

The Renal Effects of Sodium Nitroprusside in Postoperative Cardiac Surgical Patients

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Sodium nitroprusside (SNP) is frequently used to control hypertension and/or improve systemic blood flow following cardiac operations. Although SNP causes renal vasodilation when infused into isolated kidneys, the reported effects of SNP on renal vascular resistance and blood flow in intact animals and humans have varied. To define the effects of SNP in postoperative cardiac surgical patients, renal clearances and hemodynamics were measured in seven patients within 24 hours of coronary bypass grafting. Studies were delayed until patients were stabilized and had rewarmed following operation. Following baseline measurements (off SNP), SNP infusion was used to lower mean arterial pressure to 85 torr. Pulmonary wedge pressure was maintained by appropriate fluid therapy, and the measurements repeated 1 h later. SNP administration resulted in equivalent decreases in renal (-31 per cent), pulmonary (-29 per cent) and systemic (-33 per cent) vascular resistance. Notwithstanding the decrease in arterial pressure (109 ± 14 to 91 ± 9 torr, $P < 0.01$), renal blood flow increased by 20 per cent (653 ± 193 to 792 ± 210 ml · min⁻¹ · 1.73 m⁻², $P < 0.02$), in direct proportion to the increase in cardiac index (2.5 ± 0.4 to 3.0 ± 0.3 l · min⁻¹ · m⁻², $P < 0.01$). Thus, in postoperative cardiac surgical patients, SNP administration can be expected to improve renal blood flow, so long as left atrial hypotension is avoided, and the decline in systemic arterial pressure is not excessive. The improvement in renal blood flow achievable with SNP may be critical for patients with severely depressed left ventricular function in whom severe depression of renal blood flow may occur as an antecedent to acute renal failure. (Key words: Anesthesia; cardiovascular. Anesthetic technique: hypotension; induced, sodium nitroprusside. Heart: atria; cardiac output. Kidney: blood flow; function. Pharmacology: sodium nitroprusside. Surgery: cardiac.)

SODIUM NITROPRUSSIDE (SNP) is a potent vasodilator which decreases arterial blood pressure by decreasing total peripheral resistance.^{1,2} It has been used in patients in cardiogenic shock following acute myocardial infarction with dramatic improvements in hemodynamic state and prognosis.³ Similarly, SNP has been shown to increase stroke volume index and cardiac

index when used in patients with mild to moderate depression of cardiac function following open-cardiac operations.⁴

The reported effects of SNP on renal blood flow (RBF) are conflicting.^{2,5-11} Whereas SNP caused renal vasodilation in isolated canine kidneys, renal vasoconstriction was demonstrated in intact animals.⁵ In various patient populations, investigators have reported both decreased⁶ and increased renal blood flow^{2,7} following SNP administration. Possible explanations for these conflicting results include reflex renal vasoconstriction secondary to left atrial hypotension,¹²⁻¹⁸ a decline in mean arterial pressure (MAP) below the autoregulatory range for renal blood flow,¹⁹⁻²² abolition of autoregulation by vasodilator administration,²³ and a different response to SNP of the normal and the failing circulation.²⁴

Renal failure, which may be a serious postoperative complication in cardiac surgical patients, is commonly preceded by a period of depressed cardiac output with renal vasoconstriction.^{25,26} The purpose of the present study was to evaluate the effects of SNP on cardiac performance and renal perfusion in postoperative cardiac surgical patients. Since most previous studies have not compensated for SNP-induced changes in left atrial pressure, this evaluation was performed after left atrial pressure had been restored to baseline levels.

Materials and Methods

Informed consent was obtained preoperatively from seven patients scheduled for coronary artery bypass grafting. Consent procedures and study techniques conformed to appropriate ethical standards and were approved by the Committee on the Use of Human Subjects in Research at Stanford. Six of the seven patients underwent coronary bypass grafting alone. Five of these patients had normal ventricular contractility by preoperative left ventriculogram, and one patient had mild-moderate ventricular dysfunction angiographically. One patient underwent coronary bypass grafting and aortic valve replacement (for aortic stenosis). This patient exhibited left ventricular enlargement angiographically with mild-moderate depression of contractility. Two patients had a history of preoperative hypertension. Renal function was nor-

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mal in these patients at the time of chart review and selection for study [no history of renal disease, normal urinalysis, blood urea nitrogen (BUN) < 20 mg/dl]. This was also evident at the time of the postoperative study when the glomerular filtration rate averaged $105 \pm 35 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, a value appropriate for the ages of the patients.

Hemodynamic and renal function were measured using standard techniques and calculations, as previously described.^{25,26} Briefly, measurements were performed on the day of surgery, after the patients were completely rewarmed and stabilized and the post-cardiopulmonary bypass mannitol diuresis had ceased. It is the routine following open cardiac operations performed at Stanford to use sodium nitroprusside, as needed, to maintain the MAP between 75 and 85 torr in the immediate postoperative period. This routine evolved to minimize suture line stress and bleeding secondary to hypertension, and to enhance cardiac output in patients with depressed postoperative left ventricular performance.^{27,28} NP infusion was discontinued in all patients and inulin and para-aminohippurate (PAH) administration were begun. Administration of diuretics were avoided 6 hours prior to and during clearance measurement periods. SNP was the only vasoactive drug administered, hypertonic volume expansion and changes in intravenous fluid administration rates were avoided during the clearance measurements. Cardiac output was measured in duplicate by dye dilution using indocyanine green, a Water's cuvette densitometer (D-400),** and a cardiac output computer (CO-4).** Pulmonary artery and pulmonary capillary wedge pressures were measured through a quadruple-lumen Swan-Ganz 7F thermodilution catheter.†† Heart rate and MAP were measured using standard transducers and monitors.‡‡

Glomerular filtration rate was measured by the clearance of inulin, and effective renal plasma flow by the clearance of PAH. A bolus of PAH and inulin was followed by a sustaining infusion to achieve a stable plasma concentration of approximately 1 and 10 mg/dl, respectively. Three sequential 20-min urine collections were made, and the urine flow and clearance values for these three periods were subsequently averaged to yield a 1-hr clearance value. At the start and end of each collection, the bladder was completely emptied by a sterile air flush, followed by gravity drainage of the residual urine through an indwelling Foley catheter. Blood samples were obtained at the beginning and end of each collection period. Inulin,

PAH, osmolality, and sodium and potassium concentrations were determined in each plasma and urine sample. The clearance of PAH was corrected, assuming a PAH extraction value of 0.9, and renal blood flow was calculated by dividing the corrected PAH clearance by (1-hematocrit).²⁹ The renal fraction measures the percentage of total cardiac output which perfuses the kidneys and was obtained by dividing renal blood flow by cardiac output and expressing the result as a percentage. The clearance values were normalized by multiplying by $1.73/\text{the patient's body surface area}$, and expressed in, $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. Control measurements were performed 40–60 min later. SNP was then infused to lower the MAP to approximately 85 torr, and appropriate fluid therapy was given to restore pulmonary wedge pressure to baseline levels. On the average, the patients received 560 ml of whole blood and 350 ml of crystalloid during the study. Following a 30 min-stabilization period, the hemodynamic and renal function measurements were repeated. As a result of preload restoration, the MAP increased somewhat. For each variable, the results are reported as the mean \pm SD. The changes resulting from SNP administration were evaluated statistically by Student's *t* test for paired data.³⁰

Results

No complications occurred as a result of these studies. Hemodynamic and renal function measurements before and during SNP administration are summarized in tables 1 and 2. The average rate of SNP infusion was $0.76 \pm 0.71 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range 0.4–2.4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). This resulted in a decrease in mean MAP from 109 ± 14 to 91 ± 9 torr ($P < 0.01$) and an increase in cardiac index from 2.5 ± 0.4 to $3.0 \pm 0.3 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($P < 0.01$; table 1). Because of intentional blood volume expansion during SNP administration, pulmonary capillary wedge pressure and central venous pressure did not change significantly. Mean heart rate rose by 6 beats/min ($P < 0.05$). Uniform and significant decreases occurred in calculated mean systemic, pulmonic, and renal vascular resistance.

PAH clearance and renal blood flow increased significantly in all patients during SNP administration (table 2). Renal blood flow as a fraction of cardiac index remained constant at 15 per cent, and urine flow and inulin clearance remained unchanged. No significant changes occurred in the following variables (group means before and during SNP respectively): sodium excretion (0.14 ± 0.1 to $0.17 \pm 0.2 \text{ mEq/min}$); potassium excretion (0.08 ± 0.01 to $0.11 \pm 0.02 \text{ mEq/min}$); total cation excretion (0.23 ± 0.1 to $0.29 \pm 0.2 \text{ mEq/min}$); and urine/plasma osmolality ratio (2.1 ± 0.3 to 2.1 ± 0.2).

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TABLE 1. Hemodynamic Effects of Sodium Nitroprusside

SNP	MAP (torr)	PCWP (torr)	CI (ml·min ⁻¹ ·m ⁻²)	SVRI (units·m ⁻²)	PVRI (units·m ⁻²)	RVR (units)
OFF	109 (±14)	16 (±4)	2.5 (±0.4)	39 (±8)	3.8 (±1.4)	142 (±65)
ON	91 (±9)	15 (±4)	3.0 (±0.3)	26 (±5)	2.7 (±0.8)	95 (±40)
Per cent change	-17	—	+20	-33	-29	-31
P	<0.01	>0.1	<0.01	<0.01	<0.02	<0.01

Values are means ± standard deviation.

SNP = sodium nitroprusside; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index;

SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; RVR = renal vascular resistance.

Discussion

SNP administration in postoperative cardiac surgical patients was associated with a decrease in MAP and total peripheral resistance and an increase in cardiac index. These findings agree with previous studies.^{1-4,29,30} Preload was maintained in the high normal range with appropriate fluid infusion to achieve maximal hemodynamic improvement.^{27,28} SNP produced a similar decrease in peripheral, pulmonary, and renal vascular resistance. In spite of the decrease in the renal perfusion pressure (measured as MAP), an increase in blood flow to renal tubular cells was documented by increased clearance of PAH. This increase was proportional to the increase in cardiac output. Urine flow, glomerular filtration rate, and renal solute excretion, however, were unaffected. Thus, the increase in renal blood flow would not have been detected by the usual clinical indices of renal function.

Several factors may alter the renal vascular response to SNP administration. A decline in left atrial pressure may cause reflex renal vasoconstriction.¹²⁻¹⁸ A decline in renal perfusion pressure below the autoregulatory range will also decrease renal blood flow,¹⁹⁻²³ in spite of a progressive decline in renal vascular resistance until perfusion pressure falls below 30

torr,¹⁹⁻²¹ when resistance may then increase.¹⁹ Renal vasodilators may abolish the autoregulation of renal blood flow;²³ once vasodilation is maximal, renal blood flow and perfusion pressure will decline in parallel. Finally, with depression of left ventricular contractility, SNP is most effective in increasing cardiac output,²⁴ which should improve renal blood flow.³¹ The previously conflicting reports of the effects of SNP administration doubtless reflect the variable influence of these factors.^{2,6-11} Bastron and Kaloyanides⁵ reported that SNP produced marked vasodilation and an increase in blood flow in the isolated perfused canine kidney; however, in the intact animal, they found that a SNP-induced reduction in arterial pressure caused a reduction in PAH clearance.

A likely explanation for many of these conflicting reports lies in the failure to maintain left atrial pressure which, if allowed to decrease, may cause profound renal vasoconstriction. Kahl *et al.*¹² reported the effects of diminished cardiac output on renal function in anesthetized dogs using a model with two distinctively different levels of left atrial pressures. Superior vena caval obstruction decreased cardiac index, MAP, and left atrial pressure and resulted in profound renal vasoconstriction. Balloon inflation in the left atrium decreased cardiac index and MAP; however, left atrial pressure was elevated and renal vascular resistance

TABLE 2. Effects of Sodium Nitroprusside Administration on Renal Function

SNP	Flow (ml/min)	C _{IN} (ml·min ⁻¹ ·1.73 m ⁻²)	C _{PAH} (ml·min ⁻¹ ·1.73 m ⁻²)	FF	RBF (ml·min ⁻¹ ·1.73 m ⁻²)	RF (per cent)
OFF	1.3 (±0.4)	105 (±35)	354 (±101)	0.30 (±0.05)	653 (±193)	15 (±5)
ON	1.5 (±0.7)	109 (±35)	424 (±102)	0.25 (±0.04)	792 (±210)	15 (±4)
Per cent change			+19		+21	
P	>0.1	>0.1	<0.02	<0.02	<0.02	>0.1

Values are means ± standard deviation.

SNP = sodium nitroprusside; Flow = urine flow; C_{IN} = clearance of

inulin; C_{PAH} = clearance of para-aminohippurate; FF = filtration fraction; RBF = renal blood flow; RF = renal fraction.

remained unchanged. Atrial hypotension is a potent stimulus for renal vasoconstriction;^{12,13} however, left atrial hypertension results in only weak renal vasodilation.^{14,15} These reflexes can be abolished by vagotomy^{14,16} or by surgical denervation of the kidney.^{16,17} In experimental animals, plasma renin activity varies inversely with atrial pressure,^{13,16} thus humoral factors appear capable of contributing to this response. Previous studies in which SNP administration increased renal vascular resistance (or decreased renal blood flow) were performed under conditions likely to decrease atrial pressures to below normal levels; however, this variable was not measured.^{5,6,8-10,18} By contrast, in patients with congestive heart failure, left atrial pressure declined during SNP infusion but remained in the high normal range, and renal blood flow improved significantly.⁷

The decline in MAP induced by SNP provides another possible explanation for the reported reduction in RBF. The following summarizes the results from several experimental animals studies:¹⁹⁻²¹ as renal artery pressure was decreased by partial arterial occlusion from 120 to 80 torr, progressive renal vasodilation occurred, and renal blood flow remained constant (autoregulation); as arterial pressure was further decreased to 60 torr, RBF decreased, on the average by only 20 per cent; below 60 torr, the reported decline in RBF was more severe. Indeed, once renal vasodilation is maximal, renal blood flow and perfusion pressure should decline in parallel (Ohm's Law). The reported decline in RBF with SNP administration averaged 42 per cent when the MAP was lowered to 67 torr.^{5,6,9,10,18} By contrast, the improvement in renal blood flow with SNP administration reported by Cogan *et al.*⁷ occurred despite a decline in average MAP to 72 torr (the left atrial pressure declined, but remained above normal). Therefore we doubt that a decline in MAP is the primary explanation for the discrepancies reported.

In the present study the increase in renal blood flow was proportional to the increase in cardiac output. Therefore, it may be argued that the increase in renal blood flow was simply a result of the SNP-induced increase in cardiac output. However, the increase in cardiac output was presumably secondary to the decrease in systemic resistance with SNP infusion. Given the documented effects of SNP on the renal vasculature and the equivalent reductions in systemic (-31 per cent), pulmonic (-29 per cent), and renal (-33 per cent) vascular resistance during SNP infusion, it seems likely that the effects of SNP are due to direct vasodilation of all three vascular beds.

Fan *et al.*³² recently reported that nitroprusside infusion in dogs decreased renal blood flow only when

rapid infusion rates ($>7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were required to induce hypotension. Surprisingly, their data also indicated that nitroprusside infusion decreased systemic vascular resistance only slightly and failed to decrease pulmonary vascular resistance at doses up to 10 and 100 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively. The authors urged caution in the uses of high doses of nitroprusside in "resistant" patients. However, the differences between our results and theirs—especially the data on the resistance changes in the systemic, pulmonic, and renal circulations—suggest that species differences in the response to nitroprusside may be important; such differences would explain many of the discrepancies in the literature. Differences in measurement techniques and the postoperative state of our patients may also have contributed to these discrepancies.

Following cardiac operation acute renal failure usually develops in patients who exhibit a protracted period of depressed renal perfusion secondary to depressed cardiac performance.²⁶ While the renal insult in experimental acute renal failure may differ, it is noteworthy that vasodilator drugs have been demonstrated to protect kidneys from the acute renal failure which develops following complete renal ischemia.^{33,34} Our findings indicate that SNP infusion is associated with improved renal perfusion in postoperative cardiac surgical patients, so long as left atrial and arterial hypotension are not excessive. Our patients had better cardiac function than is usually seen in patients who develop acute renal failure.²⁶ Nevertheless, the frequent use of SNP to optimize hemodynamic state following cardiac operations, particularly in patients with depressed cardiac function, may be one factor accounting for the low incidence of postoperative acute renal failure recently reported.²⁵

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References

1. Tinker JH, Michenfelder JD: Sodium nitroprusside: Pharmacology, toxicology and therapeutics. *ANESTHESIOLOGY* 45: 340-354, 1976
2. Page IH, Corcoran AC, Dustan HP, et al: Cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. *Circulation* 11:188-198, 1955
3. Chatterjee K, Swan HJC, Kovshik VS, et al: Effects of vasodilator therapy for severe pump failure in acute myocardial infarction on short-term and late prognosis. *Circulation* 53: 797-802, 1976
4. Stinson EB, Holloway EL, Derby GC, et al: Control of myocardial performance early after open-heart operations by vasodilator treatment. *J Thorac Cardiovasc Surg* 73:523-530, 1977
5. Bastron RD, Kaloyanides GJ: Effects of sodium nitroprusside

- on function in the isolated and intact dog kidney. *J Pharmacol Exp Ther* 181:244-249, 1972
6. Birch AA, Boyce WH: Changing renal blood flow following sodium nitroprusside in patients undergoing nephrolithotomy. *Anesth Analg (Cleve)* 56:102-109, 1977
 7. Cogan J, Humphreys M, Carlson J, et al: Afterload reduction increases renal blood flow and maintains glomerular filtration rate in patients with congestive heart failure. *Circulation* 61:316-323, 1980
 8. Delaney TJ, Miller ED Jr: Blood flow alteration induced by saralasin or sodium nitroprusside. *ANESTHESIOLOGY* 51 (Suppl):S73, 1979
 9. Behnia R, Osborn RC, Linde HW, et al: Renal function and hemodynamics during induced hypotension in dogs. *ANESTHESIOLOGY* 51(Suppl):S81, 1979
 10. Bagshaw RJ, Cox RH, Campbell KB: Sodium nitroprusside and regional arterial haemodynamics in the dog. *Br J Anaesth* 49:735-743, 1977
 11. Wang HH, Liu LMP, Katz RL: A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. *ANESTHESIOLOGY* 46:40-48, 1977
 12. Kahl FR, Flint JF, Szidon JP: Influence of left atrial distention on renal vasomotor tone. *Am J Physiol* 226:240-246, 1974
 13. Brosnihan KB, Bravo EL: Graded reductions of atrial pressure and renin release. *Am J Physiol* 235:H175-H181, 1978
 14. Mason JM, Ledson JR: Effects of obstruction of the mitral orifice or distension of the pulmonary vein-atrial junctions on renal and hind-limb vascular resistance in the dog. *Circ Res* 35:24-32, 1974
 15. Kaczmarczyk G, Eigenheer F, Gatzka M, et al: No relation between atrial natriuresis and renal blood flow in conscious dogs. *Pfluegers Arch* 373:49-58, 1978
 16. Zehr JE, Hasbargen JA, Kurz KD: Reflex suppression of renin secretion during distention of cardiopulmonary receptors in dogs. *Circ Res* 38:232-239, 1976
 17. Korner PI, Stokes GS, White SW, et al: Role of the autonomic nervous system in the renal vasoconstriction response to hemorrhage in the rabbit. *Circ Res* 20:676-685, 1967
 18. Kaneko Y, Ikeda T, Takeda T, et al: Renin release during acute reduction of arterial pressure in normotensive subjects and patients with renovascular hypertension. *J Clin Invest* 46:705-716, 1967
 19. Selkurt EE: The relation of renal blood flow to effective arterial pressure in the intact kidney of the dog. *Am J Physiol* 147:537-549, 1946
 20. Shipley RE, Study RS: Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery blood pressure. *Am J Physiol* 167:676-688, 1951
 21. Ritter ER: Pressure/flow relations in the kidney. Alleged effects of pulse pressure. *Am J Physiol* 168:480-489, 1952
 22. Schmid HE Jr, Spencer MP: Characteristics of pressure-flow regulation by the kidney. *J Appl Physiol* 17:201-204, 1962
 23. Baer PG, Navar LG: Renal vasodilation and uncoupling of blood flow and filtration rate autoregulation. *Kidney Int* 4: 12-21, 1973
 24. Pouleur H, Covell JA, Ross J: Effects of nitroprusside on venous return and central blood volume in the absence and presence of acute heart failure. *Circulation* 61:328-337, 1980
 25. Hilberman M, Myers BD, Carrie BJ, et al: Acute renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* 77: 880-888, 1979
 26. Hilberman M, Myers BD, Derby GC, et al: Sequential pathophysiological changes characterizing the progression from renal dysfunction to renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* 79:838-846, 1980
 27. Stinson EB, Holloway EL, Derby GC, et al: Comparative hemodynamic responses to chlorpromazine, nitroprusside, nitroglycerin and trimethaphan immediately after open-heart operations. *Circulation* 51:126-132, 1975
 28. Meretoga OA, Laaksonen VO: Hemodynamic effects of pre-load and sodium nitroprusside in patients subjected to coronary bypass surgery. *Circulation* 58:815-825, 1978
 29. Stein JH: The renal circulation, in *The Kidney*. Edited by Brenner BM, Rector FC. Philadelphia, W. B. Saunders Company, 1976, pp 215-250
 30. Nie NH, Hull CH, Jenkins JG, et al: SPSS-Statistical Package for the Social Sciences. New York, McGraw-Hill Book Company, Inc. 1975
 31. Porter GA, Kloster FE, Bristow JD, et al: Interrelationship of hemodynamic alterations of valvular heart disease and renal function: Influences on renal sodium reabsorption. *Am Heart J* 84:189-202, 1972
 32. Fan F-C, Kim S, Simchon S, et al: Effects of sodium nitroprusside on systemic and regional hemodynamics and oxygen utilization in the dog. *ANESTHESIOLOGY* 53:113-120, 1980
 33. De Torrente A, Miller PD, Cronin RE, et al: Effects of furosemide and acetylcholine in norepinephrine-induced acute renal failure. *Am J Physiol* 235:F131-F136, 1978
 34. Patak RV, Fadem SZ, Lifschitz MD, et al: Study of factors which modify the development of norepinephrine-induced acute renal failure in the dog. *Kidney Int* 15:227-237, 1979