Evidence of a Shared Mechanism of Vasoconstriction in Pulmonary and Systemic Circulation in Hypertension: A Possible Role of Intracellular Calcium

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SUMMARY **We investigated the hemodynamics of the greater and lesser circulation in 35 patients with primary hypertension, as well as the effects of calcium-channel blockade, to test whether a common factor may account for the excessive vascular resistance in the two circuits and whether intracellular calcium concentration ([Ca++]i) may be involved. We proved that (1) elevated pulmonary arteriolar resistance (PAR) is not related to pulmonary blood flow and volume, pleural pressure, arterial oxygen or carbon dioxide tension and pH, left ventricular filling pressure and function; (2) systemic vascular resistance (SVR) significantly correlates with PAR; (3) calcium-channel blockade with nifedipine reduces systemic and pulmonary arterial pressures toward normal and significantly lowers both SVR and PAR; (4) the percent decrease in vascular resistance after nifedipine is related to the baseline level of resistance in both the greater and the lesser circulations.**

Failure of the mechanisms currently indicated as responsible for pulmonary vasoconstriction to explain convincingly the increased PAR, the correlation between SVR and PAR, as well as the qualitatively similar response to calcium-channel blockade suggest that a common factor produces vasoconstriction in the two circuits. A pathogenetic role of a primary disorder in [Ca++]i cannot be excluded, but remains to be proved.

BLOOD PRESSURE elevation in most patients with chronic hypertension is associated with increased peripheral vascular resistance, which is due in part to abnormal constriction of the resistance vessels.[1-3] For a time, the autoregulatory theory[4] was popular. Interest has now focused on the hypothesis that an excessive intracellular calcium-ion concentration ([Ca++]i) is the proximate cause of the disordered vasomotility.[5] This view is based on two fundamental concepts: that in smooth muscle,[6, 7] as in striate muscle,[8] calcium ions trigger contraction, and that sodium-calcium exchange plays a critical role in the control of [Ca++]i and in the tension regulation of vascular smooth muscle.[9] In hypertension, an increase in sodium gradient across the sarcolemma is reflected as an increase in [Ca++]i and therefore in steady wall tension and peripheral vascular resistance.[5]

For intracellular sodium to be raised, the delicate mechanisms that are located in the membrane and regulate the sodium and potassium content of the cell must be disturbed. Several investigators have described a defect in ion transport across the erythrocyte membrane in animal hypertension,[10] as well as in red[11-14] and white blood cells[15] of patients with essential hypertension or of their normotensive offspring.[16, 17] Impairment of the sodium pump has been found by some workers,[15] and a deficiency in the Na^+/K^+ cotransport system has been described by others.[14] As related to hypertension, these disorders are spread throughout the body and involve arteriolar smooth muscle, which is the actual culprit. Unfortunately, blood cells, which can be easily studied, are not related at all to the muscles of the vessel wall, and the theory of abnormal membrane cation transport, although attractive, will remain speculative, until more is known about the metabolism of this tissue in essential hypertension.

Based on previous observations[18-20] that pressure and arteriolar resistance in the pulmonary circulation are increased in systemic high blood pressure, we decided to investigate the hemodynamics of the lesser circulation in hypertension to determine whether there is a common factor that accounts for the vasoconstriction that involves the two circuits and whether intracellular calcium is involved.

Materials and Methods

Subjects

Thirty-five hospitalized men with primary arterial hypertension were investigated. All had blood pressure readings persistently above 180/100 mm Hg by sphygmomanometer. Uncomplicated essential hypertension was diagnosed from the patient's medical history and ordinary clinical tests. Criteria for selection of patients were absence of symptoms or signs of heart failure, pulmonary disease, valvular lesions, anginal pain, old myocardial infarction, idiopathic myocardial disese in addition to hypertension; glomerular filtration rate above 70 ml/min; normal serum concentration of sodium, potassium and chloride; regular sinus rhythm without conduction defects; no digitalis at any time in the past or antihypertensive therapy for at least 3 weeks before entry; no urgent need for treatment; and a technically satisfactory left ventricular echocardiogram. After receiving detailed information on the procedures and the possible clinical benefits, all patients consented to participate in the investigation.

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Baseline variables measured in these patients were compared with those in 14 normotensive subjects of similar age investigated previously.[20] These controls were healthy volunteers or patients in the hospital who had no signs of circulatory disorders and were not taking medications that could interfere with their cardiovascular function. The echocardiographic and hemodynamic techniques used in this study have been reported in detail.[20]

Ultrasound Methods

Echocardiography was carried out with an ECHO-Cardio-VISOR (Organon-Teknika) ultrasound unit. Patients were recumbent in a slight lateral decubitus position. The left ventricular internal dimensions were measured at end-diastole simultaneously with the R wave of the ECG and at end-systole when posterior wall and septum maximally approached each other; the distance was taken from the endocardial echo of the posterior wall to the echo of the left side of the septum. The normalized mean velocity of left ventricular circumferential fiber shortening (circ/sec) was derived from the equation

$$\frac{D_d - S_d}{LVET \times D_d},$$

where D_d is the end-diastolic diameter, S_d is the end-systolic diameter and LVET is the left ventricular ejection time.

Endovascular Techniques

Hemodynamic measurements were performed with the patients in the fasting state and supine; no premedication was given. A #7 flow-directed Swan-Ganz catheter was inserted percutaneously into an antecubital vein, floated to the pulmonary artery and advanced to the wedge position. A #6 polyethylene radiopaque catheter introduced into a brachial artery and advanced to the root of the aorta was used to monitor arterial pressure and to sample blood for cardiac output determinations. Reproducible dye-dilution curves were obtained by Gilford densitometer after rapid injection of indocyanine green dye (5 mg) into the main pulmonary artery just beyond the pulmonary valve. The area under each dye-dilution curve was measured by planimetry; cardiac output and pulmonary blood volume were calculated by the method of Hamilton et al.[21] Pressures were determined with Statham P23De and P23Db strain-gauge transducers, which were balanced against atmospheric pressure. The zero reference level for pressure recordings was 5 cm below the sternal angle. Mean pressures were obtained by electronic damping. The left ventricular ejection time was measured by recording the aortic pressure tracing on an eight-channel Gould-Brush ink recorder (model 480) at a paper speed of 100 mm/sec. The interval was calculated from the mean of five consecutive beats, each read to the nearest 5 msec. Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR) were calculated from the following formulas:

$$SVR = \frac{\overline{AP} - \overline{RAP} \times 1332 \times 60}{CO\ (ml/min)}$$

$$PAR = \frac{\overline{PP} - \overline{PWP} \times 1332 \times 60}{CO\ (ml/min)}$$

where $\overline{AP}$ = mean aortic pressure, $\overline{PP}$ = mean pulmonary arterial pressure, $\overline{RAP}$ = mean right atrial pressure, $\overline{PWP}$ = mean pulmonary arterial wedge pressure and CO = cardiac output.

Respiratory Techniques

Pleural pressure was estimated by the method of Milic-Emili et al.[22] In brief, a rubber 2-ml esophageal balloon was introduced through the nose into the esophagus, placed 45 cm from the balloon tip to the nares, and connected to a pressure transducer through a polyethylene tube. Pleural pressure and circulatory variables were recorded simultaneously on the same recording system during quiet regular respiration. Oxygen and carbon dioxide tensions and pH were determined from an arterial blood sample drawn during quiet regular respiration. The pH was determined using the apparatus described by Siggaard-Andersen et al.[23] The P_{CO_2} was obtained with the nomogram also described by Siggaard-Andersen et al.[23] Oxygen tension was determined with a Radiometer P_{O_2} electrode (type E 5046). The final values for each subject were the average of three measurements.

Procedures

Essential hypertension was diagnosed after admission to the hospital. The patients were given a standard hospital diet (approximately 100 mEq sodium/day) and were familiarized with the laboratory and the investigators to minimize the possible interference of emotional factors. Then, echocardiographic, hemodynamic and respiratory evaluation was performed and the circulatory response to a calcium-channel blocking agent (nifedipine, 10 mg sublingually) was tested. All of the steady-state measurements were performed when patients felt comfortable and heart rate and pressures had stabilized, at least 30 minutes after the endovascular procedures were completed. The baseline hemodynamic variables were measured 30 minutes and 5 minutes before nifedipine was given. The average of the two measurements was taken as the representative value of each subject. Aortic and pulmonary pressures and heart rate were monitored continuously during the 30 minutes before and the 120 minutes after nifedipine. Right atrial pressure, pulmonary wedge pressure and cardiac output were measured again 30, 60 and 120 minutes, respectively, after nifedipine.

The hypertensive patients were separated into two groups, according to the absence (group 1, 18 patients) or the presence (group 2, 17 patients) of left ventricular enlargement determined echocardiographically. The left ventricular end-diastolic minor axis was within control limits in group 1 and exceeded 1 standard deviation of control in group 2. This difference was used to define the possible backward influence of left ventricu-

TABLE 1. *Pleural Pressure, Pulmonary Blood Volume and Arterial Oxygen Tension, Carbon Dioxide Tension and pH*

	Control subjects	Hypertensive patients	
		Group 1	Group 2
Pleural pressure (mm Hg)			
Inspiratory	−5.7 ± 0.94	−5.63 ± 0.99	−5.59 ± 0.93
Expiratory	−2.03 ± 0.7	−1.97 ± 0.69	−2.05 ± 0.71
Pulmonary blood volume (ml)	1161 ± 221	1194 ± 309	1235 ± 278
P_{O_2}	91.7 ± 2.6	90.8 ± 2.6	92.3 ± 2.9
P_{CO_2}	35.07 ± 2.6	35.25 ± 2.5	34.23 ± 3.01
pH	7.433	7.436	7.428

Values are average ± SD.

The differences between hypertensive groups and control subjects are statistically not significant.

Abbreviations: P_{O_2} = arterial oxygen tension; P_{CO_2} = arterial carbon dioxide tension.

lar function on pulmonary hemodynamics, as the performance of the hypertensive left ventricle is preserved or enhanced when its dimensions are normal, and consistently compromised when it is enlarged.[24]

Statistical Analysis

The statistical significance of the differences between normal subjects and hypertensives, between the two hypertensive groups, and between values before and after nifedipine was evaluated by analysis of variance on a Hewlett Packard desktop computer.

Results

Age and body surface area were comparable in the two hypertensive groups and in the control group. Pulmonary blood volume, pleural pressure, respiratory gases and pH of the blood were also similar in the three groups (table 1).

The average values of the hemodynamic variables are reported in figure 1. Systemic systolic and diastolic arterial pressures were elevated to a similar degree in groups 1 and 2; since cardiac index was normal in the former and reduced in the latter, systemic vascular resistance was elevated in both groups, with a higher level in group 2. Averages of systolic, diastolic and mean pulmonary wedge pressures were relatively similar in the two hypertensive groups and significantly higher than normal; pulmonary arteriolar resistance was elevated in group 1 and to a larger extent in group 2. The mean velocity of circumferential fiber shortening was significantly enhanced in group 1 and reduced in group 2.

Figure 2 shows the systemic vascular resistance in each hypertensive patient plotted against pulmonary arteriolar resistance. The correlation between the two variables is significant ($p < 0.01$).

The time course of the average percent circulatory variations from baseline induced by nifedipine in hypertensive patients is shown in figure 3. In group 1, 30 minutes after administration of the drug, mean systemic arterial pressure was reduced by 15% and mean pulmonary arterial pressure was reduced by 6%. These reductions were mediated through a 30% decrease in systemic arteriolar resistance and a 17% decrease in pulmonary arteriolar resistance, associated with a 22% increase in cardiac index. Cardiac index increased because heart rate and stroke index increased. Although some recovery was observed, these circulatory variations were still consistently evident 120 minutes after nifedipine. In group 2, the response to calcium-ion

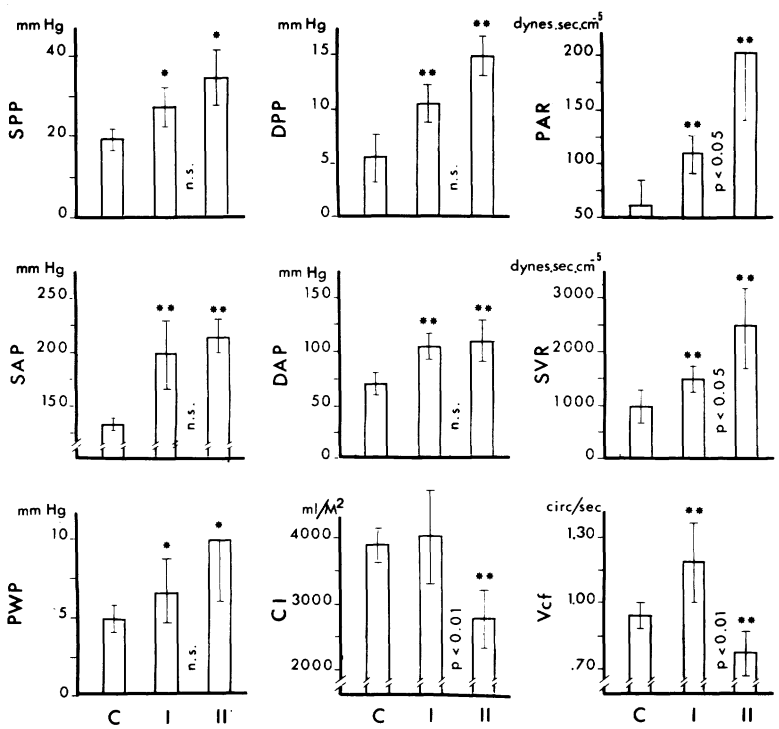

FIGURE 1. *Hemodynamic functions in 14 normotensive control subjects (C) and in two groups of patients with essential hypertension: group 1, 18 patients with normal-sized left ventricle; and group 2, 17 patients with left ventricular enlargement. Bars represent the mean for the group (± SD).* *p < *0.05*; **p < *0.01 for differences between the hypertensive groups and the control subjects. The* p *values for differences between the hypertensive groups are indicated in the figure. SPP = systolic pulmonary pressure; DPP = diastolic pulmonary pressure; PAR = pulmonary arteriolar resistance; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; SVR = systemic vascular resistance; PWP = mean pulmonary wedge pressure; CI = cardiac index; Vcf = left ventricular mean velocity of circumferential fiber shortening.*

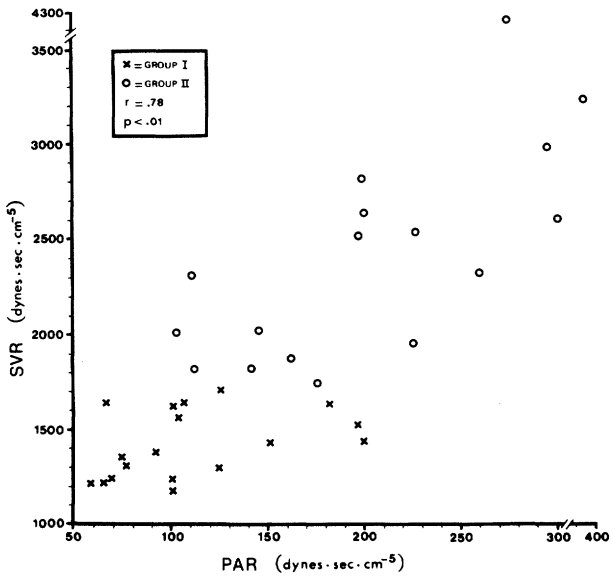

FIGURE 2. *Correlation between systemic (SVR) and pulmonary (PAR) vascular resistance in 35 untreated subjects with primary hypertension. Crosses identify patients with a normal-sized left ventricle; circles, patients with left ventricular enlargement.*

blockade was qualitatively similar to that in group 1, but was characterized by a significantly greater decrease in systemic (−40%) and pulmonary arteriolar resistance (−30%) at 30 minutes, which, despite a greater increase in cardiac index, caused a larger reduction in mean systemic (−20%) and mean pulmonary arterial pressure (−14%). The circulatory variations after calcium blockade remained significantly greater than in group 1 at both 60 and 120 minutes.

Discussion

Pulmonary systolic and diastolic pressures were equivalent among the hypertensives and significantly higher than in the normotensives. Cardiac output was normal in group 1 and reduced in group 2; since the driving pressure across the lung was augmented in both groups, pressure elevation in the pulmonary artery depended on an increased pulmonary arteriolar resistance.

Factors of different origin are conceivably involved in a change in pulmonary arteriolar resistance: pulmonary blood flow and volume, intrathoracic and alveolar pressures, left ventricular function, respiratory gases, autonomic nervous system, and vasomotor substances.[25, 26] Respiratory gases, the pH of the blood, and the pulmonary blood volume probably were not responsible for an altered pulmonary vasomotility, as they were similar in hypertensive and control subjects. Blood flow also seems unrelated to changes in pulmonary arteriolar resistance, as it was normal in one group and reduced in the other, while resistance was elevated in both groups. Pleural pressure estimated by esophageal balloon during quiet, regular respiration was equivalent in the three groups; alveolar pressure was not determined, but no reason was seen for an increase in hypertensive patients. Therefore, extramural pressures can also be excluded as important determinants of the differences between control and hypertensive patients. Elevation of left ventricular diastolic pressure may account for an increase in pulmonary arteriolar resistance. However, Atkins and collaborators[18] reported that in patients suffering from systemic hypertension, pulmonary vascular resistance is highly correlated with pulmonary wedge pressure greater than 20 mm Hg, but not with pulmonary wedge pressure lower than 20 mm Hg, even though many patients with lower wedge pressures had an increased pulmonary vascular resistance. In our hypertensive population, the pulmonary wedge pressure was less than 20 mm Hg and no correlation was found between the two variables. Finally, the pattern of the mean velocity of circumferential fiber shortening shows that cardiac muscle performance was compromised in group 2 and enhanced in group 1, which confirms previous findings of opposite functional changes in the normal-sized hypertensive heart compared with the en-

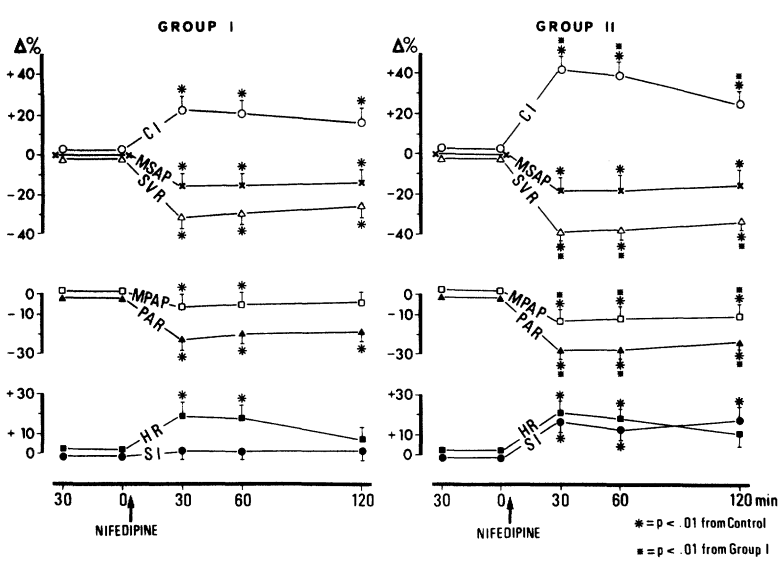

FIGURE 3. *Average (± SD) percent variations from baseline at various periods after nifedipine (10 mg) of mean systemic (MSAP) and pulmonary (MPAP) arterial pressures, systemic (SVR) and pulmonary (PAR) vascular resistance, cardiac index (CI), stroke index (SI) and heart rate (HR) in untreated patients with primary hypertension (group 1, 18 subjects with normal sized left ventricle; group 2, 17 subjects with left ventricular enlargement). *p < 0.01 vs baseline. **p < 0.01 vs group 1 at the same period.*

larged one.[20, 24] Apart from the intriguing mechanisms underlying these patterns, circumferential fiber shortening velocity values in groups 1 and 2 reasonably rule out the possibility that the elevated pulmonary arteriolar resistance in either group depends on left ventricular function.

A quantitative relationship exists in the averages of pulmonary and systemic vascular resistance in the two hypertensive groups, which suggests the alternative explanation that a common mechanism may produce vasoconstriction in the greater and in the lesser circulation. This possibility is strengthened by the significant correlation found when systemic vascular resistance was plotted against pulmonary arteriolar resistance (fig. 2).

Referring to the pathogenetic role of calcium in human hypertension, the ability of nifedipine to reduce high blood pressure toward normal through vasodilatation[27-29] does not seem as important as originally suggested.[30] In fact, since intracellular calcium is a physiologic mediator of the resting vascular smooth muscle tone,[6, 31] which is normally maintained in most resistance vessels, a vasodilating effect and some degree of blood pressure reduction after calcium-channel blockade with either nifedipine[32] or verapamil[33] also occurs in normotensive subjects. Consequently, the antihypertensive response to nifedipine, per se, does not allow us to discern whether it is caused by withdrawal of a physiologic factor or whether a disorder in $[Ca^{++}]i$ actually promotes the exaggerated vascular tone. Figure 3 shows that nifedipine lowers blood pressure in both the greater and the lesser circulation through vasodilatation, which involves systemic and pulmonary arterioles to a degree that, in either circuit, is proportional to the baseline levels of vascular resistance. Folkow[34] emphasized the structural changes in arterial and arteriolar walls in hypertension, and pointed out that an increased wall:lumen ratio can have a progressive pressor effect, and accentuate the superimposed vascular tone adjustments correspondingly. Thereby, subtraction of the physiologic vascular tone through calcium blockade might lower blood pressure in proportion to the structural vascular changes. This interpretation might explain results in systemic circulation; whether it fits our findings in pulmonary circulation remains matter of dispute, as information on the structure of the pulmonary vessels in hypertension is lacking.

The ratios of the rate coefficients for fluxes of Na^{+} and Ca^{++} across sarcolemma and for sarcolemmal sodium-calcium exchange play a critical role in the regulation of the steady-state intracellular Ca^{++} concentration. Factors that influence these ratios may, therefore, be important determinants of the vascular smooth fiber tension and blood pressure. Disorders in sodium and calcium permeability and transport in vessel smooth muscle and vasoconstrictor agents such as norepinephrine are examples of such factors. Norepinephrine tends to increase the mean $[Ca^{++}]i$ through an augmented permeability of the sarcolemma to sodium[35] and, perhaps, to calcium[36] and by triggering the release of calcium from the sarcoplasmic reticulum.[37] An excessive adrenergic drive or catecholamine release as a basic mechanism for the vasoconstriction in primary high blood pressure in man might explain the antihypertensive effect of calcium-blocking agents, but this theory, although extensively debated, has never been proved.

In conclusion, failure to explain convincingly the increased pulmonary arteriolar resistance through the mechanisms that are currently considered responsible for pulmonary vasoconstriction, the significant correlation between systemic and pulmonary vascular resistance, together with the qualitatively similar response to calcium-channel blockade, consistently suggest the possibility that a common factor causes vasoconstriction in the two circuits in patients with systemic hypertension. These data do not rule out the possibility that a disordered $[Ca^{++}]i$ is a shared mechanism for the augmented vascular tone; however, the pathogenetic role of calcium remains to be proved.

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