The Effect of Dobutamine on Cardiac Oxygen Balance, Regional Blood Flow, and Infarction Severity after Coronary Artery Narrowing in Dogs

RONALD R. TUTTLE, G. DONALD POLLOCK, GLEN TODD, BRIAN MACDONALD, RALMOND TUST, AND WILLIAM DUSENBERRY

SUMMARY We compared the acute effects of dobutamine and isoproterenol on cardiac O2 balance and regional blood flow (studied with microspheres) in eight male beagles with a narrowed left anterior descending coronary artery (LAD). The two drugs similarly increased cardiac contractility, output, and oxygen consumption. However, unlike isoproterenol, dobutamine did not accelerate heart rate or markedly lower peripheral resistance. Also unlike isoproterenol, dobutamine augmented blood flow in regions supplied by the LAD and improved oxygen balance, as indicated by significant increases in coronary sinus Po2, oxygen supply-consumption ratio, and lactic acid consumption. To determine whether dobutamine would contain infarction, we continuously infused it or saline in 24 beagles for 24 hours immediately after LAD constriction. Then, 1–3 days after LAD constriction, we assessed the infarction. In 11 of 12 dogs treated with dobutamine, infarctions could not be detected by gross examination or the distribution of microspheres, and microscopic lesions were minimal. In contrast, 10 of 12 dogs treated with saline had gross transmural infarctions, an absence of microspheres in the region supplied by the LAD, and marked microscopic damage. Therefore, prompt and persistent treatment with a powerful inotropic agent, used at doses low enough to avoid chronotropic and vascular side effects, may contain rather than extend myocardial infarction by increasing the supply of oxygen more than it increases the requirement for oxygen.

THE PURPOSE of inotropic drug therapy in patients with heart failure due to acute myocardial infarction is to force well perfused regions of the myocardium to compensate for poorly perfused regions. Such therapy should increase cardiac output and thereby improve perfusion of the whole body and the ischemic region of myocardium as well, thus containing infarction. However, there are studies showing that the powerful inotropic agent, isoproterenol, extends myocardial infarction, and these studies have created the idea that inotropic therapy should be avoided during acute myocardial infarction. However, there are good reasons to believe that it is the marked chronotropic and \( \beta_2 \) vasodilating actions of isoproterenol, rather than the drug's inotropic effect, that are responsible for its adverse effect on myocardial infarction.

Although both inotropic and chronotropic effects increase cardiac oxygen consumption (MVO2), the oxygen cost of an inotropic effect is mitigated by a reduction in ventricular volume and, thus, in wall tension. Moreover, regional oxygen requirements are not raised equally by increases in contractility and heart rate. The degree to which isoproterenol can elevate the oxygen requirement of a region through its inotropic effect is related to the rate of delivery of the drug, and because blood flow to a region supplied by an obstructed artery is limited, so is drug delivery. In contrast to the inotropic effect, the chronotropic effect is not regional. Because the chronotropic effect is related to the rate of drug delivery to the sinoatrial (SA) node, the myocardium supplied by an obstructed artery undergoes the same elevation in heart rate as does well perfused myocardium.

Vasomotor tone is present in well perfused regions, but in an ischemic region, the arterioles are maximally dilated and flow depends solely on the duration of diastole and on coronary perfusion pressure. This dependency prevents isoproterenol from improving perfusion of a region supplied by a narrowed artery because its powerful chronotropic effect shortens diastolic time. Also, \( \beta_2 \) activity on the peripheral vasculature lowers diastolic pressure and thus coronary perfusion pressure. Furthermore, the \( \beta_2 \) activity on the coronary vasculature reduces arteriolar tone in well oxygenated regions and thus diverts blood flow to well perfused regions at the expense of ischemic regions. Dobutamine is a new catecholamine in which chronotropic and \( \beta_2 \) effects have been attenuated. Studies in dogs, on isolated hearts, on cardiac tissue, and in patients with heart failure have established that, for an equivalent inotropic effect, dobutamine has less chronotropic and \( \beta_2 \) activity than does isoproterenol. Therefore, in contrast to isoproterenol, dobutamine should be able to improve blood flow to an ischemic region and contain infarction. The experiments reported here were designed to test this hypothesis.

METHODS

EXPERIMENTAL PLAN

The study was divided into two parts. In Part I, we infused isoproterenol or dobutamine into anesthetized dogs after coronary artery narrowing, to determine whether the two agonists, when administered in doses causing similar increases in cardiac contractility, cardiac
output, and Mvo2, would differ in their effects on regional left ventricular blood flow. The purpose of Part II was to determine whether 24 hours of dobutamine treatment, at a dose high enough to increase contractility and Mvo2 but low enough to avoid increasing heart rate, would contain infarction.

SURGICAL PROCEDURES

We used purebred adult male beagles of similar age and weight. Sodium thiopental (15 mg/kg, iv) was used to induce anesthesia, and halothane (1%), in a mixture of N2O (80%) and O2 (20%) was used to maintain anesthesia. A positive-pressure Harvard respiration pump ventilated the dogs, and a heating pad kept their body temperature at 37-38°C. Carotid arterial pressure was measured through a heparin-filled polyethylene catheter (PE200).

In Part I, a miniature pressure transducer (Konigsberg Instruments, P22) was placed in the left ventricle, an electromagnetic flow probe (Carolina Medical EP440-EP450) was placed around the aortic root, and the coronary sinus was cannulated. The right femoral vein was cannulated for the administration of drugs.

MEASUREMENTS

Aortic blood flow, arterial pressure, left intraventricular pressure and its derivative (dP/dt), ECG lead II, and heart rate were recorded on a Beckman Dynograph. We assessed cardiac contractility from dP/dt at an intraventricular pressure of 60 mm Hg. The value of dP/dt was divided by 60, and contractility is expressed as dp/dt/P, sec-1.17

An Instrumentation Laboratory pH/blood gas analyzer (model 513) and co-oximeter (model 182) were used to measure the following parameters on heparinized arterial and coronary sinus blood samples: pH, Pco2 (mm Hg), PO2 (mm Hg), hemoglobin (Hb)(g/100 ml), and HbO2 (%). O2 content (ml/100 ml) equaled Hb x HbO2 x 1.39. Lactic acid concentration was measured enzymatically with the lactate test combination kit (Boehringer-Mannheim).

Regional cardiac blood flows were measured with carbonized microspheres having diameters of 15 ± 5 µm and labeled with six different nuclides, of which the specific activities, expressed as mCi/g, were as follows: 43Sc = 8.74, 22Nb = 8.99, 85Sr = 13.31, 95Nb = 9.98, 99Tc = 13.45, and 125I = 9.38. To ensure homogeneity, dextran suspensions of the spheres were sonicated just before administration. Each dose consisted of no less than 430,000 spheres. To determine the portion of tissue radioactivity contributed by each nuclide, we used our modification18 of the method of Rudolph and Heymann.19

PROTOCOL FOR ACUTE EXPERIMENTS (PART I)

After the catheters and transducers were implanted, ventilation was adjusted so that arterial pH was 7.35-7.45 and PO2 was 65-80 mm Hg. To cause coronary narrowing, we tied 2-0 silk ligature around both a 20-gauge hypodermic needle and the LAD, 5-8 mm below the circumflex branch. The needle was withdrawn immediately after the knot was made, so that the artery was not totally occluded.

The first microspheres were injected 10 minutes before LAD stenosis and the second, 10 minutes after stenosis. Isoproterenol was infused intravenously into four dogs at rates of 0.05, 0.1, and 0.2 µg/kg per min. Dobutamine was similarly infused into another four dogs at rates (2, 4, and 8 µg/kg per min) that were inotropically equal to those of isoproterenol. There was no pause between infusion rates, and an interval of 10 minutes was allowed at each rate for all parameters to stabilize. During the steady state, we injected the microspheres and withdrew arterial and coronary sinus blood samples.

After injection of the last dose of microspheres, the heart was excised and the left ventricular free wall was divided into 20 sections, as indicated in Figure 1. From each of these sections we cut a slice of subendocardium (3-5 mm thick) and a slice of subepicardium (1-2 mm thick). Radioactivity was measured in all 40 slices and in the 20 remaining middle sections. Although data from the middle slices were not analyzed statistically, they were used in calculation of total coronary blood flow.

Calculations

Blood flow to each sample (ml/min per 100 g tissue) = radioactivity in sample/radioactivity injected per sample weight in grams x aortic blood flow (ml/min) x 100.

Total coronary blood flow (ml/min) = sum of blood flow in the left and right ventricular walls, interventricular septum, and right and left atria.

Peripheral resistance (mm Hg/ml per min) = mean aortic pressure/aortic blood flow.

Myocardial O2 supply (ml/min) = total coronary blood flow x O2 content of arterial blood.

Cardiac O2 consumption (Mvo2) (ml/min) = (O2 content of arterial blood – O2 content of coronary sinus blood) x total coronary blood flow.

Cardiac lactic acid consumption (mmol/min) = the difference in lactic acid concentrations between arterial and coronary sinus blood x total coronary blood flow.

PROTOCOL FOR 24-HOUR INFUSION EXPERIMENTS (PART II)

During halothane anesthesia (as in part I), a Tygon catheter was placed in the jugular vein, threaded under the skin with its tip exteriorized between the shoulders, and

![Diagram of sectioning of left ventricular free wall. The arrow marks the site of left anterior descending coronary artery (LAD) narrowing.](http://circres.ahajournals.org/)

FIGURE 1
then connected to a battery-operated (Harvard Lambda) portable infusion pump that contained either dobutamine (in a concentration that provided 2.5 μg/kg per min) or saline. We occluded the LAD as before, immediately started the infusion pump, and closed the chest. The pump was secured in a jacket worn by the dog. The dog was exubated, shortly thereafter regained consciousness, and then was given morphine sulfate (2.0 mg/kg, sc) and penicillin G (600,000 U, im). At 1–3 days after LAD constriction, the dogs were anesthetized, microspheres were injected into the left atrium, and the heart was excised.

The 20 sections of left ventricular free wall represented in Figure 1 were split longitudinally to yield two sets of 20 sections each. The radioactivity of one set was determined. The other set of 20 was fixed in formalin. Four slices were made from each of the 20. These were stained with hematoxylin and eosin, and the percentage of tissue damaged by hemorrhage, edema, degeneration, and necrosis was estimated by light microscopy. The pathologist did not know whether the samples were from dobutamine- or saline-treated dogs.

To assess the degree of LAD constriction, a cast was made by injecting a quick-hardening liquid rubber (Dow Corning 3111 RTV encapsulant and catalyst) into the coronary ostium. The diameters of the cast at the point of constriction and immediately proximal to the constriction were determined with an optical micrometer.

DRUGS

dl-Isoproterenol HCl and dl-dobutamine HCl were dissolved in sterile 0.9% NaCl containing ethylenediaminetetraacetic acid (EDTA) (1.8 mg/liter) and sodium bisulfite (0.5 mg/ml). Drug concentrations were adjusted so that, over the 24-hour infusion period, each dog received a volume of 150 ml. Dogs used as controls received 150 ml of vehicle without drug.

STATISTICS

Means ± standard errors are given. Unless otherwise noted, the P values given in the text, tables, and figures were derived from analysis of variance.

Results

PART I. COMPARISON OF THE ACUTE EFFECTS OF DOBUTAMINE AND ISOPROTERENOL

Figure 2 illustrates the effects of LAD narrowing and the subsequent responses to graded infusions of dobutamine and isoproterenol. With narrowing, there was a significant decrease in overall cardiac oxygen consumption (MvO₂) and a significant rise in left ventricular end diastolic pressure (P < 0.05). However, narrowing had no significant effect on cardiac contractility, aortic blood flow, heart rate, aortic pressure, or peripheral resistance.

After narrowing, the infusions of isoproterenol (0.05, 0.1, and 0.2 μg/kg per min) and dobutamine (2, 4, and 8 μg/kg per min) increased cardiac contractility, aortic blood flow, and MvO₂ equally, and both drugs reduced left ventricular end diastolic pressure to the preocclusion level. However, as Figure 2 shows, isoproterenol lowered pe-
peripheral resistance and increased heart rate significantly more than did dobutamine. Although the drugs increased aortic blood flow similarly, isoproterenol lowered peripheral resistance to a greater extent, and therefore maintained a lower mean aortic pressure, than did dobutamine.

**Regional Blood Flow**

Narrowing of the LAD reduced the overall mean blood flow in the left ventricular wall from 114 ± 3 to 67 ± 2 ml/min per 100 g (P < 0.01). Table I shows that flow to the anterior-apical regions was reduced more than was flow to the posterior-base regions, and in most regions the subendocardium was more affected than was the subepicardium.

Isoproterenol and dobutamine similarly increased blood flow to the subepicardium (83 ± 6 and 87 ± 5 ml/min per 100 g, respectively), but dobutamine increased flow to the subendocardium more than twice as much as did isoproterenol. Comparative values were 83 ± 6 vs. 40 ± 4 ml/min per 100 g (P < 0.001). As illustrated by Figure 3, dobutamine more effectively restored flow than did isoproterenol in the regions where flow was most diminished by LAD narrowing.

**Myocardial Oxygen Balance**

Table II shows that LAD constriction significantly reduced cardiac oxygen supply and consumption. However, the decrease in supply was greater than the decrease in consumption; thus, myocardial oxygenation was impaired, as indicated by significant decreases in the oxygen supply-consumption ratio, in coronary sinus Po2, and in cardiac lactate acid consumption.

Although dobutamine and isoproterenol similarly increased myocardial oxygen consumption, dobutamine increased oxygen supply significantly more than did isopro-

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### Table I  Blood Flow within the Left Ventricular Wall

<table>
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<th>Base to apex section</th>
<th>Blood flow (ml/min per 100 g) anterior to posterior section</th>
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<td>A</td>
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<td>Before occl.</td>
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**Epicardium**

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<td>8 ± 2</td>
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Blood flow values during dobutamine (DOB) and isoproterenol (ISO) are the averages for the three infusion rates: isoproterenol = 0.05, 0.1, and 0.2 μg/kg per min; dobutamine = 2, 4, and 8 μg/kg per min. Detailed analysis of variance will be supplied by the authors on request. Results are expressed as mean ± se.
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Figure 3 The effect of dobutamine and isoproterenol on regional blood flow within the left ventricular free wall after narrowing of the LAD. The three regions were operationally defined: the most ischemic = those sections where LAD narrowing reduced blood flow by 81% or more. These included anterior-apical regions designated in Figure 1 as 3A, 3B, 4A, and 4B. The moderately ischemic region = those sections where LAD narrowing reduced blood flow by 30-80%. These include regions designated in Figure 1 as 2A, 2B, 3C, 4C, 4D, and 4E. The least ischemic = all other sections. In these, flow was reduced by less than 30% by LAD narrowing. P values apply to the mean differences between dobutamine and isoproterenol. The means were computed from all sections within a region, and all three dose levels. Blood flow (ml/min per 100 g) for each section is given in Table 1.

terol. Therefore, dobutamine caused a significant improvement in myocardial oxygenation, as indicated by a 39% rise in the supply-consumption ratio, a 38% increase in coronary sinus Po2, and a 348% elevation in myocardial lactic acid consumption. With isoproterenol, not only were the increases in the first two parameters insignificant, but the heart produced rather than consumed lactic acid.

PART II. THE EFFECT OF 24 HOURS OF TREATMENT WITH DOBUTAMINE ON INFARCT DEVELOPMENT

Autopsies were done on eight dogs (four controls and four dobutamine-treated) from 71 to 73 hours after narrowing of the LAD and, in the other 16 dogs, from 25 to 26 hours after LAD narrowing. Because we could not detect that the time of autopsy influenced the results, the data were pooled.

On gross examination, there was evidence of infarction in only one of 12 of the hearts from dobutamine-treated dogs. In contrast, severe transmural infarction of the anterior-apical region was present in 10 of 12 of the saline-treated dogs ($\chi^2$, $P < 0.001$); the other two hearts were comparable to the 11 normal-appearing hearts from dobutamine-treated dogs.

Histology

From each of 20 subendocardial sections, four histological sections were made, giving 80 sections from each heart. Light microscopic examination of the hearts from dobutamine-treated dogs revealed no tissue damage in two, slight diffuse damage in nine, and severe damage in one. Tissue damage was slight in the hearts from two control dogs that had no gross evidence of infarction, but in the other 10 control dogs the damage was extensive and was found most severe in the anterior-apical region. These results are illustrated in Figure 4.

Microspheres

The microspheres were distributed evenly throughout the left ventricular wall in 11 of the 12 dogs treated with dobutamine. In the 12th, there was a relative absence of microspheres in the anterior-apical regions. In contrast, microspheres were distributed homogeneously in only two hearts from the saline-treated dogs. In the other 10, there was a marked paucity of microspheres in the anterior-apical regions.

Figure 5 illustrates the mean distribution of microspheres in the two groups of dogs. Analysis of variance showed that the difference between the dobutamine- and saline-treated dogs reached a high degree of statistical significance ($P < 0.0001$).

Degree of LAD Narrowing

Narrowing was severe and consistent in all dogs, regardless of treatment. The cross-sectional area of the lumen

<table>
<thead>
<tr>
<th>Index of oxygenation</th>
<th>Before occlusion</th>
<th>After occlusion</th>
<th>During dobutamine</th>
<th>During isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2 supply (ml/min)</td>
<td>15.5 ± 1.1</td>
<td>10.6 ± 1.1*</td>
<td>25.4 ± 2.1*</td>
<td>18.3 ± 2.2†</td>
</tr>
<tr>
<td>O2 consumption (MVO2) (ml/min)</td>
<td>9.5 ± 1.1</td>
<td>6.9 ± 0.8*</td>
<td>12.3 ± 1.1*</td>
<td>11.4 ± 1.7†</td>
</tr>
<tr>
<td>O2 supply/consumption ratio</td>
<td>1.71 ± 0.11</td>
<td>1.58 ± 0.10*</td>
<td>2.15 ± 0.20*</td>
<td>1.68 ± 0.09†</td>
</tr>
<tr>
<td>Coronary sinus Po2 (mm Hg)</td>
<td>24.9 ± 1.2</td>
<td>22.4 ± 1.9*</td>
<td>30.8 ± 1.4†</td>
<td>25.3 ± 1.78‡</td>
</tr>
<tr>
<td>Lactic acid consumption (mmol/min)</td>
<td>66.3 ± 13.4</td>
<td>13.3 ± 8.4*</td>
<td>59.7 ± 13.5†</td>
<td>-17.2 ± 36.9†</td>
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Values during the administration of dobutamine or isoproterenol are the means (± se) for the three infusion rates: dobutamine = 2, 4, and 8 μg/kg per min; isoproterenol = 0.05, 0.1, and 0.2 μg/kg per min.

* Statistically significant ($P < 0.05$) change from before-occlusion value.
† Statistically significant ($P < 0.05$) change from after-occlusion value.
‡ Statistically significant ($P < 0.05$) difference between the changes caused by dobutamine and isoproterenol.
FIGURE 4 The effect of dobutamine on severity of infarction as assessed by histology. The upper diagram represents the results from 12 control dogs, and the bottom diagram represents the results from 12 dobutamine-treated dogs. From each section of the left ventricular free wall (Fig. 1), four histological sections were prepared and graded by light microscopy as follows: No mark = normal tissue; + = 1-10% damage; ++ = 10-25% damage; +++ = 25-50% damage; ++++ = 50-100% damage. Therefore, the maximum possible number of marks in an individual section = 48 (4 x 12 dogs).

was reduced at the site of the ligature by a mean of 98 ± 0.5% in the control dogs and by 98 ± 0.6% in the dobutamine-treated dogs. The reductions in the two control dogs without gross appearance of infarction were 97% and 99%. In the one dobutamine-treated dog that was as severely infarcted as the control dogs, the reduction was 98%.

Discussion

When we narrowed the LAD, total cardiac oxygen consumption (MVO₂) decreased and, if the animals were left untreated, massive infarctions developed. When we infused dobutamine immediately after the narrowing, MVO₂ increased, but so did perfusion of regions supplied by the LAD, and total oxygen supply increased faster than MVO₂. Consequently, when the dobutamine infusions were continued for 24 hours, the infarction was contained. These findings suggest reexamination of the concept that inotropic therapy should be avoided during evolving myocardial infarction.

We believe that the well known detrimental effect of isoproterenol on infarct size⁴ is due to chronotropic and β₂ vascular effects, not an inotropic effect. In our experiments, isoproterenol so markedly lowered peripheral resistance that aortic and thus coronary perfusion pressure did not rise with the increased cardiac output. This, combined with the shortened diastolic time caused by the accelerated heart rate, explains the contrasting effects of isoproterenol and dobutamine on restoration of blood flow to ischemic regions. We have shown earlier that isoproterenol, infused for 24 hours in a dose that was the inotropic equivalent of the dose of dobutamine used here, killed 67% of the dogs, and the surviving 33% were more severely infarcted than dogs infused with saline.

FIGURE 5 The effect of dobutamine on severity of infarction as assessed by the distribution of radioactive microspheres. The upper diagram represents the mean results from the 12 control dogs, and the lower diagram represents the mean results from the 12 dobutamine-treated dogs. Each □ = 0.1% of the total radioactivity administered.
The salutary effect produced on regional perfusion by augmentation of coronary perfusion pressure with norepinephrine is known, but there is an important distinction between dobutamine and norepinephrine. Dobutamine is not a vasoconstricting agent. Thus it does not increase cardiac work by elevating peripheral resistance or reduce blood flow to vital peripheral organs. Moreover, the arrhythmogenic effect of dobutamine is less than that of norepinephrine.

One would anticipate that dopamine could produce results similar to our results with dobutamine. In a certain dose range, dopamine, like dobutamine, will increase cardiac contractility and cardiac output without causing vasoconstriction or marked increases in heart rate. However, the mechanisms involved in dopamine’s cardiac and peripheral actions are complex, and these make it difficult to predict the effect on myocardial infarction. In the dose range where dopamine’s vasodilating activity on the renal and mesenteric beds counter-acts its α-adrenergic vasoconstricting activity, its inotropic effect relies on release of cardiac norepinephrine. If cardiac stores of norepinephrine are low, as in heart failure, the dose of dopamine has to be increased to achieve a direct inotropic effect. With the higher dose, the powerful α-adrenergic vasoconstricting activity overrides its dopaminergic vasodilating actions, and peripheral resistance is increased.

In contrast to dopamine, dobutamine has so little α-adrenergic activity that it will not increase peripheral resistance even at high doses. After administering dopamine and dobutamine in doses producing similar increments in cardiac output in patients with chronic, low output heart failure, Loeb et al. concluded that dobutamine was superior because it decreased left ventricular filling pressure whereas dopamine increased it.

Moreover, the factors involved in the inactivation of dopamine (uptake by adrenergic nerve fibers, enzymatic oxidation, and O-methylation) make it difficult to predict its effect on infarction. In contrast, adrenergic uptake and oxidation are not involved in the inactivation of dobutamine. The pertinence of this in myocardial ischemia and infarction is that uptake and oxidation require oxygen; methylation does not. Therefore, inactivation of dobutamine would not be slowed in a region of myocardium where oxygen supply is limited by a narrowed artery. The concentration of dobutamine in an ischemic region should be lower than in regions supplied by normal arteries because the rate of drug delivery has to be lower.

In contrast to dobutamine, the amount of dopamine present in a region supplied by the narrowed artery may be higher than in well perfused regions where uptake and enzymatic oxidation are fully functional. These differences in the modes of inactivation between dopamine and dobutamine may help to reconcile our results with those of Reid et al., who found that dopamine increased infarction size in dogs when infused at the same rate at which we infused dobutamine (2.5 µg/kg per min).

The separation of inotropic and chronotropic effects achieved with the development of dobutamine is not absolute. As the dose increases, the chronotropic effect appears. We chose a dose that was large enough to augment cardiac contractility, cardiac output, and MVO₂, but low enough to avoid elevation of heart rate. If heart rate had been significantly increased, infarction size would have been increased. We recently found, in experiments similar to these (unpublished observations), that doses of dobutamine of 1–7.5 µg/kg per min do not raise heart rate and do contain infarction. Doses greater than 7.5 µg/kg per min raise heart rate and extend the infarction.

Because heart rate is a key factor, it is important to point out that the relative inotropic-chronotropic response to dobutamine depends on the dog’s physiological state as well as on dose. In conscious dogs, where the vagal reflex is not attenuated by anesthesia, remarkably large increases in contractility can occur without increases in heart rate. Recently, Willerson et al. assessed the effects of dobutamine in pentobarbital-anesthetized dogs with acute ischemia and in conscious dogs with chronic ischemia. Their data show that, in the anesthetized dogs, 20 µg/kg per min increased cardiac contractility by 92% and heart rate by 26%, and these increases were accompanied by an intensification of ischemia as indicated by an elevation of epicardial S-T segment height. At a smaller dose of 4 µg/kg per min, contractility still increased by 36%, but heart rate increased by only 6%, and there was no increase in ST-segment height. In conscious dogs, the high dose of dobutamine, 20 µg/kg per min, increased contractility by 43% without causing any increase in heart rate, and blood flow to the ischemic region was increased by 44%. However, whether the increased myocardial perfusion was adequate to meet the increased oxygen demand unfortunately was not assessed.

We occluded the LAD partially rather than completely because myocardial infarction frequently occurs in man without total obstruction. Moreover, we thought it unlikely that inotropic therapy could restore flow adequately to contain infarction through collateral vessels alone. It is also unlikely that dobutamine would have contained infarction as effectively as it did if the start of the infusion had been delayed, for reperfusion studies show that the amount of myocardium saved is proportional to how quickly blood flow is restored. The continuation of the dobutamine infusion for 24 hours was probably adequate to cover the time over which the infarction could be expected to evolve.

Extensive clinical trials will be required to reexamine the role of inotropic therapy in acute myocardial infarction. However, dobutamine can improve ventricular performance in patients with heart failure at doses low enough to avoid significant increases in heart rate, and our results indicate that when chronotropic effects are avoided, dobutamine will at least not expand infarction. Moreover, Gillespie et al. recently found that dobutamine improved ventricular performance in patients with evolving myocardial infarction without extending infarction or promoting arrhythmias.

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