Comparative Vasodilator Effects of Nitroprusside, Phentolamine, and Nitroglycerin on Hemodynamics, Regional Myocardial Function and Epicardial Electrogram in Dogs with Acute Myocardial Ischemia

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SUMMARY
The effects of nitroprusside (NP), phentolamine (PH), and nitroglycerin (NTG) were studied on systemic hemodynamics, regional contraction and epicardial ST segment in the border and non-ischemic zones of the left ventricle of anesthetized open chest dogs. The anterior descending coronary artery (LAD) was completely occluded. NP (5 µg/Kg/min) or PH (100 µg/Kg/min) was drip-infused, or a bolus injection of NTG (20 µg/Kg) was administered intravenously. The 3 vasodilator agents produced somewhat similar reductions in systemic arterial pressure. However, NP caused a greater reduction in total peripheral resistance (TPR) than in left ventricular end-diastolic pressure (LVEDP), and caused a decline, in the ischemic marginal zone, in both ST segment elevation and paradoxical systolic lengthening. PH decreased TPR without reducing LVEDP and elevated the ST segment. NTG markedly reduced LVEDP and elevated the ST segment. NTG markedly reduced LVEDP and TPR slightly. NTG improved the elevated ST segment and paradoxical systolic expansion of the segmental myocardium in the border zone. Cardiac output rose with NP and PH, whereas injected NTG caused a reduction in cardiac output. These findings suggest that NP favourably affects the ischemic myocardium mainly by reducing the afterload and that the NTG-induced improvement of myocardial ischemia can be attributed mainly to preload reduction, while PH enhances cardiac function with slight or no improvement of myocardial ischemia in the border zone.

Additional Indexing Words:
Afterload reduction LV function Segmental function Epicardial ST segment

VASODILATOR agents have been used to improve left ventricular function in patients with acute myocardial infarction and left ventricular dysfunction. However, it is not clear whether a given vasodilator has
characteristic properties in systemic hemodynamics, regional contractile performance and epicardial electrograms of the border and non-ischemic zones after coronary occlusion. The present experimental study was, therefore, undertaken to compare arterial pressure reduction with nitroprusside, phentolamine, and nitroglycerin on systemic hemodynamics, regional contraction and the epicardial ST-segment of the border and non-ischemic zones of the left ventricle after coronary occlusion.

**Materials and Methods**

Experiments were conducted in 20 mongrel dogs, weighing 10-20 Kg. They were anesthetized with intravenous sodium pentobarbital (25-30 mg/Kg) and ventilated with an intermittent positive pressure pump. The heart was exposed through thoracotomy in the left fifth intercostal space and supported with a pericardial cradle. Electromagnetic flow probes (Type MF-26, Nihonkoden) were positioned around the aortic root and the left circumflex coronary artery (LCX) for measuring cardiac output and coronary blood flow, respectively. The left anterior descending artery (LAD) was isolated just distal to the first major coronary branch, and a loose ligature was positioned for producing myocardial infarction by total occlusion of the vessel. Two catheters were inserted into the thoracic aorta via the right femoral artery. Pressures were monitored using Nihonkoden Model MP-24T strain-gauges placed at mid-chest level. Two segment-length gauges (Nihonkoden Model HDS-1T) were placed on the left ventricular surface: one was sutured on the lateral portion of the left ventricular wall perfused by LCX (normal zone), and the other was placed on the border zone between LCX and LAD which was detected by transient occlusion of LAD (marginal zone). A segment of myocardium (approximately 1.0 cm) was contained between the struts of the strain-gauges. The suture bites penetrated to a depth of approximately 2-3 mm. Epicardial electrograms were also obtained from both normal and marginal zones. Recordings were made using a multichannel jet recorder (Mingograf 804, Siemens-Elema) at a paper speed of 100 mm/sec or 2.5 mm/sec. Following control observations, LAD was completely occluded with ligature placed around the vessel. In 6 dogs at 10 min after occlusion, 20 µg/Kg of nitroglycerin (NTG) was administered as a bolus injection. Fourteen dogs received continuous infusions of 5 µg/Kg/min of sodium nitroprusside (7 dogs) or 100 µg/Kg/min of phentolamine (7 dogs) via a plastic tube inserted into the right femoral vein.

Segment-length was measured at end-systole (point D) and at end-diastole (point A), and was expressed as length from end-diastolic point during the control period. ST-segment of the electrogram was measured at 40 msec after J point.

Hemodynamic and electrographic measurements were made during the control period, at 10 min after LAD occlusion and at 1 min after injection of nitroglycerin or 10 min after onset of continuous infusion of sodium nitroprusside (NP) or phentolamine (PH).

Student's t-test for paired data was used to calculated probability values.
RESULTS

Effect of coronary occlusion:
LAD occlusion resulted in a small but significant decrease in blood pressure and rate pressure product (mean aortic pressure×heart rate) with a substantial, constant heart rate. Cardiac output decreased by 16.5–17.5% (p<0.001) and was associated with about a 10% increase in total peripheral resistance. Left ventricular end-diastolic pressure (LVEDP) was elevated significantly. Blood flow in LCX increased significantly concomitant with a reduction in coronary vascular resistance. ST segment in the marginal zone rose markedly (more than 6 mV), while in the normal zone, the ST segment did not show a significant change. The segment-length in the marginal zone was lengthened markedly at end-systole (point D) resulting in end-systolic bulging. The end-diastolic segment-length was slightly lengthened in both marginal and normal zones.

Effect of vasodilator agents:
Infusion of NP and PH at a constant rate for 10 min reduced mean arterial pressure in all dogs (Fig. 1). The preinfusion blood pressure of 90±12.2 mmHg (mean±SD) fell to 68±7.5 mmHg (−20.9%, p<0.001) during infusion of NP, while PH caused a decline in mean blood pressure from 93±
7.9 mmHg to 76 ± 7.0 mmHg (−18.3%, p < 0.001). Similarly, a bolus injection of NTG reduced the average arterial pressure from 89 ± 11.9 mmHg to 66 ± 11.0 mmHg (−22.9%, p < 0.001). A significant change in heart rate was not produced by NP or by NTG. In contrast, PH increased heart rate from 141 ± 10.9 beats/min to 153 ± 13.3 beats/min (+8.8%, p < 0.02), as illustrated in Fig. 1. LVEDP decreased after administration of NP and NTG: from 6.7 ± 2.0 mmHg to 5.5 ± 1.8 mmHg (−16.6%, p < 0.01) with NP and from 9.3 ± 2.6 mmHg to 7.1 ± 2.0 mmHg (−24.9%, p < 0.001) with NTG (Fig. 2). In contrast, PH did not produce a significant change in LVEDP.

![Fig. 2. Effects of LAD occlusion and vasodilator agents on left ventricular end-diastolic pressure (left) and cardiac output (right).](image1)

![Fig. 3. Effects of LAD occlusion and vasodilator agents on total peripheral resistance (left) and rate pressure products (right).](image2)
The decline in LVEDP was significantly greater with NTG than with NP (p<0.01) or with PH (p<0.01). Cardiac output rose during NP infusion from 0.70±0.10 L/min to 0.80±0.09 L/min (+14.5%, p<0.001) despite of the concomitant fall in LVEDP. Cardiac output increased markedly with PH treatment from 0.83±0.13 L/min to 1.02±0.11 L/min (+22.4%, p<0.001). In contrast to NP and PH, NTG reduced cardiac output further from 0.80±0.12 L/min to 0.78±0.14 L/min, but the difference was not statistically significant (Fig. 2). The calculated total peripheral resistance

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**Fig. 4.** Effects of LAD occlusion and vasodilator agents on blood flow (left) and vascular resistance (right) of the circumflex coronary artery.

**Fig. 5.** Effects of LAD occlusion and vasodilator agents on the ST segment of epicardial electrogram in the marginal area.
TPR) decreased markedly under NP (−36.1%, p<0.001) and PH (−32.4%, p<0.001) but moderately with NTG (−18.0%, p<0.01). The rate pressure product (double product) was lowered by all 3 vasodilators (Fig. 3).

Blood flow through LCX decreased by 11.8% with NP (p<0.05) and by 8.7% with NTG (p<0.05) despite a significant reduction in coronary vascular resistance. Coronary vascular resistances of 0.91±0.16 mmHg/ml/min prior to NP and 0.87±0.15 mmHg/ml/min prior to NTG fell to 0.76±0.12 mmHg/ml/min (−14.3%, p<0.02) and to 0.71±0.16 mmHg/ml/min (−18.4%, p<0.01), respectively. In contrast to NP and NTG, PH augmented coronary blood flow in LCX from 98.2±7.6 ml/min/100Gm to 120.5±14.0 ml/min/100Gm (−27.6%, p<0.01), associated with a 18.4% decrease in coronary vascular resistance (Fig. 4). Administration of NP and NTG lowered ST segment in the marginal zone.

The average preinfusion ST segment of 6.2±1.5 mV declined to 5.7±1.7 mV (−1.3±0.9 mV, p<0.02) by NP infusion, while NTG caused a reduction in the elevated ST segment from 6.8±1.2 mV to 5.3±1.1 mV (−1.5 mV).

![Fig. 6. Effects of LAD occlusion and vasodilator agents on segment-length in the marginal (left) and non-ischemic (right) zones. A. segment-length at end-diastole. D. segment-length at the onset of isometric relaxation.](image-url)
±0.7 mV, p<0.01). ST segment in the marginal zone was not affected by PH infusion. In the normal zone, ST segment was essentially unchanged by any vasodilator (Fig. 5). In both normal and marginal zones, segment-length at the end of diastole was not influenced by infusion of NP or PH. NTG, in contrast, significantly shortened (p<0.05) end-diastolic length in the normal zone. The extent of paradoxical shortening at end-systole, which appeared during preinfusion period, was significantly decreased by all 3 vasodilators. NTG produced greater improvement of paradoxical systolic expansion than NP (p<0.02) or PH (p<0.02), as illustrated in Fig. 6.

Total peripheral resistance was decreased approximately twice as much as LVEDP by infusion of NP, while NTG reduced the preload more than the
afterload. PH remarkably decreased the afterload without substantially changing the preload (Fig. 7). Fig. 8 represents changes in cardiac output and LVEDP during vasodilator treatment. An increase in cardiac output and a decrease in LVEDP were noted during NP infusion. A concomitant reduction in cardiac output with decreased LVEDP was observed after injection of NTG, and an increase in cardiac output during PH infusion was usually accompanied by substantially no change in LVEDP.

**DISCUSSION**

The vasodilator-induced reduction in arterial blood pressure is associated with reducing impedance to left ventricular ejection (afterload). A fall in the afterload might be accompanied by a reduction in end-systolic volume, and thereby increase stroke volume and ejection fraction. The present investigation in dogs with myocardial infarction examined the contrasting effects of 3 commonly employed ventricular unloading agents, nitroprusside, phentolamine, and nitroglycerin, on cardiac performance, blood flow in the adjacent coronary artery, epicardial electrogram, and segmental myocardial function. LAD occlusion decreased systemic arterial pressure and cardiac output, and increased total peripheral resistance, LVEDP and blood flow in the adjacent coronary artery with a reduction in coronary vascular resistance. ST segment was markedly elevated by LAD occlusion in association with paradoxical systolic lengthening in the marginal area. Although each drug reduced systemic arterial pressure to a similar extent, cardiac output augmentation was found with only NP and PH, and a reduction of LVEDP with only NP and NTG. Heart rate was increased only with PH infusion. Because previous studies have demonstrated that NP and NTG do not show direct inotropic action, the possible variations inherent in the myocardial stimulation response of the 2 agents cannot explain the disparate alteration in left ventricular function. Therefore, quantitative differences in agents relaxing peripheral arterial and venous smooth muscles must contribute to dissimilar secondary modifications in cardiac hemodynamics. Increased cardiac output with concomitant reduction in LVEDP by NP implies a shift in the cardiac function curve to the left and superiorly. With NP infusion, a significant increase in cardiac output has been reported in patients with ischemic heart disease or cardiomyopathy with severe congestive heart failure. An increase has also been reported in left ventricular filling pressure in patients with low cardiac output and lung edema. We confirmed these observations in dogs with experimental myocardial ischemia. NP produced greater reduction in TPR than in LVEDP: the percent reduction
in TPR was almost twice as much as that in LVEDP. A greater decline in TPR with NP suggests the predominant effect of this agent on arterioles when compared to effects on the capacitance vascular bed. In contrast, previous investigations\(^{11,12}\) demonstrated that PH has a direct positive inotropic effect on the heart, although Rabinowitz et al\(^{13}\) reported no direct PH effects on myocardial beta adrenergic receptor. In the present investigation an increase in heart rate was observed only during infusion of PH in spite of a similar quantitative reduction in systemic arterial pressure by each of the 3 drugs. These findings suggest that PH directly stimulates the beta adrenergic receptor. PH-induced increases in cardiac output have been found in patients with congestive heart failure with or without infarction.\(^{14-17}\) Wainsky et al\(^{18}\) and Chatterjee et al,\(^{19}\) however, noted an increase of cardiac output in only patients with myocardial infarction and left ventricular filling pressure above 15 mmHg. In our study the PH effect did not dependent on LVEDP. The arteriolar vasodilating effect of PH is caused by the direct relaxing effect on smooth vascular muscle.\(^{20}\) PH produced no significant fall in LVEDP. The relationship between \(\Delta \%\) LVEDP and \(\Delta \%\) TPR shows that the PH influence on arterioles clearly predominates when compared with its effect on venous capacitance. These findings agree with Kotter et al.\(^{17}\)

In our study, NTG produced a slight decrease in cardiac output in spite of a significant fall in TPR. This is consistent with the findings of other studies,\(^{21-25}\) which have shown a reduction in cardiac output after sublingual administration\(^{21-23}\) or during intravenous infusion of NTG.\(^{24,25}\) Of these vasodilator agents, NTG had the least effect on peripheral resistance. On the other hand, this agent produced the greatest reduction in LVEDP. The greater effect of NTG on venous capacitance than on arterioles is indicated by the nearly two-fold decline of LVEDP compared with TPR. Therefore, NTG lowered cardiac output as a predominant consequence of its preload-reducing action over its effect of decreasing ejection impedance. If vasodilators improve the affected myocardial oxygen supply-demand relationship in the ischemic area, the local myocardial function would be enhanced in association with a decline in ischemic injury. The present experimental study in acute myocardial ischemia indicates that NP, PH, and NTG have different regional effects. The 3 agents significantly improve segment-length in the marginal zone. The greatest improvement in segment-length was observed with NTG and the smallest improvement under PH infusion. NP and NTG accomplished this with decreasing ischemic injury, as assessed with epicardial ST segments. In contrast, the PH-induced improvement in segmental performance was accompanied by failure to decrease the ST segment elevation, in spite of a marked increase in blood flow through the adjacent
coronary artery. There are several possible explanations for these observations. The 3 agents had differing actions on oxygen supply to the ischemic myocardium. Rowe and Henderson suggested that NP improved myocardial oxygenation because of increased coronary sinus oxygen content. According to Walston et al, NP favourably affects the endocardial-epicardial distribution of coronary blood flow. Becker and associates reported that like NP, NTG administered before occlusion of LCX redistributes coronary blood flow from the epicardium to endocardium. Using the thermodilution method with heated cross-thermocouples, Hirano observed that NTG improves abnormal transmural flow distribution caused by partial coronary occlusion, without increasing total coronary blood flow. In contrast, another investigation suggested that PH might adversely affect coronary collateral flow.

Important differences between these agents are also evident in respect to the 3 major determinants of myocardial oxygen consumption: contractility, chronotropy, and wall tension. NP and NTG appear to have no direct inotropic effect, while PH has positive inotropic action either directly or indirectly. In addition, our study demonstrated that PH caused an increase in heart rate that was not seen with NP and NTG. This positive chronotropic effect of PH may be responsible for its deleterious effect on the ischemic area. Wall tension is one of the major determinants of myocardial oxygen consumption. NP and NTG may markedly decrease wall tension through decline in LVEDP, probably in left ventricular end-diastolic volume, and in systemic arterial pressure. In contrast, PH may cause a comparatively small reduction in wall tension since no significant change in LVEDP was observed.

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