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# Cardioacceleration by Atrial Pacing and Transmural Metabolite Levels in the Canine Left Ventricle[1] (40177)

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There is conflicting information in the literature concerning the effect of increasing heart rate by electrical pacing on the transmural distribution of myocardial blood flow in the left ventricle. Several reports (1–3) indicate that the rise in myocardial blood flow associated with pacing the heart at different rates between 100 and 200 beats/min is uneven transmurally and less pronounced in the subendocardium than in the subepicardium. One of these reports (3) suggests that the subendocardium undergoes a significant and preferential decline in tissue oxygen tension as heart rate is increased. In contrast, another report (4) indicates that the rise in myocardial blood flow is uniform across the ventricular wall at pacing rates up to 240 beats/min. At issue is whether the coronary circulation autoregulates the transmural distribution of myocardial blood flow sufficiently well to prevent regional myocardial ischemia under these conditions. This question of regional myocardial ischemia during cardioacceleration was examined in the present study by determining the effects of raising heart rate on the tissue levels of several metabolites sensitive to oxygen supply in the outer, middle, and inner regions of the canine left ventricle.

*Material and methods.* Experiments were performed on 37 fasted male mongrel dogs. The animals had been screened for microfilaria, medicated against rabies and for intestinal parasites, and maintained on a nourishing diet for at least 30 days. Anesthesia was induced with sodium pentobarbital (30 mg/kg, iv). Additional doses were given as required during the experiment. The trachea was intubated, and respiration was maintained with a Harvard respirator. Supplemental oxygen was added to the inspired air (approximately 10% of the inspired air volume) to ensure a normal arterial oxygen tension. Rectal temperature, measured with a Yellow Springs telethermometer, was maintained between 38 and 39° by the use of a heating pad. Pressure in the arch of the aorta was monitored through a side-hole polyethylene catheter passed retrograde from the femoral artery. Left ventricular intracavitary pressure was obtained through a needle (thin wall, no. 17) which was later inserted through the left ventricular wall. Statham pressure transducers (P23 Db) and an Electronics-for-Medicine (model DR-8) multichannel oscillograph were used to record pressures.

A right thoracotomy was performed, pacing electrodes were attached to the right atrial appendage, and the SA node was crushed. Pacing was begun at either 100 or 150 beats/min at this time. A left thoracotomy was then performed exposing the left ventricle. Heparin was administered (350 units/kg, iv) and a blood sample was drawn anaerobically from the aortic catheter for the determination of arterial $PO_2$, $PCO_2$, pH and hematocrit. Blood gas samples were read immediately on an Instrumentation Laboratory blood–gas analyzer (model 113-S1). If required, ventilation and oxygen administration were adjusted to maintain arterial $PCO_2$ between 33–40 mm Hg and $PO_2$ between 90–110 mm Hg. A final arterial blood gas sample was taken immediately before procuring a transmural left ventricular tissue sample. An arterial blood sample was also drawn and precipitated with cold 6% perchloric acid for subsequent determination of lactate (5).

A transmural tissue sample of the left ventricle was obtained under stable hemodynamic conditions while the animal was being paced at one of the following heart rates: 100, 150, or 200 beats/min. The duration of pacing at 100 or 150 beats/min was variable depending upon further surgical preparation time after crushing the S.A. node. The duration of

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pacing at 200 beats/min was 5 min. The pacing rate was raised from 150 to 200 beats/min over a 30 sec period before timing was begun. Only one tissue sample was obtained per animal, necessitating studies on three groups of animals, each paced at a specific heart rate. A special tissue borer mounted on an electric drill (6) was used to cut the sample from the base of the anterior free wall of the ventricle.

The sample was quickly placed between heavy metal tongs precooled in liquid nitrogen and compressed. The total elapsed time for cutting and compressing the sample was less than 2 sec. The frozen sample was divided into outer, middle and inner thirds, pulverized, extracted with perchloric acid and analyzed for creatine phosphate (7), adenosine triphosphate (8) and lactate (5).

*Statistical methods.* All results were analyzed by nonparametric statistical methods (9). The outer, middle, and inner layer tissue metabolite levels for all three animal groups were tested for significant differences with the Friedman two-way analysis of variance by ranks. If a statistically significant difference ($P < 0.05$) was found individual differences were analyzed by the Wilcoxon matched pairs test. Among the animal groups, outer, middle and inner region differences were tested by the Wilcoxon rank sum test. This test was also used to compare hemodynamic and blood data among the groups.

*Results.* Results obtained in the three groups of animals paced at different heart rates are presented in Table I and Figs. 1-3. Hemodynamic and arterial blood data are shown in Table I. All pressures and arterial blood values were reasonably near the physiologic range and not systematically different between groups except for the left ventricular end diastolic pressure, which was lower in animals paced at 150 and 200 beats/min than in those paced at 100 beats/min. Data on the creatine phosphate levels for the outer, middle, and inner layers of the left ventricle in animals paced at different heart rates are shown in Fig. 1. When the mean levels for the outer layer in all three heart rate groups were compared statistically no significant differences were found. Likewise, when the levels for the middle and inner layers in the different groups were compared no significant differences were found in the respective layers. The mean creatine phosphate level for the inner layer in animals paced at 200

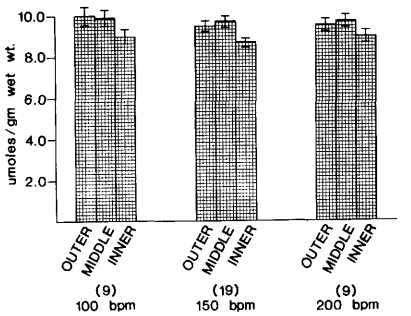

FIG. 1. Mean creatine phosphate tissue levels for the outer, middle and inner thirds of the canine left ventricle in three groups of animals paced at different heart rates. Bars denote standard errors. Values in parentheses indicate size of animal group.

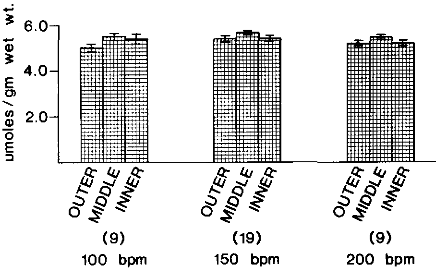

FIG. 2. Mean adenosine triphosphate tissue levels for same animals depicted in Fig. 1.

TABLE I. HEMODYNAMIC AND ARTERIAL BLOOD DATA.

| Animal group | n[a] | L. Vent. syst. press. (mm Hg) | L. Vent. end diast. press. (mm Hg) | Aortic diast. press. (mm Hg) | Hematocrit (%) | Art. Lactate (m*M*) | Art. $PO_2$ (mm Hg) | Art. $PCO_2$ (mm Hg) | Art: pH |
|---|---|---|---|---|---|---|---|---|---|
| I. Paced at 100 beats/min | 9 | 131 ± 6[b] | 8 ± 1 | 103 ± 5 | 42 ± 1 | 1.1 ± 0.1 | 103 ± 2 | 36 ± 1 | 7.40 ± .01 |
| II. Paced at 150 beats/min | 19 | 121 ± 3 | 5 ± 0 | 102 ± 3 | 43 ± 1 | 0.9 ± 0.1 | 100 ± 3 | 36 ± 1 | 7.37 ± .01 |
| III. Paced at 200 beats/min | 9 | 119 ± 6 | 4 ± 0 | 111 ± 6 | 42 ± 2 | 1.1 ± 0.1 | 99 ± 2 | 36 ± 1 | 7.39 ± .01 |
| P |  | N.S. | <0.001[c] | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |

[a] Number of animals in each group.

[b] Values are mean ± SE.

[c] Groups II and III compared to Group I.

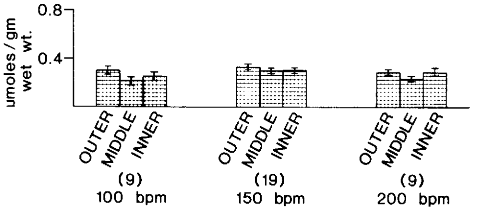

FIG. 3. Mean lactate tissue levels for same animals depicted in Fig. 1.

beats/min was 8.98 ± 0.28 (SE) μmoles/g as compared to 9.03 ± 0.34 μmoles/g in animals paced at 100 beats/min; an insignificant difference. A consistently positive finding in each animal group was a slightly but significantly lower creatine phosphate level for the inner layer compared to both the outer and middle layers of the ventricle ($P < 0.05$ in all three groups). We reported this finding previously in animals paced at 150 beats/min (6). When these interlayer creatine phosphate differences for each group were compared among the groups no significant differences were noted. Thus, the results failed to demonstrate any effect of increasing heart rate by atrial pacing from 100 to 200 beats/min on creatine phosphate levels for the outer, middle or inner layers of the left ventricle. Data on outer, middle and inner layer levels of adenosine triphosphate (Fig. 2) and lactate (Fig. 3) in the three groups were analyzed in the same manner and these data also failed to demonstrate any effect of increasing heart rate on the regional tissue levels of these metabolites. The inner layer adenosine triphosphate level in animals paced at 200 beats/min was 5.17 ± 0.13 μmoles/g as compared to 5.44 ± 0.21 μmoles/g in animals paced at 100 beats/min; an insignificant difference. The inner layer lactate level in animals paced at 200 beats/min was 0.29 ± 0.04 μmoles as compared to 0.24 ± 0.03 μmoles/g in animals paced at 100 beats/min, also an insignificant difference. In contrast to results obtained for creatine phosphate, no consistent differences between levels in the inner layer and the other two layers were found for adenosine triphosphate and lactate, and no analysis of interlayer differences between groups was performed for these metabolites.

*Discussion.* Previous studies performed to assess the effect of cardioacceleration by electrical pacing on the distribution of blood flow between the epicardium and endocardium of the left ventricle have yielded conflicting results. Neill *et al.* (1) using the microsphere method to measure regional myocardial blood flow and atrial pacing to increase heart rate in the dog, compared the subendocardial to subepicardial blood flow ratio at different heart rates between 75 and 193 beats/min. They noted, along with an increase in total myocardial blood flow, a decrease in the subendocardial to subepicardial blood flow ratio from 1.25 to 1.07. Similar results were obtained by Domenech and Goich (2) at heart rates between 100 and 170 beats/min and by Weiss (3), using the hydrogen clearance method to measure blood flow, at heart rates between 140 and 220 beats/min. In his study, Weiss also implanted oxygen sensitive microelectrodes in the ventricle to obtain information on tissue oxygen tension in the subepicardium and subendocardium at different heart rates. Results revealed a significantly lower oxygen tension in the subendocardium under control conditions and a greater drop in oxygen tension in this region than in the subepicardium with progressive increases in heart rate. In contrast, Buckberg *et al.* (4), using the microsphere method to measure blood flow, observed no changes in the subendocardial to subepicardial blood flow ratio in the canine left ventricle as heart rate was increased from 120 to 240 beats/min by atrial pacing. Total myocardial blood flow increased 50%.

An important question raised by the previous studies is whether the subendocardium experiences significant ischemia when the heart is paced at these elevated rates. It has been shown that the subendocardium is subject to a greater systolic compressive stress (10, 11) which must be compensated for by an autoregulatory mechanism if an appropriate distribution of blood flow is to occur across the ventricular wall. Opinion has varied concerning the effectiveness of such an autoregulatory mechanism (12) and some investigators (3, 13, 14) have contended that the subendocardium is relatively underperfused under normal hemodynamic conditions. Others (4, 15–17) have contended that the coronary circulation possesses considerable vasomotor reserve and that subendocardial underperfusion occurs only under rather severely altered hemodynamic conditions.

In the present study the myocardial tissue levels of creatine phosphate, adenosine triphosphate, and lactate were examined in hearts paced at different heart rates. Although the levels of these metabolites may vary for reasons other than an oxygen deficiency in various tissues, they have been shown to be acutely sensitive to a decrease in oxygen delivery in the myocardium (18, 19).

We have noted abnormalities in the myocardial tissue levels of these metabolites in animals subjected to a reduction or a brief interruption of coronary blood flow (6, 20). The results obtained in the present study failed to demonstrate any significant effects of pacing hearts at different rates over the previously considered critical range of 100–200 beats/min on the metabolite levels in the outer, middle, or inner layers of the ventricle. These negative results suggest that the coronary circulation was able to regulate the transmural distribution of myocardial blood flow sufficiently well to prevent significant regional myocardial ischemia. Although the possibility of subtle changes in regional myocardial metabolism due to underperfusion cannot be completely excluded by the present findings, the lack of any significant effects of cardioacceleration on creatine phosphate and adenosine triphosphate, the two high energy phosphate compounds most intimately associated with myocardial contraction, suggest that oxygen delivery was adequate to meet the contractile needs of the myocardium. Likewise, the lack of any significant effects on lactate suggests that oxygen delivery was adequate to meet the myocardial metabolic needs without requiring recourse to anaerobic glycolysis. Although tissue lactate levels may be influenced by the availability of glucose or fatty acids as myocardial substrate the possibility that the negative lactate findings in the present study were due to the attenuation of an ischemic response because of these variables seems remote in view of previous studies from this laboratory (6, 20–23) in which a subendocardial lactate rise was observed in the same basic animal preparation when experimental interventions designed to produce subendocardial ischemia were employed.

The present results are comparable to those obtained in animals with similarly elevated heart rates (196 ± 11 beats/min) due to isoproterenol administration (21). In those animals the myocardial tissue lactate to pyruvate ratio was examined in the outer and inner halves of the left ventricle and the values were found to be equal and not significantly different from those obtained in control animals. A positive result consisting of a higher inner ventricular lactate to pyruvate ratio was obtained in animals with proximal coronary vessel stenosis receiving isoproterenol. In light of the present results, the previous negative finding in normal animals receiving isoproterenol could not be attributed to an independent action of isoproterenol on the coronary circulation or the myocardium. It would appear that the coronary circulation responds in a similar manner to a metabolic stress imposed on the ventricle by either beta adrenergic stimulation or electrical cardioacceleration.

Our previously reported finding of a lower creatine phosphate level in the inner ventricular layer in animals paced at 150 beats/min (6) has been extended in the present study to animals paced at 100 and 200 beats/min. The interlayer differences were small, not in the form of a true transmural gradient, and independent of heart rate. These findings suggest that the uneven creatine phosphate level is not caused by uneven myocardial perfusion. Other possible explanations at this time include an uneven myocardial energy demand (6) or a lesser amount of creatine phosphate rich tissue in the subendocardium.

In a recent study similar to ours, Allison and Holsinger (24) also noted no effect of cardioacceleration on creatine phosphate, adenosine triphosphate, or lactate levels in different layers of the canine left ventricle. However, in that study all animals, including the controls, exhibited transmural gradients in these metabolites of the type we have observed only in the presence of subendocardial ischemia (20–23).

*Summary.* Creatine phosphate, adenosine triphosphate, and lactate levels were determined for the outer, middle, and inner layers of the canine left ventricle in animals paced at 100, 150 or 200 beats/min. A slightly lower creatine phosphate level was noted for the inner layer compared to the outer and middle

layers of the ventricle at all three heart rates. No evidence of a heart rate effect on metabolite levels in any of the ventricular layers was found. The results indicate that the coronary circulation autoregulates the transmural distribution of myocardial blood flow sufficiently well to maintain an adequate oxygen delivery to all layers of the ventricle under these conditions despite previous reports of a reduced subendocardial to subepicardial blood flow ratio and a lower subendocardial oxygen tension.

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