Age-related changes in cardiac structure and function in Fischer 344 × Brown Norway hybrid rats

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Hacker, Timothy A., Susan H. McKiernan, Pamela S. Douglas, Jonathan Wanagat, and Judd M. Aiken. Age-related changes in cardiac structure and function in Fischer 344 × Brown Norway hybrid rats. Am J Physiol Heart Circ Physiol 290: H304–H311, 2006. —The effects of aging on cardiovascular function and cardiac structure were determined in a rat model recommended for gerontological studies. A cross-sectional analysis assessed cardiac changes in male Fischer 344 × Brown Norway F1 hybrid rats (FBN) from adulthood to the very aged (n = 6 per 12-, 18-, 21-, 24-, 27-, 30-, 33-, 36-, and 39-mo-old group). Rats underwent echocardiographic and hemodynamic analyses to determine standard values for left ventricular (LV) mass, LV wall thickness, LV chamber diameter, heart rate, LV fractional shortening, mitral inflow velocity, LV relaxation time, and aortic/LV pressures. Histological analyses were used to assess LV fibrotic infiltration and cardiomyocyte volume density over time. Aged rats had an increased LV mass-to-body weight ratio and deteriorated systolic function. LV systolic pressure declined with age. Histological analysis demonstrated a gradual increase in fibrosis and a decrease in cardiomyocyte volume density with age. We conclude that, although significant physiological and morphological changes occurred in heart function and structure between 12 and 39 mo of age, these changes did not likely contribute to mortality. We report reference values for cardiac function and structure in adult FBN male rats through very old age at 3-mo intervals.

Cardiac structure and function are remarkably similar among mammalian species, and the use of animal models has been extremely helpful in developing treatment strategies for alleviating heart disease in humans. Extending animal studies beyond young adult ages to very old ages may provide similar gerontological studies. A cross-sectional analysis assessed cardiac changes in male Fischer 344 × Brown Norway F1 hybrid rats (FBN) from adulthood to the very aged (n = 6 per 12-, 18-, 21-, 24-, 27-, 30-, 33-, 36-, and 39-mo-old group). Rats underwent echocardiographic and hemodynamic analyses to determine standard values for left ventricular (LV) mass, LV wall thickness, LV chamber diameter, heart rate, LV fractional shortening, mitral inflow velocity, LV relaxation time, and aortic/LV pressures. Histological analyses were used to assess LV fibrotic infiltration and cardiomyocyte volume density over time. Aged rats had an increased LV mass-to-body weight ratio and deteriorated systolic function. LV systolic pressure declined with age. Histological analysis demonstrated a gradual increase in fibrosis and a decrease in cardiomyocyte volume density with age. We conclude that, although significant physiological and morphological changes occurred in heart function and structure between 12 and 39 mo of age, these changes did not likely contribute to mortality. We report reference values for cardiac function and structure in adult FBN male rats through very old age at 3-mo intervals.

Cardiac structure and function are remarkably similar among mammalian species, and the use of animal models has been extremely helpful in developing treatment strategies for alleviating heart disease in humans. Extending animal studies beyond young adult ages to very old ages may provide similar benefits to cardiovascular health of the growing aged population. In mammalian tissues, aging manifests as detrimental alterations in structure and function. Structural changes in the aging heart extend from cardiomyocyte cell loss, left ventricular (LV) hypertrophy, changes in ventricle chamber diameter, and collagen deposition (3, 13, 14), leading to overt functional changes such as lengthening of contraction and relaxation times and thus a decrease in heart rate (15). Decreases in fractional shortening, decreased LV end-systolic pressure (15, 33), and reduced cardiac output. These normal aging changes do not necessarily contribute to morbidity but are clearly associated with the general decline observed with aging. The Fischer 344 (F344) rat has been a standard model of aging with an extensive database on this genotype (29). Even though the F344 rat has been widely used in research, concerns have been raised whether this specific strain is appropriate for all gerontological studies because of its overuse and some severe age-related pathologies (53). The National Institute on Aging and the National Center for Toxicological Research responded to these concerns and found that, among others, the Fischer 344 × Brown Norway F1 hybrid rat (FBN) would complement the F344 aging studies (53). The FBN rat had significantly fewer pathological lesions compared with the F344 and a greater mean age for 50% mortality (29): ~33 mo for FBN compared with ~27 mo for F344 (46). Population analyses of the FBN show a longer maximal life span compared with F344 (~43 and ~35 mo, respectively (46)), and they provide an increased period of time in which changes associated with age can be examined in the relative absence of disease (29).

Echocardiography is a safe, repeatable, and portable technology that has been underutilized in the assessment of cardiac function in important mammalian experimental model systems (51). Studies in humans have provided visualization of structural or functional abnormalities that appear long before the detection of overt clinical disease (18). Structural and functional features of left ventricles assessed using echocardiography have been validated and have considerable accuracy compared with necropsy samples (17, 18, 42, 54). The efficacy of echocardiography in the rat model has been confirmed (10, 40, 41), and it has been used to evaluate treatment effects on cardiac function (34), to assess cardiac structural and functional characteristics of rats with surgically induced myocardial infarct (30) and hypertension (24, 32), and in genetic models of hypertrophic heart failure (37). Only recently has there been a report on baseline echocardiographic values for normal adult rats (51) and age-associated changes in the female F344 rat heart (9).

Although several studies have characterized the cardiovascular system in older rats (1, 5, 8, 9, 14, 21, 23, 33, 37), no study has examined functional and structural alterations over 30 mo of age. In this study we determined standard reference values for adult (12 mo) and aging (18 to 39 mo in 3-mo intervals) FBN male rat cardiovascular structure and function by using echocardiographic, hemodynamic, and histological measures.

Materials and methods

A total of 54 male ad libitum-fed FBN hybrid rats were purchased from the National Institute on Aging’s colony at Harlan (Oregon, WI). Baseline assessments of heart function and structure were conducted

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on rats at 12 mo and then performed at 3-mo intervals between 18 and 39 mo of age (n = 6 rats per time point) to provide an aging continuum from middle to extreme old age. All animals were healthy and free of clinical signs of short- or long-term illnesses.

In accordance with the “Guiding Principles in the Care and Use of Animals,” institutional approval was granted for this experimental protocol by the University of Wisconsin-Madison.

Heart function and structure were measured using echocardiography at all nine time points. Immediately after echocardiography, hemodynamic analysis was completed on 12- (n = 6), 18- (n = 6), 21- (n = 2), 24- (n = 4), 36- (n = 7), and 39-mo-old rats (n = 5).

Transthoracic echocardiography was performed using a Sonos 5500 ultrasonograph with a 12-MHz transducer (Philips). Noninvasive acquisition of two-dimensional guided M-mode images at the tip of papillary muscles and Doppler studies were recorded on anesthetized rats (50 mg/kg ketamine). The thickness of the posterior and anterior walls of the LV chamber and the LV chamber diameter during systole and diastole were measured using the leading edge-to-leading edge convention. All parameters were measured over at least three consecutive cardiac cycles. These parameters were used to calculate LV mass and fractional shortening as previously described (22). Pulse-wave Doppler was used to measure the velocity of blood through the mitral and aortic valves and to qualitatively examine the valve for evidence of mitral regurgitation. From these images, heart rate and the time between closure of the mitral valve and the opening of the aortic valve were calculated.

After echocardiography was completed, rats underwent hemodynamic analysis. Rats were further anesthetized (1 mg/kg

Table 1. Body weight and LV mass determinations for aging rats

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Body Weight, g</th>
<th>Postmortem LV Weight, g</th>
<th>LV Mass Estimated by Echocardiography</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>517 ± 20 (6)</td>
<td>0.84 ± 0.079 (6)*</td>
<td>0.92 ± 0.16 (6)*</td>
<td>0.84</td>
</tr>
<tr>
<td>18</td>
<td>499 ± 26 (6)</td>
<td>0.82 ± 0.033 (6)*</td>
<td>0.88 ± 0.088 (6)*</td>
<td>0.86</td>
</tr>
<tr>
<td>21</td>
<td>540 ± 40 (6)</td>
<td>0.86 ± 0.048 (6)*</td>
<td>0.85 ± 0.089 (6)*</td>
<td>0.87</td>
</tr>
<tr>
<td>24</td>
<td>594 ± 21 (3)</td>
<td>0.93 ± 0.062 (3)*</td>
<td>0.78 ± 0.057 (3)*</td>
<td>0.89</td>
</tr>
<tr>
<td>27</td>
<td>516 ± 55 (6)</td>
<td>0.85 ± 0.14 (6)*</td>
<td>0.94 ± 0.16 (6)*</td>
<td>0.92</td>
</tr>
<tr>
<td>30</td>
<td>560 ± 27 (5)</td>
<td>0.99 ± 0.14 (6)*</td>
<td>0.96 ± 0.065 (5)*</td>
<td>0.87</td>
</tr>
<tr>
<td>33</td>
<td>558 ± 50 (5)</td>
<td>1.03 ± 0.14 (6)*</td>
<td>1.12 ± 0.14 (5)*</td>
<td>0.79</td>
</tr>
<tr>
<td>36</td>
<td>468 ± 30 (7)</td>
<td>0.99 ± 0.11 (7)*</td>
<td>1.35 ± 0.227 (7)*</td>
<td>0.78</td>
</tr>
<tr>
<td>39</td>
<td>459 ± 39 (5)</td>
<td>1.09 ± 0.076 (5)*</td>
<td>1.35 ± 0.170 (5)*</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Values are means ± SD; nos. in parentheses are the number of animals analyzed. R is the correlation coefficient between the left ventricular (LV) mass determined by postmortem weighing and estimation of LV mass by M-mode echocardiography. a,b,c,d Body weights and echo LV masses with different superscripts are significantly different (P < 0.05) using ANOVA.

Fig. 1. Structural features of the aging rat left ventricle determined using echocardiography: LV mass (A), LV mass-to-body weight ratio (B), posterior wall thickness-to-body weight ratio (C), anterior wall thickness-to-body weight ratio (D), relative wall thickness-to-body weight ratio (E), and LV chamber diameter-to-body weight ratio (F). Regression analysis was performed to determine whether there was a significant effect of age on a specific left ventricular (LV) structure. ANOVA was used to determine differences among ages.
Table 2. **Echocardiographic analysis of aging rats**

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>n</th>
<th>LV/Body WT, mg/g</th>
<th>PW d, mm</th>
<th>AW d, mm</th>
<th>LVD d, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>1.77±0.27bc</td>
<td>1.9±0.1bcde</td>
<td>1.8±0.2a</td>
<td>6.9±0.5a</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>1.77±0.14c</td>
<td>1.9±0.2bcde</td>
<td>1.9±0.1b</td>
<td>6.6±0.2b</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>1.58±0.16cde</td>
<td>1.8±0.2bcde</td>
<td>1.7±0.2cde</td>
<td>6.9±0.3b</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>1.32±0.14d</td>
<td>1.9±0.1</td>
<td>1.8±0.2cde</td>
<td>6.3±0.1c</td>
</tr>
<tr>
<td>27</td>
<td>6</td>
<td>1.82±0.19bcde</td>
<td>2.0±0.2bcde, 2.1±0.1</td>
<td>6.3±0.4c</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>1.72±0.16bcde</td>
<td>1.9±0.1a</td>
<td>1.9±0.1cde</td>
<td>7.0±0.2b</td>
</tr>
<tr>
<td>33</td>
<td>5</td>
<td>2.02±0.20b</td>
<td>2.1±0.1bcde</td>
<td>1.9±0.1cde</td>
<td>7.4±0.8b</td>
</tr>
<tr>
<td>36</td>
<td>7</td>
<td>2.91±0.61ab</td>
<td>2.1±0.4</td>
<td>1.9±0.1</td>
<td>8.2±0.8a</td>
</tr>
<tr>
<td>39</td>
<td>5</td>
<td>2.95±0.33bcde</td>
<td>2.0±0.3bcde</td>
<td>1.8±0.2b</td>
<td>8.7±0.6b</td>
</tr>
</tbody>
</table>

LV/Body WT, left ventricle mass to body weight ratio; PW d, left ventricle posterior wall thickness in diastole; AW d, left ventricle anterior wall thickness in diastole; and LVD d, left ventricle diameter in diastole. a,b,c,d,e Within each column, values with different superscripts are significantly different (P < 0.05).

Sections from the 12-, 18-, 24-, 30-, and 36-mo-old animals were examined. Each LV section was delineated into quarters, and eight digital images (×20) were taken within the epicardium and eight images within the endocardium using an Olympus BH2 microscope and a Hitachi three-chip charge-coupled device camera (Hitachi, Japan). A 100-point grid was masked over the images. At each intersection of the grid, myocytes, interstitial fibrosis, or other was recorded, and the volume densities of cardiomyocytes [Vv(cm)] and fibrosis [Vv(fb)] were determined for each animal as follows: Vv = PP (structure)/PT, where P is the number of points hitting the structure and PT is the total number of test points (7). Mean volume densities for myocytes and fibrosis were determined for the whole left ventricle (1,600 test points) as well as the epicardium (800 test points) and the endocardium (800 test points).

Regression analysis was performed on the cross-sectional echocardiographic data sets to determine the effect of age on each measure. Echocardiographic, hemodynamic, and histological data also were analyzed using an ANOVA to determine differences among ages. All analyses were performed using the GLM procedure of SAS (SAS Institute, 1989). Significance was set at P < 0.05.

**RESULTS**

Body weight and echocardiographic structural features. Body weight of the rats between the ages of 12 and 33 mo remained relatively constant between 500 and 600 g. A significant decline in weight was observed at 36 mo (468 g) and 39 mo (459 g) (P = 0.0003; Table 1). LV mass as measured by wet weights obtained at necropsy gradually increased with age. At 39 mo, LV wet weights were significantly higher than those measured at 12–27 mo of age, and at 36 mo, LV weight was significantly greater than that observed at 12 and 18 mo of age (Table 1). LV mass as measured by echocardiography signifi-
Table 3. Echocardiographic analysis of heart function of aging rats

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>n</th>
<th>HR, beats/min</th>
<th>%FS</th>
<th>Peak E, cm/s</th>
<th>IVRT, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>413±13</td>
<td>58±2b</td>
<td>84±10b,c</td>
<td>0.021±0.001b,c</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>412±53</td>
<td>57±8b</td>
<td>82±16b,c</td>
<td>0.020±0.001c</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>371±14</td>
<td>69±6b</td>
<td>82±9b</td>
<td>0.016±0.003a,c,d</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>424±24</td>
<td>63±2b</td>
<td>81±4b</td>
<td>0.016±0.003a,d</td>
</tr>
<tr>
<td>27</td>
<td>6</td>
<td>417±21</td>
<td>57±3b</td>
<td>96±7b,c</td>
<td>0.019±0.003b,d,e</td>
</tr>
<tr>
<td>30</td>
<td>5</td>
<td>373±55</td>
<td>46±8b</td>
<td>100±20b,b</td>
<td>0.024±0.005b</td>
</tr>
<tr>
<td>33</td>
<td>5</td>
<td>389±22</td>
<td>44±5b</td>
<td>101±8b,b</td>
<td>0.024±0.002b,a,b</td>
</tr>
<tr>
<td>36</td>
<td>7</td>
<td>404±16</td>
<td>38±8a,d</td>
<td>98±13b,c</td>
<td>0.025±0.002b</td>
</tr>
<tr>
<td>39</td>
<td>5</td>
<td>397±37</td>
<td>30±6b</td>
<td>115±18b</td>
<td>0.027±0.004a</td>
</tr>
</tbody>
</table>

HR, heart rate. (ANOVA model showed no significant differences in HR); %FS, percent fractional shortening of the left ventricle; Peak E, peak velocity of early diastolic blood flow through the mitral valve; and IVRT, isovolumic relaxation time. Within each column, values with different superscripts are significantly different (P < 0.05).

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>n</th>
<th>HR, beats/min</th>
<th>AoP Mean, mmHg</th>
<th>LVP Peak, mmHg</th>
<th>LVEDP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>6</td>
<td>250±14</td>
<td>80±6</td>
<td>90±6</td>
<td>−3±2b</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>248±15</td>
<td>79±6</td>
<td>90±4</td>
<td>−1±2b,c</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>291±24</td>
<td>107±13b</td>
<td>105±10</td>
<td>−3±2b,c</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>293±17</td>
<td>97±11b</td>
<td>106±7a</td>
<td>−4±3a</td>
</tr>
<tr>
<td>30</td>
<td>7</td>
<td>275±126</td>
<td>72±10a,b</td>
<td>76±6c</td>
<td>0±2a,b</td>
</tr>
<tr>
<td>39</td>
<td>4</td>
<td>274±25</td>
<td>69±11a</td>
<td>71±9b</td>
<td>3±2a</td>
</tr>
</tbody>
</table>

AoP, mean aortic pressure; LVP, peak left ventricular pressure; and LVEDP, left ventricular end-diastolic pressure. Within each column, values with different superscripts are significantly different (P < 0.05).

Hemodynamic analyses. Hemodynamic analyses were performed on animals at 12, 18, 21, 24, 36, and 39 mo of age. Measures of aortic mean pressure and LV pressure in systole and diastole were recorded (Table 4). Mean aortic and peak LV systolic pressures increased significantly from 12 and 18 mo to 21 and 24 mo and then significantly decreased at 36 and 39 mo, whereas there was an increase in LV end-diastolic pressure at the oldest ages compared with the younger animals. A plot of end-systolic volume vs. percent fractional shortening (%FS), essentially a graph of the Frank-Starling curve, reveals a decrease in %FS as the left ventricle dilates, demonstrating that these aging hearts are on the descending arm of the length-tension relationship (Fig. 3). A plot of end-systolic volume vs. end-systolic pressure demonstrates a gradual decrease in elastance as the animals age (Fig. 4).
Histological analysis. Frozen cross sections of the left ventricle were taken at the midpapillary level and analyzed for volume densities of fibrosis and cardiomyocytes. Fibrotic infiltration of the left ventricle significantly increased with age [Fig. 5, A (18 mo) and B (36 mo), and Fig. 6A]. Fibrosis was more concentrated in the endocardium compared with the epicardium (Fig. 6A). The volume density of cardiomyocytes for the total left ventricle significantly decreased with age in rat hearts and was significantly less at 24 and 30 mo compared with that at 12 and 18 mo and decreased further at 36 mo (Fig. 6B).

**DISCUSSION**

The present study provides reference values for cardiac function in adult (12 mo) FBN male rats through middle to very old age (18–39 mo) at 3-mo intervals. Cardiac structural measures in the adult (12–24 mo) FBN male rat were very similar to reported values from similar ages and various other strains with respect to LV mass-to-body weight ratio (5, 8, 9, 20, 21, 28, 36, 37), anterior and posterior wall thicknesses (9, 21, 28, 37), and LV diastolic dimension (1, 5, 9, 21, 23, 28, 37). LV function in the present study was also similar to that reported in 12- to 25-mo-old rats of various strains. The %FS for the FBN rat between 12 and 24 mo of age ranged between 57 and 69%, indicating maintenance of systolic function through middle age. Other published reports for %FS ranged from 35 to 84% (1, 5, 9, 21, 23, 28, 37). This large range may be related to differences in heart rate, side effects of anesthesia, or measurement variables for different strains. LV pressure for our 12- to 24-mo-old rats also fell within one standard deviation of the ranges reported in the literature (LV pressure 105–130 mmHg) (1, 5, 8, 21, 23, 28, 33, 36, 37).

Functional cardiac measurements at old ages (27–39 mo) revealed a decline in %FS and LV pressure with age and indicated that these hearts were on the descending portion of the length-tension curve. The length-tension relationship in the heart, also known as the Frank-Starling mechanism, states that the greater the stretch or length of the LV fibers, the greater the force of contraction; however, if the fibers are overstretched, force declines. In this study a surrogate measure for the Frank-Starling relationship, a plot of end-diastolic volume vs. %FS, showed that the increased dilation of these aging hearts was detrimental as fractional shortening declined (i.e., they are on the descending arm of the length-tension relationship). A crude measure of contractility (the plot of end-systolic volume vs. end-systolic pressure) revealed a decrease in the performance of the heart similar to that recently reported using the pressure-volume relationship to measure LV function (33). The fall in %FS and LV pressure are quite striking and may be at least partially explained by the increase in fibrosis, apoptosis, and/or alterations in the β-adrenergic system. Snyder et al. (44) identified a decrease in the release of norepinephrine, which may affect blood pressure and %FS. Indeed, others also have shown a reduced response to catecholamines in aged aortas and hearts (5, 19, 25, 38, 44). Arosio et al. (5) also have reported an increase in adenosine A1 receptor gene expression in the aging rat heart, which would have a similar antiadrenergic effect.

**Fig. 5.** Fibrotic infiltration of the left ventricle in aging rats. A: midpapillary cross sections of an 18-mo-old rat left ventricle. B: a 36-mo-old left ventricle stained with Gomori trichrome for fibrosis (fibrotic tissue stained blue).

**Fig. 6.** A: Fibrotic tissue volume density (A) and cardiomyocyte volume density (B) of left ventricles in aging rats. Total volume densities were analyzed using ANOVA. a,b,c/Columns with different letters indicate significantly different values ($P < 0.05$).
Diastolic relaxation as measured by IVRT in the FBN rat progressively deteriorated with age. Values reported in the present study are remarkably similar to the findings of Boluyt et al. (9) in terms of the absolute values for IVRT and the declining relaxation with age. When IVRT is corrected for heart rate in the present study (occupying 11.58% of 1 beat), it also is similar to what has been reported previously by Forman et al. (12.25% of 1 beat) (21). This is in contrast to analysis of single cardiomyocytes from 32- to 33-mo-old female Fischer 344 × Brown Norway rats where no change in relaxation was observed with age (48). However, other rat strains do show impaired relaxation in single cardiomyocytes (4, 6, 13). The methodological differences in measuring relaxation in a whole animal versus an isolated cell preparation likely accounts for the differences. Wahr et al. (48) speculated that changes in relaxation in other rat species may be attributed to pathologies associated with aging, rather than aging itself, because the Fischer 344 × Brown Norway rat has a lower rate of age-related pathologies (29).

The impact of anesthesia on cardiac function during echocardiography in mice is dependent on strain, type of anesthesia administered, and the timing of echocardiographic measurements (39). Aging also confounds the effects of anesthetic agents and has been associated with an increased sensitivity in humans (47). Ketamine/xylazine depresses cardiac function in young mice (39). In older mice, ketamine/xylazine or halothane anesthesia resulted in a higher heart rate, compared with young mice (39). In older mice, ketamine/xylazine or halothane anesthesia resulted in a higher heart rate, compared with younger mice, when a minimally effective dose was employed (16). The two anesthetic agents differentially altered various electrographic intervals, making it difficult to determine how aging affects anesthetic pharmacodynamics. The effects of anesthesia on normal cardiac function in aging rats are unclear. In ketamine-anesthetized FBN male rats, we report an average heart rate of ∼400 ± 20 beats/min, which may be slightly elevated compared with values reported from 10 rats of an unspecified strain (296–388 beats/min) (26). Care was taken to administer anesthetic agents to effect, and no change in heart rate was observed (413 ± 13 beats/min for 12-mo-old rats and 397 ± 37 beats/min for 39-mo-old rats). These data indicate that the FBN rats had no age-related sensitivities to the effects of the anesthesia.

The cardiac extracellular matrix is composed mainly of collagen and plays a dynamic role in myocardial structure and function (35). This connective tissue framework, though, undergoes changes with age, including increased interstitial or replacement fibrosis associated with hypertrophied myocardium (52) as well as posttranslational modifications resulting in collagen insolubility (35). We identified an increase in the percentage of tissue in the left ventricle that became fibrotic with age, which is in agreement with other studies (2, 3, 14, 36). Fibrosis in the left ventricle accumulated disproportionately in the endocardium compared with the epicardium. F344 rats had similar patterns of fibrotic accumulation in the left ventricle (3). The increase in fibrosis in the endocardial region compared with the epicardial region may be due to increased inner wall stress during contraction. The blood flow to this region is likely compromised, resulting in ischemic events leading to the replacement fibrosis (3, 14). This ventricular tissue fibrosis imposes a viscoelastic burden that compromises diastole, including the rate of relaxation, diastolic suction, and passive stiffness (11).

Cardiomyocyte loss with age was evident as the volume density of cardiomyocytes decreased with the increase in fibrosis over time. In the endocardium of the aged rat left ventricle, there were many atrophied cardiomyocytes surrounded by interstitial fibrosis and significantly enlarged myocytes. Myocyte loss and hypertrophy are characteristic of the heart’s aging process, and these changes were found to precede the occurrence of ventricular dysfunction in the Fisher 344 rat (2). The mechanisms of myocyte loss are via apoptosis and/or necrosis, the necrotic process leading to an inflammatory reaction with macrophage infiltration, fibroblast activation, and scar formation. Mitochondrial dysfunction may initiate cardiomyocyte loss via the mitochondrial pathway of apoptosis. Mitochondrial DNA (mtDNA) mutations accumulate with age in nonreplicative tissues such as skeletal muscle, heart, and brain. mtDNA deletion mutations remove genes encoding critical subunits of the electron transport system, resulting in mitochondrial enzymatic dysfunction that appears to cause muscle fiber atrophy and fiber loss in aging rats (12, 49). Mitochondrial deletion mutations have been detected in both ventricles of aging FBN rat hearts, increasing in number with age (50). In turn, mtDNA mutations have been shown to activate apoptosis in cardiac tissue of mice (27, 55).

The effects of age on rat cardiovascular function were very similar to changes observed in clinically normal aging humans. Humans free of cardiovascular disease show decreasing myocardial systolic performance over time as indicated by decline in midwall fractional shortening and a decrease in cardiac index (43). In addition, normal aging in humans is accompanied by a decrease in diastolic function as indicated by an increase in IVRT (31, 45), which also was seen in our aging rats.

Reference values for cardiac structure and function in the aging FBN rat model have been presented in this study. Understanding the structural and functional changes of these aged, altered hearts and how they continue to sustain sufficient function may provide valuable insight into the postponement or prevention of cardiovascular disease.

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