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Effects of Nitroprusside on Cardiac Function, Blood Flow Distribution, and Oxygen Consumption in the Conscious Young Lamb

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Summary

Resting cardiac output is high relative to body weight during the neonatal period and there is a limited reserve for further increasing cardiac output. We assessed the effect on the circulation of reducing peripheral vascular resistance by infusing high doses of sodium nitroprusside in 1- and 3-week-old lambs. In a dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 1 h, nitroprusside caused a decrease in aortic and left atrial pressure, an increase in heart rate, and no significant changes in cardiac output or oxygen consumption. Infusing 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 2 h resulted in an initial marked decrease in aortic pressure, cardiac output, and also heart rate. Within 50 min aortic pressure gradually increased, but was still well below control levels, while cardiac output returned to control level and heart rate slowly increased. Distribution of cardiac output and organ blood flows was measured by the radionuclide microsphere method. Blood flows to the kidneys and to the skin fell markedly, but flows to other organs did not change significantly.

Sodium nitroprusside has been shown to be beneficial in the medical management of patients with acute or chronic heart failure (1, 8, 10, 20, 21, 24). Positive effects were attributed to a reduction in systemic vascular impedance or left ventricular afterload caused by arteriolar vasodilatation and to a reduction in preload secondary to venodilatation (29). Reduction in preload, however, can also result from the additional effects of nitroprusside on myocardial relaxation (6), left ventricular diastolic properties (7), and alterations in pulmonary venous compliance (32). The precise mechanisms by which nitroprusside alters the hemodynamics in physiological and pathological situations are still not completely understood; yet nitroprusside is widely used clinically. Experience with nitroprusside in the pe-

diatric age group, however, is limited and there is, as yet, no reliable information concerning its effectiveness (2, 3). In view of our observations that, in the neonate, resting cardiac output is high, and systemic vascular resistance is relatively low, we wondered what effects nitroprusside would have in the newborn animal.

The objectives of this study were to assess the influence of postnatal age on the response to nitroprusside, and to examine the changes in distribution of the cardiac output caused by nitroprusside.

MATERIALS AND METHODS

Nineteen lambs of mixed Western breed and documented birth dates were studied. They were divided into two groups; group 1 (7 lambs) was studied between 4 and 8 days (mean, 5.9 days), and group 2 (12 lambs) from 19 to 28 days (mean, 22.6 days). Throughout the study, each lamb remained with its mother and fed well.

Surgical procedures: thoracotomy. Surgical preparation, catheter care, and antibiotic administration were carried out in the 19 lambs as described previously (15). Briefly, under halothane anesthesia (0.5% in O_2), the lambs were ventilated by a Harvard pump. A left thoracotomy was performed in the third or fourth intercostal space; polyvinyl catheters (OD 1.2 mm; ID 0.75 mm) were passed from the internal thoracic artery and vein into the aorta and superior vena cava, respectively. The pericardium was incised over the main pulmonary artery to within 2–3 mm of the vagus nerve. Similar catheters were inserted through purse string sutures into the pulmonary artery and through the left atrial appendage into the body of the left atrium. A precalibrated electromagnetic 7–13 mm flow transducer (C. C. Instruments, Culver City, CA) was placed around the ascending aorta just above the coronary arteries. The ductus arteriosus was examined to ascertain that it was closed; in two of the younger lambs, it had to be ligated. An 8F polyvinyl catheter was placed in the left pleural cavity for drainage. No attempt was made to close the pericardium. All catheters and the flow transducer cable were led to the skin on the left flank and protected by a Teflon cloth pouch which was sewn to the skin after the chest had been closed in layers. Air and fluid were withdrawn from the chest.

Through a small incision in the left leg, polyvinyl catheters were passed into the femoral artery and vein. These catheters were protected by a bandage around the leg. All catheters except the one for chest drainage were filled with heparin (1000 units·ml^{-1}) and plugged.

On the day of surgery and on days 1–4 postoperatively, we injected 100,000 units ·kg^{-1} of procaine penicillin and 50 mg·kg^{-1} of dihydrostreptomycin intramuscularly. The heparin was drained from the catheters daily, after which they were flushed with 0.9% saline and refilled with heparin. We allowed the lambs at least 3 days to recover from surgery before we started our studies.

Experimental Protocols. Control protocol. The lambs were allowed to feed until 1 h prior to study. At that time they were placed in a canvas sling which supported them in an upright position. The lambs were not sedated but were blindfolded to help keep them calm. A loose mask was placed over each lamb's head to collect the mixed expired gas that was used to measure oxygen consumption by the flow-through system, as described previously (18). Data were collected only when the lambs were calm and resting. During the control period oxygen consumption, aortic blood flow minus coronary blood flow, aortic, pulmonary arterial, left atrial and central venous pressures, and heart rate were measured continuously. One-ml blood samples were withdrawn from the aorta to determine blood gases, pH, hemoglobin concentration, and O_2 saturation. Three to 5 min later, radionuclide-labeled microspheres were injected into the left atrium in all group 1 lambs and in 9 group 2 lambs. Since ambient temperature influences oxygen consumption and cardiovascular function both at rest and during stress (28), during the study we kept ambient temperature between 22–25°C, depending on the age of the lamb.

Nitroprusside protocol. After taking control measurements for 20–45 min (mean, 30 min), we infused nitroprusside in quantities of 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 to 2 h, respectively. From the onset of infusion, it took about 2–3 min to fill the catheter with nitroprusside. We measured the same variables as during the control period. Blood samples were drawn at 10 and 50 min while microspheres, if used, were injected at 10 and/or 50 min after the onset of infusion. At the end of the study, the lamb was anesthetized with an intravenous injection of sodium pentobarbital and killed.

Nitroprusside (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Five lambs were studied from each age group. For technical reasons, oxygen consumption could be measured in only three lambs from group 1. Radioactive microspheres were used only in group 1. After the infusion, we studied the lambs during a 30-min recovery period.

Nitroprusside (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$). We studied 7 lambs in group 1 and 12 lambs in group 2. Radioactive microspheres were injected at 10 and 50 min in all group 1 lambs and in 9 group 2 lambs. Because of technical problems and also with a view to other studies, measurements were made for only 2 h in 8 group 2 lambs. In these 8 lambs and in 6 group 1 lambs, oxygen consumption was measured. All group 1 and the 8 group 2 lambs were studied for 60 min after the infusion was stopped.

Measurements and calculations. Oxygen consumption was measured continuously by the flow-through system as described previously (18). Aortic blood flow minus coronary blood flow was measured with a precalibrated electromagnetic flow transducer connected to a Statham SP 2202 flowmeter. Aortic, pulmonary arterial, left atrial, and systemic venous pressures were measured with Statham P23Db pressure transducers. Heart rate was calculated from the aortic blood pressure or flow signal with a cardiotachometer. All these variables were recorded on a Beckman type RM direct-writing recorder. Blood gas tensions and pH were measured with a Radiometer blood gas analyzer with appropriate electrodes; hemoglobin concentration and blood oxygen saturation were measured with a Radiometer OSM-2 hemoximeter. Cardiac output and flow distribution were measured with 15-μm diameter radionuclide-labeled microspheres (11). As microspheres were injected into the left atrium, reference samples from the ascending and descending aorta were continuously and simultaneously drawn into preweighed syringes for 1 to 1.25 min at a rate of 7 $ml \cdot min^{-1}$. After killing the lambs, we dissected them as described previously (11). The heart was weighed, fixed in 10% formalin for 7 days, and then reweighed. The atria, great vessels, valves and chordae, and epicardial fat were removed. The right and left ventricular free walls and septum were separated and divided into three transmural layers. The different parts of the heart, organs, and tissues were incinerated in an oven; their radioactivity was determined in a 1000-channel pulse height analyzer (Inotech Inc., Fort Atkinson, WI) (11). Blood flow to the various organs and regional myocardial blood flow were calculated with the aid of a IBM 370 computer. Cardiac output was measured by determining radioactive counts of the entire animal. The weight of each tissue sample of the heart was corrected for weight change caused by fixation. Myocardial, organ, and tissue blood flows were expressed as flow/100 g of fresh weight ($ml \cdot min^{-1} \cdot 100\ g^{-1}$). The transmural distribution of left ventricular myocardial blood flow was determined by dividing blood flow to the subendocardial layer by flow to the subepicardial layer of the left ventricle, to give the endo:epi flow ratio. The systemic vascular resistance was calculated by dividing the mean aortic pressure minus central venous pressure by the left ventricular output in liters·min^{-1}, and the vascular resistance of a particular vascular bed was obtained by dividing the pressure difference at the time of microsphere injection by the blood flow to that organ or tissue expressed as $ml \cdot min^{-1} \cdot 100\ g^{-1}$.

Statistical Analysis. Results are expressed as the mean ± SE.

Within each group, the data obtained during the control period before infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside were compared with those obtained before infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside, and analyzed with a one-way analysis of variance to determine whether a given variable was different during the control periods. Subsequently, control data of group 2 were compared with those of group 1 and analyzed by one-way analysis of variance (31). Two-way analysis of variance with replication and unequal samples was used within each group to test the response to nitroprusside, the effect of the different concentrations, and their interaction. The same analysis was done to test the response to the infusion of nitroprusside of the same concentration, the effect of age, and their interaction (29). If there was a significant difference, the Neuman-Keuls test was used. A value of 0.05 was considered significant.

RESULTS

Control Period. The weights, ages, and control hemodynamic data for the two groups are shown in Table 1. There was no difference within each group between the control values obtained before the studies with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and those obtained before the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion. Between the groups we found differences in some resting cardiovascular, hematologic, and blood gas variables, as described previously by Lister *et al.* (19) (Table 1). The cardiac output and oxygen consumption per kg body weight and heart rate were significantly lower in group 2 than in group 1.

Cardiac output measured by radionuclide-labeled microspheres was, as expected, higher than that measured by the electromagnetic flow transducer (16) both in group 1 (291 ± 18, $P < 0.05$) and group 2 (228 ml $\cdot kg^{-1} \cdot min^{-1}$, $P < 0.05$). The proportion of cardiac output distributed to the bones and to the carcass, as well as the blood flows/100 g tissue, was significantly lower in group 2 (bones, $P < 0.05$; carcass, $P < 0.025$). The percentage of cardiac output to the kidneys, however, was significantly higher in group 2 than in group 1 ($P < 0.005$); actual flow/100 g to the kidney was not significantly different in the two groups. Otherwise, there were no significant differences in distribution or cardiac output or organ blood flow between the two groups in the initial control period.

Responses to nitroprusside. The time sequence of the responses to the infusion of 5 or 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside was similar in the two age groups (Figs. 1 and 2). About 2 to 3 min after the onset of infusion, mean aortic pressure fell consistently, but changes in heart rate, cardiac output, and left atrial pressure fluctuated for about 15 min. There was then a gradual adjustment and by 50 min after the onset of infusion all the hemodynamic variables were stable until the end of the infusion.

The fall in mean aortic blood pressure reached its nadir 5 to 7 min after the onset of the infusion in both groups 1 and 2, amounting to 70 and 50% of the control value, respectively. During 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside, the pressure decreased significantly from 75 ± 4 to 53 ± 5 mm Hg ($P < 0.025$) in group 1 and from 84 ± 3 to 59 ± 4 mm Hg ($P < 0.001$) in group 2. During 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside, there was a decrease from 75 ± 3 to 35 ± 4 mm Hg and from 79 ± 4 to 39 ± 2 mm Hg ($P < 0.001$), respectively. The minimum pressures obtained during 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside differed significantly ($P < 0.001$) in group 2 only. After the maximum decrease, the mean aortic pressure gradually increased to 62 ± 6 mm Hg with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside, and to 57 ± 3 mm Hg with the higher infusion rate in group 1 animals. In group 2, it increased to 72 ± 6 and 67 ± 2 mm Hg, respectively. These values were all still significantly lower than the control values except for group 1 during 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside. After the infusion was stopped, mean aortic pressure increased significantly in group 1 to 86 ± 6 ($P < 0.025$) and 83 ± 4 ($P < 0.001$) mm Hg and in group 2 to 91 ± 4 ($P < 0.005$) and 92 ± 3 ($P < 0.001$) mm Hg, respectively. In both the 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside studies, there were no significant differences between groups 1 and 2 in the pressures obtained at corresponding times before, during, and after the nitroprusside infusion.

Mean left atrial pressure was slightly lower during nitroprusside infusion in both groups 1 and 2, but the values were not significantly different from control. After the infusion was stopped at 10 $\mu g \cdot kg \cdot min^{-1}$, mean left atrial pressure rose to 3.8 ± 0.8 mm Hg in group 1 ($P < 0.025$), and to 6.9 ± 1.0 mm Hg in group 2 ($P < 0.001$), levels significantly higher than the pressures during both infusion and control periods.

Heart rate increased immediately after the onset of nitroprusside infusion in both groups. With the 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, it increased by about 22% within 3 min; this rate was maintained throughout the infusion, but heart rate fell rapidly after the infusion was stopped. With the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion, the heart rate also increased within 3 min from 212 ± 9 to 267 ± 10 ($P < 0.001$) in group 1, and from 157 ± 8 to 192 ± 8 ($P < 0.05$) in group 2; both represented a 25% rise. Heart rate then fell rapidly (within 3–5 min) to 84% of control in group 1 and to control in group 2, and again increased, but gradually (within 60 min) to reach a peak of 282 ± 8 ($P < 0.001$) in group 1 and 209 ± 5 ($P < 0.005$) in group 2; these levels were maintained until the end of the infusion when heart rate rapidly fell to control values.

Cardiac output, as measured with the electromagnetic flowmeter (thus excluding coronary blood flow), decreased rapidly after the onset of the nitroprusside infusion, reaching a nadir after 10 min. With the 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, the fall in cardiac output was not statistically significant, nor was it significant with the higher infusion rate in group 2. In group 1 animals, however, the early fall in cardiac output was significant ($P < 0.005$): from 252 ± 16 to 162 ± 18 ml $\cdot kg^{-1} \cdot min^{-1}$, a fall of 36%. Cardiac output then increased gradually, returning to control values in 50 to 60 min.

Systemic vascular resistance did not change significantly during infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside in either group. During infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the vascular resistance fell significantly immediately after onset of the infusion in both groups, reaching a nadir in about 5 min, to 62% of control values. Following this, resistance returned to control levels in about 20 min, then fell again to about 77% of control; this fall was significant only in group 2. After the infusion was stopped, systemic vascular resistance increased abruptly and then returned to control levels.

Oxygen consumption was, as reported previously, considerably

Table 1. *Control values**

	Group 1†	Group 2‡
Heart rate (beats $\cdot min^{-1}$)	212 ± 9	173 ± 10^a
Mean aortic pressure (mm Hg)	75 ± 3	77 ± 3
Left atrial pressure (mm Hg)	1.3 ± 0.4	2.4 ± 0.4
Aortic blood flow (ml $\cdot min^{-1} \cdot kg^{-1}$)§	252 ± 16	193 ± 6^b¶
Stroke volume (ml $\cdot kg^{-1}$)	1.18 ± 0.05	1.16 ± 0.09¶
Systemic vascular resistance [mm Hg (liters $\cdot min^{-1})^{-1}$]	48 ± 4	54 ± 3¶
Oxygen consumption (ml $\cdot kg^{-1} \cdot min^{-1}$)	14.2 ± 0.6‖	9.3 ± 0.4^c
pH	7.43 ± 0.1	7.43 ± 0.01
P_{O_2} (mm Hg)	75 ± 4	84 ± 3
P_{CO_2} (mm Hg)	38 ± 1	38 ± 1
O_2 saturation (%)	93 ± 1	93 ± 1
Hemoglobin (g $\cdot dl^{-1}$)	8.7 ± 0.7	6.9 ± 0.5
n	7	12

* Data shown are means ± SE. One-way analysis of variance: *vs.* group I: [a], $P < 0.05$; [b], $P < 0.005$; [c], $P < 0.001$.

† Weight, 6.5 ± 0.6 kg; age, 5.9 ± 0.7 days.

‡ Weight, 7.3 ± 0.3 kg; age, 22.6 ± 0.7 days.

§ Measured by electromagnetic flow probe.

¶ $n = 11$.

‖ $n = 6$.

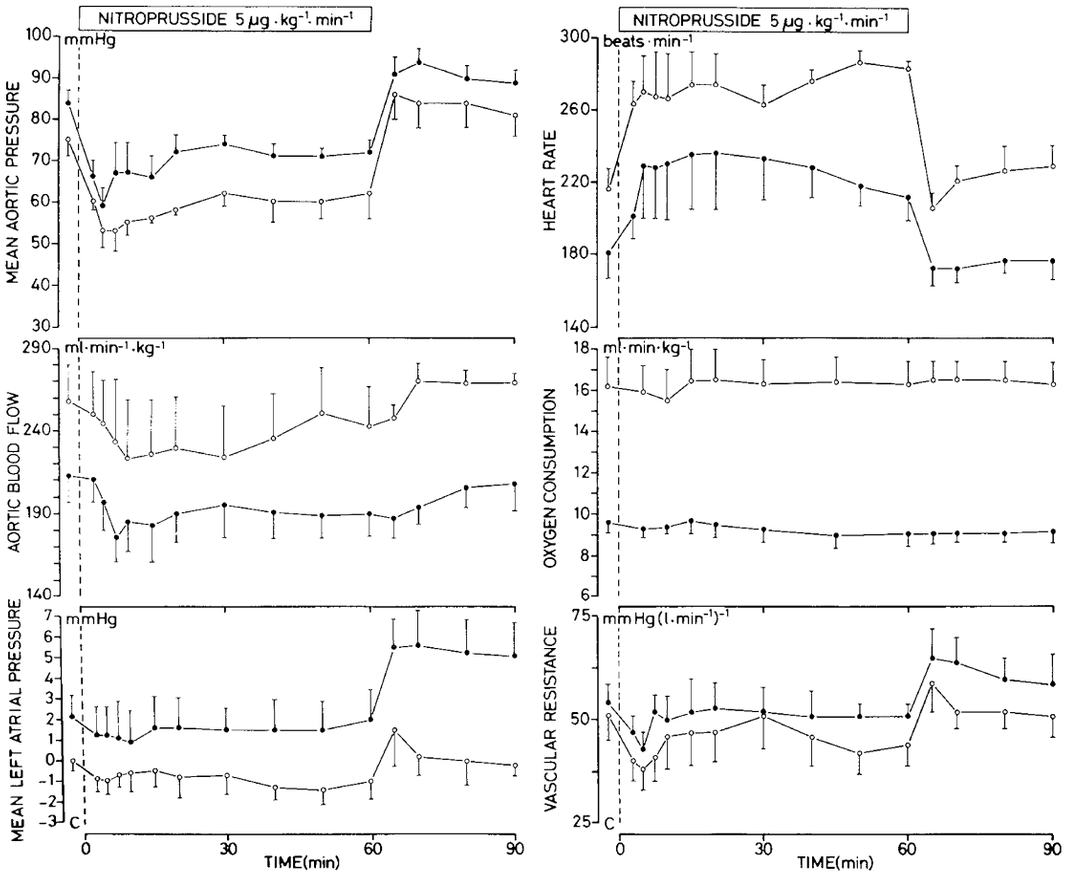

Fig. 1. Sequential effects of a 1-h I.V. infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of sodium nitroprusside, followed by a 30-min recovery period, on mean aortic pressure, aortic blood flow, mean left atrial pressure, heart rate, oxygen consumption, and vascular resistance in newborn (○) and 3-week-old lambs (●). Data are means ± SE of five experiments, except for the oxygen consumption of the newborn lambs where there were three. *C*, control (pre-infusion).

higher in group 1 as compared with group 2 lambs. Infusing 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside did not significantly alter oxygen consumption; infusing 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not change oxygen consumption in group 2 but oxygen consumption fell significantly in group 1 animals. Oxygen consumption gradually returned to control levels within 60 min after onset of the infusion.

Distribution of Cardiac Output and Organ Blood Flows. During infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside, distribution of cardiac output was examined only in the younger (group 1) animals (Table 2). The only significant changes noted were in the kidneys and the brain. The proportion of cardiac output, and actual blood flow, to the kidney fell. Renal blood flow dropped from 345 ± 31 to 213 ± 22 $ml \cdot min^{-1}$ ($P < 0.025$), 10 min after infusion. Renal vascular resistance, however, did not change significantly. Although actual cerebral blood flow did not increase significantly, cerebral vascular resistance decreased (from 1.00 ± 0.15 to 0.63 ± 0.09 mm $Hg \cdot 100\ g^{-1} \cdot min^{-1}$) 50 min after infusion.

Infusing 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased renal blood flow; in group 1 (Table 3) it was 38% of control at 10 min and 71% of control at 50 min after the infusion was started, and in group 2 (Table 4) it was 53 and 68% of control values at similar periods. The proportion of cardiac output to the kidneys fell significantly in both groups, but renal vascular resistance increased significantly only in group 1 animals 10 min after infusion. Blood flow to the skin fell significantly in both groups to 55–60 and 70% of control at 10 and 50 min, respectively. Flow to bone and total carcass fell at 10 min in group 1, but returned to control at 50 min. The percentage of cardiac output to the skin decreased significantly in both groups.

Although actual adrenal blood flow did not change significantly, adrenal vascular resistance fell in group 1. Also cerebral vascular resistance fell significantly after 50-min infusion in group 1 animals.

Myocardial blood flow and coronary vascular resistance did not change significantly in either group and the ratio of coronary blood flow to the inner and outer layers of the myocardium also did not change significantly.

DISCUSSION

Sodium nitroprusside has been used to reduce vascular resistance, or the afterload on the left ventricle, in patients with impaired ventricular performance; it has generally been administered when cardiac output is decreased (1, 7–9). During the neonatal period, cardiac output is high relative to body weight (15, 19). In infants with left-to-right shunt lesions associated with cardiac failure, such as ventricular septal defect or patent ductus arteriosus, left ventricular output is usually increased, or at least maintained. Nitroprusside infusion has resulted in varying degrees of improvement in infants and children with ventricular septal defects (2). In the early postnatal period, the effectiveness of nitroprusside could be influenced by the relatively high cardiac output and the relatively low vascular resistance, in relation to body weight. To assess whether these developmental differences influence the responses to nitroprusside, we infused the drug into lambs at different postnatal ages. The dose we used was somewhat higher than that generally used in clinical practice. We specifically selected the dose that produced a definite decrease in systemic arterial pressure, and also examined the effects of a dose double that amount.

Heart rate has been reported to increase immediately after the

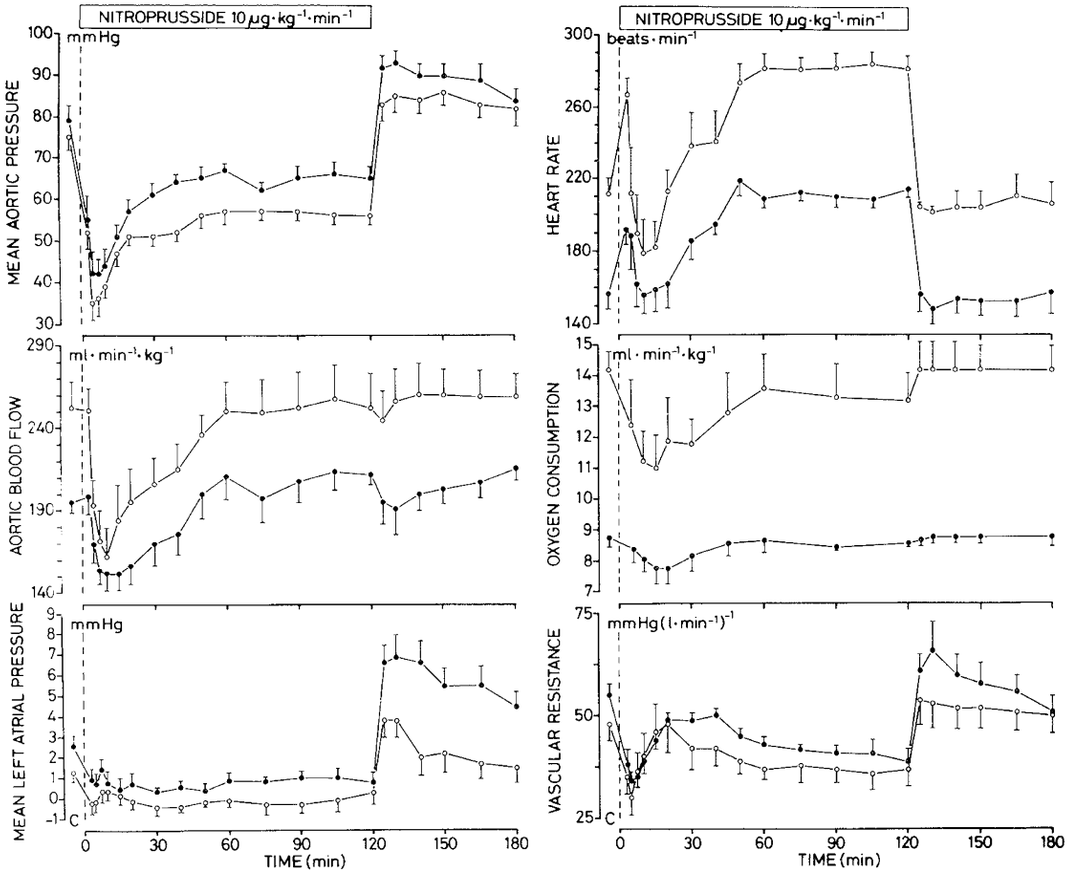

Fig. 2. Sequential effects of a 2-h IV infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of sodium nitroprusside, followed by a 1-h recovery period, on mean aortic pressure, aortic blood flow, mean left atrial pressure, heart rate, oxygen consumption, and vascular resistance in newborn (○) and 3-week-old lambs (●). Data are means ± SE of seven experiments in the newborn lambs, except for the oxygen consumption where it is six, and eight experiments in the 3-week-old-lambs. *C*, control (pre-infusion).

onset of nitroprusside infusion in normal animals (13, 23, 25) and humans (27) as well as in hypertensive individuals (4, 23). This response is probably a result of baroreceptor response to the reduced arterial blood pressure. In adult patients with cardiac failure, heart rate does not usually change with nitroprusside (7, 8, 20, 21, 28), but infants develop tachycardia (2). In our studies, the higher dose of nitroprusside resulted in an initial increase in heart rate, followed by a sudden bradycardia within 3–5 min, and then a gradual increase over 60 min. The bradycardia was particularly marked in the younger lambs and heart rate fell below control values. The cause of this bradycardia has not been established. It is possible that the immature animal does not have as prominent a sympathetic nervous system response to the baroreflex because sympathetic innervation to the heart is incomplete (17). It is also possible that increased vasopressin release in response to the arterial hypotension and reduced left atrial pressure (5, 14) may be responsible for the bradycardia because vasopressin has been shown to produce bradycardia in fetal lambs (12). On the other hand, this bradycardia could also be caused by stimulation of ventricular receptors because of the low arterial pressure and the severity of the reduced venous return (22).

Cardiac output did not change significantly after infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside into lambs of either age group, nor during infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ into the older lambs. However, the infusion of the higher dose in lambs during the 1st week after birth resulted in a marked fall of cardiac output, reaching a nadir at 10–15 min, and then gradually recovering by about 60 min after onset of the infusion. This decrease in cardiac output is probably associated in part with reduced venous return resulting from venous pooling (29), but could be related to the fall in heart rate. Cardiac output is greatly influenced by heart rate in fetal (26) as well as neonatal lambs (Rogé, Heymann, Rudolph, unpublished observations). The cause of the increase in arterial blood pressure following cessation of the infusion has not been delineated. It could be the result of baroreflex vasoconstriction and venoconstriction which has occurred in response to the decreased arterial blood pressure, and which is unopposed by the direct local vascular effect of the nitroprusside.

Distribution of cardiac output was not altered greatly in either age group. The most important changes were a reduction in the percentage of cardiac output distributed to the kidneys and to the peripheral circulation, particularly the skin. Myocardial blood flow did not change significantly at 10 or 50 min after onset of the infusion, although arterial blood pressure was reduced. There was a trend for myocardial flow to decrease at 10 min (control, 144 ± 18 *versus* 92 ± 16 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ at 10 min), but, because of wide variation, the difference was not statistically significant (Table 3). It is possible that, with additional studies, this difference would be significant. Renal blood flow fell significantly with both the high and low doses of nitroprusside. There were no substantial differences in the responses in the two age groups.

These data have implications in regard to the possible use of sodium nitroprusside in treating infants with cardiac failure. In view of the reduced heart rate and cardiac output, in association with a marked fall in arterial pressure, which occur soon after infusion of large doses, it is reiterated that the initial rate of administration should be slow. Should bradycardia occur, the infusion rate should be reduced to avoid a marked fall in cardiac output because, in association with the fall in arterial pressure,

Table 2. *Effects of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside on blood flow, distribution of cardiac output, and vascular resistance in 1-week-old lambs**

	Blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)			Cardiac output (%)			Vascular resistance ($mm\ Hg \cdot ml^{-1} \cdot 100\ g^{-1}$)		
	Control	Nitroprusside		Control	Nitroprusside		Control	Nitroprusside	
		10 min	50 min		10 min	50 min		10 min	50 min
Organ									
Adrenal	141 ± 16	153 ± 10	167 ± 20	0.09 ± 0.01	0.13 ± 0.03	0.10 ± 0.01	0.56 ± 0.05	0.43 ± 0.07	0.37 ± 0.03
Spleen	222 ± 35	126 ± 24	184 ± 56	3.03 ± 0.37	2.34 ± 0.46	2.93 ± 1.05	0.38 ± 0.07	0.51 ± 0.08	0.52 ± 0.23
Gut	99 ± 12	78 ± 12	132 ± 11	23.72 ± 1.71	24.54 ± 2.80	28.53 ± 1.95	0.84 ± 0.17	0.79 ± 0.10	0.48 ± 0.08
Liver	4.5 ± 0.7	5.0 ± 1.4	3.4 ± 1.1	0.55 ± 0.11	0.80 ± 0.23	0.39 ± 0.09	19.18 ± 4.15	17.77 ± 5.77	25.25 ± 7.81
Kidneys	345 ± 31	213 ± 22[b]	286 ± 32	8.29 ± 0.30	6.63 ± 0.26[c]	6.43 ± 0.49[c]	0.23 ± 0.02	0.28 ± 0.02	0.22 ± 0.03
Brain	82 ± 11	73 ± 8	98 ± 8	2.84 ± 0.38	3.26 ± 0.35	3.03 ± 0.33	1.00 ± 0.15	0.81 ± 0.08	0.63 ± 0.09[a]
Thyroid	77 ± 9	73 ± 15	105 ± 33	0.07 ± 0.01	0.08 ± 0.00	0.08 ± 0.01	0.99 ± 0.12	0.89 ± 0.14	0.64 ± 0.19
Heart	113 ± 10	102 ± 13	134 ± 2	4.50 ± 0.39	5.25 ± 0.65	5.05 ± 0.45	0.70 ± 0.08	0.60 ± 0.09	0.46 ± 0.05
Lungs	70 ± 11	62 ± 8	68 ± 7	5.24 ± 0.58	5.91 ± 0.47	5.26 ± 0.76	1.19 ± 0.20	0.99 ± 0.12	0.94 ± 0.17
Skin	13.3 ± 0.8	9.9 ± 1.5	11.9 ± 1.4	8.08 ± 0.80	7.45 ± 0.84	6.55 ± 0.40	5.78 ± 0.49	6.44 ± 1.11	5.60 ± 1.32
Muscle	14.1 ± 2.6	9.6 ± 1.1	16.7 ± 3.2	14.67 ± 1.30	13.79 ± 2.06	14.57 ± 1.53	6.23 ± 1.31	6.36 ± 0.93	4.42 ± 1.52
Bones	20.5 ± 1.0	17.6 ± 2.1	22.9 ± 3.7	24.74 ± 1.51	26.66 ± 2.19	23.89 ± 1.92	3.76 ± 0.35	3.54 ± 0.57	3.10 ± 0.95
Total carcass	16.6 ± 1.4	13.0 ± 1.4	18.4 ± 2.9	47.49 ± 1.70	47.89 ± 2.53	45.01 ± 1.92	4.79 ± 0.65	4.63 ± 0.55	3.89 ± 1.24
CO ($ml \cdot min^{-1} \cdot kg^{-1}$)	286 ± 25	222 ± 23	325 ± 35						
$\bar{P}ao$ (mm Hg)	75 ± 4	56 ± 1[e]	60 ± 5[d]						
HR ($beats \cdot min^{-1}$)	217 ± 11	273 ± 18[a]	283 ± 6[b]						
R_s [$mm\ Hg(liters \cdot min^{-1})^{-1}$]	46 ± 4	41 ± 4	34 ± 4						

* Data shown are means ± SE; $n = 5$. *Versus* control: [a], $P < 0.05$; [b], $P < 0.025$; [c], $P < 0.01$; [d], $P < 0.005$; [e], $P < 0.001$. CO = cardiac output; $\bar{P}ao$ = mean aortic pressure; HR = heart rate; R_s = vascular resistance.

Table 3. *Effects of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside on blood flow, distribution of cardiac output, and vascular resistance in 1-week-old lambs**

	Blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)			Cardiac output (%)			Vascular resistance ($mm\ Hg \cdot ml^{-1} \cdot 100\ g^{-1}$)		
		Nitroprusside			Nitroprusside			Nitroprusside	
	Control	10 min	50 min	Control	10 min	50 min	Control	10 min	50 min
Organ									
Adrenal	150 ± 12	202 ± 35	233 ± 32	0.09 ± 0.01	0.19 ± 0.04[c]	0.13 ± 0.01	0.52 ± 0.05	0.25 ± 0.04[d]	0.27 ± 0.03[d]
Spleen	247 ± 43	162 ± 27	204 ± 44	2.91 ± 0.59	2.99 ± 0.37	2.23 ± 0.39	0.54 ± 0.26	0.30 ± 0.05	0.36 ± 0.07
Gut	112 ± 13	68 ± 9	119 ± 18	24.73 ± 1.73	24.06 ± 2.54	24.94 ± 2.02	0.71 ± 0.06	0.68 ± 0.10	0.53 ± 0.09
Liver	10.7 ± 3.3	13.7 ± 3.5	6.2 ± 1.2	1.11 ± 0.31	2.33 ± 0.56	0.64 ± 0.12	10.03 ± 1.98	4.74 ± 1.51	10.89 ± 1.92
Kidneys	358 ± 16	135 ± 24[e]	255 ± 25[d,h]	8.12 ± 0.45	4.78 ± 0.70[c]	5.55 ± 0.45[c]	0.21 ± 0.01	0.34 ± 0.03[d]	0.23 ± 0.02[h]
Brain	98 ± 7	78 ± 7	111 ± 5	3.14 ± 0.32	4.31 ± 0.88	3.48 ± 0.36	0.80 ± 0.08	0.55 ± 0.05	0.51 ± 0.04[a]
Thyroid	83 ± 18	60 ± 11	111 ± 28	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.02	1.14 ± 0.30	0.95 ± 0.29	0.71 ± 0.20
Heart	144 ± 18	92 ± 16	184 ± 25	5.15 ± 0.64	5.22 ± 0.88	6.38 ± 0.81	0.56 ± 0.06	0.54 ± 0.09	0.34 ± 0.04
Lungs	80 ± 12	76 ± 18	61 ± 9	5.33 ± 0.78	7.89 ± 0.51	4.39 ± 0.79	1.02 ± 0.10	0.77 ± 0.18	1.07 ± 0.22
Skin	14.7 ± 0.6	7.8 ± 0.8[e]	10.7 ± 1.2[d,f]	7.98 ± 0.33	6.65 ± 0.34[c]	5.73 ± 0.29[e]	5.15 ± 0.34	5.66 ± 0.74	5.64 ± 0.76
Muscle	14.5 ± 1.4	11.0 ± 2.2	16.5 ± 1.7	14.75 ± 1.78	17.41 ± 3.04	17.26 ± 2.91	5.57 ± 0.76	4.63 ± 0.87	3.56 ± 0.31
Bones	21.5 ± 1.6	12.9 ± 2.0[d]	22.2 ± 2.0[g]	23.90 ± 1.17	21.89 ± 1.43	24.32 ± 1.03	3.56 ± 0.23	3.69 ± 0.66	2.70 ± 0.37
Total carcass	17.6 ± 1.1	11.2 ± 1.6[c]	18.0 ± 1.2[g]	46.64 ± 2.19	45.94 ± 3.40	47.31 ± 2.61	4.37 ± 0.32	4.21 ± 0.73	3.19 ± 0.27
$\dot{C}O$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	291 ± 18	184 ± 21[d]	301 ± 25[h]						
$\bar{P}ao$ (mm Hg)	75 ± 3	42 ± 4[e,j]	55 ± 2[d]						
HR ($beats \cdot min^{-1}$)	214 ± 10	181 ± 18[k]	270 ± 12[b,i]						
R_s [mm Hg(liters·min^{-1})$^{-1}$]	42 ± 3	38 ± 4	31 ± 4						

* Data shown are means ± SE; $n = 7$. Data before and during the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion were compared with those before and during the 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion in the 1-week-old lambs using two-way analysis of variance with replication and unequal samples and the Neuman-Keuls test using rank sums. *Versus* control: [a], $P < 0.05$; [b], $P < 0.025$; [c], $P < 0.01$; [d], $P < 0.005$; [e], $P < 0.001$. *Versus* 10-min nitroprusside: [f], $P < 0.05$; [g], $P < 0.01$; [h], $P < 0.005$; [i], $P < 0.001$. *Versus* corresponding times before and during 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion in the 1-week-old lambs: [j], $P < 0.01$; [k], $P < 0.001$.

Table 4. *Effects of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside on blood flow, distribution of cardiac output, and vascular resistance in 3-week-old lambs**

	Blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)			Cardiac output (%)			Vascular resistance ($mm\ Hg \cdot ml^{-1} \cdot 100\ g^{-1}$)		
		Nitroprusside			Nitroprusside			Nitroprusside	
	Control	10 min	50 min	Control	10 min	50 min	Control	10 min	50 min
Organ									
Adrenal	129 ± 12	193 ± 44	193 ± 25	0.10 ± 0.01	0.20 ± 0.05	0.17 ± 0.03	0.64 ± 0.09	0.40 ± 0.12	0.36 ± 0.05
Spleen	177 ± 29	105 ± 16	112 ± 33	3.44 ± 0.55	2.20 ± 0.22	1.97 ± 0.41	0.45 ± 0.07	0.53 ± 0.07	0.92 ± 0.32
Gut	84 ± 9	72 ± 15	84 ± 13	27.05 ± 1.97	28.17 ± 3.68	29.79 ± 2.77	1.02 ± 0.15	1.10 ± 0.42	0.95 ± 0.26
Liver	18.2 ± 7.2	18.3 ± 12.2	13.8 ± 5.3	2.26 ± 0.78	3.46 ± 2.16	2.39 ± 1.02	10.21 ± 2.40	9.70 ± 3.07	12.66 ± 3.19
Kidneys	310 ± 14	164 ± 17[e]	212 ± 20[d]	11.52 ± 0.82[j]	7.85 ± 0.87[a,i]	9.00 ± 0.90[a,i]	0.25 ± 0.01	0.32 ± 0.03	0.30 ± 0.03[g]
Brain	95 ± 9	102 ± 15	101 ± 8	3.65 ± 0.20	5.26 ± 0.65	4.54 ± 0.39	0.87 ± 0.10	0.57 ± 0.09	0.64 ± 0.07
Thyroid	91 ± 18	87 ± 30	106 ± 19	0.07 ± 0.01	0.08 ± 0.02	0.09 ± 0.01	1.10 ± 0.18	1.01 ± 0.38	0.75 ± 0.15
Heart	121 ± 19	101 ± 29	129 ± 29	4.90 ± 0.29	4.56 ± 0.45	5.72 ± 0.47	0.75 ± 0.12	0.73 ± 0.18	0.60 ± 0.08
Lungs	78 ± 26	67 ± 13	63 ± 8	6.27 ± 1.50	6.87 ± 1.30	6.56 ± 1.23	1.51 ± 0.29	0.96 ± 0.21	1.18 ± 0.23
Skin	12.7 ± 0.9	7.6 ± 1.2[b]	8.6 ± 1.3[b]	8.08 ± 0.46	6.14 ± 0.73[b]	5.79 ± 0.28[e]	6.24 ± 0.66	7.31 ± 0.84	8.55 ± 1.39
Muscle	9.8 ± 1.6	7.4 ± 1.1	8.6 ± 1.3	11.59 ± 1.07	11.27± 0.75	11.58 ± 0.72	10.17 ± 2.02	7.66 ± 1.13	8.56 ± 1.36[i]
Bones	15.2 ± 2.0[g]	13.8 ± 2.4	14.7 ± 2.2	19.03 ± 1.56[g]	21.99 ± 1.74	20.55 ± 1.37	5.91 ± 1.01	4.12 ± 0.53	4.85 ± 0.69[h]
Total carcass	12.5 ± 1.2[h]	10.0 ± 1.6	11.0 ± 1.6	38.72 ± 1.51[i]	39.40 ± 2.70	37.92 ± 1.94[i]	6.85 ± 1.04	5.55 ± 0.70	6.45 ± 0.94[i]
CO ($ml \cdot min^{-1} \cdot kg^{-1}$)	228 ± 19[g]	179 ± 24	203 ± 22[h]						
$\bar{P}ao$ (mm Hg)	76 ± 4	52 ± 5[d]	60 ± 3[c]						
HR ($beats \cdot min^{-1}$)	177 ± 12	163 ± 7	227 ± 12[b,f,h]						
R_s [mm Hg(liters $\cdot min^{-1})^{-1}$]	47 ± 5	45 ± 7	44 ± 4						

* Data shown are means ± SE; $n = 9$ during the control period and at 50 min, $n = 6$ at 10 min. Data before and during the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion were compared with those before and during the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion in the 1-week-old lambs using two-way analysis of variance with replication and unequal samples and the Neuman-Keuls test using rank sums. *Versus* control: [a], $P < 0.05$; [b], $P < 0.025$; [c], $P < 0.01$; [d], $P < 0.005$; [e], $P < 0.001$. *Versus* 10-min nitroprusside: [f], $P < 0.001$. *Versus* corresponding times before and during 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ nitroprusside infusion in the 1-week-old lambs: [g], $P < 0.05$; [h], $P < 0.025$; [i], $P < 0.01$; [j], $P < 0.005$.

coronary blood flow could be seriously reduced. A second potential disadvantage in the use of this agent is the reduced renal blood flow. This could have serious adverse effects in an infant who already has cardiac failure with limited renal function. The mechanism responsible for the reduced renal blood flow has not been established. It could be merely a result of the fall in arterial blood pressure below the range of effective autoregulation, or it could result from a renin-angiotensin mechanism induced by the fall in arterial pressure. Whatever the cause, it merits careful attention if infants are to be treated by afterload-reducing agents.

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