Pulmonary Vascular Overreactivity in Systemic Hypertension
A Pathophysiological Link Between the Greater and the Lesser Circulation

CESARE FIORENTINI, PAOLO BARBIER, CLAUDIA GALLI, ALESSANDRO LOALDI, GLORIA TAMBORINI, ELENA TOSI, AND MAURIZIO D. GUAZZI

SUMMARY This study was undertaken to test whether the emphasized systemic vasomotion during sympathetic activation in hypertension is shared by the pulmonary circulation. To this end, 10 normotensive and 29 primary hypertensive subjects were investigated during adrenergic stimulation by mental arithmetic and cold pressor test. Both stimuli induced a systemic pressor reaction in both groups, which was mediated through an increase in cardiac output and a mild reduction in vascular resistance during arithmetic and through a predominant rise in systemic vascular resistance during cold. Each of these changes was emphasized in the hypertensive population as compared with the normotensive one. Pressure in the pulmonary artery remained unchanged during cold and was slightly raised (systolic) during arithmetic in normotensive subjects. On the contrary, in hypertensive subjects systolic and diastolic pulmonary pressures were consistently augmented by both stimuli, and pulmonary arteriolar resistance (dyn sec cm$^{-2}$) rose from 92 in the baseline to 125 ($p < 0.01$) during arithmetic and to 124 ($p < 0.01$) during the cold test. This reaction is interpreted as reflecting a neurally mediated vasoconstriction and not as the consequence of mechanical or chemical changes, since no difference was observed in pulmonary wedge pressure, pleural pressure, arterial blood gas levels, and pH between controls and hypertensive subjects in the steady state and during either stressful stimulation. Baseline pulmonary arteriolar resistance was also found to correlate positively with systemic vascular resistance in the hypertensive group. When pressure changes occurred, the time course was similar in the two circuits; resistance increased to a proportionally similar degree in the two districts during the cold stimulus. All these observations support the concept that systemic and pulmonary vasculatures become oversensitive to neural activation and that the two vascular beds are exposed to the same type of dysregulation in systemic hypertension.

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KEY WORDS • arithmetic • blood gases • cold • vasoconstriction

FROM a hemodynamic viewpoint sustained primary hypertension is characterized by elevated systemic vascular resistance in the baseline$^{1-3}$ and by enhancement of the cardiovascular reactivity to sympathetic activation or catecholamine infusion.$^{4-8}$ Measurements in the pulmonary circulation have shown that the arterial pressure is higher than normal$^9$ in uncomplicated systemic hypertension$^{10,11}$ and that vascular resistance in the lungs is raised.$^{12-14}$ The causes of this abnormal vasomotion have not been elucidated, and no convincing explanation has been derived from the analysis of the mechanisms that are commonly indicated as interfering with the pulmonary vasomotility in humans,$^{14}$ such as changes in the respiratory gases and pH of the blood, pleural pressure, blood volume and flow through the lungs, or in the function of the left side of the heart and the related backward influences. These reasons, and the positive correlation existing between systemic and pulmonary vascular resistance, have suggested that a common factor responsible for vasoconstriction may be at work in the pulmonary and systemic circulation in hypertension.$^{14,15}$

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This study was undertaken to test whether the emphasized systemic vasomotion during sympathetic activation in hypertension is shared by the pulmonary vasculature. It has been proved in animals that lung vessels are sensitive to neural influences mediated through α-adrenergic and β₂-adrenergic receptors. Such evidence would be an additional aspect of parallelism between the two circuits, and the concept that both are exposed to the same type of dysregulation could become strengthened. Mental arithmetic and cold pressor test were utilized to this end, not merely because they are time-honored physiological sympathetic activators in humans, but mainly because at least in normotensive subjects these stimuli elicit a different hemodynamic response, prevalent increase in cardiac output by the former, and predominant rise in systemic vascular resistance by the latter, which might be expected to provide a tool for better understanding of the vasomotor reaction in the lesser circulation.

Materials and Methods

Our subjects were male or female patients in the hospital with primary arterial hypertension, who had repeated sphygmomanometric readings of diastolic pressure between 95 and 110 mm Hg. None of these subjects had symptoms or signs referable to sleep apnea syndromes. Diagnosis of uncomplicated essential hypertension was made on the basis of the patients' history and of the ordinary diagnostic tests, including intravenous urography and, if indicated, renal arteriography. None of the patients had heart failure, pulmonary disease, valvular lesions, anginal pain, old myocardial infarction, idiopathic myocardial disease, or marked renal damage. Only subjects who showed normal serum concentration of potassium, sodium, and chloride, who were in regular sinus rhythm without conduction, QRS voltage, or repolarization abnormalities in the electrocardiogram, who showed normal ventricular wall thickness and dimensions at the echocardiogram, and who had not received digitalis at any time in the past or antihypertensive therapy for at least 1 month before entry were included. Patients who were not able to cooperate for various reasons, or who had a priority need for treatment, were not included. The scientific aspects of the investigative program and the procedures to be undertaken were explained in detail to each patient.

Measurements in these 29 patients were compared with those in 10 hospitalized, normotensive symptom-free subjects, who showed a systolic murmur over the precordium or atypical chest pain, in whom cardiac abnormalities were excluded through cardiac catheterization and coronary angiography. These control subjects were not taking medications that could interfere with their cardiovascular or respiratory function.

Circulatory measurements were performed with the subjects in the fasting state in the supine position without premedication. A 7F double-lumen flow-directed Swan-Ganz catheter for measurements of right atrial, pulmonary arterial, and wedge pressures was inserted percutaneously with the subject under local anesthesia into an antecubital vein, floated, under fluoroscopic guidance, to the pulmonary artery, and advanced, when necessary, to the wedge position. A 7F polyethylene radiopaque catheter introduced percutaneously into a brachial artery and advanced to the root of the aorta immediately distal to the aortic valve was used to monitor aortic pressure and to sample blood for cardiac output determinations. Reproducible dye dilution curves were obtained by a Gilford densitometer (Oberlin, OH, USA) 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 a planimeter; cardiac output was calculated by the standard method of Hamilton et al. Pressures were determined with Statham P23 De and P23 Db strain gauge transducers (Oxnard, CA, USA), which were balanced against atmospheric pressure. Zero reference level for pressure recordings was 5 cm below the sternal angle. Mean pressures were obtained by electronic damping. Criteria for a satisfactory pulmonary artery wedge pressure were a change from the typical pulmonary artery pressure waveform to the typical pulmonary artery wedge pressure waveform on inflation of the balloon catheter and a mean pressure step-up on deflation of the balloon. The pulmonary artery wedge pressure was characterized by distinct a and v waveforms with the v wave occurring after the T wave of the electrocardiogram. Records were obtained on an eight-channel Gould-Brush ink recorder (model 480, Saddle Brook, NJ, USA). Systemic vascular resistance (SVR) and pulmonary arteriolar resistance (PAR), in dyn sec cm⁻⁵, were calculated from the following formulas: SVR = AP - RAP × 1332 × 60/CO (ml/min); PAR = PP - PWP × 1332 × 60/CO (ml/min), where AP, RAP, PP, and PWP are, respectively, mean aortic, right atrial, pulmonary arterial, and pulmonary wedge pressures, and CO is cardiac output.

In each subject pleural pressure was estimated by the method of Milic-Emili et al. A 2-ml rubber 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 both in the baseline and during adrenergic activation. Oxygen and carbon dioxide tensions and pH were measured on arterial blood samples drawn during regular, quiet respiration, according to methods that have been described in detail elsewhere. Circulatory measurements were performed 1 week after admission to the hospital, during which time the diagnostic laboratory work was done and the diagnosis of essential hypertension was established, and after the patients had been familiarized with the laboratory staff and the environment during 3 consecutive days to minimize the possible interference of emotional factors. Continuous recordings of electrocardiogram, heart rate (through a cardiograph), pleural pres-
sure, and aortic and pulmonary arterial pressures were obtained in the baseline condition and during two different types of stressful stimuli: painful (the standard cold pressor test with the left hand immersed to the wrist level in water at 3 °C for 3 min), and mental (patients were asked to divide a 4-digit number by a 2-digit number, while under the pressure of time; after 2 min they were informed of the result and invited to relax). Cardiac output was also determined, the wedge pulmonary pressure was measured, and systemic and pulmonary arteriolar resistances were calculated in the steady state and coincident with the largest pressure variations during stimuli. Arterial blood samples were withdrawn at the same time for respiratory gases and pH determinations. Steady state measurements were charted 30 minutes after completing the endovascular procedures, at a time when heart rate, aortic pressure, and respiration had definitely stabilized.

The two stressful tests were alternated and repeated twice in each subject at 10-minute intervals. The averages of the two measurements were taken as the representative values for the subjects. Variables immediately before each of the repeated tests were quite similar to those recorded at the beginning of the study, which indicates that between one test and the other the steady state could be reestablished. From the continuous recordings, measurements of heart rate and systolic and diastolic aortic and pulmonary pressures were taken at 10-second intervals for the duration of the stimulus and during the 40 seconds that preceded it and the 60 seconds that followed it. This method provided an exact evaluation of the delay of the circulatory changes in relation to the beginning of the stimuli, of the time for the pressor reaction to reach its peak, and of the time for reversion of pressure to the pretest level after the interruption of the stimulus.

Statistical significance of the differences between normotensive and hypertensive subjects, and between values in the steady state and during adrenergic activation, was evaluated by analysis of variance on a Hewlett-Packard desktop computer (Waltham, MA, USA).

Results

Middle-aged patients (age range, 35–55 yr) with moderate hypertension and no circulatory hyperkinesis, detectable signs of hypertensive cardiac disease, or respiratory dysfunction were purposely selected. Control subjects were well matched for sex, age, and somatic characteristics (Table 1).

Patients in this study had a normal cardiac index in the baseline and their aortic pressure elevation was due to a raised systemic vascular resistance (Figure 1). The pattern was similar in the pulmonary vascular bed, where systolic and diastolic arterial pressure and arteriolar resistance were significantly higher than in the control group (Figure 1). A positive significant correlation was found between systemic vascular resistance and pulmonary arteriolar resistance ($r = 0.79, p < 0.001$) only in the hypertensive group (Figure 2).

The average (±sd) heart rate and systolic and diastolic aortic and pulmonary arterial pressures, taken at the various moments during arithmetic and cold stimulation, for both groups is shown in Figure 3 and Figure 4 respectively. Statistical significance of the differences from the steady state and between the two groups at the various moments of the stressful stimuli is shown in the figures.
Both stimuli in both groups induced a systemic pressor reaction that was much more pronounced in the hypertensive population in terms of levels reached and magnitude of changes from baseline (Table 2). Pressure in the pulmonary artery remained unchanged during cold stimulation and was slightly raised (systolic) during arithmetic in the control subjects, while it definitely rose (systolic and diastolic) in the hypertensive population during both types of stimuli. When pressure changes occurred, the time course was similar in the two circuits and the maximal reaction was generally achieved within 60 seconds during the arithmetic test and within 90 seconds during the cold test. Values of the circulatory functions recorded at these periods are reported in Figure 1. The influences of arithmetic on the systemic circuit were different in quality from those of the cold test both in normotensive and hypertensive subjects. In both populations the pressure rise during arithmetic was mediated through a similarly increased cardiac index associated with a tendency of systemic vascular resistance to decrease; a raised systemic vascular resistance (which was much greater in hypertensive subjects) without remarkable changes in cardiac index characterized the systemic hemodynamic response to cold. As regards the pulmonary circuit, neither stimulus was effective on arteriolar resistance in normotensive subjects and the unremarkable systolic pressure rise recorded during arithmetic was attributable exclusively to the augmented cardiac index. On the contrary, in the hypertensive group, systolic and
TABLE 2. Comparison Between Changes from Baseline in Normotensive and Hypertensive Subjects During Arithmetic and Cold Pressor Tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arithmetic test</th>
<th>Cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>+7.4 ± 2.2</td>
<td>+15.4 ± 3.1</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>+13.1 ± 6.8</td>
<td>+27.8 ± 7.9</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>+8.2 ± 4.3</td>
<td>+16.5 ± 4.6</td>
</tr>
<tr>
<td>Pulmonary pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>+3.1 ± 1.8</td>
<td>+10.4 ± 2.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>+0.8 ± 1.2</td>
<td>+7.2 ± 1.4</td>
</tr>
<tr>
<td>Mean wedge</td>
<td>+1.3 ± 0.7</td>
<td>+1.2 ± 0.6</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>+643 ± 226</td>
<td>+814 ± 213</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(dyn sec cm⁻⁵)</td>
<td>−24 ± 16</td>
<td>−27 ± 14</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(dyn sec cm⁻⁵)</td>
<td>−3.5 ± 2.6</td>
<td>+29.2 ± 5.4</td>
</tr>
</tbody>
</table>

*Values represent the mean change ± SD.*

*NS = not significant.*

Diastolic pulmonary artery pressure were augmented to a similar level by both stimuli and the rise was mediated through an increase of both cardiac index and arteriolar resistance during arithmetic test and exclusively through the latter during cold test (Figure 1; Table 2). Figure 5 shows the variations from the steady state in systemic vascular resistance induced by the arithmetic and the cold test in each normotensive and hypertensive subject, plotted against changes in pulmonary arteriolar resistance. No correlation was found between vasomotor changes in the two vascular districts caused by either stimulus in normotensive subjects and...
by arithmetic in hypertensive subjects. On the contrary, a positive significant correlation was evident in the hypertensive group during cold stimulation (r = 0.81, p < 0.001).

As can be seen in Table 3, pleural pressure, carbon dioxide and oxygen tension, and pH of the arterial blood did not significantly vary during the stressful stimulations and no difference was evident between groups.

Discussion

There is little doubt that both stimuli used in this study induced adrenergic activation, of which the systemic circulatory reaction is a consequence. The critical time relationship between stimuli and circulatory events, as indicated by the continuous recordings, makes a neural adrenergic effect more likely than a humoral (adrenal) adrenergic effect. On the other hand, a typical circulatory response to cold has been observed in adrenalectomized subjects, which suggests that, although adrenal medullary catecholamine release is elicited by the cold pressor test, the pressure elevation is independent of such adrenal activity.

The disparate response to mental and painful stimuli raises some questions about the neural control of circulation during stress. Mental test elicited a pressor response that was associated with a substantial rise of cardiac index and heart rate and some reduction in cardiac index and heart rate and some reduction in humoral (adrenal) adrenergic effect. On the other hand, a typical circulatory response to cold has been observed in adrenalectomized subjects, which suggests that, although adrenal medullary catecholamine release is elicited by the cold pressor test, the pressure elevation is independent of such adrenal activity.

The factors controlling the flow of blood through the lungs are predominantly mechanical ones, and knowledge of the passive relationship between pressure and flow in the circuit becomes crucially important in the interpretation of pharmacological or physiological interventions on the pulmonary circulation. If this relationship is not linear, an alteration in resistance in circumstances when flow is changing does not necessarily imply any active change in the tone of the resistance vessels. The ratio of pulmonary driving pressure to flow curves obtained in normal persons lying down suggests that the overall pattern is not significantly different from a straight line when flow is suddenly doubled; however, the actual passive pressure flow relation with small changes in flow in humans is unknown.

In the present study, the increase in pulmonary blood flow elicited by the arithmetic test did not alter the baseline difference between the pulmonary arterial and the wedge pressure in the normotensive subjects, while a similar increase of blood flow by the same stimulus was associated with a substantial rise of the driving pressure through the lungs in the hypertensive population. This finding indicates an active vasoconstriction in this group. Particularly important is the response to the cold test during which changes in blood

<table>
<thead>
<tr>
<th>Variable</th>
<th>Steady state</th>
<th>Arithmetic test</th>
<th>Cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
<td>Normotensive</td>
</tr>
<tr>
<td>Pleural pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspiratory</td>
<td>-5.6±0.94</td>
<td>-5.6±0.78</td>
<td>-5.7±0.99</td>
</tr>
<tr>
<td>Expiratory</td>
<td>-2.0±0.69</td>
<td>-2.5±0.75</td>
<td>-2.0±0.73</td>
</tr>
<tr>
<td>Po2</td>
<td>91±2.9</td>
<td>93±2.3</td>
<td>92±2.6</td>
</tr>
<tr>
<td>Pco2</td>
<td>35±2.5</td>
<td>36±2.8</td>
<td>34±2.1</td>
</tr>
</tbody>
</table>

Values (except pH) represent the average ± SD.

Differences between the two groups in the steady state and during tests were statistically not significant.
flow were hardly noticeable in the two populations; however, in hypertensive subjects the driving pressure across the lungs rose to the same extent as during the arithmetic test, which suggests that an even greater vasomotion had occurred.

The hypothesis considered by some authors\(^\text{29}\) that pulmonary vascular pressure is influenced by the elevation of aortic pressure through the anastomoses connecting branchial arterioles with the pulmonary circulation seems untenable, since aortic pressure was also raised during stress in normotensive subjects in whom hemodynamic changes in the lesser circulation were minimal. Even though long-standing elevation of the left ventricular filling pressure may account for an increase in pulmonary arteriolar resistance, in the hypertensive population in this study the wedge pulmonary pressure was within normal limits in the steady state, and its changes during stress tests did not correlate with those of resistance.

As regards the influence of respiratory factors on the pulmonary vasomotion, no difference was detected in the measured variables (blood gases, pH, pleural pressure) between controls and hypertensive subjects, either in the baseline or during either stressfull stimulation (Table 3).

These findings suggest that a neurally mediated pulmonary vasoconstriction in the hypertensive person subjected to a mental or a physical stimulus is most likely and reasonably acceptable.

The question concerning the reasons for the enhanced vascular reactivity to adrenergic neural activation in hypertension becomes even more impelling if one considers that it is not confined to the systemic circulation. In fact, pulmonary vasculature seems involved to such an extent that stimuli (arithmetic and cold) that are ineffective on the pulmonary vasomotion in normotension become definitive vasoconstrictors when hypertension develops; and a stimulus (arithmetie) that is a weak systemic vasodilator becomes a pulmonary vasoconstrictor.

Stressful stimulations promote the release of catecholamines, and reaction of the systemic circulation is probably the result of an interplay of α-adrenergic and β-adrenergic receptor activation at the level of the heart and the vessels. A review of the studies concerned with human pulmonary circulation shows an increase in the pulmonary arterial and wedge pressures during the infusion of norepinephrine without remarkable changes in the pulmonary blood flow and arteriolar resistance; the heart rate is decreased and the systemic arterial pressure increased. The balance of evidence is against the existence of a substantial pulmonary vasoconstriction in normal humans. This hemodynamic pattern, which is reminiscent of the one observed in normotensive subjects during cold stimulation in this study, is interpreted as a composite of passive pulmonary vasodilatation caused by an increased transmural pressure consequent on displacement of blood from the systemic vascular system and of some active vasoconstriction caused by stimulation of α-adrenergic receptors.\(^\text{29}\) On this basis, one should deduce that in hypertension, for some reason, the passive pulmonary dilatation is impeded or the influence of α-adrenergic receptors is enhanced or that both factors come into action; this would provide explanation for both patterns that were observed during cold and arithmetic.

This study confirms the previous findings that in hypertension the baseline resistance to flow is raised in the two vascular circuits\(^\text{12,13}\) and that pulmonary arteriolar resistance correlates positively with systemic vascular resistance.\(^\text{14}\) It also indicates that the systemic and pulmonary vasculatures become oversensitive to neural stimulation and vascular tone increases to a degree that is proportionally similar in the two districts during the neural adrenergic activation elicited by the cold stimulus (Figure 5). These observations reinforce the concept that vasomotility of the greater and the lesser circulation in hypertension is disturbed by the same type of disorder. Whether it is a matter of changes in the lumen of the vessels,\(^\text{10,30}\) of neural or receptor adrenergic activity,\(^\text{8,31}\) of circulating hormones, or of an altered biochemistry of the contractile vascular structure\(^\text{32}\) remains obscure.

References

Institute: current research and recommendation from the subgroup of local hemodynamics. Hypertension 1980;2:342–369
Pulmonary vascular overreactivity in systemic hypertension. A pathophysiological link between the greater and the lesser circulation.
C Fiorentini, P Barbier, C Galli, A Loaldi, G Tamborini, E Tosi and M D Guazzi

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