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Rebound Hypertension after Sodium Nitroprusside Prevented by Saralasin in Rats

Thomas J. Delaney, M.D., and Edward D. Miller, Jr., M.D.†*

The role of the renin–angiotensin system in the maintenance of blood pressure during halothane anesthesia and sodium nitroprusside (SNP)-induced hypotension was evaluated. Control rats received halothane anesthesia (1 MAC) for one hour, followed by SNP infusion, 40 μg/kg/min, for 30 min, followed by a 30-min recovery period. A second group of rats was treated identically and, in addition, received an infusion of saralasin (a competitive inhibitor of angiotensin II) throughout the experimental period. In each group, SNP infusion resulted in an initial decrease in blood pressure from 86 torr and 83 torr, respectively, to 48 torr. During the SNP infusion the control animals demonstrated a progressive increase in blood pressure to 61 torr, whereas the saralasin-treated animals showed no change. Following discontinuation of SNP, blood pressure in the control animals rebounded to 94 torr, as compared with 78 torr in the saralasin-treated rats. This study indicates that with stable halothane anesthesia, the partial recovery of blood pressure during SNP infusion and the post-SNP rebound of blood pressure can be completely blocked by saralasin. This demonstrates the participation of the renin–angiotensin system in antagonizing the combined hypotensive effects of halothane and SNP. (Key words: Anesthetic techniques, hypotension, induced: nitroprusside. Anesthetics, volatile: halothane. Polypeptides: renin–angiotensin; saralasin.)

A PREVIOUS REPORT from this laboratory[1] has shown that sodium nitroprusside (SNP)-induced hypotension stimulates renin release in the rat, and the subsequent production of angiotensin II helps maintain blood pressure during the hypotensive period. Furthermore, enflurane anesthesia does not modify the renin response to SNP-induced hypotension. During this earlier study we found that SNP-induced hypotension during enflurane anesthesia was characterized by an initial large decrease in blood pressure followed by a gradual recovery. In addition, the termination of the SNP infusion was associated with a rebound of the blood pressure to significantly higher levels than pre-infusion, even though anesthetic depth remained constant. It was speculated that this effect was the result of the already increased renin activity. We have also observed clinically that the abrupt discontinuation of the SNP during stable anesthesia often results in a rebound of blood pressure to above the pre-SNP levels (occasionally to dangerous levels). The purpose of this study was to determine whether, during halothane anesthesia, the partial recovery of blood pressure during SNP infusion and the post-SNP rebound of blood pressure are attributable to increased renin (and hence angiotensin) levels, or whether other mechanisms must be invoked, *e.g.*, catecholamine release.

Methods

Fourteen male Wistar rats (250–400 g) that had been maintained on a normal-sodium diet were anesthetized throughout the study with halothane, 1.3 per cent, in air. This inspired concentration represents the approximate MAC for halothane in young rats.[2] The protocol included a one-hour control period, during which a femoral artery and vein were cannulated with PE-50 tubing and flushed with a solution of dextrose, 5 per cent, in water (D5W) and heparin. Blood pressure was monitored through the arterial cannula by a Statham P23Db® pressure transducer connected to a Brush Mark 260® recorder.

Following a one-hour control period, SNP was infused with a Harvard pump via the femoral vein catheter in a dose of 40 μg/kg/min for 30 min. SNP was weighed out daily, diluted appropriately, and infused in D5W. The total volume of SNP solution infused did not exceed 0.5 ml. Following the SNP infusion, blood pressure was monitored for another 30 min. The above-described protocol was followed for Group I (n = 8). In Group II (n = 6) the same protocol was followed and, in addition, the other femoral vein was cannulated with PE-50 tubing and an infusion of saralasin,[3] a competitive inhibitor of angiotensin II, was begun before the contralateral femoral vein and artery were cannulated. Group II was given a loading dose of 100 μg/kg over 1 min,

*Fellow.
†Associate Professor.
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Address reprint requests to Dr. Miller.

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followed by 10 μg/kg/min. It has been established that this dose blocks both the systemic vascular response to angiotensin II and the compensatory increase in cardiac output.[4] Saralasin was weighed out daily, diluted appropriately with D5W, and infused with a Harvard pump in a volume that did not exceed 2.5 ml over the two-hour period.

Arterial blood (0.3 ml) was drawn for blood-gas and *p*H analysis following the control period, following the SNP infusion, and at the conclusion of the study.

The data were analyzed using the Student *t* test for unpaired data for comparison between groups and the Student *t* test for paired data for comparisons within groups. $P < 0.05$ was considered significant.

Results

When SNP, 40 μg/kg/min, was administered, mean arterial blood pressure (MAP) decreased 35–40 torr to nearly identical levels in both groups (fig. 1). However, in Group I, the MAP made a gradual partial recovery, while in Group II it remained constant. MAP in Group I was significantly greater than that in Group II after 25 and 30 min of SNP infusion. Following the discontinuation of SNP, MAP in Group I increased to greater than control levels ($P < 0.05$ comparing MAP at −5 min with 35 min), whereas no such rebound was seen in Group II. The initial recovery blood pressure in Group I was significantly higher than that in Group II (94 torr versus 78 torr). Following the initial post-SNP value, MAP gradually declined in both Group I and Group II.

There was no significant difference between the groups with regard to P_{O_2}, P_{CO_2}, or *p*H values at the various points at which arterial blood samples were obtained (table 1). Within each group, there was a significant decrease in arterial blood *p*H with time, which was respiratory in origin.

TABLE 1. Results of Arterial Blood-gas Analysis (Mean ± SEM)

	Control	30 Min SNP	30 Min Recovery
Group I (control)			
P_{O_2}	89 ± 4	87 ± 4	80 ± 5*
P_{CO_2}	38 ± 3	38 ± 4	46 ± 4
*p*H	7.31 ± 0.01	7.31 ± 0.01	7.29 ± 0.02*
Group II (saralasin-treated)			
P_{O_2}	83 ± 4	82 ± 5	75 ± 7
P_{CO_2}	42 ± 2	40 ± 3	45 ± 4
*p*H	7.32 ± 0.01	7.31 ± 0.01	7.28 ± 0.02*

* $P < 0.05$ compared with control.

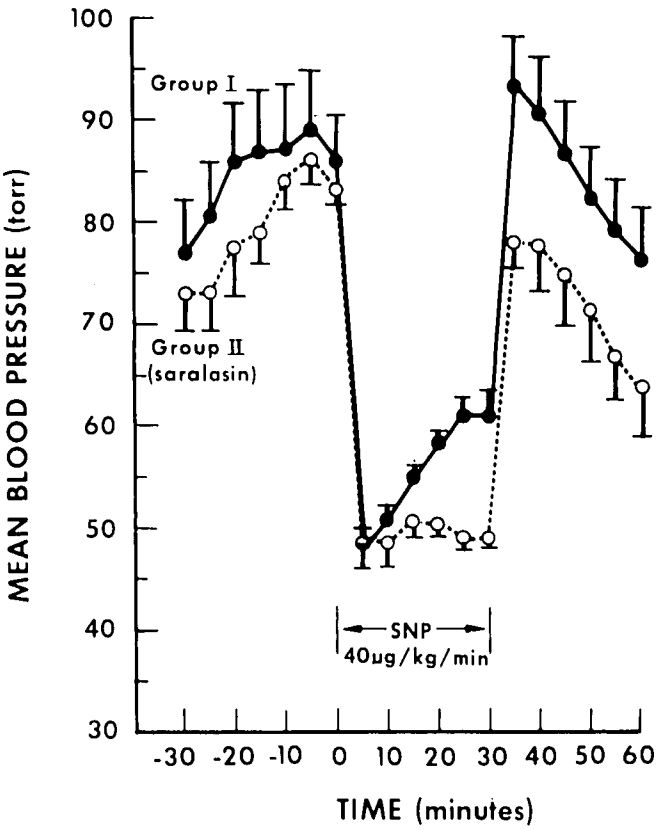

FIG. 1. Mean arterial pressures in Group I (control) and Group II (saralasin-treated). Group II failed to demonstrate partial recovery during the SNP infusion as well as the post-SNP rebound. Bars indicate ±SEM.

Discussion

In a previous study, we found that blood pressure decreased significantly when rats received infusions of saralasin during stable anesthesia produced by halothane or enflurane.[5] In contrast, in this study no statistically significant change in blood pressure occurred in the group given saralasin (Group II). The lack of compensation for the hypotension induced by halothane and SNP in Group II was somewhat surprising. This indicates that other means of blood pressure support (*e.g.*, catecholamines) are not operant in this setting. Since catecholamines were not measured in these experiments, it is not known whether catecholamine levels increased with hypotension induced by SNP, or whether their effect was attenuated by blockade of angiotensin II. In a previous report[6], catecholamine levels were found to be increased with SNP-induced hypotension during nitrous oxide–halothane anesthesia.

A consistent finding in both Groups I and II was a progressive decrease in MAP following the initial

blood pressure in the recovery period. The fact that the decrease occurred in Group II would suggest that it was not due to a gradual decline in renin–angiotensin activity. The decrease in blood pressure may indicate SNP-induced cyanide toxicity; however, there was no worsening of the metabolic acidosis to suggest this.

The results of this study indicate that with stable halothane anesthesia, the partial recovery of MAP during SNP infusion and the post-SNP rebound of MAP can be completely blocked by saralasin, a competitive inhibitor of angiotensin II. This further substantiates the importance of the renin–angiotensin system in the regulation of blood pressure during hypotensive anesthesia, and also demonstrates its role in the (potentially dangerous) post-SNP rebound of blood pressure.

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