Consequences of Regional Inotropic Stimulation of Ischemic Myocardium on Regional Myocardial Blood Flow and Function in Anesthetized Swine

Rainer Schulz, Shunichi Miyazaki, Mark Miller, Erik Thaulow, Gerd Heusch, John Ross Jr., and Brian D. Guth

Determination of the effect of inotropic stimulation on regionally ischemic and hypokinetic myocardium is complicated when intravenous administration of the inotropic agent also causes stimulation of nonischemic adjacent and distant regions, thereby altering global ventricular hemodynamics. To obviate such events, 16 anesthetized swine were studied during regional inotropic stimulation by infusion of dobutamine hydrochloride (2.5±1 μg/min) into the cannulated left anterior descending coronary artery. Coronary inflow was controlled by a pump in an extracorporeal circuit. Two groups of swine with different degrees of ischemia were studied. In the first group of animals (n=8), reduction in coronary inflow to produce a fall in coronary artery pressure (CAP) from 114±7 mm Hg to 62±2 mm Hg caused a decrease in percent systolic wall thickening (%WTh) from 34.6±8.1% to 25.4±5.8% (p<0.005). In the second group of animals (n=8), CAP was decreased to 46±5 mm Hg (control: 115±8 mm Hg) and %WTh decreased from 34.1±16.4% to 10.4±6.9% (p<0.001). Subendocardial blood flow was reduced from 1.41±0.38 ml/min/g to 0.65±0.13 ml/min/g (group 1, p<0.001) and from 1.08±0.22 ml/min/g to 0.24±0.08 ml/min/g (group 2, p<0.001). Regional infusion of dobutamine caused asynchronous ventricular contraction with early systolic augmentation in wall thickening followed by late systolic thinning. Therefore, during hypoperfusion regional myocardial function assessed by %WTh remained unchanged (26.2±5.8%, p=NS) in group 1 and decreased significantly to 1.6±5.1% (p<0.041) in group 2. Subendocardial blood flow decreased to 0.44±0.15 ml/min/g in group 1 (p<0.005) and to 0.15±0.07 ml/min/g in group 2 (p<0.012). To account for the augmented early systolic thickening that occurred during asynchronous contraction, a myocardial work index was developed in which the sum of the instantaneous left ventricular pressure–wall thickness product was calculated for estimation of regional myocardial work. Increases in this work index were apparent with the addition of dobutamine at both levels of hypoperfusion. This significant enhancement in regional myocardial function in group 2 caused a significant increase of 16% (p<0.009) in overall left ventricular power during ejection. Thus, regional inotropic stimulation with dobutamine caused enhancement of maximum work of the ischemic myocardium in the steady state despite a further decrease in subendocardial blood flow. (Circulation Research 1989;64:1116–1126)

The effect of inotropic stimulation on ischemic myocardium is of interest because of the frequent use of agents such as dobutamine in the treatment of patients with cardiac failure associated with coronary artery disease.1-3 However, the effect of such clinical intervention on ischemic myocardial function is difficult to assess in patients. In an experimental study, Goodlett et al4 found that β-adrenergic stimulation did not further impair regional high-energy-phosphate stores of an

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ischemic region and suggested that the noncontractile state of the ischemic myocardium protected it from responding to adrenergic stimulation. Buda et al3 also found little response to dobutamine in the center of an acutely ischemic region. However, Vatner and coworkers6-8 reported that β-adrenergic stimulation of ischemic myocardium with isoproterenol resulted in increased paradoxical bulging and S-T segment elevation in conscious dogs with acute ischemia. Intravenous administration of inotropic agents, however, complicates the assessment of the effect on ischemic myocardium because of simultaneous stimulation of nonischemic adjacent and distant regions with subsequent changes in ventricular hemodynamics.5

This study was undertaken for evaluation of the effects of inotropic stimulation on the ischemic myocardium, its regional blood flow, and blood flow distribution under similar global hemodynamic conditions by regional infusion of dobutamine into the ischemic myocardium. Specifically, we tested whether regional myocardial blood flow and function are matched during steady-state ischemia under conditions of regional inotropic stimulation or whether dobutamine induces a state of "relative" ischemia characterized by an imbalance between decreased flow and increased function.9-11

Materials and Methods

Sixteen swine (30-40 kg) were studied under isoflurane anesthesia. The swine were handled according to the animal welfare regulations of the University of California, San Diego, and the experimental protocol was approved by the animals committee of this institution.

Animal Model

Swine were sedated with ketamine hydrochloride (1 g i.m.) and anesthetized with thiamylal sodium (500 mg) administered through an ear vein. A tracheostomy was performed, and an endotracheal tube was positioned and connected to a respirator equipped with an isoflurane vaporizer. Anesthesia was maintained by means of isoflurane (1-2%) with oxygen, and ventilation was adjusted to keep PaCO2, PaO2, and pH within the normal range (PaCO2 35±5 mm Hg, PaO2>150 mm Hg, pH 7.35±0.05). Both carotid arteries were cannulated, one with a large polyethylene catheter that served as the blood supply for the extracorporeal circuit and the other with a small polyethylene catheter for pressure measurement and blood sampling. An internal jugular vein was cannulated before coronary perfusion for return of blood from the extracorporeal circuit, and a saphenous vein was cannulated for saline infusion. Rectal temperature was measured periodically, and swine were kept on a circulating hot water pad for prevention of hypothermia (body temperature maintained at >36.8°C).

A left lateral thoracotomy was performed in the fourth intercostal space, and the pericardium was opened and sutured to cradle the heart. Electrodes were sutured to the left atrium for electrical pacing (model 5800, Medtronic, Minneapolis, Minnesota). A micromanometer (model P7, Konigsberg Instruments, Pasadena, California) and a fluid-filled catheter were placed in the left ventricle through the apex for measurement of left ventricular pressure.

Ultrasonic crystals were then implanted in the anterior wall within the perfusion bed of the left anterior descending (LAD) coronary artery for measurement of wall thickness by use of standard techniques.12 The stability of the preparation was verified by implantation of a set of ultrasonic crystals in the lateral wall (control zone) within the perfusion bed of the left circumflex coronary artery by the transit time technique (Triton Technologies, San Diego, California). In five pigs ascending aortic blood flow was also measured with a 16-mm (inner diameter) electromagnetic flow probe and a Statham flowmeter (model SP 2200, Gould, Cleveland, Ohio).

The proximal LAD coronary artery was dissected free from surrounding tissue for a distance of approximately 2 cm. After heparinization of the swine (20,000 IU initial dose, followed by 10,000 IU/hr), the LAD coronary artery was ligated and rapidly cannulated. Perfusion pressure was measured through a distal side arm of the cannula. Pressure drop from the cannula tip to the side arm was measured in vitro by use of heparinized blood at 36.8°C over a flow range of 0–100 ml/min; the maximum difference that occurred was 1.2 mm Hg at a flow rate of 100 ml/min. Since the maximum flow rate for perfusion of the LAD coronary artery under control conditions was less than 70 ml/min, the maximum error introduced by measurement of coronary artery pressure through the side arm of the cannula was less than 1 mm Hg. Because the Statham transducer (P23Db, Hato Rey, Puerto Rico) used for measurement of coronary artery pressure was fixed to the study table, correction for the difference in height between the Statham transducer and the side arm of the cannula was determined at the end of the study. The difference in height was measured, and coronary artery pressure was corrected by application of the equation P=pg×(h2-h1), where P is the difference in pressure, p is the density, g is the gravity, and (h2-h1) is the difference in height. Because the pressure line was filled with saline solution, we calculated a correction factor of 0.7525 mm Hg/cm difference in height. Coronary artery pressure data are presented as the corrected values.

Blood was supplied by an extracorporeal circuit that included an occlusive roller pump (Masterflex, Cole-Parmer Instrument Co, Chicago, Illinois), a Windkessel, and an electromagnetic flow probe (model RC 2000, Micron Medical, Los Angeles, California) as well as two side ports, one for regional dobutamine infusion and one for microsphere injection. The microsphere injection port was proximal (just distal to pump and Windkessel) in the extra-
Figure 1. Validation of method for determination of blood flow distribution. Panel A: Regional myocardial blood flow throughout perfusion bed during low-flow conditions both with (filled symbols) and without (open symbols) inclusion of an additional mixing chamber in perfusion circuit. Absence of differences between these injections in three separate pigs indicates that thorough mixing of spheres was achieved. Panel B: Reproducibility of measurements under control perfusion conditions. Four sequential determinations of blood flow distribution across the left ventricular wall were done in three pigs under similar hemodynamic conditions. Panel C: Distribution of subendocardial blood flow throughout perfusion bed was assessed by comparison of the subendocardial flow to each of seven samples within perfusion bed with the overall mean value in each of four microsphere injections (same three pigs as in panel B). Small differences observed and random nature of the differences indicate that no preferential streaming of microspheres occurred.

Corporal circuit; spheres were injected in the opposite direction of flow to facilitate mixing with blood. The adequacy of mixing was tested in three additional swine in which a mixing chamber was included in the perfusion system. Microsphere injections were performed first under control conditions either with or without the mixing chamber; measurements were then repeated at a level of coronary artery pressure below the level used in these studies. No significant differences in absolute blood flow and blood flow distribution were observed, within the myocardium, as shown in Figure 1A. The reproduc-
The radioactivity injected was determined by totaling all counts from the perfusion bed, and coronary inflow was measured with the electromagnetic flowmeter. The number of microspheres in each tissue sample was calculated by use of the predetermined number of counts per sphere. Samples usually contained more than 1,000 spheres and never fewer than 700.

In the presence of a significant coronary collateral circulation, a regional microsphere injection, which is only able to detect antegrade blood flow, would have underestimated the absolute amount of myocardial blood flow by not accounting for retrograde perfusion. Despite the fact that many investigators have shown an absence of collateral circulation in pigs, in four additional pigs microspheres were injected into the left atrium and a reference withdrawal was taken from the aorta for measurement of the amount of collateral circulation to the LAD coronary artery perfusion bed. At the time of microsphere injection, the perfusion circuit was clamped to stop antegrade flow into the area perfused by the LAD coronary artery. After the study, the circumferential slice of the left ventricle containing the wall thickness crystal was cut into 21 transmural pieces, and myocardial blood flow was calculated. In agreement with other investigators, we could not detect any significant collateral flow in the bed perfused by the LAD coronary artery in pigs, as shown in Figure 2.

**Protocol**

Blood flow through the cannulated LAD coronary artery was adjusted in both groups to produce a coronary artery pressure of 114 or 115 mm Hg, respectively, and the first microsphere injection was made. Dobutamine hydrochloride was then infused into the perfusion system at a rate of 2.5±1 μg/min, which resulted in an increase in the first derivative of

**Blood Flow Measurements**

Regional myocardial blood flow distribution was measured by use of 12-μm microspheres (Du Pont, Boston, Massachusetts) labeled with one of the following radionuclides: ^14^Ce, ^11^In, ^51^Cr, ^18^Sn, ^10^Ru, ^99^Nb, or ^46^Sc. For each measurement, approximately 130,000 spheres suspended in saline were injected into the extracorporeal circuit perfusing the LAD coronary artery. Microspheres received from the manufacturer were diluted to adjust the number of spheres for every injection into an injection volume of 1 ml. Each microsphere injection was followed by a flush of 3 ml saline solution at a slow speed (approximately 90 sec) to avoid changes of coronary artery pressure.

After the study, the perfusion bed of the LAD coronary artery was determined by injection of trypan blue dye through the cannula into the beating heart simultaneously with an intravenous injection of euthanizing solution (T-61 [0.3 ml/lb], Hoechst-Roussel Agri-Vet Co, Somerville, New Jersey). The radioactivity content of the entire dyed area was determined for use in the calculation of regional blood flow (see below). The left ventricular samples were divided into transmural thirds, and all samples were placed in glass tubes for counting gamma radioactivity by means of a multichannel gamma counter (model 5912, Packard Instrument, Downers Grove, Illinois). Blood flow corrected for wet weight of the tissue was calculated by standard techniques modified for the coronary injection of the microspheres. Thus, the blood flow was calculated by the equation

The diagram shows the collateral flow measurements with mean flow and standard deviation for n=4. The crystal area of the perfused myocardium is also indicated. The graph is labeled as follows:

**Figure 2.** Perfusion system for left anterior descending coronary artery was clamped, and microspheres were injected into left atrium while a reference withdrawal was taken from aorta. A circumferential slice of left ventricle containing anterior wall thickness crystal (A1) was cut into 21 transmural pieces, and myocardial blood flow was calculated. No significant myocardial blood flow could be detected in area perfused by left anterior descending coronary artery, indicating lack of collateral circulation to anterior wall. S1–S7, posterior to anterior septum; A1–A4, anterior wall; L1–L3, lateral wall; P1–P5, posterior wall.
left ventricular pressure (positive LVdP/dt) by >30%. When the first steady-state condition was observed, a second microsphere injection was performed and dobutamine infusion was stopped. After all parameters were restored completely to control baseline values for no less than 2 minutes, coronary inflow was reduced to produce mild ischemia (group 1) (decrease of 25% in percent systolic wall thickening [%WTh], measured as the difference between end-systolic and end-diastolic wall thickness divided by end-diastolic wall thickness) and moderate ischemia (group 2) (decrease of 75% in %WTh). A third microsphere label was injected when regional myocardial function remained stable for over 2 minutes (after approximately 5 minutes of hypoperfusion). Dobutamine was then infused at the same infusion rate as before into the perfusion system, and as soon as a steady-state response was confirmed (mean time 5 minutes), the last microsphere injection was done and dobutamine infusion was stopped.

Data Analysis and Statistics
Data were recorded on an eight-channel recorder (model 200, Gould, Cerritos, California) and on 0.5-in. magnetic tape and were replayed and digitized for beat averaging. Fifteen sequential beats were averaged for each measurement. End diastole was defined as the zero crossing point of LVdP/dt before its maximum value. Global end systole was defined as the time of maximum excursion of the left circumflex sonomicrometer tracings occurring within 10 msec before peak negative LVdP/dt, as verified in five pigs in which aortic blood flow was measured. Hemodynamic parameters that were calculated included left ventricular peak and end-diastolic pressures, peak positive and peak negative LVdP/dt, and coronary artery pressure; heart rate was paced at the left atrium and held constant throughout the protocol. Regional function was first assessed by use of %WTh. Because regional dobutamine infusion changed the contraction pattern of the stimulated area as previously described18-21 (an augmented early systolic thickening occurred, followed by late systolic thinning, as shown in Figure 3), an additional estimation of regional work performed by the ischemic myocardium was calculated. The regional myocardial work index (WI) was estimated by calculation of the sum of the instantaneous left ventricular pressure–wall thickness product over the time of the cardiac cycle with the equation

\[ F[n] = (LVP_{[n]} - LVP_{min}) \times (WTh_{[n]} - WTh_{[n-1]}) \]
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MODERATE ISCHEMIA

- i.e. DOBUTAMINE

LEFT VENTRICULAR PRESSURE (mmHg)

ANTERIOR WALL THICKNESS (mm)

SUM OF THE INSTANTANEOUS LEFT VENTRICULAR PRESSURE-WALL THICKNESS PRODUCT (mmHg - mm)

TIME OF CARDIAC CYCLE (ms)

where LVP_{init} is the left ventricular pressure at time (n), LVP_{min} is the minimum left ventricular pressure, and WTh is the anterior wall thickness (Figure 4). Both the maximum work index of the ischemic myocardium (MAX-WORK), measured as the maximum value of W1 observed during systole, and the work index observed at end systole are reported.

In five pigs of group 2, aortic flow was measured to assess the effect of the regional inotropic stimulation on overall left ventricular pump function. Two parameters were used: 1) the integral of the product of aortic flow times left ventricular pressure throughout the time of ejection, as a calculation of overall left ventricular work during ejection, and 2) left ventricular ejection work divided by ejection time as a calculation of left ventricular power.

An analysis of variance was performed. When an overall significant difference among the groups was detected, a comparison of mean values was done using a paired t test. Data are reported as mean±SD.

Results

Global Hemodynamics

Hemodynamic data are summarized in Table 1. Heart rate was paced throughout the protocol at 124±4 beats/min in group 1 and 121±5 beats/min in group 2. During the dobutamine infusion under control conditions, peak positive LVdP/dt increased significantly by 33% (p<0.001) and 65% (p<0.001) in groups 1 and 2, respectively (group 1 vs. group 2, p=NS). Left ventricular peak (LVPP) and end-diastolic pressure (LVEDP) as well as peak negative LVdP/dt remained unchanged in both groups.

When coronary artery pressure (CAP) was reduced from 114±7 mm Hg to 62±2 mm Hg in group 1 to produce a mild reduction in %WTh, LVPP and LVEDP were unchanged. However, peak positive LVdP/dt decreased significantly by 8% (p<0.026). In group 2, when CAP was reduced to 46±5 mm Hg (control 115±8 mm Hg), LVPP fell from 96±18 mm Hg to 85±12 mm Hg (p<0.010) and both positive and negative LVdP/dt were significantly reduced by 19% (p<0.001) and 23% (p<0.009), respectively; LVEDP was unchanged. When dobutamine was then infused into the LAD coronary artery (at the same infusion rate used under control conditions), peak positive LVdP/dt increased by 29% (group 1, p<0.008) and 37% (group 2, p<0.001) (group 2 vs. group 1, p=NS), whereas LVPP and LVEDP remained unchanged in both groups.

Regional Myocardial Contractile Function

Myocardial function and blood flow data are summarized in Table 1. An original tracing is shown in Figure 3.

Anterior Wall

There were no significant differences between group 1 and group 2 in %WTh, end-systolic work.
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...and both ES-WORK and MAX-WORK fell from 250±74 to 189±63 mm Hgxmm (p<0.001). (ES-WORK, end-systolic work index; MAX-WORK, maximal work index; %pSS, systolic percent posterior segment shortening from end diastole; G1, group 1 (mild ischemia group); G2, group 2 (moderate ischemia group).)

<table>
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<th>Control</th>
<th>Ischemia</th>
<th>Dobutamine</th>
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<tr>
<td>LVPP (mm Hg)</td>
<td>G1 104±14</td>
<td>G2 96±18</td>
<td>G1 102±15</td>
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<td>p&lt;0.057</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>G1 7.2±8.5</td>
<td>G2 6.6±6.8</td>
<td>G2 8.4±8.7</td>
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<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>+LVdP/dt (mm Hg/sec)</td>
<td>G1 1.78±266</td>
<td>2.33±343</td>
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<td></td>
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<td>0.026</td>
<td>0.008</td>
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<tr>
<td>−LVdP/dt (mm Hg/sec)</td>
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<td>1.68±266</td>
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<td>CAP (mm Hg)</td>
<td>G1 114±7</td>
<td>G2 115±8</td>
<td>G1 62±2</td>
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<td>%WTh (%)</td>
<td>G1 34.6±8.1</td>
<td>G2 34.1±16.4</td>
<td>G2 25±4±5.8</td>
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<td>ES-WORK (mm Hgxmm)</td>
<td>G1 250±74</td>
<td>273±107</td>
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<tr>
<td>MAX-WORK (mm Hgxmm)</td>
<td>G1 250±74</td>
<td>323±94</td>
<td>189±63</td>
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<tr>
<td>TMF (ml/min/g)</td>
<td>G1 1.52±0.24</td>
<td>1.37±0.23</td>
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<td>ENDO (ml/min/g)</td>
<td>G1 1.32±0.34</td>
<td>1.21±0.25</td>
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<tr>
<td>%pSS (%)</td>
<td>G1 18.5±4.4</td>
<td>G2 16.5±3.8</td>
<td>G1 18.7±4.2</td>
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<td>ES-WORK (mm Hgxmm)</td>
<td>G1 225±70</td>
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<td>G1 225±70</td>
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*%pSS for group 1 vs. group 2 under control conditions.

LVPP, left ventricular peak pressure; LVEDP, left ventricular end-diastolic pressure; +LVdP/dt, peak positive first derivative of left ventricular pressure; −LVdP/dt, peak negative first derivative of left ventricular pressure; CAP, coronary artery pressure; %WTh, systolic percent anterior wall thickening from end diastole; ES-WORK, end-systolic work index; MAX-WORK, maximal work index; TMF, transmural myocardial blood flow; ENDO, endocardial blood flow; %pSS, systolic percent posterior segment shortening from end diastole; G1, group 1 (mild ischemia group); G2, group 2 (moderate ischemia group).

*%pSS for group 1 vs. group 2 under control conditions.

During the control dobutamine infusion, there was a significant increase in %WTh by 11% (p<0.002) and in MAX-WORK by 29% (p<0.001), while ES-WORK increased by only 9% (p=NS). When CAP was reduced to 62±2 mm Hg, %WTh decreased from 34.6±8.1% to 25.4±5.8% (p<0.005), and both ES-WORK and MAX-WORK fell from 250±74 to 189±63 mm Hgxmm (p<0.001). (ES-WORK and MAX-WORK were identical under these conditions since the maximum work within systole occurred at the end of systole.) When dobutamine was infused, the contraction pattern of the ischemic myocardium changed markedly (Figure 3). Calculated %WTh remained unchanged compared with the mild ischemic conditions; ES-WORK decreased by 20% (p<0.057), but in contrast, MAX-WORK was enhanced by 10% (p<0.059).

During the control dobutamine infusion there was a 15% increase in %WTh (p<0.069). Changes in ES-WORK and MAX-WORK were comparable with those described for group 1. When CAP was reduced to 46±± mm Hg, %WTh decreased by 70% (p<0.001). Regional work, estimated either as MAX-WORK or ES-WORK, decreased also by 71% (p<0.001). However, during the dobutamine infusion, a further deterioration of %WTh and ES-WORK was measured (Table 1). In contrast, MAX-WORK increased significantly by 42% (p<0.010) due to the increased wall thickening occurring in early systole.

**Posterior Wall**

During the control dobutamine infusion no change in percent systolic segment shortening (%pSS) in the control wall was observed in either group. Because of the asynchronous contraction, postischemic shortening occurred with each dobutamine infusion (Figure 3). Reduction of blood flow to the LAD coronary artery to produce a CAP of 62±2 mm Hg (group 1) or 46±± mm Hg (group 2) caused no change in %pSS. Because LVPP decreased significantly in group 2 with the onset of ischemia, there was a reduction in ES-WORK and MAX-WORK. Infusion of dobutamine during anterior wall ischemia caused similar changes when compared with infusion of dobutamine in controls (Table 1).

**Global Ventricular Function**

Changes in aortic flow were measured in five of the group 2 pigs for assessment of overall left...

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**Global Ventricular Function**

Changes in aortic flow were measured in five of the group 2 pigs for assessment of overall left
ventricular pump function. During control dobutamine infusion, global left ventricular work tended to increase compared with the control condition (8.1%, \( p=NS \)). Due to a decrease in global ejection time during the dobutamine infusion, left ventricular power (defined as systolic work divided by systolic time) increased significantly by 19.8% \( (p<0.009) \). Reduction in CAP produced significant decreases in global left ventricular ejection work and power (reductions of 26% \( [p<0.007] \) and 26% \( [p<0.011] \), respectively). With dobutamine infusion under ischemic conditions, no change in global left ventricular ejection work was observed; left ventricular power increased again by 16.3% \( (p<0.009) \).

**Myocardial Blood Flow**

Under control conditions, transmural blood flow (TMF) was 1.32±0.34 ml/min/g in group 2, respectively (group 1 vs. group 2, \( p=NS \)). Control subendocardial blood flow (ENDO) was significantly different between group 1 (1.41±0.38 ml/min/g) and group 2 (1.08±0.22 ml/min/g). With reduced coronary inflow, TMF and ENDO in both groups were reduced; endocardial blood flow decreased to 0.65±0.13 ml/min/g \( (p<0.001) \) in group 1 and to 0.24±0.08 ml/min/g \( (p<0.001) \) in group 2. During dobutamine infusion there was a significant further reduction in both TMF and ENDO in both groups, as shown in Figures 5A and 5B.

**Regional Myocardial Blood Flow–Function (or Work) Relation**

Calculations made by means of control and mild and moderate ischemia points and a polynomic fitting (Table 2) produced a good correlation between

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**FIGURE 5.** Summary of left ventricular blood flow (subendocardial in 5A and transmural in 5B) at two levels of coronary inflow (mild and moderate ischemia) both before and during dobutamine infusion. Blood flow was significantly reduced during dobutamine infusion at each level of perfusion.
fore, one goal of the present study was to investigate the effect of inotropic stimulation on hypokinetic affected by changes in global hemodynamics. There-

ations in regional function were likely to have been

Inotropic stimulation through intracoro-

nary dobutamine infusion. Furthermore, this
dysfunctional myocardium can be increased by
given amount of endocardial perfusion maximum 

%WTh and endocardial or transmural myocardial 

blood flow. (The polynomial fitting was used because in comparison with the linear fitting, a slightly higher r value was calculated; linear regression r=0.710, polynomial fitting r=0.737). When ES-WORK or MAX-WORK was plotted against endocardial blood flow, the best correlation (comparison of linear and polynomial fittings) was observed with a linear regression (Table 2). During dobutamine infusion, no shift in the relation between %WTh and endocardial blood flow was observed (Table 2, Figure 6A). When ES-WORK was plotted against endocardial blood flow, a significant shift in the slope as well as the y intercept was detected (Figure 6B); while the slope of the relation increased, the y intercept decreased significantly, indicating that with increasing severity of ischemia, ES-WORK deteriorated during dobutamine infusion. In contrast, a significant shift of the relation between MAX-WORK and endocardial blood flow was found (Figure 6C), indicating that for a given amount of endocardial perfusion maximum work was increased.

Discussion

In the present study we have shown that the maximum work performed by the ischemic and dysfunctional myocardium can be increased by regional inotropic stimulation through intracoronary dobutamine infusion. Furthermore, this increase in regional contractile performance of the ischemic myocardium also resulted in an increased overall systolic left ventricular performance.

Several studies have examined the effects of inotropic stimulation on the hypokinetic myocardium.5-8 Because in all of these studies the inotropic agent was administered intravenously, alterations in regional function were likely to have been affected by changes in global hemodynamics. Therefore, one goal of the present study was to investigate the effect of inotropic stimulation on hypokinetic myocardium without significant changes in global hemodynamics. As shown in Table 1, dobutamine infusion under control conditions did not alter left ventricular peak or end-diastolic pressures.

There was a significant difference in subendocardial blood flow under control conditions between group 1 and group 2. However, this difference in blood flow was not associated with any differences in regional myocardial function. Such differences in blood flow in this range under control conditions would not be expected to result in changes in contractile function, as shown in earlier studies by Vatner.22

The contractile performance of the regional myocardium is frequently assessed by measurement of changes in ventricular dimensions (wall thickness or segment length) occurring between end diastole and end systole. In this study, during ischemia, regional myocardial function (measured as %WTh) remained unchanged in group 1 and deteriorated in group 2 during dobutamine infusion; this result was in agreement with studies of Vatner and co-workers6-8 that used intravenous infusion of isoproterenol. However, the estimation of MAX-WORK improved significantly under these conditions. This discrepancy was the result of the ventricular asynchrony that occurred during regional inotropic stimulation, which caused a significantly reduced active-state duration in the stimulated region. Thus, conventional parameters of regional contractile function failed to account for the pronounced augmentation in function that occurred at an earlier time during systole (Table 1, Figure 3). The increase in MAX-WORK was consistently observed despite the fact that ENDO actually decreased further in each animal, resulting in a significantly steeper relation between regional ENDO and MAX-WORK (Figure 6C). This relation between regional ENDO and MAX-WORK was used because a strong dependence of regional wall function on subendocardial perfusion

### Table 2. Relation Between Regional Myocardial Blood Flow and Function or Work

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>r</th>
<th>p&lt; vs. without</th>
</tr>
</thead>
<tbody>
<tr>
<td>%WTh (a×ENDO²+b×ENDO+c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-7.68</td>
<td>35.78</td>
<td>3.75</td>
<td>0.737</td>
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<tr>
<td>Dobutamine</td>
<td>-20.40</td>
<td>61.61</td>
<td>-2.18</td>
<td>0.817</td>
<td>NS</td>
</tr>
<tr>
<td>%WTh (a×TMF²+b×TMF+c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>-3.89</td>
<td>29.67</td>
<td>1.08</td>
<td>0.736</td>
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</tr>
<tr>
<td>Dobutamine</td>
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<td>51.51</td>
<td>-8.49</td>
<td>0.814</td>
<td>NS</td>
</tr>
<tr>
<td>ES-WORK (a×ENDO+c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>152.40</td>
<td>65.20</td>
<td>0.800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>238.20</td>
<td>13.01</td>
<td>0.837</td>
<td>0.05 for a and c</td>
<td></td>
</tr>
<tr>
<td>MAX-WORK (a×ENDO+c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>65.10</td>
<td>0.802</td>
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<tr>
<td>Dobutamine</td>
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<td>88.80</td>
<td>0.860</td>
<td>0.05 for a</td>
<td></td>
</tr>
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</table>

Control values represent control and ischemic conditions without dobutamine infusion; dobutamine values represent control and ischemic condition with dobutamine infusion. %WTh, systolic percent anterior wall thickening from end diastole; ES-WORK, end-systolic work index; MAX-WORK, maximal work index; TMF, transmural myocardial blood flow; ENDO, endocardial blood flow.
was demonstrated for anesthetized animals by Gallagher et al.23 and for conscious animals by Roan et al.24 The decrease in ENDO had two likely reasons: 1) the increase in regional contractile function in early systole may favor the perfusion of the outer wall,25 and 2) as we have shown recently, with inotropic stimulation of the hypoperfused myocardium perfused by the LAD coronary artery, CAP decreases significantly because of a right ventricular vasodilatation.26

We also measured changes in global left ventricular ejection work and power in five pigs. Because the regional infusion of dobutamine produced a significant shortening in global ejection time, left ventricular power during ejection increased. Because no increase in regional function or regional work was measured in the control lateral wall during ejection, the increase in performance must have been due to the increase in regional function in the stimulated area in early systole, despite the lack of thickening in the stimulated area later during systole.

We have thus demonstrated that acutely hypoperfused and hypokinetic myocardium can respond with increased contractile performance despite a further decrease in subendocardial perfusion. An anesthetized swine preparation with flow-constant perfusion and regional inotropic stimulation is unphysiological. Nevertheless, this preparation is necessary for assessment of the regional ischemic myocardial flow–function relations during regional inotropic stimulation under conditions of controlled coronary perfusion. In contrast with the present results, in previous studies in conscious, exercising dogs during steady-state exercise-induced ischemia, the observed decreases in regional myocardial function (expressed as %WTH) and decreases in regional myocardial blood flow were well matched.9–11 It was hypothesized that during steady-state exercise-

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**Figure 6.** Summary of effect of regional dobutamine infusion on relation between regional blood flow and contractile function. Panel A: Subendocardial blood flow in anterior perfused wall plotted against percent systolic wall thickening. No difference was observed in this relation with addition of dobutamine. Panel B: Subendocardial blood flow plotted against ES-WORK showing a significant shift in slope and y intercept of relation during dobutamine infusion. Slope of relation increased, while y intercept decreased significantly. Therefore, with increased severity of ischemia, ES-WORK decreased compared with control conditions. Panel C: Subendocardial blood flow plotted against MAX-WORK showing a significant shift in slope of relation (y intercept was unchanged) with addition of dobutamine. Thus, significantly more work was performed for a given level of subendocardial perfusion when dobutamine was infused. ES-WORK, maximum value of sum of instantaneous left ventricular pressure–wall thickness product within 10-msec interval before peak negative LVdP/dt (first derivative of left ventricular pressure); MAX-WORK, maximum value of sum of instantaneous left ventricular pressure–wall thickness product within systole.
induced ischemia, "absolute" ischemia results in depression of myocardial function to a level consistent with the decrease in subendocardial or transmural myocardial blood flow. Thus, a reduction of "relative" ischemia (defined as an imbalance between myocardial blood flow and function) occurs early during exercise, as function decreases to match the reduced perfusion in the steady state. In the present study, regional ENDO and function appeared also to be matched during regional inotropic stimulation with dobutamine when function was expressed as %WTh. However, due to the asynchrony of myocardial contraction caused by the regional administration of dobutamine, %WTh was not useful in describing the increase in regional myocardial performance which occurred early in systole. A new index, MAX-WORK, was developed for adequate description of regional performance during intracoronary dobutamine infusion. When this new index was used, an imbalance between an increased regional function and a decreased regional perfusion became evident during intracoronary dobutamine infusion in ischemic myocardium. It remains to be clarified in further studies for how long such an imbalance can be maintained, what the underlying mechanisms are, and whether this imbalance is deleterious for the survival of the dobutamine-stimulated ischemic myocardium.

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Key Words • dobutamine • myocardial blood flow • myocardial contraction • myocardial ischemia
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