

Pressor Response to Norepinephrine Infusion in Patients with Pheochromocytoma

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ABSTRACT

In a patient with pheochromocytoma, norepinephrine (NE) infusion test coupled with measurement of plasma NE concentration was performed. NE turnover rate was accelerated before the surgical removal of the tumor compared to post operation, but the pressor response showed no difference between the two.

INTRODUCTION

Because of the clinical difficulty in evaluating the vascular reactivity in hypertensive patients to NE directly, the pressor response to the amount of NE infused or the amount of NE required to obtain certain pressor response has been used for this purpose^{5, 6, 8)}.

By using these methods, decreased pressor response in pheochromocytoma and the improvement after surgical removal of the tumor have been reported⁶⁾. In these studies we performed the exogenous NE infusion test to a patient with the left adrenal pheochromocytoma with simultaneous measurement of blood pressure (BP) and plasma NE level, and compared them with the previous results determining BP alone.

MATERIALS AND METHODS

The pressor response to exogenous NE in a 40 year old female with a pheochromocytoma of left adrenal gland was studied before and after the surgical removal of the tumor.

Before the operation she was withdrawn from antihypertensive medication for 2 weeks prior to the study and allowed an unrestricted diet. She was then placed in a comfortable supine position under fasting conditions in the morning period. An indwelling venous catheter was

placed in the antecubital vein in order to obtain blood samples without repeated venipuncture. Another catheter was placed in an instep vein for NE infusion. Blood pressure was monitored every minute by sphygmomanometric method, and heart rate was recorded by electrocardiogram. NE solution was prepared as 10 $\mu\text{g}/\text{kg}/\text{min}$ in 5% glucose solution. After instrumentation the patient was kept in the supine position for an additional 30 min, and then a blood sample was obtained for plasma NE determination. NE infusion rate was started with 0.08 $\mu\text{g}/\text{kg}/\text{min}$ with an infusion pump (Nihon Kohden TFV 1100), and was increased in 0.04 to 0.10 $\mu\text{g}/\text{kg}/\text{min}$ steps every 3 min until 1.20 $\mu\text{g}/\text{kg}/\text{min}$. Blood samples were also obtained at 0.08, 0.40, and 0.80 $\mu\text{g}/\text{kg}/\text{min}$ NE infusion, respectively. NE was extracted from the deproteinized plasma by alumina, and was detected by electrochemical method⁴⁾ by high performance liquid chromatography (Yanaco L-4000w).

The same study was repeated one week, 2 weeks, and 6 months after the operation.

RESULTS

1) Evaluation of pressor response by the previous method of NE infusion test

(Fig. 1) The blood pressure at the time of 6 months after the operation decreased significantly, compared with that prior to the operation

*¹⁾ 山本正治, 正岡智子, 金沢郁夫, 松浦秀夫, 梶山梧朗: 褐色細胞腫におけるノルエピネフリン負荷時の血圧反応性

Table 1. The blood pressure and the plasma NE concentration before and during NE infusion

NE Infusion Rate ($\mu\text{g}/\text{kg}/\text{min}$)		Before	0.08	0.40	0.80
Pre-ope	P. NE	0.862	1.063	2.850	3.798
	mBP	125	128	132	143
Post-ope 1W	P. NE	0.250	0.790	3.007	5.069
	mBP	85	88	103	155
Post-ope 2W	P. NE	0.142	0.830	3.610	6.245
	mBP	104	110	133	142
Post-ope 6M	P. NE	0.120	0.976	5.098	10.717
	mBP	94	94	124	134

P. NE: Plasma Norepinephrine (ng/ml) mBP: mean Blood Pressure (mmHg)

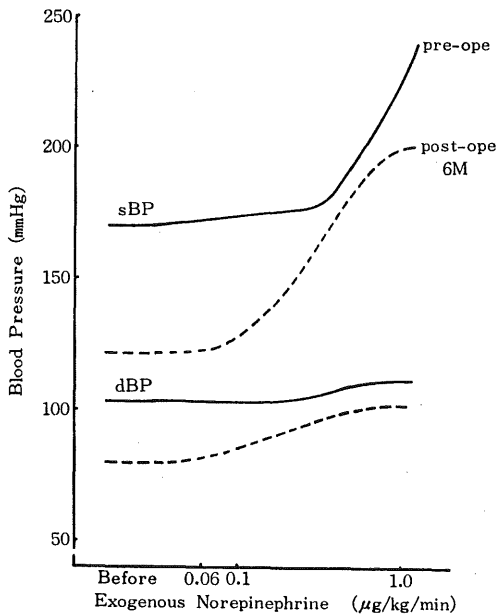


Fig. 1. The blood pressure responses to the exogenous NE before and 6 months after operation

before and during NE infusion. However, pressor response was observed from as little as $0.06 \mu\text{g}/\text{kg}/\text{min}$ of NE infusion rate postoperatively, whereas $0.30 \mu\text{g}/\text{kg}/\text{min}$ preoperatively. Fig. 2 shows the dose-response curve of mean blood pressure (ΔmBP) to exogenous NE. The curve shifted to the left after the operation, which suggested the decreased pressor response to infused NE in pheochromocytoma and its improvement after the operation as reported previously.

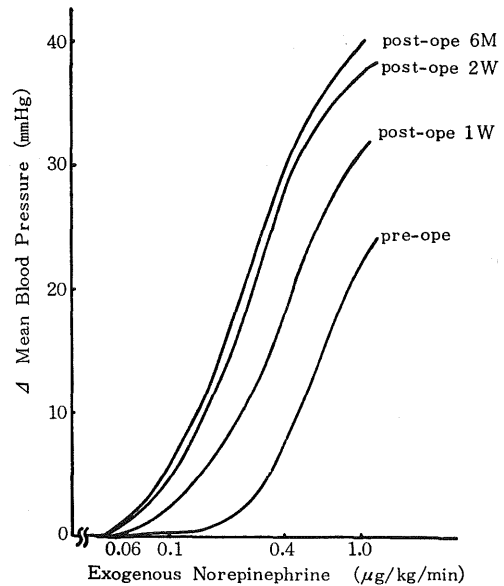


Fig. 2. The shift of the dose response curve between Δ mean blood pressure and exogenous NE before, one week, two weeks, and 6 months after operation

2) Plasma NE concentration during exogenous NE infusion

Table 1 and Fig. 3 show plasma NE concentration before and during NE infusion. The basal plasma NE concentration before the operation was markedly elevated, compared with that prior to the operation (0.862 pre-ope, 0.250 post-ope 1W, 0.142 post-ope 2W, and 0.120 ng/ml post-ope 6M, respectively). There was a linear relationship between plasma NE concentration and logarithm of NE infusion rate,

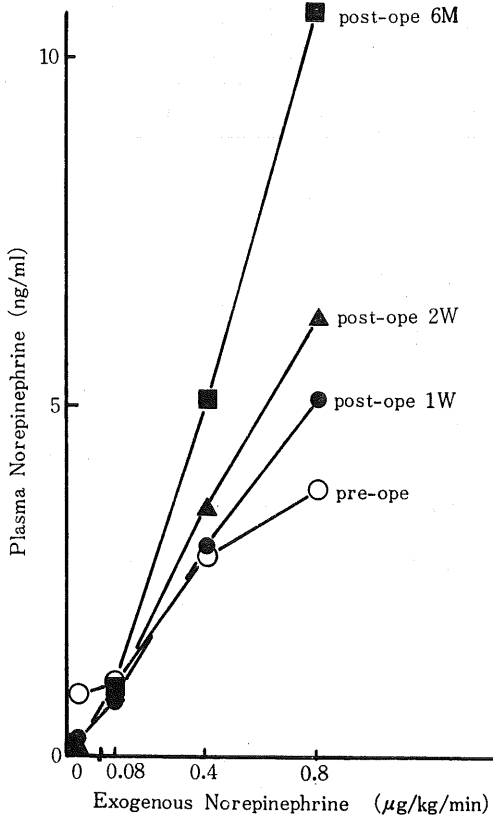


Fig. 3. The increase in plasma NE concentration during NE infusion test before operation, one week, two weeks, and 6 months after operation

but the slopes of the lines became significantly steeper after the operation.

3) The evaluation of pressor response coupled with plasma NE concentration

As shown in Fig. 4, Δ plasma NE concentration and Δ mBP showed a linear relationship of the identical slope before and after the operation.

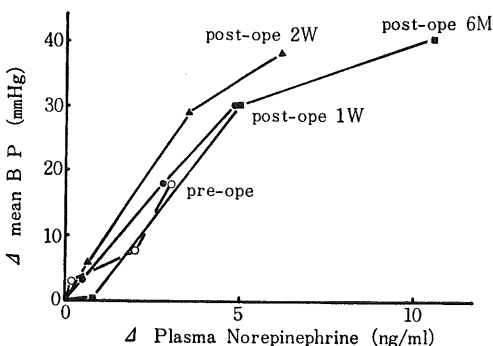


Fig. 4. The dose response curve of Δ mean blood pressure to Δ plasma NE

It means that the pressor response to plasma NE, was not affected by the presence of pheochromocytoma and the previous method shown in Fig. 2 could not have evaluated the accurate pressor response to NE.

DISCUSSION

Decreased pressor response to exogenous NE in pheochromocytoma has been reported, and attributed to decreased vascular reactivity⁶⁾. Our findings that the dose-response curve shifted to the right before the operation became normal after the operation coincided with the previous reports. If the plasma NE concentration to the exogenous NE revealed an identical slope before and after the operation, the difference of pressor response between pre- and postoperation could have been well evaluated from the result above. In the present study, the plasma NE concentration increased linearly with the logarithm of NE infusion rate. However, the slope of line became steeper after the operation, as shown in Fig. 3. Therefore, the plasma NE concentration at a given NE infusion rate is different between the pre-operative period and 1 week and 2 weeks and 6 months after the operation, and it suggests the necessity of using pressure change coupled with plasma NE concentration in evaluating the pressor response to exogenous NE. These phenomena indicate that the turnover rate of exogenous NE is different between pre- and postoperation, suggesting the increased sympathetic neural uptake of NE or NE metabolism.

In pheochromocytoma the platelet α -adrenoceptor number decreased compared with normal subjects, which fact suggests the decrease in vascular reactivity^{2,10)} which is incompatible with our results. The plasma volume, which is decreased before the operation¹⁾, becomes normal after surgical correction. Some probable influence of a change in the plasma volume on pressor response cannot be denied. These problems should be clarified by further investigation.

Because of the clinical difficulty in evaluating vascular reactivity, we used pressor response. Mean blood pressure is regulated by cardiac output and systemic vascular resistance. Cardiac output hardly changes by exogenous NE infusion^{9,10)}. Therefore, we consider that pressor response directly reflects changes in systemic vascular resistance, which is vascular reactivity,

and can be substituted for the latter.

The increased pressor response or vascular reactivity to infused NE has repeatedly been observed in hypertensive patients^{3, 5, 7, 8)}. However, such studies have not been coupled with specific measurement of plasma NE concentration. As we have shown in this study, pressor response should be evaluated by the pressure change against plasma NE concentration, and this should be considered in the evaluation of pressor response in hypertensive patients, too.

REFERENCES

1. **Brunjes, S., Johns, V. J., Jr. and Crane, M. G.** 1960. Pheochromocytoma: postoperative shock and blood volume. *New Eng. J. Med.* **262**: 393.
2. **Davies, I. B., Sudera, D. and Sever, P. S.** 1981. Endogenous agonist regulation of α -adrenoceptors in man. *Clinical Science (Suppl.)* **61**: 207s-210s.
3. **Goldenberg, M., Pines, K. L., Baldwin, E. F. et al.** 1948. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. *Am. J. Med.* **5**: 792-806.
4. **Hallman, H., Farnebo, L.-O., Hamberger, B. and Jonsson, G.** 1978. A sensitive method for the determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life. Sci.* **23**: 1049-1052.
5. **Krakoff, L. R., Vlachakis, N. D. and Mendlowitz, M.** 1980. Effect of posture, isometric hand-grip exercise, and norepinephrine infusion in normal-renin hypertensive patients. *Frontiers in Hypertension Research*: 290-296.
6. **Leonetti, G., Terzoli, L., Bianchini, G., Ruppoli, L., Lipira, R. and Zanchetti, A.** 1981. Noradrenaline reactivity in patients with phaeochromocytoma before and after surgical correction. *Clinical Science (Suppl.)* **61**: 211s-213s.
7. **Mendlowitz, M., Naftchi, N. E., Gitlow, S. E. and Wolf, R. L.** 1965. Vascular responsiveness in hypertensive and hypotensive states. *Geriatrics* **20**: 797-807.
8. **Philipp, T., Distler, A., Cordes, U. and Wolff, H. P.** 1978. Plasma noradrenaline and the pressor action of exogenous noradrenaline in normotensive subjects and patients with essential hypertension. *Clinical Science and Molecular Medicine* **55**: 61s-63s.
9. **Sato, K., Kondo, S. and Aoki, A.** 1982. The effects of noradrenaline on the hemodynamics in the essential hypertensive patients. *J. of Japanese College of Angiology* **22(6)**: 693. (in Japanese)
10. **Sever, P. S., Roberts, J. C. and Snell, M. E.** 1980. Phaeochromocytoma. *Clinics in Endocrinology and Metabolism* **9**: 543-568.