Effect of Acute Exercise Stress in Cardiac Hypertrophy:  
I. Correlation of Regional Blood Flow and 
Qualitative Ultrastructural Changes 

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Ultrastructural myocardial cell changes were determined in eight miniswine after the 
development of pressure-overload hypertrophy induced by supra-valvular aortic constriction. 
Four miniswine served as control animals. Regional myocardial blood flows were measured at 
rest and during exercise stress with radioactive microspheres after two days and one month of 
aortic constriction. Exercise stress, causing the heart rate to increase to 85 percent of its 
maximum, was imposed twice weekly for 7 minutes on four pressure-overloaded animals and 
the four control animals to elicit differences between the control and experimental groups that 
might not occur at rest. After one month of pressure overload the swine were killed and 
myocardial samples were processed for electron microscopy. Ultrastructural changes similar to 
those in hypertrophied hearts were present throughout the left ventricular walls of the pressure-
overloaded animals. Other changes consistent with ischemic injury were present in the subendocardial regions of pressure-overloaded animals subjected to exercise stress. These 
changes included disorganization of myofibrils, disintegration and broadening of Z-bands, 
swelling and aggregation of mitochondria, electron-dense deposits in mitochondria, decreased 
cristal density and vacuolization of mitochondria, intracellular edema, margination and 
clumping of nuclear chromatin, and a decrease of glycogen granules. Regional ischemia in the 
subendocardium of these animals was confirmed by functional studies which showed decreased 
regional myocardial blood flow to the subendocardium during exercise and S-T segment 
elevation for the first 2-10 days after inducing pressure overload. The ischemia, as shown by 
flow studies, during exercise stress persisted in the compensatory stage of hypertrophy although 
S-T segments returned to normal. Thus, the combined effect of pressure overload and exercise 
stress can produce focal subendocardial ischemia in the compensated, hypertrophied heart. 

INTRODUCTION 

The morphologic changes occurring in the pressure-overloaded heart depend on the 
severity of the pressure overload and how rapidly it is imposed on the heart [1–4]. 
Clinically, ischemia has been induced in patients who have enlarged hearts without 
coronary artery disease by suddenly increasing the workload, e.g., by exercise stress 
test [5]. This suggests that an imposed physiologic stress, i.e., exercise, on the 
hypertrophied heart may result in ischemic myocardial injury. The mechanism 

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inducing this ischemia is thought to be a relative diastolic hypoperfusion due to heterogeneous intramyocardial compressive forces [6–8].

Recently, our laboratory reported that although regional myocardial blood flows of pressure-overloaded animals at rest were similar to those of control animals, when exercise stress was imposed, after two days and one month of pressure overload, endocardial blood flows decreased 45 percent below control exercise levels [9]. Electrocardiographic and light microscopic findings indicated that significant ischemic injury had occurred during the early uncompensated state of developing cardiac hypertrophy. The return of the electrocardiograms to normal and the absence of recent, acute lesions on light microscopy correlating with the stable, compensated stage of hypertrophy, even though the endocardial hypoperfusion persisted during exercise stress, suggested that (1) wall stress decreased in the stable, compensated stage of hypertrophy, resulting in decreased oxygen demands; (2) coronary reserve in the stable, compensated hypertrophied heart was adequate to meet the metabolic demands; or (3) the morphologic changes occurring when exercise stress was imposed on the stable, compensated hypertrophied heart were acute and could only be identified at the ultrastructural level. We undertook this study to determine what ultrastructural changes, if any, occurred in the stable, compensated stage of cardiac hypertrophy when acute exercise stress was imposed.

METHODS

Animal Preparation

We used Yucatan miniswine, weighing about 45 kg, who were trained to run on a treadmill for periods up to 15 minutes at speeds up to four mph. Twelve animals were randomly selected for this study. Out of these, eight were used for supra-valvular banding of the ascending aorta.

All animals underwent left thoracotomy under halothane anesthesia and oxygen administration. Catheters were placed in the supra-valvular aortic chamber proximal to the constricting band, the left ventricle, and the left atrium. The aorta was constricted with nylon cable that had been covered with dacron mesh in eight animals. Constriction was increased until peak supra-valvular systolic aortic pressure increased 75–100 mm Hg above the pre-constriction control level of 142 ± 3 mm Hg. A Biotronex aortic flow transducer was placed on the aorta between the aortic valve and the constricting band. An electrode was placed on the epicardium of the anterior surface of the heart and a hook electrode was placed on the endocardium [10]. All catheters and cables were tunneled subcutaneously to the back where they were exteriorized. After surgery four constricted animals were randomly selected to be a nonexercised hypertrophy group. Four other animals were similarly instrumented but without aortic constriction to serve as controls.

Experimental Design

The animals were separated into three experimental groups. Group 1 (N = 4) were control animals who were instrumented and exercised but did not have aortic constriction. Group 2 (N = 4) were aortic constricted animals who were exercised and had cardiac hypertrophy at autopsy. Group 3 (N = 4) were aortic constricted animals who were not exercised, but had cardiac hypertrophy at autopsy. Cardiac hypertrophy was considered present if the heart weight/body weight ratio exceeded 3.65 g/kg, since this value represents the 99 percent confidence limit of the control values.

Two days after surgery a resting heart rate was obtained in all animals. Phasic
aortic pressure and left atrial pressure were monitored using Elema-Schonander pressure transducers and a Mingograf 81 Elema-Schonander 16-channel recorder. Aortic flows were monitored using a Biotronex 310 flow meter. At rest myocardial blood flows were determined by injecting a dose of radioactive microspheres into the left atrium. The animals to be exercised were placed on a treadmill and run until a heart rate of 240 beats/min (about 85 percent of maximal) was obtained. A second dose of microspheres was given after the heart rate stabilized at 240 beats/min for at least two minutes. Groups 1 and 2 animals were monitored twice weekly at rest and during exercise of seven minutes' duration which elicited a heart rate of 240 beats/min. Both groups 1 and 2 were exercised two times per week. Group 3 animals were monitored only weekly. Radioactive microspheres for myocardial blood flow measurements were given at two and 30 days after surgery. The animals were killed 24 hours after the final experimental microsphere study.

**Microsphere Method and Postmortem Studies**

Radiolabeled microspheres were used to measure the distribution of blood flow throughout the myocardium. Our methods have been described in detail elsewhere [11]. Briefly, we obtained polystyrene microspheres, 7–10um in diameter and labeled with $^{46}$Sc, $^{85}$Sr, $^{95}$Nb, and $^{141}$Ce (3M Company, St. Paul, MN). These were suspended in a 10 percent solution of dextran. After the radioactivity per unit volume of these microspheres was established, the microspheres were vigorously mixed, and measured volumes, containing about $6 \times 10^6$ microspheres, were injected through the left atrial catheter at rest and during exercise. Blood flows for the various regions of the myocardium were calculated using the aortic flow measured with the aortic flow probe. These flows are expressed as regional myocardial blood flow ($RMBF$) in ml/min/per 100 gm using the formula:

$$RMBF = cpm/g \ T/cpm \ I \times AF \times 100,$$

where $cpm/g \ T$ is the counts per minute per gram of tissues, $cpm \ I$ is the counts per minute injected, and $AF$ is aortic flow (ml/min).

After completion of the study, the hearts were excised and the coronary arteries were immediately perfused with a 3 percent gluteraldehyde solution buffered with 0.1M sodium cacodylate PH 7.2–7.4. The perfusion pressure was 100 mm Hg. The free wall of the right ventricle, left atrium, the great vessels, valves, surface vessels, and epicardial fat were removed. The left ventricle was then weighed. Two cm thick slices were taken from base to apex and subdivided into anterior, posterior, and septal walls. These were further subdivided into epicardial, mid-wall, and endocardial regions. Samples of 1 to 3 gm were placed in counting vials with formalin.

The tissue was analyzed for the distribution of the microspheres on a Packard-Auto-Gamma Spectrometer, model 5912, equipped with a multichannel analyzer. The spectrometer measured the energy emitted in the photo peak window of each isotope. From these measurements the radioactivity per gram of tissue was calculated according to our previous methods [11] using a Hewlett-Packard 9825A programmable calculator. Mean values and paired "t" tests were used for statistical analysis.

**Light and Electron Microscopy Procedures**

Tissues, about 0.5 cm$^3$, were cut from the epicardium and endocardium of the fixed left ventricular wall. Samples were taken from the posterior and lateral regions of the apex, base, and the area midway between the base and apex. No samples, however,
were taken from the anterior wall of the left ventricle because of the possibility of damage to the tissues as a result of instrumentation. Blocks of the tissues were immediately transferred to 3 percent buffered gluteraldehyde in 0.1 M sodium cacodylate pH 7.2–7.4 to avoid any damage. These blocks were further cut into small strips, 2 × 3 mm, taking care that the tissues remained wet and were further fixed for 24 hours in 3 percent buffered gluteraldehyde at 4°C. After three washings in 0.1 M sodium cacodylate buffer, pH 7.2–7.4, tissues were postfixed in 2 percent osmium tetroxide, in 0.1 M sodium cacodylate buffer, pH 7.2–7.4, for two hours at 4°C. Further washing in cacodylate buffer was followed by dehydration in graded concentrations of 35, 50, 70, 95, and 100 percent of acetone. Infiltration was done for 10 hours with a mixture of 50 percent acetone and 50 percent araldite resin. Tissues were embedded, using flat molds, in araldite resin of the composition: araldite 502, 30 ml; DDSA (Dodecenylsuccinic anhydride), 20 ml; DMP-30 [Tri(Dimethylaminomethyl)phenol], 1 ml; these supplies were purchased from Pelco, Tustin, CA. Polymerization was done at 60°C for 2–3 days. Thick sections, 0.5–1μm, were cut with glass knives and stained with Toluidine blue for light microscopy. Tissues which were abnormal by light microscopic examination were excluded from ultrastructural studies. Thin sections, showing silver to silver-grey interference colors, were cut with diamond knife (DuPont) on LKB III ultratome and picked up on 200–300 mesh copper grids. The sections were stained with saturated uranyl acetate solution in 50 percent ethanol for 15 minutes and Reynolds lead citrate solution for two minutes. Electron microscopy was done on Zeiss 10 transmission microscope. Ultrastructural examination was conducted on both longitudinal and cross sections from eight regions of left ventricle, each being subdivided into endocardial and epicardial zones. Electron micrographs were printed on 8 × 10 inch photographic paper at various magnifications.

To quantify the extent of myocardial necrosis or fibrosis present in the different regions, we superimposed a metric grid (1 cm/side) on the projected image of each histologic slide. The image was projected with a diameter of about 25 cm. We used an electronic digitizer, Graf Pen GP-3, to count the number of test grid intersections lying on necrotic or fibrotic tissue. A Hewlett-Packard 9825A desktop calculator was programmed to control the digitizer, accumulate the counted points, and calculate the percentage of the area of each myocardial region, i.e., epicardial, midwall, and endocardial, that was necrotic. At least 50 fields were measured in each myocardial region.

RESULTS

Since body weights were similar in the three groups, the ratio of left ventricular weight to body weight was used as an index of the degree of cardiac hypertrophy present. Left ventricular/body weight ratio (gm/Kg) was 3.34 ± .12 (SEM) in control animals and was significantly increased in groups 2 and 3, 5.23 ± .25 and 4.84 ± .24, respectively (P < .05).

Systemic Hemodynamics

Systemic hemodynamic measurements for the three groups are presented in Table 1. Resting heart rates at two days and one month after surgery were markedly similar in all groups. Likewise, both groups were able to achieve similar heart rates during exercise, indicating a similar workload. Supra-valvular systolic pressure at rest increased significantly after aortic banding and remained constant during the month.
TABLE 1
Systemic Hemodynamics

|                 | Rest                  | Exercise               |
|-----------------|-----------------------|------------------------|
|                 | 2 Day | 1 Month | 2 Day | 1 Month |
| Heart Rate      |        |         |       |         |
| (beats/min)     |        |         |       |         |
| Group 1         | 85 ± 9 | 87 ± 5  | 245 ± 6† | 248 ± 6† |
| Group 2         | 99 ± 9  | 95 ± 5  | 242 ± 6† | 240 ± 8† |
| Group 3         | 100 ± 5 | 97 ± 5  | —      | —       |
| Supra-Valvular  |        |         |       |         |
| Systolic Pressure (mm Hg) |        |         |       |         |
| Group 1         | 135 ± 4 | 131 ± 4 | 180 ± 7† | 181 ± 6† |
| Group 2         | 224 ± 10* | 225 ± 11* | 227 ± 19*† | 291 ± 15*† |
| Group 3         | 218 ± 10* | 220 ± 8*  | —      | —       |

Values are means ± SEM.
*P < 0.05, compared to group 1
†P < 0.05, compared to resting value within group
N = 4 for each group

During exercise it increased significantly (P < 0.05) at two days in group 2 and increased more between two days and one month.

Regional Myocardial Blood Flow

Regional myocardial blood flow in the three groups is presented in Table 2. At rest epicardial blood flow was similar in all three groups. However, groups 2 and 3 had significantly (P < 0.05) greater endocardial blood flows than did group 1. This change was also reflected in the increased ratios of endocardial to epicardial flow in groups 2 and 3. At one month endocardial blood flow in groups 2 and 3 returned to control levels.

During exercise both increased myocardial blood flow. Within each group the flow increases were similar at both two days and one month after surgery. However, endocardial blood flow in group 2 is significantly less than observed in group 1. Epicardial blood flow during exercise was similar in all groups.

S-T Segment Changes

S-T segment changes recorded in both epicardial and endocardial electrodes are shown in Table 3. Significant changes (P < 0.001) in S-T segments were found between groups 1 and 2 at two days during exercise, however, at 14 days no significant differences were observed among all three groups.

Light Microscopic Changes

In group 1, control miniswine, there was very little necrosis or fibrosis present on routine histologic sections. The extent of damage was greater in the epicardial regions. This difference probably represents injury at the time of surgical instrumentation.

In those animals developing hypertrophy, groups 2 and 3, a greater amount of necrosis or fibrosis was present in the epicardial, midwall, and endocardial regions. In the non-exercise-stressed animals, group 3, the amount was less than 1 percent of
|                | Rest |                          | Exercise |                          |
|----------------|------|--------------------------|----------|--------------------------|
|                | 2 Days | 1 Month | 2 Days | 1 Month |
|                | Endo | Epi | Endo | Epi | Endo | Epi | Endo | Epi |
| Group 1        | 95 ± 4 | 79 ± 7 | 99 ± 4 | 85 ± 4 | 290 ± 20 | 261 ± 20 | 298 ± 30 | 271 ± 21 |
|                | [1.20 ± .04] | [1.16 ± .04] | [1.12 ± .07] | [1.10 ± .08] |       |       |       |       |
| Group 2        | 118 ± 15* | 78 ± 8 | 103 ± 8 | 85 ± 6 | 187 ± 28* | 260 ± 25 | 205 ± 29* | 309 ± 35 |
|                | [1.51 ± .08]* | [1.21 ± .07] |       |       | [0.72 ± .05]* |       | [0.66 ± .05]* |       |
| Group 3        | 121 ± 13* | 91 ± 11 | 92 ± 6 | 84 ± 6 |       |       |       |       |
|                | [1.33 ± .08] | [1.10 ± .06] |       |       |       |       |       |       |

Values are mean ± SEM.

*P < 0.05, compared to group 1 at rest or during exercise
Mean endocardial/epicardial flow ratios ± SEM are in brackets.
## EXERCISE STRESS IN CARDIAC HYPERTROPHY

### TABLE 3

|             | 2 Days |          | 14 Days |          |
|-------------|--------|----------|---------|----------|
|             | Rest   | Exercise | Rest    | Exercise |
| Group 1     | .56 ± .19 | .53 ± .18 | .30 ± .10 | .37 ± .15 |
| Group 2     | .78 ± .21 | 4.51 ± 1.5* | .54 ± .15 | .74 ± .31 |
| Group 3     | .59 ± .20 |          | .40 ± .10 |          |

Values are mean ± SEM  
*P < 0.001, compared to group 1 during exercise at 2 days

As the exercise-stressed, hypertrophying animals, group 2, showed a significant increase of regional myocardial necrosis or fibrosis, particularly in the subendocardial region. The amount of necrosis or fibrosis present in the subendocardial region and visible on light microscopy was significantly greater in group 2 compared to group 3, 3.50 ± 0.71 vs. 0.96 ± 0.20 percent, respectively (P < 0.05).

### Ultrastructural Changes

At least 16 blocks from both epicardial and endocardial regions of each animal that were normal on light microscopy were examined for ultrastructural changes. Non-necrotic or non-fibrotic tissues were selected for study to determine if early ultrastructural changes, not visible on light microscopy, were present indicating cellular injury related to the most recent exercise stress episode. In group 1, control miniswine, the ultrastructural features of the myocardial cell were normal (Fig. 1).

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**FIG. 1.** Control animal. Longitudinal section of left ventricular myocardium obtained from the subendocardial region shows densely packed mitochondria and regularly arranged sarcomeres. ×30,000.
In those animals developing hypertrophy, groups 2 and 3, ultrastructural changes similar to those described before in cardiac hypertrophy were observed in both endocardial and epicardial regions (Fig. 2). These changes comprised a decrease of mitochondrial matrix density, partial vacuolization of mitochondria, slight disorientation of myofibrils, disorganization and widening of Z-bands, widening of intercalated discs, swelling of sarcoplasmic reticulum, and intracellular edema. Also increased cell diameters, and some nuclear changes, i.e., slight margination of nuclear chromatin, were present on both electron and light photomicrographs.

The hypertrophying animals that were exercise-stressed during the stable, compensated state of hypertrophy, group 2, showed severe ultrastructural changes in the endocardial regions which were similar to lesions described in acute myocardial ischemia. These changes included disintegration of the myofilaments, increased separation of the filaments, Z-band changes (Fig. 3), aggregation of swollen mitochondria with decreased cristal densities, mitochondrial deposits, decrease of glycogen granules, swollen sarcoplasmic reticulum, widening of the intercalated discs with irregular, increased longitudinal foldings (Fig. 4), intracellular edema, and margination of nuclear material. These changes were present in 10 percent of the photographs examined in two animals and 50 percent of the photographs examined in the other two animals. Such changes were observed only in the subendocardial region. These findings, combined with the microsphere blood flow results, suggested that exercise stress induced ischemia during the late, stable, compensated phase of pressure overload induced hypertrophy caused injury to the subendocardial region of the myocardium.

DISCUSSION

Many experimental models of cardiac hypertrophy have been used for the understanding of the different functional, structural, and biochemical alterations that occur during the development of hypertrophy and failure in the heart. The model we used produced similar increases in left ventricular mass to those reported by other investigators [12-20]. The ultrastructural changes observed in the endocardial and epicardial regions were also similar to those reported, by other investigators, in the hypertrophied heart. This suggests that our model provides investigators an opportunity to study changes occurring with exercise stress at different stages of developing cardiac hypertrophy.

The time required for functional adaptation to occur after the induction of pressure overload varies. Meerson [4] states that functional adaptation of the myocardium occurs within 5-10 days of the start of pressure overload while others [16] state adaptation requires 1-3 weeks. Experimental hypertrophy induced by chronic pressure overload remains relatively constant after two weeks [16]. We have observed in pigs that heart weight/body weight ratios after eight months of pressure overload were similar to those reported in this study after one month of pressure overload [21]. These findings indicate that sufficient time had elapsed in this study for a relatively stable, compensated hypertrophy to occur. Breisch et al. [18] have shown that ultrastructural features are maintained in this stable hypertrophy in the absence of failure.

Changes in wall stress may account for regional myocardial flow changes in different stages of developing hypertrophy. Circumferential wall stress is greater near the endocardium and decreases toward the epicardium according to Streeter [22]. During left ventricular dilation, which may occur in the early uncompensated stage of developing hypertrophy, wall stress should increase even more in the subendocardial
FIG. 2. Non-exercised, hypertrophied animal. Longitudinal section of left ventricular myocardium obtained from the subendocardial region shows partial vacuolization of mitochondria, some disruption of myofilaments, and slight broadening of Z-band. ×30,000.

FIG. 3. Exercised-stressed, hypertrophied animal. Longitudinal section of left ventricular myocardium obtained from the subendocardial region. The aggregating mitochondria are swollen and show decreased cristal density. The sarcomeres are disorganized and show streaming of Z-band material. ×12,000.
FIG. 4. Exercise-stressed, hypertrophied animal. Longitudinal section of left ventricular myocardium obtained from the subendocardial region. The myofibers are disrupted. Mitochondria are swollen and partially vacuolated. The intercalated disc regions are broad and have accumulations of Z-band material. Intracellular edema is present. ×22,000.

region [23]. Bishop and Melsen [1] have described ultrastructural changes in experimental cardiac hypertrophy induced by sudden pressure overload. These changes occurred most frequently in the subendocardial region. In our study the ultrastructural changes also occurred most frequently in the subendocardial region. Since wall stress increases more in the inner layers of the heart wall when pressure overload is induced [23], these findings suggest that wall stress is a major factor in inducing such ultrastructural changes. However, wall stress changes could alter myocardial flow to the subendocardial region resulting in ischemia which induces the morphologic changes.

The presence of subendocardial ischemia is of special interest. Our electrocardiographic findings show subendocardial ischemia during the acute stage of pressure overload. Although other causes of S-T segment elevation may be possible, e.g., stretching of myocardial fibers and changes in autonomic tone, the observed decrease in blood flow to the subendocardial region during the acute stage of pressure overload, particularly when exercise stress is superimposed, supports the presence of ischemia. Although the S-T segments return to normal after ten days of pressure overload, the underperfusion of the subendocardial region persists and is accentuated by superimposed physiologic stress. The absence of S-T segment changes with exercise 14 days after aortic constriction may reflect changes in conductance of the electrode due to surrounding zones of fibrosis. Others [7,24] have postulated that ischemia may be present in the subendocardial region of the hypertrophied heart. Hatt et al. [25] have shown cellular changes associated with ischemia to predominate in the subendocardial region of the hypertrophied heart. The ultrastructural lesions
we observed in the exercise-stressed animals indicate that the stable, compensated hypertrophied heart is vulnerable to ischemic injury when a physiologic stress is superimposed.

The decrease in blood flow to the subendocardial region may also be due to morphologic alterations in the resistance vessels of the subendocardium. Such changes have been reported in patients with aortic stenosis [26] and could increase coronary vascular resistance resulting in redistribution of myocardial blood flow. Increased coronary vascular resistance has been observed at rest in our hypertrophied animals in the stable, compensated stage [9] and may reflect such vascular changes, although Keefe et al. [15] suggest that the increased resistance may be due to the increased muscle mass.

Our earlier study suggested that ischemia was a key stimulus in the early, uncompensated stage of hypertrophy. Of special interest in this study is the occurrence of ischemic injury in the late, stable, compensated stage when a physiologic stress, i.e., exercise, is superimposed. These findings indicate that at all stages of hypertrophy the subendocardial region is most susceptible to ischemic injury, particularly when additional stress is superimposed.

REFERENCES

1. Bishop SP, Melsen L: Myocardial necrosis, fibrosis, and DNA synthesis in experimental cardiac hypertrophy induced by sudden pressure overload. Circulation Res 39:238-244, 1976
2. Buchner JF: Qualitative morphology of heart failure: Light and electron microscopic characteristics of acute and chronic heart failure. In Methods and Achievements in Experimental Pathology, Vol 5. Edited by E Bajsuz, G Jasmin. Basel, S Karger, 1971, pp 60-120
3. Hatt PY: La cellule myocardiques dans les surcharges cardiaques mecaniques aspects ultrastructuraux. In Colloque Les Surcharges Cardiaques (heart overloading). Edited by PY Hatt. Paris, INSERM, 1972, pp 13-37
4. Meerson FM: A mechanism of hypertrophy and wear of the myocardium. American Cardiol 15:755-760, 1965
5. Harris CN, Aranow WS, Parker DP, et al: Treadmill stress-test in left ventricular hypertrophy. Chest 28:353-357, 1973
6. Barnard RJ, MacAlpin R, Kattus AA, et al: Ischemic response to sudden strenous exercise in healthy men. Circulation 48:936-942, 1973
7. Buckberg GD, Fixler DE, Archie JP, et al: Experimental subendocardial ischemia in dogs with normal coronary arteries. Circulation Res 30:67-81, 1972
8. Monroe RG, La Farge CG, Gamble WJ, et al: Left ventricular pressure-volume relations and performance as affected by sudden increases in developed pressure. Circulation Res 22:333-344, 1968
9. White FC, Sanders M, Peterson T, et al: Ischemic myocardial injury after exercise stress in the pressure overloaded heart. Am J Pathol 97:473-488, 1979
10. Guyton RA, McClanathan JH, Newman GE, et al: Significance of subendocardial S-T segment elevation caused by coronary artery stenosis in dog. American J Cardiol 40:373-380, 1977
11. Bishop SP, White FC, Bloor CM: Regional myocardial blood flow during acute myocardial infarction in the conscious dog. Circulation Res 38:429-438, 1976
12. Bishop SP: Effect of aortic stenosis on myocardial cell growth, hyperplasia, and ultrastructure in neonatal dogs. In Recent Advances in Studies on Cardiac Structures and Metabolism. Vol 3. Edited by NS Dhall. Baltimore, University Park Press, 1973, pp 637-656
13. Malik AB, Geha AS: Cardiac function, coronary flow and MVO₂ hypertrophy induced by pressure and volume overloading. Cardiovascular Res 11:310-316, 1977
14. Mueller TM, Marcus ML, Kerber RE, et al: Effect of renal hypertension and left ventricular hypertrophy on the coronary circulation in dogs. Circulation Res 42:543-549, 1978
15. O'Keefe DD, Hoffman JIE, Cheitlin R, et al: Coronary blood flow in experimental canine left ventricle hypertrophy. Circulation Res 43:43-51, 1978
16. Sasayama S, Ross J Jr, Franklin D, et al: Adaptations of the left ventricle to chronic pressure overload. Circulation Res 38:172-178, 1976
17. Bishop S, Franklin D, Ross J Jr, et al: Ultrastructural alterations of hypertrophied canine left ventricular subendocardium. Circulation 50 (Suppl III): 13, 1974
18. Breisch EA, Bone AA, Phillips SJ: Myocardial morphometrics in pressure overload left ventricular hypertrophy and regression. Cardiovasc Res 14:161–168, 1980
19. Imamura K: Ultrastructural aspect of left ventricular hypertrophy in spontaneously hypertensive rats: A qualitative and quantitative study. Japanese Circulation 42:979–1002, 1978
20. Maron BJ, Ferrans VJ: Ultrastructural features of hypertrophied human ventricular myocardium. Progress in Cardiovascular Diseases 21:207–238, 1978
21. Singh S, White FC, Bloor C: The changes in the ultrastructure of pressure overloaded swine myocardium. J Molecular Cell Cardiol 11 (Suppl I): 58, 1979
22. Streeter DD Jr, Vaishnau RN, Patel DJ, et al: Stress distribution in the canine left ventricle during diastole and systole. Biophysical J 10:345–363, 1970
23. LeWinter MM, Kent RS, Kroener JM, et al: Regional differences in myocardial performance in the left ventricle of the dog. Circulation Res 37:191–199, 1975
24. Holtz J, von Restorff W, Bard P, et al: Transmural distribution of myocardial blood flow and/or coronary reserve in canine left ventricular hypertrophy. Basic Res Cardiol 72:286–292, 1977
25. Hatt PY, Jouannot P, Moravec J, et al: Development and reversal of pressure-induced cardiac hypertrophy. Basic Res Cardiol 73:405–421, 1978
26. Nacye RL, Liedtke AJ: Consequences of intramyocardial arterial lesions in aortic valvular stenosis. Am J Pathol 85:569–580, 1976