Extent of Baroreceptor Resetting in Response to Sodium Nitroprusside and Verapamil

HELIO C. SALGADO AND EDUARDO M. KRIEGER

SUMMARY We investigated the effect of sodium nitroprusside, verapamil, and hemorrhage on the resetting of the aortic baroreceptors of normotensive control rats to hypotension, and the reversal of resetting of baroreceptors of one-kidney, one clip hypertensive rats to normotension. Using whole-nerve recording, the extent (%) of resetting (or reversal of resetting) observed 15 minutes after a maintained fall in mean arterial pressure (MAP) was evaluated by the ratio between changes of systolic threshold pressure for baroreceptor activation and changes of control diastolic pressure exhibited by the rats, multiplied by 100. Three groups of normotensive control rats showed a MAP decrease to hypotensive levels of 33%, 39%, and 41%, respectively, with sodium nitroprusside, verapamil, and hemorrhage. The corresponding extent of resetting was 96±3%, 39±2%, and 46±4%, respectively. Only in the group treated with verapamil did MAP and systolic threshold pressure not revert completely to normotensive levels 15 minutes after the end of drug infusion. Three groups of one-kidney, one clip hypertensive rats showed MAP normalization of 30%, 37%, and 31%, respectively, with sodium nitroprusside, verapamil, and hemorrhage. The corresponding extent of reversal of resetting to normotension was 107±3%, 40±2%, and 60±9%, respectively. Again, only in the group treated with verapamil did MAP and systolic threshold pressure not revert to hypertensive levels 15 minutes after infusion. Besides indicating that different vasodilators can differently modulate the rapid (15-minute) resetting (or reversal of the resetting) due to similarly maintained fall in MAP, these data suggest that verapamil has a nonspecific effect on the baroreceptors, whereas sodium nitroprusside appears to affect baroreceptor transduction.

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KEY WORDS • hypertension • hypotension • reversal of resetting • hemorrhage • pressoreceptors • calcium antagonist

THERE has been a substantial accumulation of data showing that acute baroreceptor resetting occurs within minutes (5–20 minutes) of a sustained rise or fall in the conditioning procedure. Data from this and other laboratories have provided evidence that the conditioning pressure is the main driving force for rapid resetting. The extent of partial resetting (5–20 minutes) has been reported to vary, probably because of differences in species or methodological approaches. The fact that resetting occurs in vitro at a rate similar to that found in intact animals led to the conclusion that rapid resetting does not require neurohumoral regulation. In this respect, Dorward et al. demonstrated similar resetting regardless of whether mean arterial pressure (MAP) was altered by vasoactive drugs (sodium nitroprusside, phenylephrine) or by controlled bleeding in sympathetic-blocked rabbits. However, studies of the role of calcium entry blocking agents, namely, verapamil and nifedipine, on baroreceptor activity have shown opposite effects of these drugs on the sensitivity of the carotid sinus baroreceptors of the dog. These observations may suggest that different substances act differently on the baroreceptors according to their intrinsic vasodilator mechanism. Thus, the extent of rapid resetting may also depend on the vasoactive drug.

In the present study we investigated the role of sodium nitroprusside and verapamil in the rapid (15-minute) resetting of baroreceptors of normotensive control rats (NCR) to hypotension, and the reversal of resetting of baroreceptors of chronic one-kidney, one clip hypertensive rats (1K1C) to normotension. The effects of both vasodilators were compared to the effect obtained with controlled hemorrhage that caused a fall in conditioning pressure similar to that induced by the vasoactive drugs.

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Materials and Methods

The experiments were performed on Wistar NCR and 1K1C weighing 300 to 650 g. Hypertension was produced in the 1K1C under ether anesthesia by constriction of the main left renal artery with a silver clip, followed by contralateral nephrectomy. The development of hypertension (2–6 months) was monitored in conscious 1K1C by using a tail plethysmographic method.

The method used for studying the whole aortic nerve activity in rats anesthetized with sodium pentobarbital (30 mg/kg i.p.; Abbott Laboratories, São Paulo, Brazil) has been described elsewhere. Sodium nitroprusside (E. Merck, Darmstadt, FRG) or verapamil (Knoll Pharmaceutical) was infused into the right femoral vein. In the experiments of controlled hemorrhage, the animals were bled and reinfused with blood through the left femoral artery. In all experiments the arterial pressure was monitored continuously with a thermal recorder (Model 7754 A, Hewlett-Packard, Palo Alto, CA, USA). The index used to evaluate the extent of aortic baroreceptor resetting to hypotension in NCR or the extent of resetting reversal to normotension in 1K1C was the ratio \( \left( \frac{SP_a}{CDP} \right) \times 100 \), where \( SP_a \) stands for changes in systolic threshold pressure (pressure at which the baroreceptors cease firing) and \( CDP \) stands for changes in control diastolic pressure. This ratio is similar to that used by Munch et al. except that we used control diastolic pressure instead of MAP.

The NCR and 1K1C were anesthetized with sodium pentobarbital. After isolating the whole aortic nerve from the cervical sympathetic trunk, the vessels were cannulated for pressure recording and venous infusion of drugs or hemorrhage. After recording carotid pressure (pressure transducer, Statham Instruments, Hato Rey, Puerto Rico) simultaneously with the aortic nerve discharges (differential amplifier, Model 113, Princeton Applied Research, Princeton, NJ, USA) on the oscilloscope (Model 502-A, Tektronix, Beaverton, OR, USA), the animals were submitted to acute changes in arterial pressure by withdrawing and reinfusing blood into the femoral artery in order to assess control baroreceptor activity. The data reported are the average of at least two sets of acute changes in blood pressure. To deal with the hysteresis shifts of the whole aortic nerve, the systolic threshold pressure was always determined when the arterial pressure was increased slowly above threshold. After the control measurements, the animals received intravenous verapamil (100 \( \mu \)g/kg/min) or sodium nitroprusside (4 \( \mu \)g/kg/min) or they were submitted to controlled hemorrhage. The controlled bleeding or the dose of each drug used was selected to produce a fall in MAP of approximately 35% of the control value. Baroreceptor activity was recorded again 15 minutes after the beginning and 15 minutes after the end of infusion as described for the control period.

Results

Normotensive Control Rats

The effects of hemorrhage on baroreceptor resetting to hypotensive levels is shown at the bottom of Figure 1. Controlled bleeding for 15 minutes caused a 41% fall in MAP (76 ± 5 vs. 130 ± 5 mm Hg in controls). The systolic threshold pressure followed only partially the diastolic pressure changes, showing an extent of resetting of 46 ± 4%. Fifteen minutes after returning arterial pressure to normal by means of blood reinfusion, the threshold pressure was also back to control levels associated with the recovery of arterial pressure.

During nitroprusside infusion (see Figure 1, top), the MAP fell 33% (73 ± 4 vs. 109 ± 4 mm Hg in controls), followed by an equivalent downward displacement of the systolic threshold pressure for baroreceptor activation. The extent of resetting was 96 ± 3%, indicat-
ing complete baroreceptor resetting to the maintained hypotensive level. This value was significantly different from that obtained with hemorrhage (46 ± 4%). Fifteen minutes after ceasing the infusion of nitroprusside, both the arterial pressure and the threshold pressure had already returned completely to control values, indicating a total reversal of baroreceptor resetting to normotension.

When verapamil was infused (see Figure 1, middle), the MAP dropped 39% (68 ± 3 vs 111 ± 3 mm Hg in control), but the downward shift of the systolic threshold pressure was not equivalent to the fall in diastolic pressure, representing an extent of resetting to hypotensive levels of 39 ± 2%. This value did not differ significantly from that obtained with hemorrhage (46 ± 4%), but it did differ from that obtained with nitroprusside (96 ± 3%). Thus, verapamil caused only a partial resetting to hypotension as observed with hemorrhage. Fifteen minutes after ceasing the infusion of verapamil, the arterial pressure recovered slightly, whereas threshold pressure did not change.

Renal Hypertensive Rats

The controlled hemorrhage in 1K1C (Figure 2, bottom) caused a 31% drop in MAP (123 ± 6 vs 179 ± 7 mm Hg in controls) that was partially followed by systolic threshold pressure. The extent of reversal of resetting caused by hemorrhage was 60 ± 9%. This value indicated partial reversal of baroreceptor resetting to normotensive levels. Reinfusion of blood elicited a prompt recovery of arterial pressure to the original hypertensive levels. Fifteen minutes later, the 1K1C showed an upward shift of the threshold pressure, indicating complete recovery of baroreceptor activity to hypertensive levels.

Nitroprusside infusion (see Figure 2, top) caused a 30% fall in MAP (125 ± 5 vs 179 ± 7 mm Hg in controls) associated with an equivalent downward displacement of systolic threshold pressure. The extent of the reversal of resetting 15 minutes after blood pressure normalization was 107 ± 3%. This value is significantly different from that obtained with hemorrhage (60 ± 9%) and indicates a complete reversal of resetting toward normotensive levels. Immediately after the infusion was stopped, arterial pressure recovered to hypertensive levels. Fifteen minutes after ceasing the infusion of nitroprusside, the threshold pressure was completely back to control levels, indicating a total shift of baroreceptor activity toward hypertensive levels.

The infusion of verapamil elicited a 37% drop in MAP (109 ± 11 vs 174 ± 16 mm Hg in controls). The extent of the partial reversal of resetting to normotension was 40 ± 2%, differing significantly from the reversal caused by nitroprusside (107 ± 3%) but not from that caused by hemorrhage (60 ± 9%). Fifteen minutes after the end of verapamil infusion, the arterial pressure had only partially returned to hypertensive levels, without a significant change in threshold pressure.

**Discussion**

After 15 minutes of nitroprusside infusion the aortic baroreceptors of intact animals showed complete resetting (96 ± 3%) to hypertensive levels in NCR and complete reversal of resetting (107 ± 3%) to normotensive levels in 1K1C. In both cases the systolic threshold pressure and the control diastolic pressure dropped proportionally, indicating a complete shift of baroreceptor activity to the new resting conditioning pressure. Immediately after ceasing the infusion of nitroprusside, arterial pressure recovered to control levels in both groups, as did threshold pressure of baroreceptor activation. After detecting decreased
myocardial contractility in response to carotid occlusion due to the effect of nitroprusside, Robie suggested that this drug can act on the components of the baroreceptor reflex mechanism. Later, Dorward et al. showed that nitroprusside produced a rapid and reversible shift of 40% in the whole aortic nerve baroreceptor function curve of rabbits. In the present study we confirmed the latter observation in the rat, but we found that the extent of resetting was larger; actually, the resetting (and reversal of resetting) was complete and not partial. This finding suggests a possible involvement of nitroprusside in baroreceptor transduction; however, the exact mechanism by which nitroprusside affects the baroreceptor resetting is not clear.

When verapamil was used to decrease the arterial pressure, the behavior of the baroreceptors was different. Even though verapamil caused a slightly greater fall in MAP than nitroprusside in NCR as well as in 1K1C, the extent of resetting in NCR and the extent of reversal of resetting in 1K1C were significantly smaller in both cases. These findings indicate that different vasodilators are able to modulate the extent of resetting (and reversal of resetting), depending, probably, on the intrinsic vasodilator mechanism of each vasoactive substance. When Heesch et al. studied the effect of verapamil on the baroreceptors of the dog, they found that this calcium channel blocker decreased the baroreceptor discharges at both low (<10^{-5} M) and high (>10^{-3} M) concentrations. These data were partially confirmed by Kunze et al. who showed that verapamil was effective in reducing the baroreceptor discharges only at high concentrations; this suggests that verapamil does not directly affect baroreceptor function at low doses. This hypothesis is supported by the fact that the slow recovery of arterial pressure after verapamil infusion in the present study did not significantly change threshold pressure. Moreover, we recently observed (unpublished results) that 1 to 4 hours after ceasing verapamil infusion in NCR and 1K1C arterial pressure had not fully recovered and that threshold pressure also showed a partial recovery proportional to the degree of pressure rise. Thus, in this case arterial pressure appears to be the only driving force for threshold pressure shift.

When the fall in MAP was induced in both models by hemorrhage, the extent of resetting (46 ± 4%) and the extent of reversal of resetting (60 ± 9%) were not significantly different from the values obtained with verapamil. These findings not only suggest a nonspecific effect of verapamil on the resetting (and reversal of resetting), which is probably not related to voltage-dependent calcium channels, but also corroborate previous observations by Kunze et al. in an aortic arch–aortic nerve preparation in the rat.

Different authors have pointed to arterial pressure level as the main driving force for rapid baroreceptor resetting. However, the striking difference in the extent of resetting (or reversal of resetting) induced by sodium nitroprusside compared to verapamil or hemorrhage points to the possibility of a modulatory mechanism causing a downward shift of the baroreceptor activity that depends on the vasodilator substance acting in concert with the conditioning pressure. The data obtained in the present study support the hypothesis of modulation of rapid resetting depending on the vasodilator mechanism. However, they do not support previous data obtained from rabbits, showing that rapid resetting is the same whether arterial pressure is altered by vasoactive substances (e.g., nitroprusside) or by rapid changes of blood volume. This discrepancy may depend on differences in species (rat vs rabbit) or methodological approach. Nevertheless, the extent of acute resetting described in rabbits was smaller (approximately 40%) than that presently observed in rat when hypotension was produced by bleeding or verapamil infusion.

The intrinsic mechanism by which rapid resetting occurs is unknown, but several hypotheses have been proposed. Coleridge et al. attributed the rapid resetting to viscoelastic relaxation or creep of the aortic wall. This hypothesis is supported by data showing that resetting can occur even in the absence of smooth muscle. Rapid resetting has some characteristics that appear to be inconsistent with the viscoelastic mechanism, however. Thus, resetting could be a property not only of the elastin-collagen environment of the ending, but also of the receptor ending itself. On the other hand, rapid resetting is not affected by chronic changes in aortic wall, and this is confirmed also by the reversal of resetting in the present study, since 1K1C with hypertension of long duration (up to 6 months) behaved similarly to those with hypertension of shorter duration (up to 2 months). Finally, a third mechanism proposed by Heesch et al. suggests that changes in the activity of an electrogenic sodium pump may play a role in acute resetting.

In summary, the present study indicates that sodium nitroprusside efficiently modulates the rapid (15-minute) resetting of the aortic baroreceptors of NCR to hypertension and also the rapid reversal of resetting of baroreceptors of 1K1C to normotension. In both cases the downward shift of the baroreceptor discharges was proportional to the fall in arterial pressure. After ceasing the infusion of sodium nitroprusside, both groups presented a prompt (15-minute) upward shift of baroreceptor discharges to control levels after the recovery of arterial pressure. On the other hand, the effects of verapamil and hemorrhage were similar, both caused partial resetting (NCR) to hypotension; in contrast to nitroprusside and hemorrhage, only verapamil affected partial reversal of resetting (1K1C) to normotension. A comparison of the effects of the vasoactive drugs with hemorrhage suggests that the effect of verapamil on baroreceptors is nonspecific, while nitroprusside seems to affect baroreceptor transduction.

References
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H C Salgado and E M Krieger

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