Effects of Nitroglycerin and Nitroprusside on Large and Small Coronary Vessels in Conscious Dogs

Pilar Macho, M.D., and Stephen F. Vatner, M.D.

SUMMARY The effects of nitroglycerin (NTG) and nitroprusside (NPR) were examined in conscious dogs on measurements of left circumflex coronary blood flow and coronary diameter and on calculations of late diastolic coronary resistance (LDCR) and left circumflex coronary internal cross-sectional area (CSA). The effects of infusions of NTG, 8 μg/kg/min for 7 minutes, and NPR, 2.5 μg/kg/min for 7 minutes, were compared. These doses of NTG and NPR induced similar effects on mean arterial and left ventricular (LV) systolic and end-diastolic pressures, heart rate and LV dP/dt. However, NTG induced significantly greater ($p < 0.05$) increases in CSA than NPR, while NPR induced significantly greater ($p < 0.05$) reductions in LDCR than NTG. Just before cessation of infusion, CSA rose by 29.2 ± 4.7% with NTG and by 22.7 ± 3.9% with NPR, while LDCR fell by 8.8 ± 3.3% with NTG and by 21.6 ± 2.7% with NPR. Moreover, the effects of NTG on CSA were significantly more sustained than those for NPR. Thus, NTG and NPR in conscious dogs, in doses that exert similar general hemodynamic effects, elicit qualitatively similar but quantitatively different effects on small vs large coronary vessels. Whereas NTG induced significantly less dilation of small coronary vessels, it exerted significantly larger and longer lasting effects on large coronary arteries.

THE EFFECTS of nitroglycerin (NTG) and nitroprusside (NPR) on coronary vessels have been a subject of considerable interest, because these agents are used frequently in patients with ischemic heart disease and congestive heart failure. Whereas NTG1-9 and NPR10 have been shown to decrease coronary vascular resistance in normal human subjects and experimental animals, their relative effects on large and small coronary vessels is unclear. Most information regarding the effects of these drugs on large coronary vessels is indirect. Studies in open-chest anesthetized animals, in which large coronary vessel resistance was assessed by the pressure drop from the aorta or left main coronary artery to a distal coronary arterial branch, indicate that NTG dilates large coronary vessels.7-9 However, in a recent study by Malindzak et al.,10 large coronary vessel resistance was assessed in the same manner, but increased substantially. Arteriographic studies in man also indicate that NTG11 and NPR12 dilate large coronary vessels. Additional indirect evidence that NTG dilates large coronary vessels is derived from its salutary effect on collateral blood flow in the presence of regional myocardial ischemia.13-15 The beneficial effects of NPR are more controversial; it has been shown either to enhance16, 17 or reduce18, 19 collateral flow to ischemic myocardium.

We have developed techniques to measure coronary arterial diameter directly and continuously in conscious dogs.17 The goal of the present investigation was to use this method to compare quantitatively the effects of NTG and NPR, when equidepressor doses of the two drugs were administered systemically.

Methods

Mongrel dogs that weighed 28–38 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. The transducers were implanted through a thoracotomy in the fifth left intercostal space. Miniature 7-MHz ultrasonic transducers (2 × 1 mm, 12 mg) were implanted on opposing surfaces of the left circumflex coronary artery 3–6 cm from its origin. The ultrasonic transducer were covered with Insl-X (Insl-X Products Corp.) and attached to a Dacron backing. This was sutured to the outer adventitia of the coronary artery using Ethicon 6-0 suture. Electromagnetic (Zepeda Instruments) or Doppler flow probes were implanted 1–3 cm distally on the same vessel. A miniature pressure gauge (Konigsberg Instruments, Inc.) was implanted in the left ventricle, and in some dogs also in the descending thoracic aorta. Heparin-filled Tygon catheters (Norton Co.) were implanted in the left atrium and descending thoracic aorta. One week later, at the time of the experiment, using local anesthesia with 2% lidocaine, a Millar microtip pressure manometer was introduced into the aorta through the femoral artery in the dogs without a solid-state aortic pressure gauge. The Millar transducer was advanced into the left ventricle and withdrawn to the aortic root.

Arterial pressure was measured with the Millar microtip manometer, or with the miniature pressure gauges, which were calibrated before and after the experiments by a mercury manometer and cross-calibrated during the experiment with the aortic pressure measurements derived from the aortic catheter attached to a Statham P23Db manometer. Left ventricular (LV) pressure was measured with the implanted miniature gauge, which was calibrated in vitro with a mercury manometer and cross calibrated in vivo with measurements of pressures from the aortic and left atrial catheters. Coronary blood flow was measured using a Benton square-wave electromagnetic flowmeter or a Doppler ultrasonic flowmeter.

Phasic coronary arterial diameter was measured instantaneously and continuously with an improved ultrasonic dimension gauge.17-19 The instrument gener-
ates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of \( \sim 1.5 \times 10^6 \) mm/sec between the 7-MHz piezoelectric crystals, giving a record of instantaneous external coronary arterial diameter. To measure these relatively small dimensions accurately, the instrument used in this study was further modified to minimize the acoustic disturbance generated by the electrical excitation of the transmitting crystal. This was accomplished by placing 1000-Ω rheostats in parallel with the crystals at the exciter output and receiver input. These rheostats were adjusted to minimize the ringing observed in the receiving crystal, without substantially affecting the amplitude of the received echo. In addition, the basic 1-MHz repetition rate of the dimension gauge was changed to 2 MHz. This doubled the amplitude of the output voltage and also permitted precise calibrations in 0.5-μsec steps. The frequency response of the dimension gauge is flat to 100 Hz. The drift of the instrument is minimal and in these experiments never exceeded 0.01 mm in 6 hours. Drift was eliminated by repeated calibration references, which were obtained regularly throughout the experiment. The received ultrasonic signal was monitored continuously on an oscilloscope. In this manner, any major change in alignment of the crystals would be detected readily in the received signal and invalidate the experiment.

The experiments were conducted with the conscious dogs lying quietly, 1-2 weeks after operation. Measurements of left circumflex external coronary arterial diameter, aortic pressure, LV pressure, LV dP/dt, left circumflex coronary blood flow, and heart rate were continuously recorded during control, infusion of the drugs and for 1 hour after administration of the drugs. In 15 dogs, NTG and NPR were administered as i.v. infusions of 8 and 2.5 μg/kg/min for 7 minutes, respectively. These doses were selected to induce equidepressor effects. The equidepressor effects of these doses were confirmed. The drugs were administered at least 2 hours apart and, in some cases, on separate days. The initial drug to be examined was selected randomly. At the end of the experiments, the dogs were sacrificed to confirm placement of the ultrasonic transducers, to determine coronary arterial wall thickness, and to examine the vessel histologically. Significant fibrosis at the crystal implant site was not observed in these dogs.

The data were recorded on a 14-channel Bell and Howell tape recorder and played back on two multichannel oscillographs (Gould-Brush). Mean pressures and coronary diameters were assessed using RC filters with 2-second time constants. LV dP/dt was derived by differentiating the LV pressure signal using a Philbrick operational amplifier (Teledyne Philbrick) connected as a differentiator and having a frequency response of 700 Hz. A triangular wave signal with known slope (rate of change) was substituted for the pressure signal to calibrate the differentiator directly. The heart rate was measured continuously with a cardiograph triggered by the LV pressure pulse.

While external diameter was measured continuous-ly, the internal radius was calculated by determining at autopsy the thickness and mass of a segment of coronary artery with known length from the point at which the piezoelectric crystals were located. Thus, wall volume could be calculated as the quotient of mass and density (\( d = 1.06 \) g/cm³). After the wall volume, wall thickness value, and the external diameter were known, the internal coronary diameter was calculated. Internal cross-sectional area (CSA) was calculated as the product of \( r \) and the square of the internal radius. Late diastolic coronary resistance (LDCR), which reflects primarily small coronary vessel resistance, was calculated as the quotient of late diastolic arterial pressure and late diastolic coronary blood flow.

The mean ± SEM were calculated for all the variables. The t test for paired comparisons was used to compare the effects of NTG and NPR at equivalent points in time and analysis of variance was used to compare multiple responses of both drugs to their control values.29

Results

Results are expressed as percent change from control. Control values and absolute changes from control are shown in table 1. Coronary blood flow, LDCR, coronary diameter and CSA refer to the left circumflex coronary artery.

Effects of Nitroglycerin (fig. 1)

Mean arterial pressure fell during infusion and was 9.8 ± 1.8% below control at the end of the infusion and returned to control by 5 minutes after the infusion. LV systolic pressure followed a similar pattern. LV end-diastolic pressure decreased during the infusion by 5.6 ± 0.5 mm Hg and remained depressed for 15 minutes after the infusion. Heart rate increased during the infusion by 38 ± 6% and returned to control rapidly after infusion. LV dP/dt increased only initially by 9.7 ± 2.0% and was no longer significantly elevated at the end of the infusion. Mean coronary diameter and CSA increased, reaching peak values of 5.7 ± 0.6% and 29 ± 4.7%, respectively, at the end of the infusion and were no longer significantly elevated 45 minutes later. Mean coronary blood flow rose by 13 ± 3.7% initially during the infusion, returned to control by the end of the infusion and fell below control by 15 ± 3.2% at 3 minutes after the infusion and returned to control 30 minutes later. LDCR demonstrated a biphasic pattern, decreasing by 16 ± 4.2% at 1 minute of infusion and remaining depressed during the infusion, but then increasing by 14 ± 3.1% above control at 3 minutes after infusion and remaining elevated for 5 minutes after infusion.

Effects of Nitroprusside

Mean arterial pressure decreased during the infusion, was depressed by 11 ± 1.7% at the end of the infusion and was no longer different from the pre-NPR control after the infusion. LV systolic pressure...
followed a similar pattern. LV end-diastolic pressure fell by 4.1 ± 0.3 mm Hg during the infusion and remained depressed for 5 minutes after infusion. Heart rate increased by 46 ± 6 beats/min during the infusion and returned to control at 3 minutes after infusion. LV dP/dt increased at the beginning of the infusion by 12 ± 2.9% and then returned to control during the infusion. Mean external coronary diameter and CSA increased at the beginning of the infusion and increased by maximum values of 4.9 ± 0.7% and 23 ± 3.9%, respectively, at the end of infusion and were not significantly elevated 15 minutes after infusion. Mean coronary blood flow rose by 32 ± 5.6% initially, returned toward control during the infusion and fell by 18 ± 5.1% at 3 minutes after the infusion and returned back to control by 15 minutes after infusion. LDCR followed a biphasic pattern, decreasing by a maximum of 30 ± 2.5%, remained depressed throughout the infusion period, but then increased by 15 ± 4.8% at 5 minutes after the infusion, and returned to control 30 minutes after infusion.

Comparison of the Two Drugs (table 1)

The two drugs elicited equivalent changes in arterial and LV systolic and end-diastolic pressures, heart rate and LV dP/dt (fig. 2). However, during the infusion NPR induced significantly greater increases in mean coronary flow and decreases in LDCR (fig. 3), while NTG induced significantly greater effects on CSA (fig. 4). At 15 minutes after infusion, when arterial pressure was essentially at control levels, only the changes in coronary diameter and CSA were significantly different for the two drugs. At this time NTG still elicited significant large vessel dilation but NPR did not. Thus, NTG not only induced significantly greater increases in CSA, but the effects were also significantly longer.

Discussion

A vasodilator can affect myocardial performance and blood flow in the presence of coronary artery dis-
ease in many ways. By decreasing preload and afterload, myocardial oxygen requirements decrease, which is a potentially beneficial effect of vasodilator therapy. However, the hypotensive action can exacerbate inadequate perfusion of ischemic coronary vessels, which are critically dependent upon perfusion pressure, or it can elicit increases in heart rate and myocardial contractility through reflex mechanisms. Finally, the direct action of the drugs on coronary vascular tone must be considered. It is generally believed that agents that dilate the large, conductive coronary arteries are preferable in the presence of myocardial ischemia than those that dilate primarily resistance vessels. By dilating the large conductive vessels, which include collateral channels, blood flow can be enhanced to the ischemic part of the heart. In contrast, dilating resistance vessels would be of little benefit to the ischemic area, where vessels are already nearly maximally dilated. In addition, dilation of resistance vessels in normal myocardium could be deleterious by inducing a "coronary steal." The doses of NTG and NPR induced equivalent reductions in mean arterial pressure, LV systolic and end-diastolic pressures, and secondary, reflex increases in heart rate and LV dP/dt. Although both drugs elicited qualitatively similar coronary vascular effects, there were quantitative differences. NPR elicited significantly greater effects on small coronary vessels, as reflected by larger increases in mean coronary blood flow and decreases in LDCR. In contrast, NTG induced significantly greater increases in CSA. Not only were the increases larger, but they were also more sustained (fig. 4).

The results of studies on the effects of NTG and NPR have conflicted. NTG has been shown to reduce and increase large coronary vessel resistance, as assessed by calculations of pressure changes from the central aorta to a distal coronary artery. The results of the present investigation are in agreement with the studies of Fam and McGregor, Cohen and Kirk, and Likoff et al., but are opposite of those of Malindzak et al. It is unclear why Malindzak et al. have different results, but it is important to note that coronary perfusion pressure decreased to extremely low levels in their study, to 55% of control. In most other studies and in the clinical setting, severe hypotension with NTG is not generally observed. Thus, the overwhelming evidence from this and other studies indicates that NTG is a potent dilator of coronary vessels, with a predilection for large coronary arteries. This has been observed in patients with coronary artery disease and in experimental models. A recent study in isolated coronary arteries by Harder et al. supports...
this concept at the cellular membrane level. In that study, NTG blocked action potentials selectively in large rather than small coronary arteries.29

The evidence that NPR dilates large coronary vessels is more controversial. Several studies have assessed the effects of NPR on collateral blood flow to ischemic myocardium, with the assumption that collateral channels are representative of large coronary

Figure 2. Responses to nitroglycerin (NTG) and nitroprusside (NPR) (average ± SEM) in measurements of heart rate, mean arterial pressure (AP) and left ventricular (LV) dP/dt. All responses are presented as percent change from control. The p values indicate significant changes from control.

Figure 3. Changes in late diastolic coronary resistance (LDCR) in response to nitroglycerin (NTG) and nitroprusside (NPR) (average ± SEM). All responses are presented as percent change from control.
vessels. These studies have shown that NPR either enhances collateral blood flow\textsuperscript{14, 16} or reduces it.\textsuperscript{5, 18} In the present study, the large coronary vessels uniformly responded with vasodilation. While the present experiments were carried out in normal, healthy, conscious dogs without myocardial ischemia, there is also evidence in patients with coronary artery disease to support the position that NPR dilates large coronary arteries. Yeh et al. found that intracoronary NPR dilated normal and stenotic coronary arteries in man.\textsuperscript{12} Furthermore, a preliminary report by Doerner et al.\textsuperscript{28} using computer averaging techniques to assess large coronary dimensions,\textsuperscript{29} indicated that NPR was as potent as NTG in dilating normal and stenotic coronary vessels in patients. Our results indicate that NPR dilates large coronary arteries, but is less potent in magnitude and duration than NTG. Thus, the differences between preliminary results of Doerner et al.\textsuperscript{28} and those in the present investigation are quantitative and not qualitative. It is likely that these quantitative differences, particularly with regard to time course, are more easily appreciated using direct and continuous measurements of coronary arterial dimensions.

In summary, in normal conscious dogs, both NTG and NPR dilate large coronary vessels. However, NTG exerts slightly but significantly larger effects than NPR. Although in the normal coronary circulation, the contribution of large coronary vessels to total coronary resistance is minimal,\textsuperscript{7} in the presence of myocardial ischemia, changes in large coronary vessel dimensions could be crucial in regulating the flow toward ischemic areas. Thus, the results of the present investigation suggest that both NTG and NPR could be useful in the treatment of myocardial ischemia if arterial pressure is well maintained. Of the two drugs, the relatively more potent effect of NTG on large coronary arteries compared with its effects on resistance coronary vessels, in combination with its larger duration of action, suggest that the drug is less likely to induce coronary steal or other deleterious effects, particularly if arterial pressure is well maintained.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Changes in cross-sectional area (CSA) in response to nitroglycerin (NTG) and nitroprusside (NPR) (average ± SEM). All responses are presented as percent change from control.}
\end{figure}

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Elevation of Thromboxane B₂ Levels in Patients with Classic and Variant Angina Pectoris

MICHIHKO TADA, M.D., TSUNEHIKO KUZUYA, M.D., MICHITOSHI INOU, M.D., KAZUHISA KODAMA, M.D., MASAYOSHI MISHIMA, M.D., MAKOTO YAMADA, M.D., MAKOTO INUI, M.D., AND HIROSHI ABE, M.D.

SUMMARY Thromboxane A₂ (TXA₂), a vasoconstrictive prostanoid, causes intense spasm of isolated coronary vessels and increases platelet aggregability. To define the role of TXA₂ in the pathogenesis of angina pectoris, plasma levels of thromboxane B₂ (TXB₂), a biologically inactive product of TXA₂, were determined in the coronary sinus (CS), aorta (AO) and peripheral vein of 30 patients with angina pectoris. Determinations were made by radioimmunoassay using anti-TXB₂ antisera and [²H]TXB₂. Acidic lipids were extracted from plasma after treatment of samples with ethylendiamine tetraacetic acid (EDTA) and indomethacin. The 18 patients with effort angina and angiographically documented coronary stenosis (≥ 75%) showed a marked increase in peripheral TXB₂ (mean ± SD 505 ± 178 pg/ml plasma) compared with 24 normal subjects (254 ± 89 pg/ml plasma; p < 0.01). When AO and CS TXB₂ levels were determined in 10 cases with simultaneous measurements of CS blood flow during atrial pacing, calculated TXB₂ release in coronary circulation at rest (−2.3 ± 14.8 ng/min) markedly rose during pacing-induced myocardial ischemia (34.7 ± 50.6 ng/min; p < 0.01), while in four control subjects with normal coronary arteries the values at rest (−1.0 ± 5.0 ng/min) did not change significantly at peak pacing (−1.5 ± 10.9 ng/min). All 12 patients with variant angina had a marked increase in peripheral TXB₂ (802 ± 249 pg/ml plasma; p < 0.01); two of five cases who were subjected to coronary sampling showed increased TXB₂ levels both in CS and AO during a spontaneous attack or attacks induced by ergonovine or by atrial pacing, which were accompanied by coronary vasospasm and fluctuation of CS blood flow. These results indicate that increased TXA₂ production in the coronary circulation may be at least partly responsible for coronary vasoconspasm and angina.

MYOCARDIAL OXYGEN DEMANDS are met by variations of coronary blood flow, which may be mediated by endogenous chemical substances, such as adenosine, prostaglandins and catecholamines. Among these, prostaglandin-like substances (prostanoids) have recently been considered in the ischemic myocardium to serve as potent determinants of coronary vascular tone and regional blood flow. Such vasoactive prostanoids were identified as thromboxane A₂ and prostaglandin I₂, which possess opposite effects on the control of vascular tone. Thus, thromboxane A₂, which is produced by an enzyme of platelet micromes, causes vasoconstriction and increases platelet aggregability; prostaglandin I₂, which is produced by an enzyme of vascular micromes, causes vasodilation and decreases platelet aggregability. Thromboxane A₂ and prostaglandin I₂ are extremely labile substances, with half-lives of 30 seconds and 10 minutes, respectively. Thus, they are readily converted to thromboxane B₂ and 6-keto-prostaglandin (PG) F₁₀, respectively, biologically inactive and chemically stable catabolites, which are...
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P Macho and S F Vatner

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