary, changes in both structural components and possibly in vascular smooth muscle function contribute to a reduction of arteriolar stiffness and impaired myogenic responsiveness in coronary resistance arteries with advancing age. Exercise training enhances myogenic responsiveness and mitigates the increase in wall-to-lumen ratio in aged coronary resistance arteries. The coronary resistance vasculature is subjected to constant intermittent compressive forces, and regulation of flow distribution is critical to the maintenance of diastolic flow to the endocardium in particular. The age-related shift to more compliant resistance arteries in which myogenic function is impaired could contribute to the maldistribution of coronary blood flow and an increased risk for ischemic events in the aged myocardium. Exercise training, even at an advanced age, may restore both mechanical and functional capacity of the vascular smooth muscle and the vascular wall of coronary resistance arteries, promoting improved distribution of coronary blood flow and oxygen delivery in the endocardial and epicardial microcirculation.

ACKNOWLEDGMENTS

The authors thank Xueling Teng and Shige Tsuda for technical support.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grants R01-HL-77224 and R01-HL-90937.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


J Appl Physiol • doi:10.1152/japplphysio1.01296.2013 • www.jappl.org