Lability of Arterial Pressure After Baroreceptor Denervation Is Not Pressure Dependent

Howard J. Jacob, Richard H. Alper, and Michael J. Brody

The mechanisms of increased arterial pressure lability after sinoaortic deafferentation remain unknown. We have shown previously in rats with chronic sinoaortic deafferentation (7–14 days after sinoaortic deafferentation) that ganglionic blockade significantly reduced mean arterial pressure and arterial pressure lability. The present study investigated the possibility that lability is related to the level of arterial pressure. Rats were instrumented chronically and heart rate and mean arterial pressure were sampled every 5 seconds in the conscious, freely moving state. Graded sustained increases in pressure (+10 to +82 mm Hg) produced by constant infusion of angiotensin II, phenylephrine, or vasopressin did not affect lability (standard deviation of 30-minute sampling period); whereas, graded hypotension (—10 to —70 mm Hg) produced by infusions of adenosine, nitroprusside, or nisoldipine appeared to reduce lability. Analysis of covariance and orthogonal polynomial curve fitting demonstrated a significant correlation between the decrease in mean arterial pressure and the decrease in lability produced by nisoldipine but not by adenosine or nitroprusside. Lability does not appear to be solely dependent on the level of arterial pressure because lability was reduced by adenosine when pressure was maintained at control levels by simultaneous infusion of phenylephrine. We conclude that 1) arterial pressure lability is not influenced by elevation of arterial pressure but can be reduced when pressure is lowered by certain vasodilators and 2) pressure alone does not appear to be the major determinants of lability because it can be attenuated by vascular smooth muscle relaxants even when pressure is maintained. (Hypertension 1989;14:501–510)

Removal of the carotid sinus and aortic arch baroreceptors results in the inability to buffer moment-to-moment changes in pressure resulting in arterial pressure lability. Lability is the most consistent feature after sinoaortic deafferentation (SAD) and has been shown to exist in all species in which SAD has been studied.1–19 Bilateral lesions of the nucleus tractus solitarius (NTS) remove primary baroreceptor nerve terminals and afferent nerves via degeneration resulting in arterial pressure lability.5,20–23 Despite the marked variability of pressure, mean pressure is the same or only slightly increased in animals without baroreceptor reflexes.6,15,24

Our laboratory has been investigating the mechanisms of arterial pressure lability. We reported previously that interruption of the sympathetic nervous system with the ganglionic blocker chlorisondamine or the combined administration of the α-adrenergic receptor antagonist prazosin and yohimbine reduced mean arterial pressure (MAP) and lability.4,5,21 Because the decrease in lability produced by blocking sympathetic nervous system transmission was associated with a fall in arterial pressure, it was important to determine if lability was reduced by the interruption of neural activity or the result of the reduction in pressure. This distinction is critical in the elucidation of the mechanisms of arterial pressure lability.

In animals after SAD, arterial pressure remains near control levels despite the marked lability in arterial pressure. This suggests that secondary mechanisms, perhaps pressure sensitive, may be responsible for maintaining the MAP near control levels.
We hypothesized that, if secondary pressure-sensitive mechanisms are responsible for maintaining pressure within control levels, it should be possible to exceed the capacity of these systems to return pressure to control levels. Pressure-sensitive systems should increase the degree of lability as pressure is moved further away from the control level up to the saturation pressure where the pressure-sensitive systems become inactive and lability is abolished. We investigated this hypothesis by increasing and decreasing arterial pressure over a wide range of pressures in an attempt to saturate this secondary control system.

To determine if the level of pressure per se alters lability in rats with chronic SAD, we studied the effect of graded increases and decreases in arterial pressure produced by continuous infusion of peripherally acting vasoconstrictor and vasodilator agents. The results suggest that the degree of arterial pressure lability and the level of arterial pressure are not inherently related. In addition, these data suggest that MAP is not maintained near control levels by secondary mechanisms that are pressure sensitive.

**Materials and Methods**

**Sinoaortic Baroreceptor Deafferentation**

Male Sprague-Dawley rats (250–375 g) were anesthetized with ketamine (120 mg/kg) and acepromazine maleate (1.2 mg/kg) given intraperitoneally. The method of SAD used was first described by Krieger.14 Each animal was fixed in a supine position, and a midline 2.5-cm incision was made in the neck, exposing the muscles that overlay the trachea and carotid bifurcation. The sternohyoideus muscles were reflected to expose the vagus, superior cervical ganglion, superior laryngeal nerve, and the carotid bifurcation. The superior cervical ganglion and superior laryngeal nerve were isolated and resected, removing input from the aortic arch baroreceptors. The carotid sinus was stripped of all fibers and adventitia to expose the internal, external, and common carotid arteries. These vessels were then painted with a 10% phenol in ethanol solution to remove any baroreceptor afferents that may remain. After this procedure was completed bilaterally, the incision was sutured closed and each rat was injected intramuscularly with 60,000 units of penicillin G benzathine and penicillin G procaine in aqueous suspension (Flo-Cillin, Bristol, Syracuse, New York). The rats were then allowed at least 7 days to recover.

Success of the denervation was determined before the experiment was begun by a phenylephrine challenge: a bolus dose of phenylephrine (2–5 μg/kg i.v.) sufficient to increase pressure at least 50 mm Hg was given. If there was a bradycardia of less than 25 beats/min, the rats were considered to be deafferented. The infusions of the vasoactive agents during the experiment altered arterial pressure but failed to elicit a compensatory change in heart rate. These data further suggest that the sinoaortic deafferentation was complete.

**Blood Pressure and Heart Rate**

Two days before the experiments were begun, the rats were reanesthetized with the ketamine and acepromazine maleate mixture, and catheters (PE-50 fused to PE-10, Clay Adams, Parsippany, New Jersey) were placed in the lower abdominal aorta via the femoral artery for the direct measurement of arterial pressure and the abdominal vena cava via the femoral vein for drug infusions. The catheters were filled with heparinized saline (50 units/ml) to prevent clotting and were plugged with paraffin-filled 23-gauge hypodermic needles. For the experiments that involved simultaneous infusions, a catheter was placed in the abdominal aorta, and two catheters were placed in the left jugular vein just rostral to the clavicle. These jugular catheters enabled one or two agents to be infused. All catheters were tunneled subcutaneously under the skin of the back and exited between the scapulae.

Arterial pressure was measured with a Century CP-01 pressure transducer (Century Technol. Co., Inglewood, California) connected to a Beckman recorder R611 (Beckman Instrs., Inc., Schiller Park, Illinois). Heart rate was derived by using a Beckman 9857B cardiocacheter that was triggered from the arterial pulse pressure. Heart rate, MAP (derived electronically with a low pass filter), and pulse pressure were recorded on the chart paper. All experiments were carried out in conscious, freely moving rats in their home cage with food and water removed.

Heart rate and MAP were recorded on an IBM-XT computer. Data were collected at a frequency of 0.2 Hz for 30 minutes with a computerized data acquisition system. MAP and heart rate were each calculated from 360 sample values.

**Arterial Pressure and Lability**

Experiments consisted of five test periods, with each period lasting 30 minutes. One period, designated as control, during which 0.9% saline (Abbott Laboratories, North Chicago, Illinois) was infused, was used to obtain the pretreatment MAP and lability, expressed as the standard deviation of the MAP. During the other four periods varying concentrations of vasoconstrictor or vasodilator agents were infused to alter the level of arterial pressure. Sample periods were initiated when the change in MAP had reached a plateau. To control for the effects of time and infusion, the same protocol was used except that saline was infused during all five sample periods. The flow rate was maintained at 7.9 μl/min; however, low drug solubility occasionally required an increase in the flow rate rather than an increase in the drug concentration. The maximum infusion rate used was 41.7 μl/min.

Three vasoconstrictor agents, angiotensin II (13–345 ng/kg/min), phenylephrine hydrochloride (0.71–
**Vasodilators and Lability**

A repeated-measures design was used to compare the effects of the three vasodilators adenosine, nisoldipine, and nitroprusside on arterial pressure and lability. These experiments were similar to the previously described protocol for the vasodilators with the following exceptions: 1) Each rat received all three vasodilators and saline, and 2) the same drug concentration was used in each rat. Each rat received adenosine (60.3, 220.3, 380.3, and 533.3 μg/kg/min), nisoldipine (2, 11, 20, and 30 μg/kg/min), and nitroprusside (1.4, 3, 6, and 12 μg/kg/min) at a constant infusion rate of 16 μl/min. Control infusions of saline were maintained at 18 μl/kg.

**Simultaneous Infusions**

Adenosine and phenylephrine were infused simultaneously using two catheters placed in the jugular vein. There were four 30-minute sample periods, with one period as the control when saline was infused into both catheters. During each of the other three periods, either saline and adenosine, saline and phenylephrine, or adenosine and phenylephrine were infused into the rats in a randomized sequence.

**Drugs**

Adenosine, angiotensin II, phenylephrine hydrochloride, and [Arg]vasopressin acetate were prepared in 0.9% saline. Each agent was infused separately to produce graded levels of increased pressure.

To produce decreases in pressure, three vasodilator agents were infused: adenosine (60–600 μg/kg/min), nisoldipine (2–29.9 μg/kg/min), and sodium nitroprusside dihydrate (1–4 μg/kg/min). Adenosine and nitroprusside were prepared in 0.9% saline. Nisoldipine was prepared in 50% polyethylene glycol 400 (Fischer Scientific Co., Fair Lawn, New Jersey) and 50% 0.9% saline. The polyethylene glycol and saline mixture was infused during the control period for nisoldipine studies.

**Statistical Analyses**

**Effect of arterial pressure on lability.** The relation between change in lability versus change in MAP was determined by regression analysis. Each experiment resulted in four data points, one for each level of pressure produced by the four different concentrations of the same agent. Because lability (standard deviation of MAP) is not normally distributed, data were analyzed after a log transformation. The correlation coefficient was calculated for each line with Pearson’s correlation coefficient analysis. The slope of the line derived from the saline infusions was the average of the individual slopes for each of the lines. To determine if the slope of the line from the saline experiments was different from zero, a one-sample t test was used. The slopes of the lines for each of the vasoconstrictors were analyzed by a one-way analysis of variance, where the slopes of the lines for each agent were compared against each other and the saline results. The slopes of the lines for the vasodilators were generated and analyzed in the same way.

**Vasodilators and lability.** Orthogonal polynomials were used to compare the effect of each vasodilator agent on MAP and lability. The purpose of this comparison was to determine whether there was a significant relation between changes in arterial pressure and changes in lability. For these analyses a mathematical description of the shape of the curve for each vasodilator for MAP versus log dose and for the log of the standard deviation (lability) versus log dose. These analyses provided the best fit of the curve shapes by a method analogous to the least-squares method for linear regression. The mathematically derived shapes of the curve for MAP versus log dose and lability versus log dose were then compared statistically. Differences between the two curves for each agent were tested with an analysis of variance. A significant F test indicated that the drug changed arterial pressure and lability independently. Comparisons were also made between the effects produced by each agent.

In addition, an analysis of covariance with repeated measures was used to compare the variate (lability) and covariate (MAP) was used to examine whether the level of lability was dependent on the level of MAP, and as before, comparisons were made between agents. The changes in the covariate were adjusted to remove biases due to different levels of MAP as described by Weiner.

**Heart rate and lability.** Heart rate variability, log of standard deviation, was compared among the four treatment groups and within the four treatment groups with a two-way analysis of covariance with repeated measures.

**Adenosine during phenylephrine infusions.** The MAP and lability were analyzed by a one-way analysis of variance with repeated measures. The effects of the control period, saline and adenosine, and adenosine and phenylephrine infusions were compared against each other to determine their effects on lability and MAP separately. All data were considered significant if p<0.05.

**Results**

**Effect of Saline Infusions**

Continuous infusions of saline were used as control in these experiments. In Figure 1, the effect of a saline infusion is shown in representative recordings of heart rate, MAP, and pulse pressure in a rat with chronic SAD.
The average slope of the line for these control experiments is shown in Figure 2. The data are graphed as change in lability (standard deviation) versus change in MAP; however, statistics were carried out using the log of the standard deviation for lability. The slope of the line compares the change in pressure versus the change in lability during saline infusions. In these control experiments, lability was not significantly changed during the 3-hour test period, indicating that neither the infusion volume nor time influenced arterial pressure lability or the level of arterial pressure.

**Effect of Increasing Arterial Pressure**

Pressure was increased and maintained for 30 minutes at various levels by a constant infusion with three different vasoconstrictor agents: angiotensin II, phenylephrine, or vasopressin. Because the degree of lability, measured by the slope of the line correlating the change in pressure with the change in lability, was not altered with any of the agents, a common slope of the line for all vasoconstrictor agents was derived (Figure 3). These data indicate that increasing arterial pressure over a wide range, 10–82 mm Hg above the control level of MAP, has no effect on the degree of lability.

**Effect of Decreasing Arterial Pressure**

To investigate the role of decreased arterial pressure on lability, three vasodilator agents were infused. Examples of the effects of adenosine and nisoldipine are shown in Figure 4. All three agents, adenosine, nisoldipine, and nitroprusside, produced a negative linear slope suggesting that, as arterial pressure was decreased, the degree of lability was decreased (Figure 5). However, some of the infu-
sions produced a significant effect. These data indicated that the degree of arterial pressure lability was not related to the level of arterial pressure. We were concerned that the high inherent variability between rats prevented us from showing a correlation between decreasing arterial pressure and lability. The effects of each of the four drug infusions on arterial pressure and lability were compared against the initial control infusion period with orthogonal polynomial curve fitting and analysis of covariance as described in Materials and Methods. Figure 6 illustrates the results for adenosine, nitroprusside, nisoldipine, and saline infusions. The results for adenosine show curve shapes that are statistically different ($p < 0.05$). This means that the decrease in arterial pressure is independent of the decrease in lability. A similar finding was noted with nitroprusside. In contrast, the curve shapes for arterial pressure and lability derived from the experiments with nisoldipine are not different statistically, suggesting that a relation between arterial pressure and lability exists with this agent. As anticipated, control saline infusions had no effect on arterial pressure or lability. Analysis of covariance yielded the same statistical findings as orthogonal polynomial curve fitting. The analysis showed that, in the case of both adenosine and nitroprusside, changes in pressure and lability were independent.

**Effect of Vasodilators on Lability**

To determine if the vasodilators adenosine and nisoldipine reduced arterial pressure lability by reducing heart rate variability, a two-way analysis of variance with repeated measures was used to compare the effect of dose and the effect of different agents on heart rate variability. There was no significant difference between either dose or agent (Table 1), indicating that the vasodilators adenosine and nisoldipine did not reduce heart rate variability. These data demonstrate that arterial pressure lability is not reduced by reduction of heart rate variability.

**Effect of Adenosine When Arterial Pressure is Maintained**

To better determine if a causal relation exists between the decrease in lability and the decrease in MAP, pressure was maintained at or near control levels by an infusion of phenylephrine while adenosine, at a concentration that significantly decreases arterial pressure lability, was infused simultaneously. A representative recording is shown in Figure 7, and the data are summarized in Figure 8. These data illustrate that lability was reduced without altering pressure and suggest that adenosine reduced lability by a direct action on vascular smooth muscle and not by reducing MAP. These data, combined with those showing that nitroprusside decreases pressure without an equivalent decrease in lability, strongly suggest that decreasing pressure alone does not alter the degree of arterial pressure lability. The simultaneous infusions of adenosine and phenylephrine maintained lability at a level not different from adenosine alone despite the fact that pressure was returned to control levels.

**Discussion**

This study was designed to evaluate if there is an interaction between the level of arterial pressure and the degree of arterial pressure lability in rats with chronic SAD. We have shown in previous studies that ganglionic blockade or combined $\alpha_1$- and $\alpha_2$-adrenergic receptor blockade produced a significant decrease in lability in rats with chronic sinoaortic deafferentation. Buchholtz and Nathan (Buchholtz et al. and Buchholtz and Nathan) also reported that in rats with bilateral lesions of the NTS, prazosin plus atropine and propranolol abolished lability and also significantly decreased MAP. These two studies indicated that decreases in lability were also associated with decreases in MAP.

Since the level of MAP in rats after SAD is similar to that of the sham-operated rats, it is conceivable that secondary baroreceptor reflex mechanisms such as the cardiopulmonary receptors or baroreceptors in the renal and mesenteric circulations are involved. These secondary systems could be responsible for maintaining pressure near control levels and, while attempting to correct for
moment-to-moment changes in MAP, could produce marked lability of arterial pressure. The baroreceptors are most sensitive between 120 mm Hg and 140 mm Hg, whereas above 150 mm Hg, the stimulus response curve becomes flat. Therefore, we hypothesized that, if pressure was maintained at high or low-levels outside the range of these putative baroreceptor reflex systems and outside the range of pressures seen in chronic SAD animals, it might be possible to abolish the lability.

The experiments described in this study demonstrate that increasing the arterial pressure over a wide range of 10–82 mm Hg had no effect on the degree of arterial pressure lability. Although all three pressor agents tested in these experiments did not alter lability, our laboratory showed earlier that increasing pressure with para-chloroamphetamine is capable of increasing MAP and decreasing lability. Overall, these data suggest that increasing pressure alone is not sufficient to influence the lability because only one of the pressor agents altered lability.

Because we were examining lability at different levels of arterial pressure, the statistical expression of lability becomes critical. At least two approaches...
Figure 5. Plot showing effect on lability of decreasing arterial pressure with three vasodilator agents. Change in lability is plotted against change in mean arterial pressure (MAP). Slopes for each vasodilator agent are shown. One-way analysis of variance was used to compare slopes of adenosine (n=8), nitroprusside (n=8), nisoldipine (n=6). Tukey's honestly significant difference test showed that nisoldipine was statistically different than the other vasodilators and saline. SD, standard deviation.

are possible: 1) the use of coefficient of variation (CV), an index that factors standard deviation (SD) for baseline pressure or 2) SD alone. The results and interpretation are quite different with these two indexes of lability; however, our data suggest that CV is not an appropriate estimation of lability. Figure 1 shows clearly that, as pressure is increased, the degree of lability remains relatively constant despite a calculated decrease in CV. Figure 4 clearly shows that lability is decreased by the infusion of adenosine, yet the CV is lower after the first dose of adenosine than the last dose despite the fact that lability is clearly abolished by the last dose of adenosine.

We believe that the SD of the MAP is the most appropriate index of lability for the following reasons. First, we are interested in the absolute changes in the variation and the CV measures the percent variation about the mean. Second, as discussed above, the statistical adjustment with CV does not support what is seen in the representative tracings (Figures 1 and 4). Third, SD is the most common expression of lability in the literature on lability. Fourth, use of the CV assumes that, at a given level of pressure, absolute changes are influenced by the level of pressure, and this study indicates that the level of pressure alone does not necessarily influence the degree of arterial pressure lability.

Decreasing the arterial pressure per se does not always influence the degree of arterial pressure lability. Adenosine, nisoldipine, and nitroprusside produced a similar decrease in pressure but not an equivalent decrease in lability. The results do show, however, that during hypotension produced by adenosine or nisoldipine, a decrease in lability was produced.

The results with the vasodilator agents did not completely answer the question regarding the potential causal relation between the decrease in pressure and the decrease in lability. To address this question, we infused phenylephrine (to maintain the pressure near control level) simultaneously with adenosine. The results of this experiment indicate that adenosine is capable of reducing lability even when pressure is maintained at control levels. This important result suggests that adenosine reduces lability by some direct mechanism such as an effect on vascular smooth muscle and not indirectly by decreasing pressure. We were unable to sustain pressure effectively with a simultaneous infusion of nisoldipine and phenylephrine; however, since neither adenosine nor nitroprusside reduced lability simply by decreasing pressure, we predict that a similar explanation would also hold for nisoldipine.

Figure 6. Plots showing comparisons between effects of vasodilators on lability versus mean arterial pressure (MAP). Effect of decreasing pressure on lability was analyzed with a repeated-measures design, orthogonal polynomial curve fitting, and an analysis of covariance. Shapes of curves for lability and MAP were compared for infusions of adenosine, nitroprusside, nisoldipine, and saline. There was no significant correlation between decrease in pressure and decrease in lability with infusions of adenosine and nitroprusside. There was, however, a correlation between decrease in MAP and decrease in lability with nisoldipine. Saline failed to produce a change in arterial pressure or lability. SD, standard deviation.
Table 1. Effect of Adenosine, Nisoldipine, and Nitroprusside on Heart Rate Variability

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
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<td>Adenosine</td>
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<td>23±4</td>
<td>22±5</td>
<td>18±4</td>
<td>11±1</td>
</tr>
<tr>
<td>Nisoldipine</td>
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<td>23±9</td>
<td>27±9</td>
<td>14±2</td>
<td>13±1</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>23±4</td>
<td>17±3</td>
<td>17±2</td>
<td>16±1</td>
<td>22±5</td>
</tr>
<tr>
<td>Saline</td>
<td>22±5</td>
<td>24±3</td>
<td>23±7</td>
<td>24±4</td>
<td>29±5</td>
</tr>
</tbody>
</table>

Values given are mean±SD.

Evoniuk et al30 showed that adenosine influences sympathetic transmission by interacting with at least three sites: sympathetic ganglia, sympathetic nerve terminals, and sympathetically innervated end organs. Adenosine and phenylephrine act at different receptors; therefore, phenylephrine can still act postsynaptically to induce vasoconstriction. However, adenosine is capable of reducing lability even in the presence of phenylephrine, suggesting that adenosine is either decreasing oscillations in sympathetic activity by acting at the sympathetic ganglia or adenosine is acting on the vascular smooth muscle to prevent lability.

This finding is further corroborated by the fact that neither adenosine nor nisoldipine reduces arterial pressure lability by reducing heart rate variability. This is an important result because it could also be hypothesized that changes in cardiac output reduce arterial pressure lability. The results from this study suggest that changes in cardiac output would have to be mediated through changes in force of contraction and not heart rate because neither the heart rate nor heart rate variability were significantly altered by either adenosine or nisoldipine despite the reduction in the lability. These data also suggest that arterial pressure lability is the result of changes in total peripheral resistance.

The mechanisms that produce the fluctuations in total peripheral resistance remain unknown; however, several investigators6,10,15 have attributed lability to postural changes. Although postural changes certainly do influence lability, Junqueira and Krieger13 have demonstrated that arterial pressure lability increases markedly in REM sleep when postural changes do not occur. We have observed dramatic changes in arterial pressure in animals that have not exhibited any postural change.

Another possibility is that the vasodilators produce a sedentary state when pressure is reduced. If the reduction in MAP resulted in a sedentary state, then it would be expected that nitroprusside, which reduced MAP to similar levels as adenosine and nisoldipine, would also reduce lability to equivalent levels. In this study, we did not observe any notice-

![Image of heart rate, mean arterial pressure, and pulse pressure recordings](http://hyper.ahajournals.org/Downloadedfrom)
The mechanism of lability appears to contain a central component that can be interrupted by blockade of sympathetic activity. The data from this study suggest that adenosine and nisoldipine may act directly on the peripheral vasculature to reduce lability, indicating a potential peripheral component to the arterial pressure lability.

In conclusion, the level of arterial pressure alone does not alter the degree of arterial pressure lability. Because it is not possible to change the level of pressure mechanically without markedly altering hemodynamic status, maintenance of the pressure at different levels by constant infusions of vasoactive agents provides the best approach for evaluation of the effect of pressure on lability. The results obtained with this approach suggest that agents that alter the level of pressure and change the degree of lability not only change the level of pressure but also alter the mechanisms of arterial pressure lability. Because pressure alone does not appear to influence the degree of arterial pressure lability, secondary pressure-sensitive regulatory mechanisms probably do not play a role in the maintenance of the MAP near control levels or induction of the lability of arterial pressure. If pressure-sensitive mechanisms were involved in maintaining pressure near control levels, there should be a better correlation between MAP and lability; for example, the lability should be increased the further the arterial pressure is from the control levels because these secondary mechanisms would cause larger changes in the pressure in an attempt to return pressure toward control levels.

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References


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