Effect of Maximal Coronary Vasodilation on Transmural Myocardial Perfusion during Tachycardia in the Awake Dog

ROBERT J. BACHE AND FREDERICK R. COBB

SUMMARY We studied the influence of active coronary vasomotion on transmural myocardial perfusion during tachycardia. Regional myocardial blood flow was estimated in chronically prepared awake dogs by injecting radioactive microspheres (7–10 μm in diameter) into the left atrium. Studies were performed during ventricular pacing at 100, 150, 200, and 250 beats/min under control conditions with intact coronary vasomotor tone, and during maximal coronary vasodilation induced by intravenous infusion of adenosine. During control conditions, mean myocardial blood flow was 1.27 ± 0.12 ml/min per g of myocardium at a heart rate of 100 beats/min, and increased regularly with increasing heart rates. Transmural myocardial perfusion remained essentially uniform as heart rates were increased from 100 to 250 beats/min. During administration of adenosine, mean myocardial blood flow increased to 5.49 ± 0.39 ml/min per g at a heart rate of 100 beats/min, and transmural myocardial perfusion was uniform. As heart rates were increased, flow to the subendocardium decreased as a linear function of heart rate while subepicardial flow was maintained so that the ratio of subendocardial-subepicardial flow fell from 1.00 at a heart rate of 100 beats/min to 0.40 at a heart rate of 250 beats/min. The reduction of subendocardial perfusion with increasing heart rate was most marked in the deepest myocardial layers. This rate-dependent decrease in subendocardial blood flow resulted in a decrease in mean myocardial blood flow with increasing heart rates (mean change at 250 beats/min = –18%; P < 0.05). These data indicate that active coronary vasomotion is necessary for maintenance of uniform transmural myocardial perfusion during tachycardia.

DURING CARDIAC systole, myocardial contraction results in selective impedance to arterial inflow into the subendocardial myocardium. Uniform net transmural myocardial perfusion consequently depends on a reverse gradient of blood flow favoring the subendocardium during diastole. Although tachycardia induced by ventricular pacing or by treadmill exercise decreases the interval of diastolic coronary perfusion, previous studies have demonstrated that uniform transmural myocardial perfusion is maintained nevertheless during these interventions. It has been proposed that as the duration of diastole decreases with increasing heart rate, active coronary vasomotion results in appropriate compensatory decreases in subendocardial vascular resistance to maintain uniform transmural myocardial perfusion. If this is the case, then paralysis of the coronary arterioles should prevent this compensatory vasomotor autoregulation and reveal the actual mechanical effect of heart rate on transmural myocardial perfusion. The present study was undertaken to test this hypothesis. The effects of heart rate on transmural myocardial perfusion were observed while coronary vasomotor paralysis was induced by administration of adenosine. Heart rates from 100 to 250 beats/min were produced by electrical pacing. A control group of dogs was studied at identical heart rates to observe transmural myocardial perfusion when coronary autoregulation was intact. Studies were performed in chronically instrumented awake dogs to eliminate the inimical effects associated with general anesthesia and acute surgical trauma.

Methods

Thirteen adult mongrel dogs weighing 20–38 kg were anesthetized with sodium thiamylal (25–30 mg/kg) and ventilated with a Harvard model 607 respirator. A left thoracotomy was performed through the fourth intercostal space and the pericardium opened. A polyvinyl chloride heparin-filled catheter, 3 mm outside diameter, was introduced into the left internal thoracic artery and advanced into the arch of the aorta. A similar catheter was introduced into the left atrial cavity through the left atrial appendage and secured in place with a purse string suture. A bipolar epicardial pacing electrode was sutured to the region of the right ventricular outflow tract. The catheters and pacing wire were tunneled dorsally into a subcutaneous pouch at the base of the neck but were not exteriorized to protect them from damage. The pericardium was loosely closed and the thoracotomy incision repaired.

Studies were carried out 39–84 days after the initial surgery. All dogs were active, fully recovered from the effects of surgery, and appeared to be in good health. Hematocrits ranged from 37% to 54% (mean = 44%). The dogs were trained to lie quietly on their right sides during the period of study. The catheters and pacing wires were exteriorized from the subcutaneous pouch through a 1-cm skin incision using 2% lidocaine infiltra-
tion anesthesia. Aortic and left atrial blood pressures were recorded with a Statham P23Db pressure transducers. Lead II of a standard electrocardiogram was obtained. Data were recorded with a Hewlett-Packard model 3917-A magnetic tape recorder and a Sanborn model 958-100 eight-channel direct-writing oscillograph. The laboratory was dimly illuminated and kept free from noise or other activity that might disturb the dog. After the recording instruments were connected, a 45- to 60-minute interval was allowed for the dog to adjust to the laboratory conditions.

Measurements of distribution of myocardial blood flow were made by injecting into the left atrium microspheres 7-10 μm in diameter labeled with gamma-emitting radionuclides 141Ce, 85Sr, 51Cr, or 46Sc (3M Company). The microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran and 0.05% polysorbate-80. This stock solution was diluted in 10% dextran so that 1.0 ml, the volume injected, contained approximately three million microspheres. Injection of this quantity of microspheres resulted in no change in heart rate or arterial or left atrial pressure. Prior to injection, microspheres were mixed by alternate agitation for at least 15 minutes in an ultrasonic bath and a vortex agitator. Complete dispersion of microspheres was verified by examination of a drop of microsphere suspension with a light microscope prior to injection.

Measurements of regional myocardial blood flow were performed in each dog during four separate periods of ventricular pacing at rates of 100, 150, 200, and 250 beats/min. Pacing was accomplished using a Grass model 588 physiologic stimulator delivering 3-msec square wave pulses 25% above threshold voltage through a stimulus isolation unit. Arterial and left atrial pressures were recorded continuously to ensure steady state hemodynamic conditions. After 4 minutes of pacing at each rate, 1.0 ml of microsphere suspension was injected into the atrial catheter and flushed in with 3 ml of normal saline. This injection and all subsequent microsphere injections were made over a 5-second interval. Beginning simultaneously with each microsphere injection and continuing for 90 seconds, a reference sample of arterial blood was collected from the aortic catheter at a constant rate of 15 ml/min with a model 1210 Harvard withdrawal pump. Pacing was continued for 2 minutes after injection of microspheres. A 10-minute interval was allowed between pacing periods, and the order in which pacing interventions were performed was randomized. A different isotope was used for each of the four pacing rates.

The above-described study was carried out in six dogs to provide control measurements when the coronary vasculature was allowed to respond normally to increasing ventricular rates. In seven additional dogs, the identical protocol was followed except that maximal coronary vasodilation was produced by infusion of adenosine, 4 μmol/kg of body weight/min, iv, using a Harvard model 901 syringe pump. This dosage of adenosine previously has been shown to result in maximum dilation of the coronary vasculature since (1) no further increase in coronary flow was observed during infusion of larger dosages of adenosine and (2) no further increase in flow occurred following brief periods of coronary occlusion.

Adenosine was dissolved in warm normal saline so that the desired dosage would be delivered by an infusion rate of 0.7 ml/min. The infusion of adenosine was begun 10 minutes before the first pacing intervention was begun and continued at a constant rate until the conclusion of the study.

After completion of the study, the dogs were killed with a lethal dose of pentobarbital and the hearts were removed and fixed in 10% buffered formalin. The atria, right ventricle, aorta, and large epicardial blood vessels were dissected from the left ventricle and discarded. The left ventricle then was sectioned into four transverse sections of approximately equal thickness parallel to the mitral valve ring. The two central sections which constituted 62 ± 4% of the left ventricular weight were divided into six regions: anterior free wall, septum, posterior free wall, posterior papillary muscle region, lateral wall, and anterior papillary muscle region, as previously described.

Each region was sectioned into four equal transmural layers from the epicardial to the endocardial surface, weighed, and placed in vials for counting. For the remainder of this paper, these layers will be referred to as “layers 1 through 4,” layer 1 being the layer closest to the epicardium, and layer 4 the layer closest to the endocardium.

Radioactivity was determined with a Beckman model 167776 gamma spectrometer, and window settings corresponding to the peak energies emitted by each radioactive nuclide were used. The activities recorded in each energy window and the corresponding sample weights were entered into a digital computer programmed to correct for contaminant activity contributed by the associated nuclides and for background activity, and to compute the corrected counts/min per g of myocardium. Since we knew the rate of withdrawal of the reference sample (Qr), the radioactivity (C0) in the reference sample, and that the ratio of flow and radioactivity was uniform throughout because complete mixing of microspheres with blood occurred during passage through the left ventricle, we used myocardial radioactivity (Cm) to compute myocardial blood flow (Qm) as:

\[ Q_m = Q_r \cdot C_m/C_r. \]

Regional myocardial blood flows to rings 2 and 3 were analyzed by multiple paired t-tests that compared each region and layer in ring 2 with the corresponding specimen in ring 3. The P values were adjusted by the Bonferroni inequality that corrects for performing multiple tests on correlated data; i.e., each P value was multiplied by the number of paired t-tests performed on each set of data, and a P value of 0.05 was required for statistical significance. Both during control conditions and during adenosine infusion, no statistically significant difference in myocardial blood flow was found between any region in ring 2 and the corresponding region in ring 3; consequently, data from corresponding regions of rings 2 and 3 were pooled for subsequent analysis. Similarly, myocardial blood flow to the corresponding layers of each circumferential region were compared by multiple paired t-tests. Both during control conditions and during adenosine
infusion, no significant difference existed between the corresponding layers of any regions. Consequently, data from the corresponding layers of all six regions were combined. Thus, during each intervention, all myocardial blood flow data were reduced to the mean values representing the four transmural layers.

Heart rate, mean arterial pressure, and mean left atrial pressure were measured directly from the recordings. Left ventricular ejection time was taken as the mean of six consecutive heart beats measured at a paper speed of 100 mm/sec. The diastolic pressure-time index (DPTI) was estimated by planimetric integration of the area under the diastolic aortic pressure curve and subtracting from it the mean left atrial pressure as described by Buckberg and associates. The ratio of endocardial to epicardial blood flow (endo/epi) was obtained by dividing flow to layer 4 by the corresponding flow to layer 1. Data analysis within each group was performed by Student's t-test for paired data, while analysis of data between the control and adenosine group of animals was performed by Student's t-test for unpaired data.

**Results**

In six dogs comprising the control group, heart rate during sinus rhythm was 74 ± 8 beats/min (range, 45–95 beats/min), mean aortic pressure was 88 ± 5 mm Hg (range, 75–112 mm Hg), and mean left atrial pressure was 6 ± 2 mm Hg (range, 1–10 mm Hg). As shown in Table 1, arterial pressure did not change significantly during ventricular pacing from 100 to 250 beats/min. Left atrial pressure was unchanged at rates up to 200 beats/min, but increased to 11 ± 2 mm Hg during pacing at 250 beats/min (P < 0.01). Left ventricular ejection time per beat was regularly and significantly decreased with each increment in pacing rate (P < 0.01). Both the duration of diastole and the percentage of time spent in diastole, as well as the DPTI, decreased significantly with each increment in pacing rate (P < 0.05).

In seven dogs comprising the adenosine group, mean heart rate during sinus rhythm prior to administration of adenosine was 75 ± 5 beats/min (range, 56–96 beats/min), mean arterial pressure was 101 ± 3 mm Hg (range, 85–112 mm Hg), and mean left atrial pressure was 5 ± 2 mm Hg. None of these values were significantly different from the control group (P > 0.1). During sinus rhythm, infusion of adenosine resulted in a decrease in mean arterial pressure to 88 ± 3 mm Hg (range, 75-100 mm Hg), while mean heart rate increased to 97 ± 4 beats/min (range, 92–108 beats/min; P < 0.01). In two dogs, the heart rates during sinus rhythm with adenosine administration exceeded 100 beats/min; consequently, measurements at a heart rate of 100 beats/min were obtained from only five of the seven dogs during adenosine administration. During sinus rhythm, adenosine administration did not significantly alter left atrial pressure. Both during sinus rhythm and ventricular pacing, arterial pressure and left atrial pressure during adenosine administration were not significantly different from those of the control group. As in the control group, mean arterial pressure did not change significantly during ventricular pacing from 100 to 250 beats/min, whereas left atrial pressure was significantly elevated during pacing at 250 beats/min (Table 1). At each heart rate, left ventricular ejection time was slightly longer in the adenosine group than in the control group; both the duration of diastole and the DPTI were slightly less in the adenosine group than in the control group.

In the control group of dogs, mean myocardial blood flow during ventricular pacing at 100 beats/min was 1.27 ± 0.12 ml/min per g of myocardium, and flow was uniformly distributed across the wall of the ventricle (Table 2). As heart rates were increased from 100 to 250 beats/min, flow to myocardial layers 1, 2, and 3 increased regularly with each increment in heart rate (P < 0.05). Flow to layer 4 also increased regularly with heart rate, but this increase achieved statistical significance only with the increment in heart rate from 100 to 150 beats/min (P < 0.01). Only at a heart rate of 150 beats/min did flow to the subendocardium significantly exceed flow to the subepicardium (ENDO/EPi = 1.18; P < 0.05).

At a heart rate of 100 beats/min, mean myocardial blood flow in the group of dogs receiving adenosine was 332 ± 31% higher than in the control group (P < 0.01), while the transmural distribution of myocardial blood flow was uniform (Table 2). As heart rates were increased above 100 beats/min, mean myocardial blood flow de-

### Table 1 Hemodynamic Measurements in Six Dogs during Control Conditions (CON) and in Seven Dogs during Intravenous Infusion of Adenosine (ADEN), 4 μg/kg per Min

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Mean left atrial pressure (mm Hg)</th>
<th>Mean diastolic pressure (mm Hg)</th>
<th>Left ventricular ejection time (sec/beat)</th>
<th>Duration of diastole (sec/min)</th>
<th>Fraction of time in diastole (%)</th>
<th>Diastolic pressure time index (mm Hg·sec/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>ADEN</td>
<td>CON</td>
<td>ADEN</td>
<td>CON</td>
<td>ADEN</td>
<td>CON</td>
<td>ADEN</td>
</tr>
<tr>
<td>100</td>
<td>94 ±5</td>
<td>92</td>
<td>6</td>
<td>4</td>
<td>91</td>
<td>87</td>
<td>0.189 ±0.011</td>
</tr>
<tr>
<td>150</td>
<td>99 ±5</td>
<td>93</td>
<td>5</td>
<td>4</td>
<td>92</td>
<td>88</td>
<td>0.152 ±0.169</td>
</tr>
<tr>
<td>200</td>
<td>100 ±4</td>
<td>97</td>
<td>2</td>
<td>2</td>
<td>93</td>
<td>86</td>
<td>0.131 ±0.141</td>
</tr>
<tr>
<td>250</td>
<td>96 ±4</td>
<td>89</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>83</td>
<td>0.107 ±0.116</td>
</tr>
</tbody>
</table>

Data were obtained at paced ventricular rates of 100–250 beats/min. All values are mean ± SE.

* P < 0.05 for comparison of control vs. adenosine-treated groups at each heart rate.
† P < 0.05 for comparison with values obtained at a heart rate of 100 beats/min.
Table 2  Transmural Left Ventricular Blood Flow

<table>
<thead>
<tr>
<th>Layer</th>
<th>Ventricular pace 100 (ml/min per g)</th>
<th>Ventricular pace 150 (ml/min per g)</th>
<th>Ventricular pace 200 (ml/min per g)</th>
<th>Ventricular pace 250 (ml/min per g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CON 1.21±0.14 5.27±0.59</td>
<td>ADEN 1.55±0.18* 5.09±0.54</td>
<td>CON 1.69±0.25* 6.08±0.57</td>
<td>ADEN 1.85±0.17* 6.19±0.63</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.33±0.13 5.59±0.45</td>
<td>1.67±0.18* 5.74±0.29</td>
<td>1.78±0.23* 5.77±0.43</td>
<td>1.96±0.15* 5.55±0.67</td>
</tr>
<tr>
<td>3</td>
<td>1.34±0.13 5.84±0.59</td>
<td>1.78±0.18* 5.14±0.26</td>
<td>1.94±0.25* 5.45±0.24</td>
<td>2.10±0.17* 3.86±0.41</td>
</tr>
<tr>
<td>4</td>
<td>1.31±0.12 5.57±0.42</td>
<td>1.80±0.16* 4.11±0.24</td>
<td>1.86±0.20* 3.38±0.22</td>
<td>1.89±0.13* 2.47±0.28</td>
</tr>
<tr>
<td>Mean</td>
<td>1.27±0.12 5.49±0.39</td>
<td>1.70±0.16* 5.02±0.24</td>
<td>1.82±0.20* 4.94±0.22</td>
<td>1.95±0.13* 4.52±0.28</td>
</tr>
<tr>
<td>ENDO/EPI</td>
<td>1.10</td>
<td>1.00</td>
<td>1.18*</td>
<td>0.81*</td>
</tr>
</tbody>
</table>

Regional myocardial blood flow (mean ± se) observed in four transmural layers from epicardium (layer 1) to endocardium (layer 4) in six awake dogs during control conditions (CON) and in seven dogs during maximal coronary vasodilation induced by intravenous infusion of adenosine (ADEN), 4 μM/kg per min. Data were measured at paced ventricular rates from 100 to 250 beats/min. ENDO/EPI = ratio of flow to layer 4 to flow to layer 1. *P < 0.05 for comparisons with value obtained at a heart rate of 100 beats/min.

Discussion

In the present study, subendocardial perfusion in the control group of dogs was maintained equal to or greater than subepicardial perfusion at all heart rates. This suggests that appropriate adjustments of coronary vascular resistance occurred during tachycardia to augment subendocardial blood flow during the abbreviated interval of diastole. A similar linear relationship was demonstrated between the ENDO/EPI ratio and the DPTI

\[ \text{ENDO/EPI} = 0.000392 \times \text{DPTI} - 0.354; r = 0.71. \]

In contrast to the control situation, during adenosine infusion, maximum coronary vasodilation existed across the left ventricular wall so that no regional vasomotor adjustments were possible. In this situation, ventricular flow ratios and the duration of diastole during ventricular pacing at 100, 150, 200, and 250 beats/min in seven dogs with maximal coronary vasodilation produced by intravenous infusion of adenosine, 4 μM/kg of body weight/min.

![Figure 1](https://example.com/figure1.png)
pacing revealed the direct mechanical effects of heart rate on transmural left ventricular perfusion, free from any compensatory adjustments normally produced by active coronary vasomotion. As heart rates were increased, flow to the subendocardium decreased as a direct function of the rate-dependent decrease in the interval of diastole, and subepicardial flow was unaffected by heart rate. In the control situation, the decreased interval of diastole associated with tachycardia could be countered by a selective decrease in diastolic subendocardial vascular resistance to maintain uniform net transmural perfusion; however, no such vasomotor adjustments could occur in the dogs receiving adenosine. These findings indicate that active coronary vasomotion is essential for maintenance of uniform transmural myocardial perfusion at heart rates of 150 beats/min or higher. The present data are in agreement with the previous report by Domenech and Goich that, in open chest dogs in which coronary vasodilation was produced by intracoronary dipyridamole, increasing heart rates from 100 to 180 beats/min resulted in no change in subepicardial blood flow, while subendocardial flow fell significantly. Using radioactive microspheres 15 μm in diameter to estimate transmural myocardial perfusion, these workers found an ENDO/EPI ratio of 1.20 at a heart rate of 100 beats/min which decreased to 0.70 at a heart rate of 180 beats/min.

Of interest was the finding that despite coronary vasomotor paralysis during adenosine infusion, transmural myocardial perfusion was uniform at a heart rate of 100 beats/min. This implies that a gradient of vascularity exists, independent of active coronary vasomotion, which favors perfusion of the subendocardium during diastole. The finding of uniform transmural myocardial perfusion during coronary vasomotor paralysis at a heart rate of 100 beats/min is in agreement with the recent report of Downey and associates that transmural myocardial perfusion in the open chest dog was uniform during coronary vasodilation at the peak of the reactive hyperemic response following a 90-second coronary artery occlusion, as well as during coronary vasodilation produced by intracoronary papaverine. It is of interest that the mechanical effect of increasing heart rate on myocardial perfusion was manifest only in the inner half of the left ventricular wall, whereas perfusion of the outer half was not affected by increasing heart rate. It has been demonstrated previously that when coronary perfusion is confined to systole, the outer half of the left ventricular wall is perfused relatively normally, whereas reduced perfusion is observed in the inner half of the left ventricular wall in proportion to the depth of the muscle layer. This finding suggests that during systole, tissue pressure in the outer half of the left ventricular wall is considerably below aortic pressure so that myocardial blood flow may continue relatively unimpeded. In deeper myocardial layers, however, the increasing time spent in systole as heart rates were increased resulted in a reduction of blood flow, both as a function of heart rate and as a function of the depth of the myocardial layer (flow to layer 4 being uniformly less than flow to layer 3 at all heart rates). Both theoretical and experimental considerations indicate that myocardial tissue pressure increases from epicardium to endocardium during ventricular contraction. In areas in which intramyocardial tissue pressure exceeds capillary outflow pressure, systolic perfusion dynamics may be represented by a series of vascular waterfalls where the interaction of intravascular driving pressure and surrounding tissue pressure determines the degree of impedance to blood flow. The present data suggest that during systole a vascular waterfall mechanism operates to limit flow in the inner half of the left ventricular wall, while perfusion of the outer half was relatively unaffected as the duration of systole increased during increasing heart rates.

Burton demonstrated that when the transmural pressure of a vessel (expressed as the difference between intraluminal driving pressure and surrounding tissue pressure) falls to a certain critical level, collapse of the vessel occurs and flow ceases. He has termed this critical closing pressure. Since tissue pressure in the inner left ventricular wall has been demonstrated to approach or exceed aortic pressure during systole, critical closing pressures for the intramural vessels of the inner left ventricular wall must be attained with each systole. In this situation, flow is a discontinuous function since it cannot smoothly approach zero but must rather cease abruptly as critical closing pressure is attained; flow cannot again resume until tissue pressure falls sufficiently so that the intramural vessels again reopen. This is in contrast to areas in which critical closing pressure is never achieved during systole, so that blood flow can rise and fall as a continuous function of the degree that intraluminal pressure exceeds tissue pressure. It may be that in areas of myocardium where vascular closure occurs during systole, a more marked reduction of flow would occur as the number of systoles per minute increased. Thus, if a finite time is required for the vessels to reopen as myocardial compression abates at the end of each systole, the increasing number of such opening events required as heart rate is increased would be expected to result in further underperfusion in regions where closure of the vessels occurred during systole. Consequently, it is possible that this phenomenon of systolic vascular closure may have contributed to the decreasing perfusion of the inner left ventricular wall which occurred with increasing heart rates.

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References
Electrophysiological Responses of Cardiac Muscle to Isoproterenol Covalently Linked to Glass Beads

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With the technical assistance of Deborah Buccigrossi

SUMMARY We investigated the effects of isoproterenol aryl glass beads on the electrical properties of cardiac muscle and related these to our previous results concerning biochemical and contractile effects (Ingebretsen et al., Circ Res, 40: 474-484, 1977). Beads (10–15) were placed near one end of guinea pig papillary muscles mounted horizontally in a bath perfused with Krebs-Henseleit solution at 30°C and stimulated at 0.2 Hz. The beads produced increased tension and elevation and slight lengthening of the plateau potential when [K+]o = 3.8 mM. After depolarization to a resting potential of −49 mV with [K+]o = 22 mM, isoproterenol beads restored contraction to a comparable extent as occurred with 10−8 M soluble drug. During field stimulation, action potentials were initiated at the site of bead application and spread decrementally. When beads were placed distal to the site of point stimulation, virtually no excitation could be obtained from cells in the vicinity of the beads. When they were placed close to the stimulating electrode, the slow increase in excitability and typical slow action potentials spread to the other end of the muscle. These potentials had the characteristics associated with the slow inward Ca2+ current. The slow channel blocker, D-600, blocked responses to isoproterenol beads. Tetrodotoxin caused responses similar to those obtained with K+ depolarization. The beads probably act by stimulating only a small fraction of the papillary muscle catecholamine receptors. Spread of action potentials from these sites and propagated tension depend on Ca2+ influx, but the nature of an intermediate messenger involved in the propagation of contraction is unknown.

CATECHOLAMINES covalently linked to glass beads exert effects on various heart muscle preparations. These include positive inotropic and chronotropic effects, and glycogen phosphorylase activation. Only a small number of catecholamine glass beads may suffice to induce a contractile effect comparable to the response to micromolar concentrations of soluble catecholamine. It was noted, however, that in contrast to the free drug, cyclic adenosine 3',5'-monophosphate (cyclic AMP) might not be involved as a mediator of bead action. The inotropic effects of beads were not associated with a detectable elevation in cyclic AMP concentrations measured in a major fraction of the papillary muscle. Furthermore, evidence has been presented that catecholamine release from the beads is negligible if the beads are properly prepared and used. Therefore, leakage does not account for the observed effects of the beads. These results pose important questions as to the mechanism of action of immobilized catecholamines, such as: (1) how is intense local activation of adrenergic receptors translated into an increase in contractility of a large fraction of the muscle fibers? and (2) if cyclic AMP is not the messenger of the propagated response, what is the mediator? Change of ionic permeabilities of the sarcolemma is an an

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A preliminary report of this work has been presented (Fed Proc. 35: 373, 1975).

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