Cardiac Hypertrophy in Response to an Isometric Training Program in the Cat

Kathryn H. Muntz, William J. Gonyea, and Jere H. Mitchell

SUMMARY  Cats were operantly conditioned to perform isometric exercise to determine the effect of this type of training program on heart morphology. The hearts of 11 cats trained for 2-9 months were removed and weighed. Heart weight-to-body weight ratios were increased significantly in the exercised animals over 15 controls (3.86 vs. 2.91 g/kg, P < 0.001). Body weights were not significantly different between the two groups. All chambers of the heart were larger in the exercising animals, compared to controls, as evidenced by a significant increase in both left (2.58 vs. 1.95 g/kg, P < 0.001) and right ventricular weight-to-body weight ratios (0.77 vs. 0.55 g/kg, P < 0.002), and increased atrial weight-to-body weight ratios (0.51 vs. 0.37 g/kg, P < 0.01). The same conclusions were reached when the heart weights were not normalized to body weight. To study the progression of cardiac hypertrophy throughout the exercise regimen, we implanted radiopaque markers in the left ventricle of cats and monitored wall thickness on a monthly basis in these animals, using biplane cinefluorography. Eleven cats implanted with markers were trained for 1-6 months. Left ventricular wall thickness increased in the trained animals after 1 month (13.15%) and continued to increase until, at 6 months, wall thickness was increased 32.5% from the initial measurement. The increase in wall thickness for the exercise period was correlated with the amount of isometric work that the cat performed, both total isometric work (r = 0.71, P < 0.05) and the mean daily isometric work (r = 0.76, P < 0.01). Males exercised longer, on the average, than females (5 vs. 3 months) and did significantly more total isometric work and mean daily isometric work, even after work was normalized to body weight. Males also exhibited larger increases in wall thickness than females (29.7% vs. 2.4%, P < 0.005). The change in wall thickness was significantly correlated with lean body mass (r = 0.95, P < 0.05). In addition, muscle fiber diameter was significantly larger in exercised animals than in controls (19.88 vs. 13.35 µm, P < 0.001). There was more variability in fiber size in the exercised animals, indicating that all fibers did not increase to the same extent. Circ Res 49: 1092-1101, 1981

ONE WAY the myocardium responds to an increased workload is by enlarging its mass. Accordingly, exercise increases the work of the heart, but the nature of myocardial hypertrophy has not been precisely defined in different forms of physical activity. Cardiac hypertrophy has been studied extensively in animals subjected to a pathological pressure overload, such as aortic banding (Meerson, 1968; Zak and Rabinowitz, 1979).

It has been shown that there is a marked increase in mean arterial pressure which accompanies the isometric contraction of even a small mass of skeletal muscle. There is little change in mean arterial pressure with dynamic exercise, the overload presented to the heart being a volume overload (Tuttle and Horvath, 1957). Dynamic exercise can induce cardiac hypertrophy, both in experimental animals and in humans (Barnard, 1975; Scheuer and Tipton, 1977). It has been unclear, however, whether an increase in heart mass accompanies an isometric training program. In this regard—in an attempt to produce more of an isometric load, rats with weights attached have been trained to climb an incline—and left ventricular hypertrophy resulted. This was not, however, a purely isometric model (Jaweed et al., 1974).

Increased left ventricular wall thickness has also been demonstrated in human athletes, by means of echocardiography (Morganroth et al, 1975; Howald et al., 1977; Longhurst et al., 1980). These athletes performed high-resistance exercise such as rowing or wrestling. Again, neither form of exercise is exclusively isometric training.

There are several problems with the aforementioned studies which deserve comment. First, the studies were not longitudinal, so preadaptation cannot be ruled out. Another problem is that, in all of these studies, a combination of isometric and dynamic exercise was performed; thus it is difficult to determine which exercise is having an effect on heart mass. Because of these problems, we chose a model which would allow us to examine heart mass changes and left ventricular wall thickness changes in cats operantly conditioned to perform isometric exercise. Lean body mass was measured in some of the animals in order to correlate it with changes in wall thickness. Left ventricular fiber diameter was measured histometrically in the mid-myocardial region upon termination of the exercise program.
Methods

Behavioral Training Program

Diepstra et al. (1980) found it possible to condition cats operantly to perform isometric exercise. It was shown that this model produced an increase in arterial pressure similar to that seen in humans performing isometric exercise. Animals used in those experiments were adult cats of either sex, with no selection as to breed.

Briefly, the procedure involved training 23-hour food-deprived cats to extend the right forelimb through a tunnel in a training enclosure and grasp a hinged bar, holding it against a microswitch for 15 seconds. The microswitch activated a manually preset electronic clock and a buzzer which provided audio feedback as long as the microswitch was kept closed. At the end of a successful holding interval, the feeder was triggered, which provided a food reward for the cat. Weights attached to the bar via a pulley provided the load the cat must hold. After the cat was trained, it was started at a weight of 100 g. The weight was increased by 20 g every 2 days and the cats were trained 5 days a week. Twenty-three-hour food deprivation was continued throughout training program, so that the only source of food, except on one of the resting days, was that received in the training enclosure. Body weight was obtained on all animals daily to make sure they were getting enough nourishment. The cats were trained until they refused to exercise against the increasing weight. This varied from 2 to 9 months, with 4 months as an average exercise period.

Heart Weights

The hearts of 11 cats that had been exercised for 2-9 months at different intensities were removed and weighed, along with the hearts of 15 control cats. The atria were removed from the ventricles at the atrioventricular septum, and the free wall of the right ventricle was dissected from the interventricular septum. The atria, the right ventricle, and the atrioventricular septum, and the free wall of the right ventricle were removed and weighed, resulting in a mean wall thickness of each animal. The distance between the anterior bead and clip and the posterior bead and clip were localized by biplane cinefluorography, which consisted of a simultaneous anterior-posterior and a lateral cinefluorogram. In this way the beads and clips were visualized in a motion picture. A steel sphere of known diameter was used to determine the projecting distance for analysis of each film. To facilitate fluoroscopy, the cats were tranquilized with 10 mg/kg ketamine hydrochloride. Concomitant electrocardiograms were taken to correlate the film with the cardiac cycle. Measurements of the distance between the anterior bead and clip and the posterior bead and clip were made from the film, using a digitizing system, and the distances were calculated on a PDP 12 computer. These measurements represented anterior and posterior wall thickness, respectively. The average wall thickness through three heart beats was used as an indication of wall thickness. This represented approximately 60 measurements. The anterior and posterior measurements were then averaged, resulting in a mean wall thickness of each animal. The distance between the two beads was used to estimate internal diameter of the left ventricle. The cats were subjected to fluoroscopy at the initiation of the exercise program and at monthly intervals thereafter. The initial fluoroscopy was taken 2-3 weeks after surgery. Because of variability among animals inherent in the technique of bead and clip insertion, wall thickness measurements for each animal were evaluated as the percentage of the initial wall thickness measurement.

In aligning the equipment, one could not be sure that the animal was placed in exactly the same position each time, so to determine whether the position of the cat during fluoroscopy influenced wall thickness, we constructed a wooden model. The model, which had beads and clips attached that approximated the position of the markers in the intact animal, was placed in front of the fluoroscope and filmed while spinning. A coefficient of
variation was calculated on 25 frames of the spinning model. We obtained a coefficient of variation of 3.6% on the anterior wall thickness and of 3.9% on the posterior wall thickness.

When the same control animal was fluoroscoped 3 times in one week, the coefficient of variation was 2.5% on anterior wall thickness and 2.9% on posterior wall thickness.

**Isometric Work**

Isometric work was calculated on a daily basis on all 11 exercised cats implanted with beads and clips, according to Monod (1972), as the product of the force (g) and the time (t) it was maintained.

\[ \text{Isometric work} = \text{force (g)} \times \text{time (sec)}. \]

This is work in a physiological and not a physical sense. Time was calculated by multiplying the number of events performed on the day in question by the holding interval for each event (15 seconds). Time was then multiplied by the weight held (g) to obtain an assessment of isometric work for that day. Monthly isometric work was determined, and mean daily isometric work was calculated by dividing the monthly isometric work by the number of days exercised during that month. Total isometric work for the entire exercise period also was calculated, as was mean daily isometric work performed during the exercise regimen. Because of variation in body size, all assessments of isometric work were normalized to body weight. Thus the results are expressed as gram seconds per kilogram (g sec/kg).

**Lean Body Mass**

Lean body mass determinations were made according to densitometric methods developed in guinea pigs (Rathbun and Pace, 1945). For this method to be used in cats, the composition of the lean body mass had to be similar to that of guinea pigs. It has been determined that the lean body mass has a similar composition in many mammalian species, including the guinea pig and the cat (Spray and Widdowson 1950); thus it was felt that this method would be appropriate.

The measurements were made on 7 exercised animals that were implanted with beads and clips. In addition, these measurements were made on 8 control animals. After the hearts were removed from the animals, the cats were shaved. Body specific gravity was determined on the animal by the water displacement method. The animal was weighed to the nearest gram by suspension in air. Then it was suspended in a tank of 25°C water and weighed. Care was taken to ensure that no air was trapped in the thorax, and the weight was allowed to stabilize to permit air in the ears and pharynx to surface.

The specific gravity of the animal could be calculated readily according to the formula:

\[ \text{Specific gravity} = \frac{\text{weight in air}}{\text{weight in air} - \text{weight in water}} \]

The percentage of body fat then was calculated from the specific gravity according to the following formula derived in guinea pigs (Rathbun and Pace, 1945):

\[ \% \text{ Fat} = 5.501/\text{specific gravity} - 5.031. \]

Percent lean body mass was determined by subtracting % fat from 100. Lean body mass was calculated by multiplying the % lean body mass by the animal's body weight.

**Histological Quantification**

Ten trained animals and 8 control cats were anesthetized with Nembutal intravenously (35 mg/kg), and given 1000 units of sodium heparin.
5 minutes, the hearts were extirpated. The aorta was cannulated and the heart perfused retrogradely with a warm saline rinse (37°C) at 90 mm Hg until the coronary vessels were cleared (5 minutes). The hearts then were perfused with a solution of 2% glutaraldehyde in 0.2 M phosphate buffer (pH 7.3) for 15 minutes, and stored in the primary fixative in the refrigerator. In some hearts, capillaries were not open and cleared of blood, so an analysis was not performed.

Some of the tissue was processed for electron microscopy to check the state of contraction as well as the fixation. The sarcomeres were at resting length and the tissue was adequately fixed. A block of tissue was removed from the lateral wall of the left ventricle halfway between the mitral valve and the apex, and post-fixed in 2% glutaraldehyde for at least 24 hours. It was then processed routinely for light microscopy and embedded in methyl methacrylate. The tissue was positioned so that the vertical axis of the left ventricle from the epicardium to the endocardium was sectioned. With this orientation, most of the fibers of the midmyocardial region were cut in cross-section.

Sections were cut at 5 μm using an AO rotary microtome, and were stained with periodic acid Schiff's reaction for polysaccharides. This stain was used because the glycocalyx coat around the muscle cell stains very darkly, facilitating fiber diameter measurement.

Muscle fiber diameters were measured in the mid-myocardial region of the sections. Three cross-sectional fields were selected randomly from the midmyocardial region, and were photographed at 250×. Black and white prints (8 X 10) were made. A magnification correction factor was calculated for each photograph by measuring the distance between two objects under the microscope using a micrometer, and then measuring the distance between the two objects on the photograph. The photographs then were placed on a digitizing tablet, and the diameter of the muscle cells digitized. The diameters of the cells were calculated from the digitized points by a Dec System 10 computer. The greatest width of the least diameter was used as an indication of fiber size (Dubowitz and Brook, 1973). Only those cells with a centrally located nucleus were analyzed. One hundred to 300 fibers from each animal were measured. The coefficient of variation on measuring a single field 3 times by this method was 0.67%. Cell frequency distributions of fiber size were calculated at 2-μm intervals by the computer on each animal.

Statistical Analyses

When two groups were compared, a two-sample t-test was used unless the data were expressed as a percentage or Bartlett's test for equal variances determined that variances between the two groups were not equal. In these instances, the nonparametric Mann Whitney two-sample test was used (Zar, 1974). A significance level of 0.05 was used for these and all subsequent analyses.

Body weight was analyzed separately in the exercised and control groups, using a single factor analysis of variance to determine whether body weight changed over time. Bartlett's test determined that nonparametric analysis should be employed for wall thickness measurements. A Kruskall-Wallis analysis of variance was used, and a nonparametric multiple comparison test for unequal sample sizes was employed (Noether, 1976). This analysis was used to compare mean daily isometric work performed each month. Simple correlations were performed between several of the variables and correlation coefficients calculated. All values are expressed as the mean ± standard error of the mean.

Results

Heart Weights

Heart weight-to-body weight ratios were significantly increased in exercised animals over controls, although body weights between the two groups were not significantly different. Figure 2 shows that the heart weight-to-body weight ratio was increased 32% in the exercised group, compared to the control group. The cats were exercised for 2-9 months.

Left ventricular weight-to-body weight ratios were significantly increased in the exercised group, compared with control values. However, there was no significant difference in left ventricular weight-to-right ventricular weight ratios between the 2 groups, as seen in Figure 3.

Right ventricular weight-to-body weight ratios were significantly increased over controls, as well as
LVW/BW LVW/RVW

FIGURE 3 Left ventricular weight-to-body weight ratios (LVW/BW) and left ventricular weight-to-right ventricular weight ratios (LVW/RVW) in exercised and control animals (mean ± SEM).

atrial weight-to-body weight ratios (Fig. 4). Thus, all chambers of the heart exhibited cardiac enlargement in response to the training program.

There was no significant difference in water content between the hearts of the 5 exercised cats and the 11 control cats, indicating that the increase in heart weight was not due to edema.

When the hearts were not normalized to body weight, the same conclusions were reached. Total heart weight, both left and right ventricular weights, and atrial weights all were significantly increased in the exercised over control animals (Table 1).

Left Ventricular Wall Thickness Study

The 11 exercised animals in this study trained for periods of 1–6 months; 6 of these animals were male, and 5 female. Males trained for 5.33 ± 0.49 months and females trained for 3.00 ± 0.55 months.

The animals performed an average of 11.18 ± 1.04 events per day throughout the training period.

Of the 8 cage confined control animals, 6 were confined for 5 months, and 2 for 3 months; 6 of these animals were female and 2 were male. In the experimental control group studied for 2 months, 2 animals were male, and 1 female.

Body weight did not change significantly over time in either the exercised animals or the control animals.

Left Ventricular Wall Thickness

There was a significant increase in wall thickness in the exercised animals on a monthly basis (p < 0.01) (Fig. 5). Wall thickness increased 13.1% after 1 month of training and, by 6 months of training, wall thickness increased 32.5% from the initial measurement.

In contrast, there were no significant increases in

![Graph showing changes in left ventricular wall thickness](image)

FIGURE 5 Changes in left ventricular wall thickness in cats exercised for up to 6 months. Wall thickness is expressed as the percent of the initial measurement (mean ± SEM).

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 15)</th>
<th>Exercised (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HW (g)</td>
<td>10.23 ± 0.60</td>
<td>14.07 ± 0.80*</td>
</tr>
<tr>
<td>LVW (g)</td>
<td>6.88 ± 0.43</td>
<td>9.44 ± 0.56*</td>
</tr>
<tr>
<td>RVW (g)</td>
<td>2.06 ± 0.14</td>
<td>2.79 ± 0.21*</td>
</tr>
<tr>
<td>AW (g)</td>
<td>1.29 ± 0.09</td>
<td>1.84 ± 0.18*</td>
</tr>
<tr>
<td>HW/BW (g/kg)</td>
<td>2.91 ± 0.09</td>
<td>3.66 ± 0.15†</td>
</tr>
<tr>
<td>LVW/BW (g/kg)</td>
<td>1.95 ± 0.05</td>
<td>2.58 ± 0.09‡</td>
</tr>
<tr>
<td>RVW/BW (g/kg)</td>
<td>0.98 ± 0.03</td>
<td>0.77 ± 0.06‡</td>
</tr>
<tr>
<td>AW/BW (g/kg)</td>
<td>0.37 ± 0.02</td>
<td>0.51 ± 0.06†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

* P < 0.05.
† P < 0.01.
‡ P < 0.001.
wall thickness in the cage-confined control animals for up to 5 months, and in the experimental control group studied for 2 months.

Internal diameter did not change with the exercise program. It was 1.91 ± 0.11 cm at the initiation of the exercise program and 2.01 ± 0.23 after 6 months of training.

**Isometric Work**

Mean daily isometric work increased significantly throughout the exercise program (Table 2).

When isometric work/kg for the entire exercise period was correlated with the change in wall thickness from initial to final measurement, a correlation coefficient of 0.71 was obtained ($P < 0.02$). A significant correlation was found between mean daily isometric work/kg for the entire exercise period, and change in wall thickness ($r = 0.76, P < 0.01$) (Fig. 6).

There was a significant difference in the amount of isometric work performed by males and females, both when expressed as total isometric work/kg, and when expressed as mean daily isometric work/kg. This was accompanied by a significant difference between sexes in left ventricular wall thickness changes (Fig. 7).

**Lean Body Mass**

There was no significant difference in percent lean body mass between exercisers and control animals. Exercisers were 80.11 ± 2.43% lean body mass and controls were 79.07 ± 2.82%. When percent lean body mass was compared between all males and all females, a significant difference was found. Males were 84.25 ± 2.18% lean body mass and females were 75.46 ± 1.43% lean body mass ($P < 0.02$). When percent lean body mass of the exercised animals was correlated with wall thickness change in the 7 exercised animals, a coefficient of 0.86 was found ($P < 0.02$). When body weight in the exercised group was correlated with wall thickness change, a coefficient of 0.87 was obtained ($P < 0.02$). However, when actual lean body mass was correlated with wall thickness change, the coefficient was very high ($r = 0.95, P < 0.002$) (Fig. 8).

**Fiber Diameter**

Mean fiber diameter was increased from 13.35 ± 0.85 μm in control animals to 19.68 ± 0.82 μm in exercised animals ($P < 0.001$). Figure 9 shows photomicrographs of the midmyocardial region from a control and an exercised animal. A mean frequency distribution based on 100 fibers was calculated at 2-μm intervals in the exercised and controls groups. These data are expressed graphically in Figure 10. It can be seen from this graph that the entire population of fiber sizes is shifted to larger values in the trained group. It is also obvious that the distribution curve of diameters is much wider in the trained group, with a much larger range of fiber sizes.

**Table 2** Monthly Isometric Work

<table>
<thead>
<tr>
<th>Month</th>
<th>Mean daily isometric work/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7,485 ± 1,380 (n = 11)</td>
</tr>
<tr>
<td>2</td>
<td>14,550 ± 4,189 (n = 10)</td>
</tr>
<tr>
<td>3</td>
<td>15,290 ± 1,957* (n = 10)</td>
</tr>
<tr>
<td>4</td>
<td>14,250 ± 3,232 (n = 7)</td>
</tr>
<tr>
<td>5</td>
<td>21,600 ± 4,560* (n = 5)</td>
</tr>
<tr>
<td>6</td>
<td>20,010 ± 4,784*† (n = 4)</td>
</tr>
</tbody>
</table>

* Results are expressed as mean ± SEM.
† $P < 0.02$ when compared with month 1.
$P < 0.02$ when compared with month 2. All other comparisons were nonsignificant.
Discussion

Although it has long been recognized that endurance type exercise induces cardiac hypertrophy, little is known about the effect of isometric exercise on heart size. Using echocardiography, Morganroth et al. (1975) examined the hearts of 56 athletes. They found an increase in left ventricular end-diastolic volume and left ventricular mass in athletes trained in dynamic type exercises, such as running or swimming, but left ventricular wall thickness was normal. In isometric exercisers such as wrestlers and shot putters, they found normal end-diastolic volumes, but found that left ventricular wall thickness and mass were significantly increased compared to normal subjects. Another echocardiographic study found increased left ventricular wall thickness in rowers compared to long distance runners, swimmers, and untrained subjects. The increase in wall thickness was attributed to a pressure load while rowing (Howald et al., 1977). In addition, it was recently determined that competitive weight lifters had increased left ventricular mass over both heavy and light control subjects (Longhurst et al., 1980).

The data from this study have clearly demonstrated that long-term isometric exercise produces an increase in the size of the heart. The reasons for the hypertrophy are speculative. Whereas hypertension or aortic banding certainly induces cardiac hypertrophy by placing a pressure overload on the heart, the overload is continuous. Studies of intermittent pressure overload indicate that when the pressure is maintained for a brief period of time (seconds) no hypertrophy results (Folkow and Rubenstein, 1966). However, when the intermittent overload is maintained for hours or days (Sizemore et al., 1973; Marcus et al., 1977), cardiac hypertrophy is the result. In our investigations, cats per-
formed an average of 11, 15-second events per day, and this is a very short exposure to an increased pressure load. Previous studies with this model have determined that left ventricular systolic pressure increases 23% when the animal is pressing against a resistance of 300 g. Left ventricular hypertrophy could be anticipated because the pressure load is on the left ventricle. It is interesting that both right ventricular and atrial hypertrophy were seen in response to the exercise. Right ventricular hypertrophy could be explained if pulmonary artery pressure were increased during isometric exercise. We are not aware of any published study of pulmonary artery pressures recorded during isometric exercise, and these studies would be useful to do, using this model.

Right ventricular weight has not often been reported in investigations of left ventricular hypertrophy in response to a pathological pressure overload. In a study by O'Keeffe et al. (1970), dogs with a balloon around the aorta for 6 weeks developed both left and right ventricular hypertrophy. The reason for this is unknown, and may be related to the structure of the fibers of the heart. A similar phenomenon may be occurring in our animals. However, right ventricular hypertrophy in the cat might result from an intermittent increased pressure load on the right ventricle.

Another possible explanation of the cardiac hypertrophy is that sympathetic activation to the myocardium increases the work of the heart by increasing contractility. Left ventricular contractile force has been shown to increase during the performance of isometric exercise by humans (Krayenbuel et al., 1972). It has been demonstrated with the experimental model used in this study that isometric exercise induces a significant increase in the maximum rate of left ventricular pressure rise (dP/dT) over pre-exercise values (Diepstra et al., 1980), and dP/dT has been shown to be a sensitive indicator of contractility (Wallace et al., 1963). Isoproterenol, a drug that increases myocardial contractility, is known to induce cardiac hypertrophy when administered in small repeated doses (Stanton et al., 1968). In this regard, it has been reported that exercised rats that have been sympathectomized by chemical means did not develop cardiac hypertrophy, although control animals did (Oatman-Smith, 1976). Unfortunately, blood pressure recordings were not obtained, so the possibility that the treatment decreased arterial blood pressure cannot be ruled out. It seems possible that the hypertrophy seen in isometric exercisers could be a combination of two effects, increased pressure load and increased contractility.

It was apparent that there was a relationship between the amount of work that the animals performed and wall thickness changes during the exercise program. Those cats that had performed more isometric work developed larger increases in wall thickness than cats that performed less work. Longhurst et al. (1980) found increased left ventricular mass in competitive weight lifters, but a smaller increase in amateur body builders, an indication that the intensity of the exercise influences the degree of hypertrophy.

In contrast, Morganroth et al. (1975) found no differences in left ventricular wall thickness or mass between world class runners and college runners, despite the fact that the college athletes manifested inferior times. No correlation was reported to exist between the estimate of training level and echocardiographic left ventricular mass or chamber size in champion childhood swimmers (Allen et al., 1977). The method for evaluating training level was not described, however.

There have also been conflicting animal studies with regard to the effect of the intensity of training on heart size, but most studies indicate that there is a relationship between the two parameters. In swimming rodents, investigators have found that there is a correlation between intensity of training and the presence or absence of hypertrophy (Leon and Bloor, 1968; Oscai et al., 1971a). In female rats, free running produced no hypertrophy, whereas forced treadmill running did (Jaweed et al., 1974). Bloor et al. (1970) reported that, in swimming rats, different intensities and different durations of exercise programs produce different degrees of hypertrophy. In none of the human or animal studies was it possible to obtain a direct estimate of the total amount of work performed by the subjects.

Although wall thickness did increase, the internal diameter of the left ventricle did not increase, which was evidence that left ventricular volume did not increase. This type of hypertrophy is called concentric hypertrophy and is characteristic of a chronic pressure overload (Grant et al., 1965). With a chronic volume overload such as dynamic exercise, the ventricular volume will increase significantly.

No sex differences were reported in the degree of cardiac hypertrophy found in police cadets in response to an endurance training program (DeMaria et al., 1978), although the increase in end-diastolic volume and mass in female hockey players was not as great as that seen by the same investigators in male endurance exercises (Zeldis et al., 1978). The findings on sex differences in experimental animals subjected to endurance exercise have been conflicting, with some reports of greater cardiac enlargement in females (VanLierre and Northrup, 1957; Oscai et al., 1971b) and others reporting greater increases in males (Tepperman and Pearlman, 1961). Although, in this study, there was a relationship between isometric work and wall thickness change, it was not established whether the difference in isometric work between sexes was directly responsible for the larger increases in wall thickness seen in males, or if the difference was related to unknown factors. It is unclear whether females, if
they could be motivated to perform, would exhibit wall thickness increases similar to males. A recent echocardiographic study found a significant correlation between lean body mass and left ventricular mass in controls and athletes, although the correlation coefficient was very low 0.276, $P < 0.03$ (Longhurst et al., 1980). Although in the present investigation, only 7 exercised animals were studied, significant correlations were found with wall thickness change and % lean body mass ($r = 0.86$). An even higher correlation was found with actual lean body mass and wall thickness change ($r = 0.95$). The reason that such a high correlation was found may relate to the fact that the cats were in a training program which was very similar for all animals. In the human study, though, both athletes—in a diversity of training programs—and controls were combined.

Because no assessment of lean body mass was made prior to the exercise regimen, it is not known whether the animals increased their lean body mass in proportion to the increased wall thickness or whether animals with a higher initial lean body mass exercised longer, thus demonstrating larger wall thickness increases. In exercised animals, the percent lean body mass was not larger than that of control animals, which implies that the isometric exercisers did not increase lean body mass.

Fiber diameters increased from 13.35 $\mu$m in control animals to 19.68 $\mu$m in exercised animals. One drawback of the study is that the state of contraction is unknown, although electron microscopy of some of the tissue indicated the tissue was in diastole. In future studies arrest with KCl might be beneficial.

The diameter changes were similar to those seen in racing greyhounds, although descriptions in this study of preparation of the tissue and measurements of fiber diameters were vague (Carew and Covell, 1978). Changes of similar magnitude in fiber diameter have been reported in pressure-induced pathological hypertrophy in experimental animals and humans (Roberts and Wearn 1941; Lowe and Bates 1948; O'Keefe et al., 1978), although some investigators have reported increases in fiber diameter that are smaller (Korecy and Rakusan, 1977) and increases that are greater (Karser et al., 1925; Meerson 1962).

Interestingly, the frequency distributions of fiber diameters in exercised animals were not only shifted to larger values, but the variability of fiber sizes was increased in the exercised animals over controls. If diameter changes were not only shifted to larger values, but the variability of fiber sizes was increased in the exercised animals over controls. If one examines the few cell frequency distributions of myocardial fiber size reported in the literature, this same phenomenon can be seen in humans with simple hypertension (Lowe and Bate 1948), and in rats with aortic banding (Dowell et al., 1976; Korecy and Rakusan 1977). This finding implies that some of the fibers are increasing to a greater extent than others. The fibers in the heart do not run exactly parallel to one another, so fibers may be subjected to different tensions when an increased load is placed on the myocardium. Differential enlargement of myocardial fibers has been demonstrated in different regions of the heart in pathological pressure overload (Anversa et al., 1978).

There was no correlation in this study of fiber size and wall thickness change, or fiber size and isometric work. There was considerable variation in fiber size in the control animals, and since the initial fiber size is unknown, it is impossible to know the change in fiber size in each animal.

In summary, we have shown that isometric exercise does induce cardiac hypertrophy in the cat, as demonstrated by increased heart weight-to-body weight ratios in exercised over control animals. Studies using biplane cinefluorographic analysis of left ventricular wall thickness indicated that the increase in wall thickness was related to the amount of isometric work that the cat performed. Males performed significantly more isometric work than females and exhibited greater increases in wall thickness. There was a significant correlation between lean body mass and the change in wall thickness. Muscle fiber diameter was significantly larger in the exercised animals, when compared to control measurements. The controlling mechanisms for the cardiac hypertrophy seen in isometric exercise are unresolved.

Acknowledgments

We are grateful for the technical assistance of James Harper and Jean Ann Dixon, and the secretarial assistance of Helen Patterson.

References


Carew TE, Covell JW (1978) Left ventricular function in exercise-induced hypertrophy in dogs. Am J Cardiol 42: 82-88


CARDIAC HYPERTROPHY WITH ISOMETRIC EXERCISE/Muntz et al.


Lowe TE, Bate EW (1948) The diameter of cardiac muscle fibers: A study of the diameter of muscle fibers in the left ventricle in normal hearts and in the left ventricular enlargement of simple hypertension. Med J Aust 1: 467-469


Wallace AG, Skinner NS, Mitchell JH (1963) Hemodynamic determinants of the maximal rate of left ventricular pressure. Am J Physiol 205: 30-36


Cardiac hypertrophy in response to an isometric training program in the cat.
K H Muntz, W J Gonyea and J H Mitchell

doi: 10.1161/01.RES.49.5.1092

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/49/5/1092.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/