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HYPERTENSION

Pulmonary Vascular Supersensitivity to Catecholamines in Systemic High Blood Pressure

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Pulmonary pressure and arteriolar resistance are elevated in uncomplicated primary systemic hypertension. This study was carried out in 16 men with this form of hypertension and in 9 healthy men to compare 1) their pulmonary vascular reactivity to endogenous catecholamines released during mental arithmetic and cold pressor tests, and 2) the dose-response relation to exogenous epinephrine and norepinephrine. Arithmetic and cold pressor tests were associated, respectively, with a predominant increase in plasma epinephrine and norepinephrine concentration; changes were significantly greater in hypertensive men. During the two tests, pulmonary arteriolar resistance in the normotensive group was reduced by 13% and augmented by 7% of baseline, respectively, whereas it was raised by 31 and 70%, respectively, in the hypertensive group. In normal subjects, the dose (μg)-response (Δ dynes) relation to epinephrine was 1 = −4, 2 = −9, 3 = −9 and 4 = −10; to norepinephrine it was 2 = +3, 4 = +6, 6 = +7 and 8 = +7. In hypertensive patients, the respective relations were 1 = +18, 2 = +44, 3 = +59 and 4 = +77; and 2 = +39, 4 = +54, 6 = +76 and 8 = +98. Group differences were highly significant. In each of these circumstances, the driving pressure across the lungs was significantly augmented in the hypertensive but not the normotensive group.

Both epinephrine and norepinephrine have a vasoconstrictor influence on the lesser circulation as a consequence of vascular overreactivity. The opposite changes in resistance between normotensive and hypertensive subjects produced by epinephrine suggest that a constrictor vascular supersensitivity becomes active in the pulmonary circuit with the development of systemic high blood pressure.

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Pressure in the pulmonary artery among hypertensive patients is significantly higher (1) than in normotensive individuals (2). The associated increase in vascular resistance in the lungs (3,4) is not explained by changes of mechanical or chemical factors that are currently involved in the pulmonary vasomotion in humans (5).

The hypothesis has been advanced that the greater and lesser circulations share a common primary vasoconstrictor mechanism in hypertension (4,6), and a positive correlation has been found between systemic and pulmonary vascular resistance (7). In addition, stimulation of the sympathetic nervous system through mental arithmetic and cold pressor tests (8) in subjects with essential hypertension resulted in increases in blood pressure and vascular resistance in the lung which were undetectable or much less pronounced in normotensive individuals. Although these findings suggested a neurally mediated pulmonary vascular overreactivity (9), the exaggerated responses to stress could either be a primary alteration in smooth muscle sensitivity (abnormalities of vascular receptors or excitation-contraction coupling) or organ structure (increased wall thickness and lumen encroachment). They could also reflect abnormal levels of external activation (autonomic nervous system or other regulatory components). These points were considered of pathophysiologic importance, and the present study was intended to contribute to their clarification.

Methods

Study subjects. Sixteen hypertensive men (mean age 45 ± 3.8 years; mean weight 73 ± 6 kg) and nine healthy normotensive men (mean age 47 ± 4.6 years; mean weight 71 ± 5.2 kg) had mental arithmetic and cold pressor tests as well as epinephrine and norepinephrine infusions. All

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subjects underwent testing in the hospital. Hypertensive individuals showed repeated supine diastolic pressure readings between 95 and 110 mm Hg and had never received antihypertensive therapy. None of them had priority need for treatment, evidence of cardiac, lung or cerebrovascular disease or an underlying renal or endocrine cause of hypertension. Respiratory gases and pH of the arterial blood were normal, and symptoms or signs referable to sleep apnea syndrome (10) were absent. Normotensive men were subjects with atypical chest pain in whom coronary disease was excluded by angiography. They were not undergoing any form of treatment. The scientific purposes of the program and the investigative procedures were explained in detail to each patient.

Hemodynamic procedures. For the right-sided pressure and cardiac output measurements, a triple lumen 7F thermodilution balloon-tipped catheter (Edwards Laboratories) was inserted percutaneously into an antecubital vein and advanced to the pulmonary artery or, when necessary, to the pulmonary wedge position. Systemic arterial pressure was derived from the right brachial artery through insertion of a Teflon catheter needle. Endovascular procedures were accomplished under local anesthesia. Pressures were determined with Statham strain gauge transducers, with the zero reference level 5 cm below the sternal angle. The pulmonary artery wedge pressure was characterized by a distinct A and V waveform, with the V wave occurring after the T wave on the electrocardiogram. Cardiac output was determined by the thermodilution method. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were derived from the following formulas: $SVR = (\overline{AP} - \overline{RAP} \times 1332 \times 60)/CO$ (ml/min); $PAR = (\overline{PP} - \overline{PWP} \times 1332 \times 60)/CO$ (ml/min), where $\overline{AP}$, $\overline{RAP}$, $\overline{PP}$ and $\overline{PWP}$ are, respectively, mean systemic, right arterial, pulmonary and pulmonary wedge pressures and CO is cardiac output. The circulatory variables and pleural pressure, estimated by the method of Milic-Emili et al. (11), were recorded on the same recording system (Gould-Brush eight channel recorder, model 480). Arterial oxygen and carbon dioxide tension and pH were determined by methods reported previously (4).

Physiologic and pharmacologic tests. Most of the testing sessions occurred in the morning, 1 week after admission to the hospital and after the patients had been familiarized on 3 consecutive days with the investigators, equipment expert and environment. They were instructed not to smoke or ingest alcohol or caffeine-containing foods for 24 hours before testing. After the subjects had been supine for at least 30 minutes, blood samples (10 ml) were drawn through the intraarterial needle for catecholamine and blood gas determinations. Thereafter, they were subjected to mental arithmetic (division over a period of 2 minutes of a four digit number by a two digit number while under the pressure of time) and cold stimulation (the standard cold pressor test of 3 minutes' duration) (8). The two stressful tests were alternated and repeated twice in each patient at 10 minute intervals. Averages of the two measurements were taken as the representative value for the subject.

After a 20 minute rest period, the subjects received (through the proximal port of the venous catheter placed at the level of the right atrium) infusion of epinephrine (8 μg/ml in 5% dextrose in water) or norepinephrine (16 μg/ml in 5% dextrose in water) at initial doses of 0.5 and 1 μg/min for 3 minutes, respectively. These drugs were infused in random order. The infusion doses were increased (different speed with a constant infusion pump) in doses of 1, 2, 3 and 4 μg/min and of 2, 4, 6, and 8 μg/min, respectively, with a minimal 15 minute washout period between each infusion until there was an increase in systolic blood pressure similar to that attained during the mental arithmetic and cold stimulation tests, respectively, or tachycardia of 30 beats/min was observed. The reason for this was to contain the pressure reaction to pharmacologic tests in the hypertensive subjects within the limits of response to physiologic stimuli. In most instances these effects were obtained with the largest doses just indicated. In three hypertensive subjects, the upper arbitrary limit of the circulatory reaction was reached with intermediate doses. Continuous records of heart rate (cardiotachograph) and pleural, aortic and pulmonary pressures were obtained throughout the studies. Cardiac output and pulmonary wedge pressure were measured, and systemic and pulmonary arteriolar resistance were calculated at baseline and during the largest pressure variations. These were generally recorded at the end of each phase. At the same periods during physiologic stimuli, arterial blood sampling was repeated for measurement of plasma epinephrine and norepinephrine concentrations and during both physiologic and pharmacologic tests for assessment of the respiratory gases and pH.

Plasma catecholamine concentration was evaluated by high performance liquid chromatography with electrochemical detection (12).

Statistical analysis. Data obtained at baseline study and at the end of each phase were expressed as mean ± SD. Statistical analysis was carried out using either one-way or two-way analysis of variance as appropriate. Dose-responses were tested for significance by a one-tailed *t* test.

Results

The two patient groups were well matched for age and somatic characteristics. Baseline pleural pressure, arterial oxygen and carbon dioxide tension and pH were similar to normal in the hypertensive men, and in neither group did they change significantly during stressful stimulations or catecholamine infusions.

Responses to physiologic stimuli. Averages of the circulatory variables and epinephrine and norepinephrine plasma

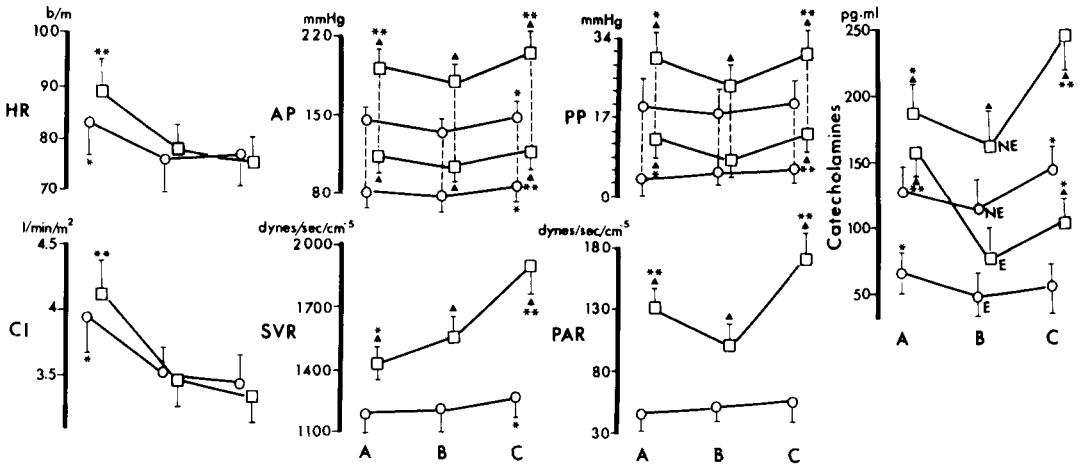

Figure 1. Mean (±SD) hemodynamic values and plasma catecholamine concentrations at baseline and during arithmetic and cold pressor tests in the normotensive (○) and hypertensive (□) study patients. A = arithmetic test; AP = aortic pressure (systolic and diastolic); B = baseline; C = cold pressor test; CI = cardiac index; E = epinephrine; HR = heart rate; NE = norepinephrine; PAR = pulmonary arteriolar resistance; PP = pulmonary pressure (systolic and diastolic); SVR = systemic vascular resistance; ▲ = differences from the corresponding value in the normotensive group significant at $p < 0.01$; * and ** = differences from baseline significant at $p < 0.05$ and < 0.01, respectively.

concentrations at baseline and at the moment of maximal pressure reaction to the mental arithmetic and cold pressor tests are illustrated in Figure 1. Plasma concentrations of epinephrine and norepinephrine were higher in the hypertensive group in the steady state and were augmented during both stimuli. The increase in epinephrine was more pronounced during the mental test, and that of norepinephrine was unequivocally preferential during the physical cold stimulus. The humoral reaction was greater in the hypertensive group in terms of levels reached and variations from baseline (epinephrine response to arithmetic: normotensives + 19± 6 pg/ml, hypertensive men + 79± 12 pg/ml; norepinephrine responses to cold: normotensive men + 33± 7 pg/ml, hypertensive men + 85± 11 pg/ml).

The circulatory changes were the following: In the systemic circulation, blood pressure increased with both stimuli in both groups, but to a greater extent in the hypertensive group; in both groups the systemic pressure increase during mental arithmetic was mediated through a similar increase in cardiac index, associated with a tendency of the vascular resistance to decrease, while a raised systemic vascular resistance (which was greater in hypertensive men) with hardly noticeable changes in cardiac index characterized the systemic hemodynamic response to cold. In the pulmonary circuit, neither stimulus affected pressure and arteriolar resistance in the normotensive control subjects, while both stimuli augmented pulmonary systolic and diastolic pressures to similar levels in the hypertensive patients; the increase was mediated through increments in both flow and resistance during mental arithmetic and exclusively through the latter during the cold pressor test. Changes in cardiac output occurred in parallel with those in heart rate, which in both groups was augmented by the mental stimulus and slightly reduced by the physical stimulus.

Responses to pharmacologic stimuli. In many respects, the hemodynamic response of the greater and lesser circulations to exogenous epinephrine (Fig. 2) and norepinephrine (Fig. 3) were qualitatively and, at the largest infusion doses, quantitatively similar to the response recorded during the mental arithmetic and cold pressor test, respectively. The only qualitative difference was the slight and significant stepwise reduction in the systolic and diastolic blood pressures in hypertensive subjects during epinephrine infusion as a result of a more substantial decrease in systemic vascular resistance (−385 dynes at 4 μg/min) compared with the arithmetic test (−136 dynes). As specifically referred to the pulmonary circulation, the finding was duplicated that either compound was ineffective in normotensive subjects and unequivocally increased pulmonary pressure and resistance in hypertensive subjects.

Figure 4 is a log dose-response plot showing the increase in systemic and pulmonary arteriolar resistance with increasing doses of norepinephrine in the normotensive and hypertensive patients. Dose-response curves in both groups have similar-shaped configurations, but the curves for the hypertensive group were steeper and shifted to the left. Variations in systemic resistance of all hypertensive patients were outside the range of values in normotensive subjects at 6 and 8 μg·min ($p < 0.01$), and variations in pulmonary resistance at all infusion rates beyond the threshold exceeded the normal values ($p < 0.01$).

Figure 5 is a log dose-response plot showing variations of the same variables with increasing doses of epinephrine in the same patient groups. Epinephrine had a depressor

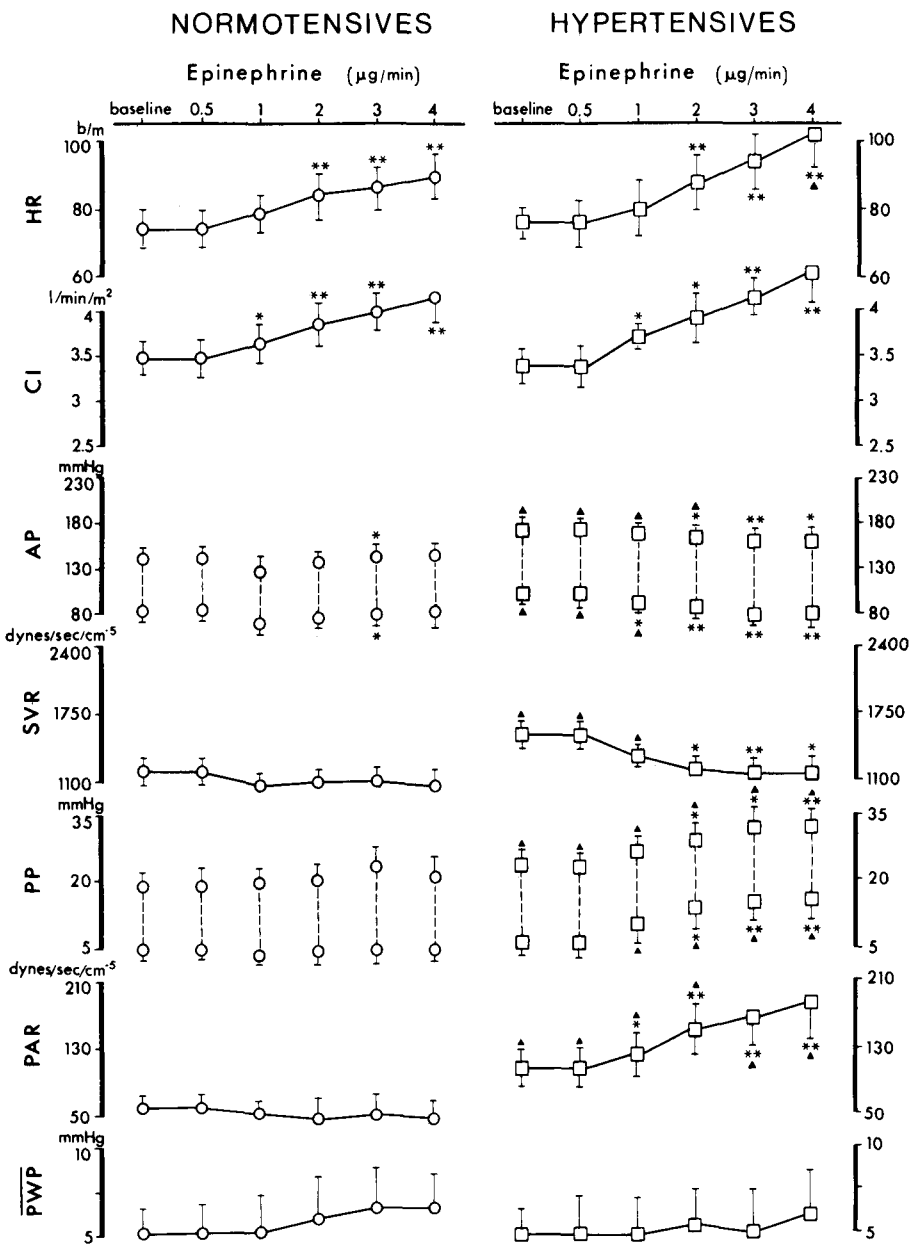

Figure 2. Hemodynamic responses to scalar doses of intravenously infused epinephrine in the normotensive and hypertensive study patients (mean ± SD). PWP = mean pulmonary wedge pressure; other abbreviations and symbols as in Figure 1.

effect on systemic vascular resistance; this was more pronounced in the hypertensive group ($p < 0.01$ at 2, 3 and 4 μg·min). The vasomotor influence of epinephrine on the pulmonary bed was opposite in the two groups, arteriolar resistance being mildly depressed in normotensive subjects and substantially enhanced in hypertension so that differences in changes were significant ($p < 0.01$) at any step beyond the threshold (0.5 μg·min).

Discussion

There are two initial questions that need clarification. 1) Do the circulatory alterations during physiologic stimuli depend on endogenously released catecholamines and are the responses to mental arithmetic and cold stimuli essentially mediated through release of epinephrine and norepinephrine, respectively? 2) Do changes in pulmonary arteriolar resistance during the tests in the hypertensive group reflect active vasomotion?

Epinephrine and norepinephrine release during physical and mental stimuli. Many comparative studies have reported higher levels of catecholamines in hypertensive than in normotensive subjects. They have also shown that these differences are small when blood is sampled under quiet rest conditions, but the catecholamine response to tests, whether physical (such as cold exposure) or psychologic (such as mental arithmetic), is exaggerated in patients with essential hypertension (13,14). In hypertension as in normotension there is a preferential increase in plasma norepinephrine during the physical stimuli and of plasma epi-

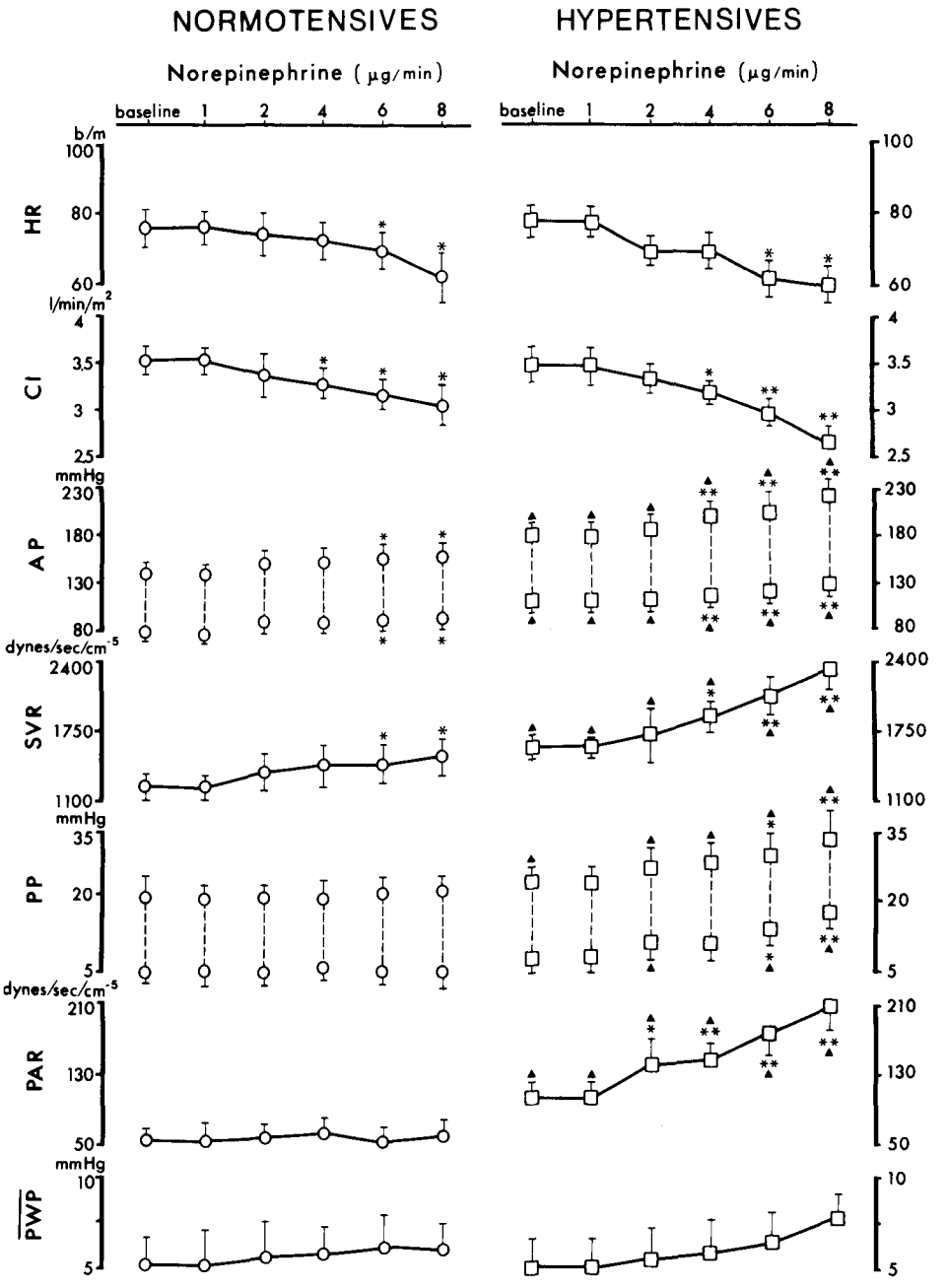

Figure 3. Hemodynamic responses to scalar doses of intravenously infused norepinephrine in the normotensive and hypertensive patients (mean ± SD). Abbreviations and symbols as in Figures 1 and 2.

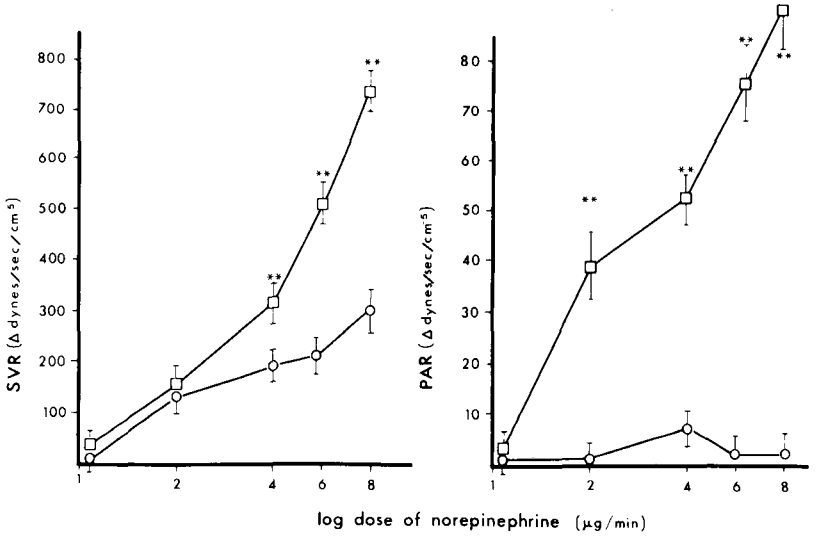

Figure 4. Systemic and pulmonary vasomotor responses evoked by norepinephrine in the normotensive (○) and hypertensive (□) study patients (mean ± SD). **Ordinate** = changes in systemic vascular (SVR) and pulmonary (PAR) arteriolar resistance; **abscissa** = log dose of norepinephrine; ** = differences from the corresponding value in the normotensive subjects significant at $p < 0.01$.

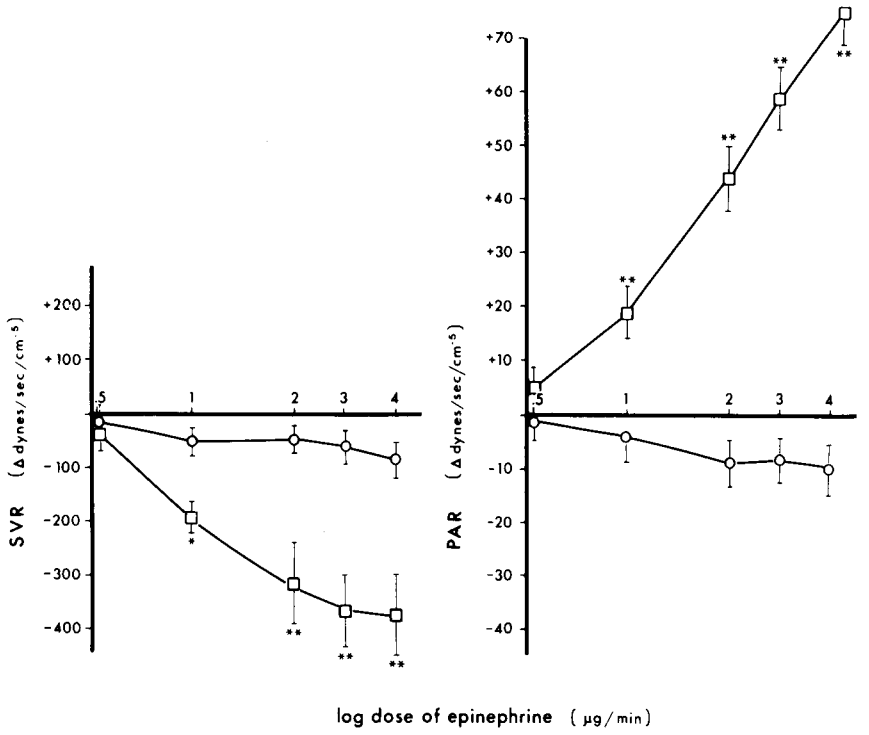

Figure 5. Systemic and pulmonary vasomotor responses evoked by epinephrine in the normotensive (○) and hypertensive (□) study patients (mean ± SD). * and ** = differences from the corresponding value in the normotensive subjects significant at $p < 0.05$ and < 0.01, respectively; abbreviations and format as in Figure 4.

nephrine during psychologic stimuli (13,14). On the other hand, the documentation is unequivocal that the classic cardiac and systemic vascular effects (15) of exogenously administered norepinephrine are duplicated by the cold pressor test and that those of epinephrine are in part reproduced by the mental arithmetic test, either procedure having been performed in the same subject in this study. The less pronounced vasodilation during mental arithmetic as compared with that during epinephrine infusion and the pressure increase during the physiologic rather than the pharmacologic stimulus in the hypertensive group were probably due to a relative selectivity of the physiologic test, which also elicited a small increase in the norepinephrine plasma concentration. These considerations support a positive response to the first question.

Pulmonary vasomotor changes during systemic hypertension. Among the factors controlling the flow of blood through the pulmonary circuit, those of mechanical origin are predominant, and knowledge of the passive relation between pressure and flow is essential in the interpretation of pharmacologic or physiologic interventions that also involve the heart and the systemic circuit. If this relation is not linear, changes in resistance when flow is also changing may not necessarily reflect an active vasomotion. The evidence in the dog is that this relation is linear (16), and the same seems true of normal human subjects in the supine position when flow is suddenly doubled (17); the actual passive pressure-flow relation with small changes in flow in humans, however, is not known. In this study, the increase in pulmonary blood flow promoted by the endogenously released (mental arithmetic test) and exogenously administered epinephrine slightly reduced the baseline difference between the pulmonary artery and wedge pressures in the normotensive men while a similar increase in flow by the same stimuli in the hypertensive men was associated with a substantial increase in the driving pressure across the lungs (Fig. 2). It follows that changes in pulmonary arteriolar resistance under the influence of endogenous (Fig. 1) and exogenous (Fig. 5) epinephrine actually reflect an active vasoconstriction in this group. Of particular significance is the response to norepinephrine released during the cold pressor test and to norepinephrine infused exogenously. In both circumstances, blood flow tended to become reduced to a similar extent in the two patient groups; however, in hypertensive men, the driving pressure through the lungs became as great as during the influence of epinephrine, suggesting that an even greater vasomotion had occurred (Fig. 3 and 4). Respiratory factors should be considered extraneous to these phenomena because the measured variables (pleural pressure, arterial blood gases and pH) were comparable at baseline and during the tests.

Catecholamine concentration as a reflection of neurogenic vascular response. Although catecholamine concentrations in body fluids are utilized as indicators of the adrenergic discharge and neural participation in essential hypertension (18), there are good reasons to be cautious about their application for assessing neurogenic contributions (19). Endogenous catecholamine assays in this study, therefore, are taken as qualitative and not quantitative indicators. Because of this, no inference will be drawn as to whether the underlying mechanism of the exaggerated systemic blood pressure reactivity to endogenously released

norepinephrine does or does not reflect abnormal levels of external (neural) vascular activation. The exogenous norepinephrine tests show that the pressure reactivity is associated with vascular overreactivity, but does not contribute to discerning whether or not the latter derives from a specific abnormality in vascular sensitivity.

Catecholamine concentration and pulmonary vascular overreactivity. Conclusions may be different when the pulmonary circulation is considered. It was documented that norepinephrine, either endogenous or exogenous, is not appreciably effective on the pulmonary vascular tone in normotensive individuals and that, in agreement with findings in the cat (20), epinephrine shows a slight vasodilating action in this group. Such an effect was unequivocal from the dose-response curve. In marked contrast with these results, in hypertension both catecholamines, from either source, had a pressor and vasoconstrictor effect. The dose-response plot showing the increase in resistance with increasing doses of norepinephrine documents the existence of vascular overreactivity. Although some evidence has been reported (21) of a tendency to increase the pulmonary artery medial thickness in spontaneous hypertensive rats, there is no information in human subjects concerning the possibility of duplication in the lesser circulation of the structural vascular changes occurring in the greater circulation in hypertension (22). The question, therefore, concerning the relation between constrictor overreactivity and structure of the pulmonary vessels remains open. However, the observation that, during the release of endogenous epinephrine and especially during exogenous infusion, normotensive subjects responded with vasodilation while hypertensive patients developed substantial vasoconstriction is not in favor of increased wall thickness and lumen encroachment because a greater decrease rather than an increase in resistance would be anticipated. This opposite vasomotor pattern suggests that a constrictor pulmonary vascular supersensitivity becomes active with the development of systemic hypertension. The baseline levels of circulating catecholamines, which were higher in hypertensive than in normotensive men, do not seem responsible for these changes because if this was the case, vascular responsiveness might have even become decreased.

Conclusions. A review of the studies concerned with the influences of catecholamines on the lesser circulation in humans shows an increase in the pulmonary artery and wedge pressures under the influence of norepinephrine without remarkable changes in arteriolar resistance and blood flow through the lungs. The balance of evidence is against the existence of substantial pulmonary vasoconstriction in normal humans. This pattern is interpreted as resulting from passive vasodilation as a consequence of displacement of blood from the periphery and some vasoconstriction caused by stimulation of alpha-adrenergic receptors (17). On this basis, one should deduce that in hypertension, in addition to an impedance to the pulmonary passive dilation, there is an enhancement of active pulmonary vasoconstriction. These changes may derive from abnormalities in the number or quality (23) of adrenergic receptors or other regulatory components (24), or in the biochemistry involved in the excitation-contraction coupling (7). Were the latter mechanism proved, then the hypothesis of a generalized membrane phenomenon responsible for enhancement in vascular contractility in hypertension (25) would be reinforced on clinical grounds.

References

1. Ferlinz J. Right ventricular function in adult cardiovascular disease. Prog Cardiovasc Dis 1982;25:225–67.
2. Fowler NO, Westcott RN, Scott RC. Normal pressure in right heart and pulmonary artery. Am Heart J 1953;46:264–7.
3. Atkins JM, Mitchell HC, Pettinger WA. Increased pulmonary vascular resistance with systemic hypertension: effect of minoxidil and other antihypertensive agents. Am J Cardiol 1977;39:802–7.
4. Olivari MT, Fiorentini C, Polese A, Guazzi MD. Pulmonary hemodynamics and right ventricular function in hypertension. Circulation 1978;57:1185–90.
5. Fishman AP. Dynamics of the pulmonary circulation. In: Dow P, ed. Handbook of Physiology, Section 2: Circulation, Volume 2. Washington: American Physiological Society, 1963:1667–743.
6. Overbeck HW, Berne RM, Chien S, et al. Report of the Hypertension Task Force of the National Heart, Lung, and Blood Institute: current research and recommendations from the Subgroup on Local Hemodynamics. Hypertension 1980;2:342–69.
7. Guazzi MD, Polese A, Bartorelli A, Loaldi A, Fiorentini C. Evidence of a shared mechanism of vasoconstriction in pulmonary and systemic circulation in hypertension: a possible role of intracellular calcium. Circulation 1982;66:881–6.
8. Fiorentini C, Barbier P, Galli C, et al. Pulmonary vascular overreactivity in systemic hypertension. A pathophysiological link between the greater and the lesser circulation. Hypertension 1985;7:995–1002.
9. Guazzi MD, De Cesare N, Fiorentini C, Galli C, Moruzzi P, Tamborini G. The lesser circulation in hypertension. Circulation (in press).
10. Kales A, Cadieux RJ, Shaw LC, et al. Sleep apnoea in a hypertensive population. Lancet 1984;II:1005–8.
11. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 1964;19:207–11.
12. Jenner DA, Brown MJ, Lhoste FJM. Determination of α-methyldopa, α-methylnoradrenaline, noradrenaline and adrenaline in plasma using high performace liquid chromatography (HPLC) with electrochemical detection. J Chromatogr 1981;224:507–12.
13. Herd JA. Cardiovascular response to stress in man. Ann Rev Physiol 1984;46:177–85.
14. Conway J. Hemodynamic aspects of essential hypertension in humans. Physiol Rev 1984;64:617–60.
15. Weiner N. Norepinephrine, epinephrine, and the sympathomimetic amines. In: Goodman LS, Gilman A, eds. The Pharmacological Basis of Therapeutics. New York: Macmillan, 1980:138–75.
16. Shoukas AA, Brunner MJ, Frankle AE, Greene AS, Kallman CH. Carotid sinus baroreceptor control and the role of autoregulation in the systemic and pulmonary arterial pressure-flow relationships of the dog. Circ Res 1984;54:674–82.
17. Harris P, Heath D. The Human Pulmonary Circulation. New York: Churchill Livingstone, 1977:128–30, 182–8.

18. Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. Hypertension 1983;5:86–9.

19. Folkow B, Di Bona GF, Hjemdahl P, Torén PH, Wallin G. Measurements of plasma norepinephrine concentrations in human primary hypertension. A word of caution on their applicability for assessing neurogenic contribution. Hypertension 1983;5:399–403.

20. Hyman AL, Nandiwada P, Knight D, Kadowitz PJ. Pulmonary vasodilator responses to catecholamines and sympathetic nerve stimulation in the cat. Evidence that vascular β-2 adrenoceptors are innervated. Circ Res 1981;48:407–15.

21. Mc Murtry IF, Petrun MD, Tucker A, Reeves JT. Pulmonary vascular reactivity in the spontaneously hypertensive rat. Blood Vessels 1979;16:61–70.

22. Schwartz SM. Smooth muscle proliferation in hypertension. State-of-the-art lecture. Hypertension 1984;6(suppl I):I-56–61.

23. Ohsuzu F, Strauss HW, Homcy CJ. The lung beta-receptor in the spontaneous hypertensive rat. Jpn Circ J 1984;48:1203–9.

24. Ellsworth ML, Gregory TJ, Newell JC. Pulmonary prostacyclin production with increased flow and sympathetic stimulation. J Appl Physiol: Respirat Environ Exercise Physiol 1983;55:1225–31.

25. Blaustein MP, Hamlyn JM. Sodium transport inhibition, cell calcium, and hypertension. The natriuretic hormone/Na^+-Ca^+ exchange/hypertension hypothesis. Am J Med 1984;77(4A):45–59.