Analysis of Cardiac Actions of Nitroprusside
in Intact Dogs and in Isolated Atria

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Summary
The effects of intravenous administration of sodium nitroprusside to a donor dog on cardiac pacemaker activity and contractility were investigated in a cross-circulated dog heart preparation; i.e., the isolated atrial muscle was perfused with blood from a pentobarbital anesthetized donor dog. Intravenous administration of nitroprusside (1–10 µg/Kg) caused a hypotension with tachycardia, and occasionally with bradycardia. This effect was blocked by atropine injections into the donor dog, but no significant chronotropic and inotropic changes were observed in the isolated atria. Larger doses (over 100 µg/Kg) of nitroprusside produced positive chronotropic and inotropic effects in isolated atria, which were inhibited completely by propranolol. Moreover, direct intraarterial injection of nitroprusside (10–1,000 µg) had no significant chronotropic and inotropic effects in isolated atria, although acetylcholine (0.01–0.1 µg) induced negative chronotropic and inotropic effects. From these results, it is concluded that nitroprusside has no direct cardiac effect and that it causes a release of catecholamines in doses which produce a profound hypotension.

Additional Indexing Words:
Nitroprusside  Donor dog  Isolated atrium  Propranolol

SODIUM nitroprusside is a potent vasodilator, which acts on vascular smooth muscle, and it has been employed in the treatment of hypertensive states and severe congestive heart failure.1),5) The pattern of cardiovascular responses to nitroprusside depends on several interactions, including a systemic hypotensive effect and secondary reflex effects.3),6)–8) Heart rate is usually increased by nitroprusside in the dog. However, either inconsistent changes or an initial increase followed by a decrease in heart rate have also been reported during nitroprusside infusions in anesthetized dogs.7)–9) In
anesthetized dogs, cardiac output has been found to be consistently or transiently increased,\textsuperscript{7,10,11} unchanged\textsuperscript{8} or reduced,\textsuperscript{12} and stroke volume and cardiac work are usually reduced during the administration of nitroprusside. A positive inotropic effect, an increase in myocardial compliance or a reduced venous return due to vasodilation would offer explanations for the fall in end-diastolic pressure.\textsuperscript{3} On the other hand, a reduced contractile force is less likely than a direct negative inotropic action of nitroprusside on the heart, because it has been reported that nitroprusside does not modify the contractile state of the myocardium.\textsuperscript{3,13–15} In the present study, we made an attempt to investigate a direct action of nitroprusside at concentrations which induced hypotension, using a canine atrial preparation cross-circulated by a donor’s arterial blood.\textsuperscript{16,71}

**Methods**

Seventeen adult mongrel dogs of either sex, weighing 9 to 15 Kg, were anesthetized intravenously with sodium pentobarbital (30 mg/Kg). After treatment with 2,000 units of sodium heparin, the right atrium was excised and plunged into cold Tyrode’s solution at 4–10°C. The sinus node artery was cannulated via the right coronary artery in the isolated atrium and perfused with blood conducted from the carotid artery of the donor dog by the aid of a peristaltic pump (Harvard Apparatus, Model 1210). A constant perfusion pressure of 100 mmHg was maintained at a flow rate of 4.5–5.0 ml/min. The atrium was suspended in a bath filled with blood at a constant temperature of 37°C. The upper part of the crista terminalis of the atrium was connected directly to a force displacement transducer (Grass FTO3B) by a silk thread. Bipolar platinum electrodes were placed in contact with the atrial wall. The atrial rate was measured with a cardiotachometer triggered by the electrogram.

The donor dogs, weighing 9 to 16 Kg, were also anesthetized intravenously with 30 mg/Kg of sodium pentobarbital. Sodium heparin (1,000 units/Kg) was administered intravenously at the beginning of the perfusion and 200 units/Kg was added at 1-hr intervals. The systemic blood pressure of the donor dog was measured from the cannulated left femoral artery with a pressure transducer (Nihon Kohden RP-2), and heart rate was measured with cardiotachometer triggered by the R wave of lead II in the ECG. Details of the isolated and blood-perfused canine atrial preparation were described in previous papers.\textsuperscript{16,17}

The drugs used in these experiments were: (dl)-norepinephrine hydrochloride (Sankyo), acetylcholine chloride (Daiichi), atropine sulfate (Takeda),
(dl)-propranolol hydrochloride (Sumitomo Chemicals), and sodium nitroprusside (Wako Pure Chemical). Each drug was administered into either the jugular vein of the donor dog or the cannulated sinus node artery of the isolated atrium.

**Results**

1. **Cardiovascular effects of sodium nitroprusside administered to the dog**

When nitroprusside was administered intravenously to the donor dog, a hypotensive effect was induced in a dose-related manner (Fig. 1). The threshold dose for inducing hypotension was about 3 μg/Kg. A single injection of 10 μg/Kg of nitroprusside caused a clear hypotension in the donor dog, i.e., a decrease by 19±1.5 mmHg in 5 dogs. The heart rate either increased slightly or changed biphasically. At the same time, in isolated atria which were perfused with the donor's blood, both the developed tension and the atrial rate were stable, and they never changed significantly with doses up to 10 μg/Kg. At 100 μg/Kg, a marked decrease in systemic blood pressure was observed (55±4.8 mmHg in 5 dogs), and the heart rate usually increased. This was frequently accompanied by bradycardia (Fig. 1). In the isolated atrium, positive chronotropic and inotropic effects were observed about 3 min after the intravenous nitroprusside administration. This delay is the time required to the drug to pass through the circuit. At increasing doses, the hypotension and changes in heart rate were much greater in the donor dog, and were accompanied by greater positive chronotropic and inotropic effects in the isolated atrium. The data are summarized in Fig. 2. After treatment with 100 μg/Kg of atropine, a large dose of nitroprusside caused only tachy-

![Fig. 1. Effects of intravenous nitroprusside on the systemic blood pressure and heart rate of the donor dog and chronotropic and inotropic effects on the isolated atrium.](image)
Fig. 2. Dose-response curves to percentage changes in the systemic blood pressure and heart rate of donor dogs and on the developed tension and atrial rate of isolated atria. Nitroprusside was given intravenously at doses of 1, 10, 100, and 1,000 µg/Kg. Vertical bars show the standard errors of the mean. Control systemic blood pressure and heart rate in the donor dog were 96 ± 4.0 mmHg (mean ± SEM), and 157 ± 13 beats/min, respectively, and control developed tension and atrial rate in isolated atria were 2.2 ± 0.2 Gm and 97 ± 5 beats/min, respectively.

2. Blocking effect of intraarterial propranolol on positive chronotropic and inotropic responses to intravenous nitroprusside in the cross-circulated preparation

When 0.01–0.1 µg of norepinephrine was injected into the sinus node artery, positive chronotropic and inotropic effects were induced in a dose-dependent manner. These were inhibited significantly by 3–10 µg of propranolol. When a relatively large dose of nitroprusside (100 µg/Kg) was administered intravenously to the donor dog, marked positive chronotropic and inotropic responses were produced in the isolated atrium. As shown in Fig. 3, an intravenous nitroprusside-induced, positive chronotropic and inotropic effect was completely blocked by intraarterial treatment with propranolol. The data are summarized in Fig. 4.

3. Comparison of chronotropic and inotropic effects of nitroprusside and acetylcholine in isolated dog atria

When acetylcholine was injected into the sinus node artery of the isolated dog atrium, negative chronotropic and inotropic effects were induced in a dose-related manner, as previously reported. Intraarterial nitroprusside showed no chronotropic and inotropic changes in a dose range of 10–
Fig. 3. Blocking effects of intraarterial propranolol on positive chronotropic and inotropic effects in an isolated atrium, induced by intravenous administration of nitroprusside to a donor dog.

Fig. 4. Effects of propranolol on positive chronotropic and inotropic responses to intraarterial norepinephrine and to intravenous nitroprusside.

100 µg. An extremely large dose of 1,000 µg of nitroprusside induced slightly negative chronotropic and inotropic effects, but they were not significant. Fig. 5 shows a tracing of typical responses to intraarterial acetylcholine and nitroprusside in the same preparation. The data are summarized in Fig. 6.
A small dose of acetylcholine caused a negative inotropic effect without influencing the chronotropism. Increasing doses of acetylcholine caused both negative chronotropic and inotropic effects.

**DISCUSSION**

In the present study, intravenous administration of nitroprusside caused
a dose-related hypotension in the whole animal, as previously reported by a number of authors. However, chronotropic responses to nitroprusside were not uniform, for hypotension was accompanied by either tachycardia or bradycardia, as reviewed by Kreye. In anesthetized dogs, nitroprusside reportedly induces inconsistent changes in heart rate, although in the conscious animal, an increased heart rate is usually observed. Since nitroprusside-induced bradycardia was inhibited and reversed to tachycardia by treatment with atropine, nitroprusside may cause a stimulation of vagal tone in addition to reflex tachycardia in pentobarbital-treated dogs. As shown in this study, nitroprusside had no significantly chronotropic effects when given directly to the isolated atrial preparation. Therefore, these changes in heart rate in the intact animal may be due to an alteration in the tonic activity of the autonomic nervous system. Intravenous administration of nitroprusside to the donor dog caused an increase in both developed tension and atrial rate in the isolated atrium when given in doses greater than 100 µg/Kg. Since positive chronotropic and inotropic responses to intravenous nitroprusside were suppressed significantly by a relatively small dose of propranolol, they are probably due to a release of catecholamines from the donor dog.

In this study, intraarterial injections of nitroprusside had no chronotropic and inotropic effects, but acetylcholine produced marked negative effects in the same preparations. Both nitroprusside and acetylcholine produce an increase in myocardial cyclic guanosine 3'5'-monophosphate (cyclic GMP). Acetylcholine-induced increases in this cyclic nucleotide appear to be correlated with decreased contractile force. However, recent data suggest that the contractile effects of choline esters on cardiac muscle are not mediated by cyclic GMP. Diamond et al have reported that nitroprusside increases atrial cyclic GMP levels, but does not decrease the twitch tension developed by cat atrial strips. However, acetylcholine decreases twitch tension without increasing myocardial cyclic GMP levels. Cyclic GMP can be elevated by treating rat atria with nitroprusside, without producing a choline ester-like contractile effect. Recently, it was shown that dibutyryl cyclic GMP had neither a chronotropic nor an inotropic effect on the isolated and blood-perfused dog atrium. In the present study, although we confirmed that nitroprusside produces a hypotension, it has no significant, direct chronotropic and inotropic effects in the dog, and that chronotropic and inotropic effects caused by a large doses of nitroprusside can be attributed to a reflex release of catecholamines.
REFERENCES


