The Effect of Nitroglycerin and Nitroprusside on Intramural Carbon Dioxide Tension during Acute Experimental Myocardial Ischemia in Dogs

L. DAVID HILLIS, CARL DAVIS, AND SHUKRI F. KHURI

SUMMARY There is continuing controversy over the effects of nitroglycerin and nitroprusside on myocardial ischemia. In 36 open-chest, anesthetized dogs with normal left ventricular filling pressures, intramural carbon dioxide tension (PmCO₂) was measured directly with a mass spectrometer during repeated 10-minute coronary artery occlusions separated by 45-minute periods of reflow. Simultaneously, regional myocardial blood flow (RMBF) in the ischemic area was quantified by the microsphere technique. In all dogs the increase in PmCO₂ from before to 10 minutes after the first occlusion (ΔPmCO₂) exceeded that during subsequent occlusions. In those dogs not receiving an intervention (controls), ΔPmCO₂ during the third occlusion was similar to that during the second occlusion. When nitroglycerin was administered before the third occlusion, it caused a significantly smaller elevation in ΔPmCO₂ than that which occurred during the control second occlusion, and transmural RMBF to the ischemic region was not altered. In contrast, sodium nitroprusside sufficient to reduce mean systemic arterial pressure to the same extent as nitroglycerin caused no change in ΔPmCO₂ and a significant decrease of transmural RMBF to the ischemic region. Thus, in the dog with normal left ventricular filling pressures, nitroglycerin reduces myocardial carbon dioxide tension, but nitroprusside given to produce similar hemodynamic alterations exerts no effect on intramural PCO₂. Circ Res 48: 372-378, 1981

DURING the past few years, numerous studies have demonstrated that left ventricular failure in the setting of acute myocardial infarction can be treated effectively by a reduction of left ventricular afterload and/or preload. In this clinical setting, both sodium nitroprusside (Franciosa et al., 1972, 1978; Chatterjee et al., 1973, 1976) and nitroglycerin (Gold et al., 1972; Delgado et al., 1975; Flaherty et al., 1975, 1976; Baxter et al., 1977) have been shown to reduce left ventricular filling pressures and to augment cardiac output. However, the effect of these pharmacological agents on the extent and severity of myocardial ischemic injury is not well characterized, either in the presence or absence of associated left ventricular failure. In the dog, nitroglycerin has been shown to exert a salutary influence on myocardial ischemia regardless of the left ventricular filling pressure (Myers et al., 1975; Hillis et al., 1979) and in patients with acute myocardial infarction and elevated filling pressures it has proved highly beneficial (Gold et al., 1972; Borer et al., 1975; Come et al., 1975; Flaherty et al., 1975). In contrast, the effect of sodium nitroprusside on myocardial ischemic injury, either with or without left ventricular failure, has not been clarified (Awan et al., 1976; Chiariello et al., 1976). The present study was performed, therefore, to assess the relative effects of nitroglycerin and nitroprusside on myocardial ischemia and transmural regional myocardial blood flow in the dog with normal left ventricular filling pressures.

Methods

The studies were performed in 36 mongrel dogs of both sexes weighing between 12 and 27 kg and anesthetized with sodium pentobarbital, 30 mg/kg. In each dog a cuffed endotracheal tube was positioned properly, after which the respiratory rate and tidal volume were maintained constant throughout the experiment with a mechanical respirator (Harvard Apparatus Co.). Since previous studies have demonstrated that carbon dioxide tension within the myocardial interstitium correlates closely with that in arterial blood (Khuri et al., 1975a), arterial carbon dioxide tension was not quantified in these animals. Systemic arterial and left atrial pressures were monitored continuously through catheters inserted into the left common carotid artery and the left atrial appendage, respectively, with a Statham P23Db strain gauge (Statham Instruments, Inc.). The left jugular vein was catheterized and used as a route for administration...
of fluids and drugs. The thorax was opened through the 5th left intercostal space and the heart sus-
pended in a pericardial cradle, so that the anterior aspect of the left ventricle was well exposed. The
midportion of the left anterior descending coronary artery was dissected free so that it could be occluded when desired.

Measurement of Intramural Carbon Dioxide Tension

The Perkin-Elmer mass spectrometer (model 1100B) (Perkin-Elmer Corporation) was used to monitor
\( \text{Pmco}_2 \) as previously described (Khuri et al., 1975b, 1979; Hillis et al., 1979). In each dog, 1-2
spectrometer probes (EXTC Teflon catheters, Chemetron Corporation) were placed in the left ven-
tricular myocardium; they were inserted through a small nick in the epicardium and advanced gently
until their sensing surfaces were entirely within the myocardium and their longitudinal axes approxi-
mately parallel to the epicardial surface. Each probe was secured with a single suture. In 21 dogs both
probes were placed in the area of distribution of the occluded left anterior descending coronary artery,
as judged by cyanosis. In the other 15 dogs, only one probe was placed in this area. Carbon dioxide
tension was measured continuously from each probe.

Measurement of Transmural Regional Myocardial Blood Flow (RMBF)

In 30 of the 36 dogs, RMBF was quantified with radioactive microspheres. Five minutes after each
coronary artery occlusion, approximately 2 \times 10^6 microspheres, 7-10 \mu m in diameter (suspended in
4-5 ml of solution) and labeled with \( ^{125}\text{I}, ^{57}\text{Co}, ^{85}\text{Sr}, ^{46}\text{Sc}, \) or \( ^{113}\text{Sn}, \) were injected into the left atrium over a period of 15 seconds. During the next 15 seconds the catheter was flushed with 4 ml of normal saline. Simultaneously, blood was withdrawn from the ca-
rotid artery at a constant rate of 15.3 ml/min for 60 seconds. The microspheres were suspended in a 50%
sucrose solution to which two drops of polysorbate 50 (Twist 50) had been added. Prior to injection they were ultrasonicated for 30 minutes, then vig-
oroously shaken by hand.

At the end of the experiment, the dogs were killed, the hearts removed, and transmural myocar-
dial specimens obtained for analysis of radioactivity. From each heart, two such specimens [average
weight, 3.0 \pm 0.2 g (mean \pm SD)] were obtained, each from the myocardium immediately surrounding
the sensing surface of the mass spectrometer probe. The radioactivity of these specimens and that of the arterial blood samples was determined in a well scintillation counter (Nuclear Chicago, model 4233). Cardiac output and regional myocardial blood flow were calculated as described previ-
ously (Kaihara et al., 1968; Utley et al., 1974).

Experimental Protocol

In all dogs, three occlusions of the coronary ar-
tery were performed, each lasting 10 minutes, with a 45-minute interval between occlusions for reflow. Transmural RMBF was measured at the midpoint of each occlusion. \( \text{Pmco}_2 \) was recorded continuously throughout each experiment. The dogs were assigned to one of three groups. In group A (13 dogs), three successive coronary artery occlusions were performed without the administration of an inter-
vention; therefore, these animals served as controls. Groups B and C were identical to the control group except that 10 minutes before the third occlusion they received one of two interventions: group B (12 dogs), nitroglycerin, 300 \mu g as an intravenous bolus followed by a continuous intravenous infusion of 3-
5 \mu g/kg per min, the exact dose adjusted so that mean systemic arterial pressure declined by 20 mm
Hg but did not fall below an absolute level of 60 mm Hg; and group C (11 dogs), sodium nitroprus-
side, 1.5 \mu g/kg per min intravenously by continuous infusion, with the exact dose adjusted so that mean arterial pressure fell by the same amount.

After release of the third coronary artery occlu-
sion, \( \text{Pmco}_2 \) was allowed to return to baseline; then the dogs were killed. The hearts were excised and dissec
ted to ensure that the entire sensing surface of each probe was completely within the myocardial
cavity. Then, transmural specimens of myocardium were obtained for determination of radioactivity.

Data Analysis

For each dog, heart rate, mean systemic arterial
pressure, and mean left atrial pressure were re-
corded during each coronary artery occlusion. For each spectrometer probe the rise in \( \text{Pmco}_2 \) with each occlusion was assessed and expressed as \( \Delta \text{Pmco}_2 \), in millimeters Hg. Likewise, transmural RMBF was measured 5 minutes after each occlu-
sion, i.e., midway during the occlusion period, by the injection of radioactive microspheres. In each of the 21 dogs in which both spectrometer probes were placed in the ischemic area, the two values for \( \Delta \text{Pmco}_2 \) during each coronary artery occlusion were averaged. The Appendix contains the values for \( \Delta \text{Pmco}_2 \) during the second and third occlusions for the individual spectrometer probes in these 21 dogs. Each parameter—\( \Delta \text{Pmco}_2 \), RMBF, heart rate, mean systemic arterial pressure, and mean left atrial pressure—was compared within each of the three groups during successive coronary artery oc-
clusions. Thus, for each dog during each occlusion, one value for each parameter was used for data analysis. For each parameter an analysis of variance was performed to determine if some groups were different from others, after which the groups were compared by the Newman-Keuls multiple compar-
ision procedure (Noether, 1971; Zar, 1974).
Results

For the 36 dogs, a total of 57 probes were placed in the ischemic myocardium. Pmco2 before the first coronary artery occlusion was $48.3 \pm 13.1$ mm Hg (mean $\pm$ sd), and with the occlusion it increased to $121.4 \pm 35.9$ mm Hg ($\Delta$Pmco2 = 73.1 $\pm$ 30.9 mm Hg). During this first occlusion, $\Delta$Pmco2 was 68.7 $\pm$ 29.0 mm Hg for the 13 control dogs and 75.7 $\pm$ 31.6 mm Hg for the 23 dogs that received either nitroglycerin or nitroprusside. The second coronary artery occlusion caused a significantly smaller rise in Pmco2 ($P < 0.001$) than with the first occlusion. Pmco2 before the first occlusion was $51.6 \pm 20.0$ mm Hg. During the first occlusion, APmco2 and RMBF during the third occlusion were similar to the values obtained during the second occlusion ($47.0 \pm 19.9$ mm Hg and $48.3 \pm 17.6$ mm Hg, respectively). During this first occlusion, heart rate for the 36 dogs was $134 \pm 14$ beats/min (NS), and during the second occlusion it was $131 \pm 12$ beats/min (NS). The mean systemic arterial pressure during the first occlusion (100.4 $\pm$ 13.5 mm Hg) was changed significantly during nitroglycerin infusion (Fig. 1). RMBF in the ischemic tissue was reduced significantly during nitroprusside administration, and mean left atrial pressure fell slightly but insignificantly (Table 1). Transmural RMBF to the ischemic region did not change significantly during nitroglycerin infusion (Fig. 2) and $\Delta$Pmco2 with the third occlusion (48.3 $\pm$ 17.6 mm Hg) was significantly less ($P < 0.01$) than with the second occlusion (58.2 $\pm$ 19.0 mm Hg) (Table 1, Fig. 1).

Group B (Nitroglycerin-Treated)

The infusion of nitroglycerin caused a reduction in mean systemic arterial pressure (from 96.3 $\pm$ 7.5 to 75.8 $\pm$ 5.4 mm Hg) but no change in heart rate or in mean left atrial pressure (Table 1). Transmural RMBF to the ischemic region did not change significantly during the infusion of nitroglycerin (Fig. 2). $\Delta$Pmco2 with the third occlusion (48.3 $\pm$ 17.6 mm Hg) was significantly less ($P < 0.01$) than with the second occlusion (58.2 $\pm$ 19.0 mm Hg) (Table 1, Fig. 1).

Group C (Nitroprusside-treated)

The infusion of nitroprusside caused a reduction in mean systemic arterial pressure of the same magnitude as that induced by nitroglycerin (from 96.0 $\pm$ 14.6 mm Hg during the second occlusion to 75.9 $\pm$ 9.5 mm Hg during the third occlusion). Heart rate did not change with nitroprusside administration, and mean left atrial pressure fell slightly but insignificantly (Table 1). Transmural RMBF was reduced significantly during nitroprusside infusion ($P < 0.01$) (Table 1, Fig. 2), and $\Delta$Pmco2 was not altered by nitroprusside (Table 1, Fig. 1).

Discussion

Several pharmacological agents, including nitroglycerin and sodium nitroprusside, have been used to reduce left ventricular afterload and/or preload in patients with acute myocardial infarction. Although these agents have been shown to reduce left ventricular filling pressure and to augment cardiac output in patients with left ventricular failure (Franciosa et al., 1972, 1978; Gold et al., 1972; Chatterjee et al., 1973, 1976; Delgado et al., 1975; Flaherty et al., 1975, 1976; Baxter et al., 1977), their influence both on the severity of myocardial ischemic injury and on blood flow to the ischemic myocardium remains controversial. Several studies in experimental animals and in humans have demonstrated that nitroglycerin administered in a dose sufficient to induce a modest reduction of systemic arterial pressure diminishes myocardial ischemia regardless of left ventricular filling pressure (Borer et al., 1975; Hillis et al., 1979; Come et al., 1975; Flaherty et al., 1976). In contrast, some studies have shown that sodium nitroprusside reduces myocardial ischemia (Awan et al., 1976), as reflected by the magnitude of precordial ST segment elevation, whereas others have demonstrated that nitroprusside actually worsens myocardial ischemic injury.
TABLE 1 Values for ΔPmco₂, RMBF, Heart Rate, Mean Arterial Pressure, and Mean Left Atrial Pressure during Occlusions 2 and 3

<table>
<thead>
<tr>
<th></th>
<th>Group A (Controls)</th>
<th>Group B (Nitroglycerin)</th>
<th>Group C (Nitroprusside)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPmco₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>occ 2</td>
<td>47.0 ± 19.9</td>
<td>58.2 ± 19.0</td>
<td>49.9 ± 19.3</td>
</tr>
<tr>
<td>occ 3</td>
<td>47.1 ± 19.4</td>
<td>48.3 ± 17.6*</td>
<td>48.2 ± 15.5</td>
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<tr>
<td>RMBF (ml/100 g per min)</td>
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<td></td>
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<tr>
<td>occ 2</td>
<td>28.5 ± 12.8</td>
<td>18.6 ± 12.4</td>
<td>28.5 ± 22.1</td>
</tr>
<tr>
<td>occ 3</td>
<td>28.8 ± 9.4</td>
<td>23.8 ± 11.9</td>
<td>18.1 ± 16.6*</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<td></td>
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</tr>
<tr>
<td>occ 2</td>
<td>129 ± 12</td>
<td>133 ± 15</td>
<td>131 ± 8</td>
</tr>
<tr>
<td>occ 3</td>
<td>124 ± 11</td>
<td>129 ± 14</td>
<td>128 ± 15</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<td></td>
<td></td>
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<tr>
<td>occ 2</td>
<td>104.6 ± 8.3</td>
<td>96.3 ± 7.5</td>
<td>96.0 ± 14.6</td>
</tr>
<tr>
<td>occ 3</td>
<td>104.5 ± 7.8</td>
<td>75.8 ± 5.4*</td>
<td>75.9 ± 9.5*</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>occ 2</td>
<td>5.2 ± 4.3</td>
<td>4.0 ± 2.3</td>
<td>5.3 ± 2.8</td>
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<td>occ 3</td>
<td>5.6 ± 4.0</td>
<td>4.0 ± 1.7</td>
<td>4.1 ± 2.3</td>
</tr>
</tbody>
</table>

All values are mean ± SD. ΔPmco₂ = rise of intramural CO₂ tension during coronary occlusion; RMBF = transmural regional myocardial blood flow; occ = occlusion.

* P < 0.01 when compared to values during the second occlusion.
recent studies have demonstrated that the magnitude of rise of PmccO2 during the hour after coronary artery occlusion corresponds closely to the severity of ischemic injury, as assessed histologically and in terms of the reduction of regional myocardial blood flow (Khuri et al., 1979). These same studies have shown that changes in intramural oxygen tension following coronary artery occlusion are unreliable in the quantification of myocardial ischemia. For this reason, the present study examined the effects of nitroglycerin and nitroprusside on PmccO2 but not Pmco2.

The accumulation of carbon dioxide within the ischemic myocardium probably results, first, from increased tissue production and, second, from decreased washout. As ischemia is initiated, the myocardium shifts from aerobic to anaerobic metabolism, resulting in the production of lactic acid (Liedtke et al., 1976). The increased concentration of hydrogen ion within the extracellular space accelerates the generation of CO2 from HCO3−. Simultaneous with this augmented production of CO2, there is a reduction of CO2 clearance. The local accumulation of carbon dioxide within the myocardial interstitium, therefore, probably reflects the balance between tissue carbon dioxide production and its clearance by local coronary blood flow. However, the relative extent to which increased carbon dioxide production and diminished tissue washout are responsible for the increase in myocardial carbon dioxide tension that occurs during ischemia has not been determined (Khuri et al., 1975b).

In the present study, each dog underwent three successive 10-minute coronary artery occlusions, each separated by 45 minutes of reflow. In all animals, the rise of PmccO2 during the initial occlusion was greater than during subsequent occlusions. This consistent reduction may be due to a prolonged depression of contractility in the ischemic tissue caused by the first occlusion. Previous studies have demonstrated that brief periods of myocardial ischemia cause a prolonged depression of myocardial function (Heyndrickx et al., 1975). The fall of ΔPmccO2 clearly is not caused by a smaller reduction in RMBF during the second occlusion when compared to the first; for all dogs, RMBF during the first occlusion averaged 25.3 ± 19.6 ml/100 g per min, and during the second occlusion it was 25.0 ± 17.0 ml/100 g per min (NS). Subsequent to the first coronary artery occlusion, ΔPmccO2 and RMBF were similar in the control dogs during the second and third occlusions.

In the present study, left ventricular filling pressure did not rise abnormally during myocardial ischemia in any of the 36 dogs. Great care was exercised to reduce mean systemic arterial pressure by 20 mm Hg in all dogs but never to reduce mean pressure below 60 mm Hg. Therefore, the animals included in this study, first, did not have abnormal left ventricular filling pressures and, second, achieved only a modest reduction of mean systemic arterial pressure. In this setting, nitroglycerin reduced the severity of myocardial ischemia (as reflected by a diminution of intramural carbon dioxide tension) without altering transmural regional myocardial blood flow to the ischemic tissue. In contrast, nitroprusside did not alter myocardial ischemia and caused a distinct decline of transmural regional myocardial blood flow. Since the present study did not attempt to quantify PmccO2 and transmural regional myocardial blood flow in dogs with myocardial ischemia and concomitant left ventricular failure, it is unknown what effects nitroglycerin and nitroprusside would have on myocardial ischemic injury in the setting of left ventricular failure.

The disparate effects of nitroglycerin and nitroprusside on the severity and extent of myocardial ischemic injury cannot be explained satisfactorily by the hemodynamic alterations they cause, since both agents were administered so that mean systemic arterial pressure fell similarly. However, as this and other studies have demonstrated (Chiarlelo et al., 1976), the two drugs exert a substantially different effect on the coronary vascular bed. Previous investigations have suggested that nitroglycerin acts primarily to dilate the large conductance vessels, at the same time exerting little or no effect on the small resistance vessels (Fam and McGregor, 1964, 1968; Wimbury et al., 1969; Cohen and Kirk, 1973). This predominant effect on the conductance vessels may account for a maintenance of flow in the ischemic area despite a distinct fall in perfusion pressure. In contrast, nitroprusside may reduce collateral flow to the ischemic area both by diminishing coronary arterial perfusion pressure and by dilating the small resistance vessels, thereby creating a "coronary steal." As a result, the blood from a relatively underperfused zone (which is already influenced by a maximal metabolic dilating stimulus) may be shunted to the adjacent nonischemic myocardium, where the vascular resistance still can be influenced pharmacologically.

In conclusion, nitroglycerin and nitroprusside commonly are employed to reduce left ventricular afterload and/or preload, oftentimes in the setting of active ischemic heart disease. Although both agents effectively reduce left ventricular filling pressure in the setting of left ventricular failure with acute myocardial infarction, their influence on myocardial ischemic injury and on myocardial blood flow differs substantially. Nitroglycerin diminishes the severity of myocardial ischemia without altering transmural myocardial blood flow. On the other hand, nitroprusside exerts no discernible effect on myocardial ischemia and precipitously lowers transmural myocardial blood flow. Since the present study was performed in open-chest, anesthetized dogs in which acute myocardial ischemia was induced in the absence of both left ventricular failure and systemic arterial hypertension, the extrapola-
tion of these results to patients with extensive coronary artery disease, left ventricular failure, and/or systemic arterial hypertension should be made carefully. Nevertheless, in this model, intravenous nitroglycerin and nitroprusside appear to exert substantially different effects on myocardial ischemic injury (as reflected by the rise of intramural carbon dioxide tension) and transmural regional myocardial blood flow. In the setting of acute myocardial ischemia and infarction, therefore, nitroglycerin may be preferable to nitroprusside in the patient in whom a reduction of systemic arterial pressure is desired.

Acknowledgments

The authors acknowledge the expert technical assistance of Janice McNatt, the secretarial help of Juanita Alexander, and the statistical assistance of Dr. Gregory Dehmer. The helpful criticisms and suggestions of Dr. J.T. Willerson are greatly appreciated.

Appendix

Values for ΔPmco2 during Occlusions #2 and 3 for Each Mass Spectrometer Probe in the 21 Dogs in Which Both Probes Were Placed in the Ischemic Area

<table>
<thead>
<tr>
<th>Dog</th>
<th>Probe #1</th>
<th>Occlusion #2</th>
<th>Average</th>
<th>Probe #1</th>
<th>Occlusion #3</th>
<th>Average</th>
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<td>Control #3</td>
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<td>51</td>
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<td>48</td>
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<td>NTG #8</td>
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<td>72</td>
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<td>35</td>
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<td>27</td>
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</tbody>
</table>

NTG = nitroglycerin; NP = nitroprusside.

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intronavenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction. Br Heart J 38: 612-621
Franciosa JA, Limas CJ, Guilha NH, Rodriguez E, Cohn JN (1972) Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. Lancet 1: 650-654

Carnitine Transport in Isolated Adult Rat Heart Myocytes and the Effect of 7,8-diOH Chlorpromazine

JOSEPH BAHL, THOMAS NAVIN, ALBERT A. MANIAN, AND RUBIN BRESSLER

SUMMARY We studied the carnitine transport system in isolated adult rat heart myocytes able to tolerate physiological concentrations of calcium. Carnitine uptake occurred against a concentration gradient and was inhibited by 2,4-dinitrophenol (2,4-DNP). The transport system had a Km of 80 μM and a Vmax of 110 pmol/mg protein per hour. The carnitine precursor deoxycarnitine, acetylcarnitine, and both the D and L isomers were effective inhibitors of uptake. The transport of carnitine was not dependent on sodium ions, but was stimulated by decreasing concentrations of calcium ions. Decreased uptake was observed in the presence of β-adrenergic agonists and antagonists, dibutyryl cyclic AMP, local anesthetics, and ouabain. No significant alteration of uptake was effected by atripine, carbachol, or a variety of tricyclic agents. The auto-oxidation product of 7,8-dihydroxychlorpromazine (7,8-diOH CPZ) decreased carnitine efflux from myocytes, which were highly permeable to low molecular weight compounds. We found that this effect was not substrate specific, and is discussed as possibly resulting from a change in the arrangement or state of polymerization of subcellular structural components. Circ Res 48: 378-385, 1981

CARNITINE is an essential cofactor for long-chain fatty acid oxidation (Fritz, 1963). There is no cardiac synthesis of carnitine, but intracardiac concentrations of carnitine are greater than plasma concentrations, suggesting an uptake system. Because of recent studies on the beneficial effects of carnitine on cardiac arrhythmias and function in the ischemic state (Vick et al., 1976; Foltz et al., 1978),...
The effect of nitroglycerin and nitroprusside on intramural carbon dioxide tension during acute experimental myocardial ischemia in dogs.

L D Hillis, C Davis and S F Khuri

doi: 10.1161/01.RES.48.3.372

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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