Effect of Dopamine and Calcium on Lipolysis and Myocardial Ischemic Injury following Acute Coronary Occlusion in the Dog

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ABSTRACT

Ischemic myocardial injury was quantified as the sum of S-T segment elevations in epicardial electrocardiogram recordings (ΣS-T) following acute coronary artery occlusions in 17 dogs. ΣS-T rose from 3 ± 1 mv to 26 ± 4 mv (P < 0.001) following occlusion. Myocardial contractility was similarly stimulated by intravenous infusions of dopamine or calcium. At reocclusions of the coronary artery, ΣS-T increased to 73 ± 12 mv (P < 0.001) with dopamine and to 41 ± 7 mv (P < 0.001) with calcium; the difference was statistically significant (P < 0.005). Arterial concentrations of free fatty acids (FFAₐ) were raised from 248 ± 33 μEq/liter to 888 ± 161 μEq/liter (P < 0.005) with dopamine, but administration of calcium did not influence FFAₐ. After inhibition of lipolysis with β-pyridyl carbinol, no difference in ΣS-T or FFAₐ was observed; the mean values were 31 ± 4 mv for ΣS-T and 144 ± 13 μEq/liter for FFAₐ. Myocardial lipolysis was suggested in three experiments in which β-pyridyl carbinol reduced ΣS-T with dopamine, although FFAₐ remained unchanged. These measurements suggest that dopamine-induced lipolysis contributes significantly to the enlargement of ischemic injury in the myocardium following acute coronary artery occlusion, probably due to the metabolic stimulation of myocardial oxygen requirements. Test doses of dopamine given to seven patients raised FFAₐ by 225 ± 87 μEq/liter (P < 0.03).

KEY WORDS β-pyridyl carbinol coronary insufficiency inotrophy free fatty acids myocardial infarction myocardial free fatty acid uptake S-T segment elevation man epicardial electrocardiogram

Methods

ANIMAL PREPARATION

A total of 17 healthy mongrel dogs of both sexes (8–20 kg) were fasted overnight and anesthetized with sodium pentobarbital (25 mg/kg, iv) followed by maintenance doses of 50 mg. Thoracotomy was performed through an incision in the left fifth intercostal space, and the heart was suspended in a pericardial cradle. Ventilation was...
performed through a cuffed endotracheal tube with a positive-pressure respirator (Cyclator MK. II). Throughout the experiments, arterial blood was examined 4–10 times for oxygen saturation (CO-oximeter model 182), pH, and PCO₂ (radiometer) (14). Mean values ± SE were as follows: oxygen saturation 95.2 ± 0.5%, pH 7.399 ± 0.015, and PCO₂ 37 ± 7 mm Hg.

**HEMODYNAMIC MEASUREMENTS**

Electrocardiographic registrations were performed with a mobile cotton wick electrode at 9–11 anatomically well-defined sites on the epicardial surface (4, 6). Together with conventional limb leads, the recordings were made on an Elema-Schönander Mingograf 42B (Stockholm) with a sensitivity of 1 mv/mm deflection and a paper speed of 25 mm/sec. Signals of 10 mv (10 cycles/sec, sinus) were used for calibration.

We selected 4–5 sites centrally in the area supplied by the coronary artery to be occluded, 4–5 other sites adjacent to this zone, and 1 control site at a remote; unaffected region of the left ventricular surface. S-T segment elevation is reproducible following several reocclusions of the vessel provided that recovery periods of 30–45 minutes are allowed (4, 5) and irreversible myocardial cell injury does not occur during the first 20 minutes of coronary artery occlusion (15). Therefore, ischemic electrocardiographic changes were compared during subsequent experimental interventions. The occlusions were performed on a branch of the left anterior descending coronary artery that was dissected free for a distance of 1–1.5 cm. The sum of S-T segment elevations from all sites in each dog after 15 minutes of occlusion (ΣS-T) was used as an overall estimate of the severity of ischemic injury. A control epicardial electrocardiogram (ECG) was recorded at all sites immediately before each occlusion, thus excluding any preexisting S-T segment elevation. Deflections > 2 mv were regarded as indicative of myocardial ischemia.

Left ventricular pressure was measured with a Statham P23Gb transducer connected to a short catheter introduced through the ventricular apex. The first derivative of left ventricular pressure, dP/dt, was continuously recorded with a differentiating circuit connected to the output of the pressure channel. Phasic aortic blood flow was measured by an electromagnetic flowmeter on the ascending aorta, and left ventricular stroke volume was determined by planimetry of the aortic flow curves. Left ventricular pressure, dP/dt, heart rate, and aortic blood flow were continuously monitored on a Sanborn multichannel oscillograph.

Heart rate was kept constant in three experiments (dogs 9–11) by pacing the right atrium with 1-msec pulses at an effective voltage of 1.5–3 v.

In two experiments (dogs 11, 12) instantaneous changes in left ventricular dimensions were monitored by ultrasound transmission between two piezoelectric crystals (0.5 × 1 × 3 mm) sewn into the well-oxygenated region of the left ventricular wall 8–12 mm apart (16), thus permitting estimates of instantaneous inner radius and wall thickness; V₁max was calculated from corresponding values of left ventricular pressure and dP/dt (17) at 10-msec intervals during the isovolumetric period of left ventricular pressure (18) using the value K = 28 as the series elasticity constant (19).

**METABOLIC MEASUREMENTS**

Arterial blood (8 ml) was sampled through a catheter inserted into a femoral artery and immediately centrifuged at 0°C for plasma separation. In three experiments (dogs 5, 10, 11) coronary sinus blood was simultaneously withdrawn through a catheter introduced via a jugular vein. Arterial plasma concentrations of free fatty acids (FFA₀) were determined by the method of Dole (20) as modified by Trout et al. (21). Arterial plasma concentrations of calcium were determined by flame photometry.

**EXPERIMENTAL PROCEDURE**

After control observations of ΣS-T, left ventricular pressure, dP/dt, heart rate, and cardiac output, the coronary artery was occluded by a Mayfield clip. Cyanosis and visible reduction in systolic movement quickly appeared in an epicardial area 4–8 cm². Hemodynamic parameters were redetermined 5, 10, and 15 minutes after occlusion, and blood samples were collected after 15 minutes of occlusion. The clip was then removed, and a recovery period of 30 minutes was allowed.

Dopamine (100–150 µg/min, iv) or calcium (1–2 mEq/min, iv) was then administered. A new steady hemodynamic state was usually attained within 10 minutes. The coronary artery was reoccluded at the same place after 15 minutes of calcium administration or 30 minutes of dopamine administration, and the protocol described above was repeated. In five experiments (dogs 1, 3, 9, 10) occlusion with calcium preceded occlusion with dopamine; in the remaining experiments the converse experimental sequence was used.

After 1 hour of recovery, a new control occlusion was performed. The alternate drug to be tested was then administered to reach the same value of dP/dt obtained before; this procedure was followed by reocclusion of the coronary artery.

β-Pyridyl carbinol (7–12 mg/min, iv) was administered and continued during the remaining two occlusions in which dP/dt was similarly raised by infusions of dopamine and calcium; the experimental protocol was performed as described above. In five experiments (dogs 1, 6, 7, 9, 10) occlusion with calcium preceded occlusion with dopamine; in the remaining experiments the converse sequence was used.

In two experiments (dogs 13, 14) the effects of glucagon (100–150 µg/min, iv) and dopamine were compared. The same experimental procedure was followed with glucagon replacing calcium.

In three additional experiments (dogs 15–17) dopamine (30–50 µg/min) was administered to the coronary circulation by an occluding pump. A minute artery branch close to the left coronary bifurcation was ligated.
MYOCARDIAL ISCHEMIC INJURY

Contr Occl Occl Ca Occl Dop Contr

CORONARY OCCLUSIONS

FIGURE 1

Epicardial electrocardiogram (ECG) recordings from 5 of 11 sites in one experiment (dog 4). Contr = control conditions prior to or after occlusions, Occl = coronary artery occlusion alone, Occl + Ca = occlusion performed during calcium infusion, and Occl + Dop = occlusion performed during dopamine infusion. Lipolysis was intact. All recordings, except control, were obtained after 15 minutes of ischemia. The occlusions were performed on a branch of the left anterior descending coronary artery (LAD) indicated by II. Site 1 was in an unaffected epicardial area and showed no S-T segment changes throughout the experiment. Sites 2 and 7 showed S-T segment elevation during dopamine infusion, but no ischemic ECG changes during occlusions alone or occlusions with calcium. Sites 4 and 5 showed S-T segment elevation in control occlusions, which were enhanced during calcium and dopamine infusions. The S-T segment elevations during dopamine administration always exceeded those obtained during calcium administration and extended the area with ischemic ECG changes as illustrated by single and double hatching (left). A = ascending aorta, PA = pulmonary artery, RV = right ventricle, and LV = left ventricle.

leaving a negligible basal infarction without measurable hemodynamic consequences. A thin catheter (0.63 mm, o.d.) was advanced to the main left coronary artery lumen; heparin (1,200-1,500 IU, iv) was used to prevent coagulation, and the correct position of the catheter and the absence of arterial thrombus formation was verified by postmortem examination. Coronary artery occlusions that gave rise to cyanosis and ECG changes clearly distant from the permanent basal infarction were performed with and without coronary administration of dopamine and with intravenous administration of dopamine to reach the same value of dP/dt in all instances. The same recording procedure described above was followed. Occlusions were then repeated during intravenous infusion of β-pyridyl carbinol. An hour and a half after β-pyridyl carbinol administration was terminated, a simple control occlusion ended the experiments.

MEASUREMENTS IN MAN

Test doses of dopamine (6-15 mg, iv) were given to seven patients during cardiac surgery. Blood samples (10 ml) were withdrawn from the catheterized femoral or radial artery 30-50 minutes after establishment of cardiopulmonary bypass, 45-60 minutes after terminating assisted circulation, and after 10-20 minutes of dopamine infusion. Analysis of FFA was performed as described above. Diagnosis and surgical treatment of the patients are listed in Table 3.
Coronary Artery Occlusions with Intact Lipolysis

Table 1 gives the results obtained with control occlusions and occlusions in which similar increments in dp/dt were effected by calcium and dopamine infusions. Compared with control occlusions, \( \Sigma S-T \) was elevated by both agents \( (P < 0.001) \). However, \( \Sigma S-T \) rose more with dopamine than it did with calcium in all experiments \( (P < 0.005) \). Figure 1 shows ECG recordings from one experiment.

Dopamine increased FFAs by an average of 258 \( \pm \) 61\% \( (P < 0.005) \), although administration of calcium did not change FFAs. The arterio-coronary sinus difference of free fatty acids (FFA\(_{ac}\)) increased markedly during dopamine infusion (Fig 2). FFAs and FFAs\(_{ac}\) reached stable levels after 20-30 minutes of dopamine infusion.

Left ventricular systolic pressure was raised, and left ventricular end-diastolic pressure was reduced proportionally by the two agents (Table 1). Cardiac output rose by 38.8 \( \pm \) 5.2\% with calcium and by 38.9 \( \pm \) 4.9\% with dopamine from a control level of 1,800 \( \pm \) 170 ml/min. Calcium infusion did not change heart rate, but tachycardia was seen in some experiments with dopamine. In three experiments in which heart rate was kept constant by atrial pacing, the difference in \( \Sigma S-T \) during occlusions with calcium and dopamine was clearly present. \( V_{\max } \) rose on the average from 15.5 cm/sec to 21.7 cm/sec with dopamine and from 16.0 cm/sec to 21.4 cm/sec with calcium.

Administration of calcium or dopamine had no effect on \( \Sigma S-T \) before coronary artery occlusions or changes of heart rate. Alternating the sequence of drug administration did not influence the different ECG responses obtained with calcium and dopamine. \( \Sigma S-T \) at control occlusions did not change significantly with time during the experiments. Plasma concentrations of calcium rose from 4.8 \( \pm \) 0.2 mEq/liter to 15.5 \( \pm \) 1.5 mEq/liter during infusion of calcium.

**Statistics**

Each dog or patient served as its own control. Student's t-test for paired data was used to calculate probability values (22); \( P > 0.05 \) was regarded as not statistically significant.

**Results**

Establishment of the control artery occlusion was followed by a rise in \( \Sigma S-T \) from 3 \( \pm \) 1 mv to 26 \( \pm \) 4 mv, whereas left ventricular systolic and end-diastolic pressure, dp/dt, heart rate, cardiac output, and FFAs remained unchanged.

**Effect of Dopamine and Calcium with Intact Lipolysis**

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### EFFECT OF DOPAMINE AND CALCIUM WITH INHIBITED LIPOLYSIS

Continuous intravenous infusion of β-pyridyl carbinol reduced FFA\textsubscript{a} from 231 ± 35 μEq/liter to 188 ± 161 μEq/liter.

### Table: Left Ventricular End-Diastolic Pressure (mm Hg) and Heart Rate (beats/min)

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<th>Occl + Dop</th>
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| Arterio-coronary sinus difference of free fatty acids (FFA\textsubscript{a-cs}) during coronary artery occlusions. Lipolysis was inhibited in two occlusions with β-pyridyl carbinol. Occl = coronary artery occlusions alone, Occl + Ca = occlusions performed during calcium infusion, and Occl + Dop = occlusions performed during dopamine infusion. Circles = dog 5, triangles = dog 10, and squares = dog 11.

**FIGURE 2**

**FIGURE 3**

Comparison of coronary artery occlusions performed during intravenous administration of dopamine and glucagon. Two occlusions were made after lipolysis was inhibited with β-pyridyl carbinol. dP/dt = maximal value of left ventricular pressure rise, FFA\textsubscript{a} = arterial plasma concentrations of free fatty acids, Σ ST = sum of S-T segment elevations in 10-11 epicardial ECG recordings, Occl = coronary artery occlusions alone, Occl + Dop = occlusions performed during dopamine infusion, and Occl + Glu = occlusions performed during glucagon infusion. Circles = dog 13 and squares = dog 14.
Myocardial contractility was increased to the

TABLE 2
Coronary Artery Occlusions with Inhibited Lipolysis Caused by Treatment with β-Pyridyl Carbinol

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Abbreviations are the same as in Table 1.

*Atrial pacing
†Probability value for comparison of paired data at occlusions with dopamine vs. occlusions with calcium.

COMPARISON BETWEEN GLUCAGON AND DOPAMINE

In eight of the dogs, coronary artery occlusions were performed during dopamine before and after antilipolytic agent treatment. In five of the dogs, coronary artery occlusions were performed during glucagon both before and after antilipolytic agent treatment. In all of these situations, myocardial contractility was increased to the same extent by dopamine and glucagon, regardless of whether or not the antilipolytic agent had been given. When the antilipolytic agent was given, myocardial contractility was increased to the same extent by either drug, regardless of whether or not the antilipolytic agent had been given. When the antilipolytic agent was given, myocardial contractility was increased to the same extent by either drug, regardless of whether or not the antilipolytic agent had been given.
same extent by intravenous and intracoronary infusions of dopamine. Intracoronary infusion of dopamine did not affect the arterial FFA levels (Fig. 4) either at intact or inhibited lipolysis. S-T segment elevation in excess of the control occlusion values was higher during intravenous infusions of dopamine than it was during coronary infusions, and ΣS-T during coronary dopamine infusion was further reduced by β-pyridyl carbinol in all experiments. Left ventricular systolic pressure, left ventricular end-diastolic pressure, heart rate, and cardiac output remained fairly constant in the three occlusions with dopamine.

Simple control occlusions were performed with intact and inhibited lipolysis in the same dogs. Although β-pyridyl carbinol did not effect other hemodynamic changes, ΣS-T was higher with intact lipolysis than it was during β-pyridyl carbinol administration in all three dogs.

**LIPOLYTIC EFFECT OF DOPAMINE IN HUMANS**

Dopamine (6–15 mg, iv) administered for 10–20 minutes caused a rise in FFA of 79 ± 27% (P < 0.03) in seven patients (Table 3). Five of the patients had been subjected to major cardiac surgery involving assisted circulation 45–60 minutes prior to administration of dopamine; however, no differences in FFA were found before, during, or after cardiopulmonary bypass (335 ± 73, 341 ± 101, and 328 ± 65 μEq/liter, respectively). Administration of dopamine was associated with a rise in systolic arterial blood pressure from 103 ± 5 mm Hg to 134 ± 11 mm Hg (P < 0.005) and in diastolic blood pressure from 69 ± 5 mm Hg to 83 ± 11 mm Hg (P < 0.02). A significant increase in coronary flow was also noted (6.9 ± 1.0 ml/min/100 g to 10.2 ± 1.2 ml/min/100 g, P < 0.005). The dP/dt₃₀₀₀₀ mm Hg/sec of the left ventricle was increased (Fig. 3) from 1490 ± 230 mm Hg/sec to 1850 ± 250 mm Hg/sec (P < 0.001). A significant increase in left ventricular contractility (≤ 0.03) was observed in all patients.

**TABLE 3**

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<td></td>
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<td></td>
<td><strong>8.9</strong></td>
<td><strong>328 ± 65</strong></td>
<td><strong>583 ± 95</strong></td>
<td><strong>&lt; 0.03</strong></td>
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FFAₐ — arterial plasma concentration of free fatty acids.
*Cardiopulmonary bypass.

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pressure from $64 \pm 2$ mm Hg to $73 \pm 4$ mm Hg ($P < 0.05$), but chronotropic effects were not consistent.

**Discussion**

The use of S-T segment elevations in epicardial ECG recordings to assess myocardial ischemic injury is qualified by their close correspondence to depletion of myocardial creatine phosphokinase activity (4, 23). Furthermore, epicardial S-T changes are associated with significant ischemic hemodynamic and metabolic changes such as raised left atrial pressure, increased myocardial oxygen extraction and myocardial lactate production (24), and diminished myocardial tissue oxygen tension (6). Since a previous investigation (4) and the present study showed complete recovery of the S-T changes when occlusion was restricted to prevent permanent cell injury (15) and since subsequent occlusions showed good reproducibility of the S-T changes, the effect of different interventions on the extent of ischemic injury can be assessed.

The most important finding in the present investigation was that acute myocardial ischemic injury following coronary artery occlusion was more increased during dopamine administration than it was during calcium administration, although myocardial contractility was similarly stimulated by the two drugs. A rise in left ventricular end-diastolic pressure or heart rate and a reduction in arterial blood pressure increase S-T segment elevations (4, 5). These parameters were similarly changed by the two drugs in this study and accordingly could not explain the differences in ischemic injury.

More increased S-T segment elevations with dopamine compared with those with calcium could not be demonstrated after treatment with β-pyridyl carbinol. The difference should thus be related to myocardial consumption of FFA (25). β-Pyridyl carbinol abolished dopamine-induced lipolysis, which caused a rise in arterial FFA concentrations by 250% and increased the myocardial arteriovenous difference even more. Although myocardial uptake of FFA could not be measured in these experiments, proportionality between arterial concentrations and myocardial arteriovenous differences of FFA have previously been found (26-28). β-Pyridyl carbinol, which is readily converted to nicotinic acid by the liver (29), blocks the action of the hormone-sensitive lipase (30), and arterial concentrations and myocardial arteriovenous differences of FFA have previously been found to be slightly reduced when lipolysis is inhibited by β-pyridyl carbinol (8, 10). It is well established that the lipolytic action of the hormone-sensitive lipase is mediated through the adenylate cyclase system (31). Evidence exists that nicotinic acid reduces adipose tissue levels of cyclic 3', 5' adenosine monophosphate (32), and stimulation of phosphodiesterase activity has been suggested from experiments in vitro (33).

The inotropic effects of catecholamines on myocardial oxygen consumption have been related to increased mechanical activity of the heart (3, 34). However, it has recently been shown that enhanced myocardial uptake of FFA increases myocardial oxygen consumption despite unchanged mechanical activity; this increase can be demonstrated whether arterial concentrations of FFA are raised by administering catecholamines (8-10) or by infusing triglycerides and heparin (7, 10). Intrinsic myocardial lipolysis has also been suggested during adrenergic stimulation (35) and during anoxia (36). Recently, evidence has been provided that β-pyridyl carbinol reduces both acute S-T segment elevations following coronary artery occlusions and myocardial creatine phosphokinase activity 24 hours later probably by inhibiting myocardial lipolysis evoked by release of endogenous catecholamines (13). This finding is corroborated by the present observation at constant arterial FFA levels that S-T segment elevation after coronary occlusions alone or during non-adrenergic stimulation with calcium (six of eight dogs) was higher before than after administration of β-pyridyl carbinol. Our findings that the S-T segments were increased less during stimulation with dopamine when the arterial FFA levels remained unchanged and that they could be further reduced by β-pyridyl carbinol imply that an activated myocardial lipolysis and an increased myocardial FFA uptake might be determinants of the extent of ischemic injury following coronary artery occlusion in dopamine-stimulated hearts.

The precise mechanism for a FFA-stimulated increase in myocardial oxygen requirements has not yet been completely established. Increased energy-requiring esterification of FFA occurs following increased availability of FFA, especially during hypoxia (37), and in vitro studies have suggested that fatty acids uncouple respiratory chain phosphorylation (38). This effect of FFA might influence cardiac function as suggested by the observation that high availability of FFA to the oxygen-limited heart depresses cardiac function (39).
Myocardial oxygen requirements and coronary blood flow increase following inotropic stimulation with dopamine (40), calcium (9, 41), and glucagon (9, 42). During conditions in which lipolysis is not activated, a similar rise in myocardial oxygen consumption is expected when the contractile indexes \(\frac{dP}{dt}\) and \(V_{max}\) are similarly raised and left ventricular systolic pressure, left ventricular end-diastolic pressure, heart rate, and cardiac output remain constant (3); S-T segment elevation following coronary artery occlusion was similar under these conditions.

Some reservations should be proposed for the chronotropic effects. Dopamine causes tachycardia in a dose-dependent manner (43); increased heart rate was observed in some of our experiments and may explain the increased S-T segment elevation (4). However, when heart rate was kept constant by atrial pacing, a larger increase in S-T segment elevation with dopamine compared with that with calcium could still be clearly demonstrated. Moreover, nonadrenergic stimulation of the heart by glucagon (9) revealed even greater S-T segment elevation during dopamine administration despite a more pronounced tachycardia during glucagon infusion.

Administration of dopamine, calcium, or glucagon did not cause significant changes in epicardial ECG recordings before coronary occlusions were established in the present experiments, although S-T segment elevation in intracellular and surface ECG recordings have been demonstrated after coronary perfusion with high-calcium solutions (44). If such calcium-induced S-T segment elevations were significantly present in our experiments when coronary occlusions were performed during calcium administration, the extent of ischemic injury might have been overestimated; on the other hand, the difference between dopamine and calcium might be even more pronounced than the difference that was actually observed.

Administration of dopamine to patients undergoing cardiac surgery was associated with enhanced lipolysis as evidenced by raised arterial FFA concentrations. The operative procedure and the use of cardiopulmonary bypass, including bubble oxygenator and heparin, did not affect the arterial FFA levels. The arterial blood pressure was increased by dopamine, but left ventricular systolic pressure remained unchanged in the dogs. This difference might be related to the higher doses of dopamine given the patients (12 \(\mu g/\text{kg min}^{-1}\)) compared with those given the dogs (8 \(\mu g/\text{kg min}^{-1}\)) or the pressor effect of dopamine might be more prominent in human diseased hearts than it is in healthy dog hearts (43). In the dog experiments, 20–30 minutes elapsed before stable levels of FFA\(_a\) and FFA\(_a,\) reached. Thus, it is likely that infusion of dopamine to the patients over a longer period might have raised FFA\(_a\) even more.

Nicotinic acid has been suggested to raise cardiac output due to peripheral vasodilation in patients (45). Coronary arteries also subjected to vasodilation might explain reduced ischemic S-T changes. \(\beta\)-Pyridyl carbinol in the doses used, however, did not change cardiac output or left ventricular pressure, and it has previously been shown (13) to have no discernible effect on coronary blood flow or retrograde flow in occluded and cannulated coronary arteries. Furthermore, any coronary vasodilating effect of \(\beta\)-pyridyl carbinol could not explain why the difference in S-T segment elevation between dopamine and calcium was eliminated by \(\beta\)-pyridyl carbinol administration.

Although calcium scarcely represents a therapeutic alternative in cardiogenic shock due to hazards of hypercalcemia, dopamine has been shown to improve cardiac function in dogs (46-49) and patients (1, 2) suffering acute coronary insufficiency or following cardiac surgery (50). The therapeutic effect is brought about by the remaining well-oxygenated myocardium that is capable of increasing its mechanical activity. Extension of the present finding obtained in dogs to patients with cardiogenic shock should be done with caution. Smaller coronary artery branches were occluded to avoid acute pump failure or serious arrhythmia, which by itself might influence the S-T changes. However, the present results suggest that the administration of dopamine to patients with cardiogenic shock might increase the attendant myocardial infarction but that this effect might be reduced by inhibition of catecholamine-induced lipolysis.

Acknowledgment

We are indebted to Miss Inger Bjerkedal and Mrs. Björg Kokkinn for skillful technical assistance.

References

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Circ Res. 1974;34:349-359
doi: 10.1161/01.RES.34.3.349

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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