Plasma noradrenaline as a measure of baroreflex sensitivity in hypertensive man

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Summary

1. Changes in plasma noradrenaline levels and heart rate were used as measures of baroreflex sensitivity in six hypertensive subjects given serial incremental doses of sodium nitroprusside (intravenously) to lower blood pressure.

2. The rises in both heart rate and plasma noradrenaline concentration were linearly related to the decrement in blood pressure and inversely related to the severity of the hypertension.

3. A positive correlation between rise in heart rate and rise in plasma noradrenaline was found for each subject. With increasing severity of hypertension, a greater increase in heart rate occurred for each increment in plasma noradrenaline concentration.

4. Baroreflex sensitivity can be assessed by relating changes in heart rate to change in arterial pressure; however, this method does not distinguish the relative contributions of the vagal and sympathetic components of the autonomic neural response or variations in the chronotropic response to sympathetic stimulation.

5. Changes in plasma noradrenaline levels in response to graded reductions in blood pressure may be a more appropriate measure of baroreflex sensitivity than the methods currently used in clinical investigation.

Key words: baroreflex sensitivity, heart rate, nitroprusside, noradrenaline.

Introduction

Plasma noradrenaline concentration is considered to be a useful measure of the activity of the sympathetic nervous system [1], particularly during cardiovascular stress produced by isometric [2, 3, 4] or dynamic [5, 6, 7] exercise, change from recumbency to upright posture [4, 6, 8], exposure to cold [4, 6, 7, 9], the Valsalva manoeuvre [7] or a change in sodium balance [1, 7, 10]. One of the major factors determining the level of activity of the peripheral sympathetic nerves, and thus plasma noradrenaline levels, is the arterial baroreceptor, and the activity of the baroreflex arc is of prime importance in the maintenance of blood pressure homeostasis.

Baroreflex sensitivity can be expressed in terms of the change in heart rate (HR) for each unit change in arterial pressure [4, 11-14]. However, practical and theoretical considerations limit this approach. Firstly, the change in heart rate in response to an alteration in blood pressure is not directly related to the level of sympathetic nerve activity in subjects receiving β-adrenoceptor antagonists. [15]. Secondly, HR is controlled by a balance between the level of activity of the vagal and the sympathetic efferent nerves innervating the heart, and cardiovascular stress causes alteration in both vagal and sympathetic nerve activity [2, 16, 17]. Thirdly, alteration in the sensitivity of the cardiac β-adrenoceptors to noradrenaline may contribute to variations in the relationship between changes in HR and blood pressure. Lastly, only the cardiac effects of an alteration in sympathetic nerve activity are measured. Since peripheral vascular resistance is affected by the sympathetic but not the parasympathetic nervous system, the neural regulation of vascular tone might be better reflected by plasma noradrenaline levels [18].

In an attempt to circumvent some of these...
limitations, we have evaluated changes in both HR and plasma noradrenaline concentration as indicators of baroreflex sensitivity in supine hypertensive patients during activation of the baroreflex arc produced by sequential stepwise reductions in mean arterial pressure (MAP) with sodium nitroprusside.

**Methods**

Six patients (ages 47–55 years) with essential hypertension were studied in hospital. All anti-hypertensive medication except hydrochlorothiazide was stopped at least 6 days before the study. The diet contained 137 mmol of sodium/day. The patients fasted from midnight, and remained supine throughout the study. All intravenous catheters were inserted at 07.00 hours, and both blood pressure and heart rate were recorded every 10 min between 07.00 and 09.00 hours. At 09.00 hours sodium nitroprusside was infused intravenously (dosage range 0.10–2.60 μg min⁻¹ kg⁻¹), and blood pressure (Arteriosonde) and HR were measured every 2 min during the administration of nitroprusside. Venous blood was withdrawn during the ninth minute of each infusion period and analysed for noradrenaline and adrenaline by a single isotope radioenzymatic assay [19]. Control MAP and control HR are expressed as the mean of the 12 values obtained before nitroprusside. The change in MAP (ΔMAP) and in HR (ΔHR) were taken to be the difference between control values and the mean of the last three values recorded during each period of infusion. The change in plasma noradrenaline (Δnoradrenaline) and adrenaline (Δadrenaline) were taken as the difference between the control values obtained immediately before nitroprusside was administered and the value obtained during the ninth minute of each infusion period.

**Results**

An average of six (range four to eight) stepwise decrements in MAP were elicited in each patient. The maximal reduction in MAP averaged 25 mmHg (range 14 mmHg in the least hypertensive to 40 mmHg in the most hypertensive patient). Linear regression analysis of the data obtained from each patient revealed a highly significant relationship between ΔMAP and the logarithm of the nitroprusside dose (P < 0.01). The maximal rise in HR, averaged 27 beats/min (range 18–37 beats/min). Within each subject, a highly significant positive correlation (P < 0.05) existed between the decrease in MAP and the resulting increase in HR.

The mean control plasma noradrenaline concentration was 205 pg/ml (range 141–329 pg/ml). No relationship was noted between the severity of the hypertension and the levels of either noradrenaline (r = 0.10) or adrenaline (r = 0.09) in the plasma. The stepwise decrements in MAP were accompanied by stepwise increments in plasma noradrenaline concentration in all subjects (P < 0.05). Moreover, a significant correlation existed between the rise in plasma noradrenaline concentration and the corresponding increase in HR in each patient (P < 0.05). Small increments in plasma adrenaline levels were significantly correlated with the fall in MAP in only two subjects. A considerable range of interindividual variation was found in the slopes of these relationships (Table 1).

To determine if control MAP affected the slopes of these relationships, the data were considered collectively by graphing the slopes of the best-fit regression lines against the control MAP for each patient. This revealed a positive correlation between control MAP and the slope of ΔMAP/log dose of nitroprusside (r = 0.96, P < 0.01). Moreover, a negative correlation was noted between control MAP and the slopes of

<table>
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<th>Subject no.</th>
<th>Control MAP (mmHg)</th>
<th>Slope of ΔMAP/log nitroprusside dose</th>
<th>Slope of ΔHR/ΔMAP</th>
<th>Slope of Δnoradrenaline/ΔMAP</th>
<th>Slope of ΔHR/Δnoradrenaline</th>
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</table>

Table 1. Effect of nitroprusside infusions on blood pressure, heart rate and plasma noradrenaline relationships

The slopes of the relationships between changes in the mean arterial blood pressure (ΔMAP, mmHg), in heart rate (ΔHR, beats/min) and in plasma noradrenaline (Δnoradrenaline, pg/ml) produced by serial incremental intravenous infusions of nitroprusside, over a dose range of 0.10–2.60 μg min⁻¹ kg⁻¹ are shown. Subjects are numbered according to pre-drug blood pressure, with patient no. 1 having the lowest blood pressure.
both the $\Delta$HR/$\Delta$MAP relationships ($r = -0.91, P < 0.05$) and the ANMA/ANAR relationships ($r = -0.70$). Lastly, a positive correlation existed between control MAP and the slopes of the ANMA/NAR relationships ($r = 0.70$). The last two correlations narrowly failed to reach statistical significance, perhaps as a result of the small numbers of subjects studied.

**Discussion**

The sensitivity of the arterial baroreceptors to a change in blood pressure is an important determinant of the ability of the autonomic nervous system to maintain cardiovascular homeostasis. We have attempted to isolate the sympathetic neural component of the baroreflex arc in hypertensive humans by considering the changes in HR and plasma noradrenaline concentration caused by stepwise decrements in MAP. Within each patient, both the increase in HR and plasma noradrenaline concentration were found to exhibit linear relationships to the fall in blood pressure induced by sodium nitroprusside. In addition, linear relationships were observed between the increase in HR and the increase in plasma noradrenaline concentration. These observations support the physiological relevance of the sympathetic nervous system to plasma noradrenaline concentration. The latter relationship was significant inverse correlation with control MAP. Several factors may account for this difference. Firstly, the response of HR to a change in blood pressure may be more tightly regulated, since the combined influences of the cardiac sympathetic and parasympathetic nerves serve to modulate changes in heart rate. Secondly, the metabolic disposition of noradrenaline, which may vary considerably between individuals [20], will have a substantial influence on plasma noradrenaline concentration. However, the analysis of ANMA/NAR provides a useful method of assessing the sympathetic neural component of the baroreflex arc.

One important finding of this study is that the response of sympathetic nerve activity to a decrease in blood pressure is depressed as a function of severity of the hypertension. Patients with higher control MAP showed smaller increments in plasma noradrenaline concentration for any given decrement in MAP and a larger decrease in MAP for any given dose of nitroprusside. Conversely, a larger increase in plasma noradrenaline concentrations occurred in response to a decrease in MAP in the patients with lower control MAP. The latter patients exhibited a small vasodepressor response as the dose of nitroprusside was increased. We interpret these results to mean that the mildly hypertensive patients have a sensitive baroreflex such that the vasodilatory effects of nitroprusside are effectively counteracted by a large increase in the release of the vasoconstrictor noradrenaline.

In addition, we have found that the relationships between changes in MAP, HR and plasma noradrenaline concentration are more complex than previously described. Consideration of ANMA/NAR as a function of control MAP indicated a trend among the more severely hypertensive patients toward a greater increase in HR for any given rise in plasma noradrenaline concentration. This observation could reflect changes in the interaction of the cardiac sympathetic and parasympathetic nerves, the density of cardiac $\beta$-adrenoceptors or the responsiveness of the effector organ to noradrenaline, any of which may be related to the severity of the hypertension.

The graded relationship between response and stimulus obtained in the present studies provides a more quantitative estimation of the sympathetic neural component of the baroreflex arc than do other manoeuvres. Other researchers [15] have used nitroprusside to activate the sympathetic nervous system and increase plasma noradrenaline levels, but only two fixed doses were given. Our approach permits the expression of the data as regression lines with statistical estimates of variability and definition of the slopes of the relationships. In addition, the usual manoeuvres used to activate the sympathetic nervous system, such as change in posture, exercise, isometric hand grip, cold pressor test and psychological stress, appear to involve differential activation of sympathetic nerve activity and adrenal catecholamine release, implying that different neural pathways are activated in each case [21].

**References**


