Factors Contributing to Resistant Hypertension

Cardiac Considerations

FETNAT M. FOUAD-TARAZI

SUMMARY Medical treatment of hypertension has beneficial effects in the prevention of complications of the disease and in prolongation of survival. Nevertheless, the control of hypertension may sometimes be difficult. In this respect, the heart itself may interfere with blood pressure control because of increased cardiac output or because of cardiogenic reflexes that could conceivably not only initiate but also perpetuate peripheral vasoconstriction. The resultant persistence of hypertension may induce further cardiac changes that will in turn perpetuate the rise in blood pressure.

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KEY WORDS • resistant hypertension • heart • blood pressure

THERE is no doubt that successful medical treatment of hypertension has had beneficial effects in the prevention of complications of this disease and resulted in prolongation of survival. Flexibility in the choice of drugs and in adjustment of doses has been made possible by the availability of multiple new effective medications that have specific pathophysiological mechanisms of action. Moreover, long-acting specific therapeutic agents have helped improve patients’ compliance during long-term treatment.

Nevertheless, the control of hypertension may sometimes be difficult to achieve despite the skillful efforts of the treating physician. Of the many possible means leading to such ineffectiveness of therapy, the cardiac factors are of special interest because of the newly recognized role of the heart in the initiation and perpetuation of hypertension. The mechanisms by which the heart itself may interfere with blood pressure control may be due to cardiac pumping ability and cardiogenic reflexes. On the other hand, the heart may suffer both structurally and functionally from the persistence of high pressure and its associated hemodynamic abnormalities. In that sense, the persistence of blood pressure elevation will accentuate the effects of hypertension on the heart, whereas the resultant cardiac changes will perpetuate hypertension (Figure 1).

Blood Pressure and Cardiac Structural Changes

Most correlations between left ventricular (LV) mass and afterload have used blood pressure levels. In this respect, studies in experimental animals and in hypertensive patients failed to reveal any strong quantitative relationship between arterial pressure levels and cardiac hypertrophy except in renal hypertensive rats. Moreover, normal hearts despite severe and prolonged hypertension were seen at autopsy, whereas enlarged hearts were found in patients with modest pressure elevation. In other studies, definite cardiac hypertrophy was recognized in young children and adolescents with borderline hypertension, while Sen and associates reported increased ventricular weight in spontaneously hypertensive rats before the development of significant or sustained hypertension. These findings should not be interpreted to mean a complete dissociation between afterload and LV structural changes because blood pressure per se does not reflect accurately the resistance to ejection from the left ventricle. On the other hand, more correct measures of afterload such as aortic impedance and LV wall stress have not been used as determinants of LV mass.

This lack of parallelism between rise in arterial pressure and increase in cardiac weight was attributed to the presence of other factors contributing to left ventricular hypertrophy (LHV), including the modulating effect of adrenergic disturbances that have been described in relation to both the pathophysiology of hypertension and antihypertensive therapy.

Irrespective of its mechanism, the occurrence of LHV in hypertension induces further changes, which are structural in the coronary circulation and functional in the myocardium. These new changes could well result in the persistence of hypertension despite appropriate therapy as described later.

Resistant Hypertension and LV Function

Contrary to the multiple reports of normal systolic function in hypertension, LV diastolic function was reported to be reduced. A diminished rate of LV filling...
was found in hypertensive patients in whom cardiac output, ejection fraction, and velocity of ejection were still normal. These findings have been confirmed by several other investigators and coincided with the previous report of Tarazi et al. of the presence of abnormal P waves (left atrial enlargement) in the absence of abnormal signs of LVH in hypertensive patients. The pathophysiological basis of this abnormality is not known. It could reflect the functional impact of slight increases in LV wall thickness, decreases in coronary blood flow, or reductions of adrenergic activity. Its physiological importance is just beginning to be evaluated. Some emerging suggestions indicate that this abnormality in LV diastolic function could alter the inhibitory afferent vagal reflexes from the cardiopulmonary area and, thus, maintain high blood pressure.

Coronary Blood Flow in Hypertension

We have observed that LV function (dP/dt) of the isolated, isovolumic hypertrophied hearts of renal hypertensive rats was strongly influenced by myocardial flow rate. Indeed, clinical observations have pointed out that the hypertrophied heart needs a higher driving pressure to maintain coronary flow within normal ranges. These observations were supported by studies of coronary flow in hypertension showing that at rest, in vivo coronary flow was normal when expressed per unit mass of myocardium. However, in response to vasodilator stimuli, there was often found, albeit not always, a reduced capacity for coronary vasodilation. As a result of such impairment in coronary reserve, additional cardiac work loads may induce ischemic myocardial injury, particularly in the subendocardial region. The situation becomes even more complex if, in addition to the effects of hypertrophy, the effects of coronary atherosclerosis and of antihypertensive therapy are added. Interference with the vasodilating capacity of coronary vessels may aggravate the effects of coronary stenosis. Also, addition of powerful vasodilators to control resistant forms of hypertension may produce reflex increases in heart rate and increases in myocardial oxygen demand. As a result, foci of ischemia may develop and, in turn, generate afferent reflex pressor mechanisms as described in detail later.

The Heart as a Cause of Resistance to Antihypertensive Therapy

Resistant hypertension is essentially diagnosed in a patient receiving multiple antihypertensive therapy. To that extent, one may attribute the cardiac causes of resistance to therapy to either 1) the counteracting mechanisms evoked by antihypertensive therapy, 2) the initiation of pressor reflex mechanisms, or 3) the loss of inhibitory reflex mechanisms.

Increased Cardiac Output as a Cause of Resistant Hypertension

High cardiac output alone is not necessarily associated with an increase in blood pressure. More relevant to the level of blood pressure is the relation of the increased output to the systemic resistance. Patients with resistant hypertension are usually taking several drugs, among which are powerful peripheral vasodilators, for example, minoxidil. The initial reduction in total peripheral resistance (TPR) induced by such drugs may produce countereffects that thwart their antihypertensive effectiveness; for example, selective arteriolar dilation without associated venodilation (e.g., minoxidil) produces a marked increase in cardiac output because of two hemodynamic events: the decreased afterload and the reflex stimulation of sympathetic activity. The rise in cardiac output may be sufficient enough to compensate for the reduction in TPR so that blood pressure remains unchanged. In our experience, addition of a β-blocker to minoxidil treatment will normalize cardiac output and institute blood pressure control (Table 1). Moreover, the reflex sympathetic activation induced by powerful vasodilators increases renin release with resultant blunting of blood pressure response to the vasodilator; this latter mechanism has not been substantiated, however, in long-term follow-up of patients.

Theoretically, hypertrophied hearts with reduced β-receptor density will not be expected to increase heart rate significantly in response to reflex sympathet-

### Table 1. Pulmonary Hypertension and Minoxidil

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Minoxidil</th>
<th>Minoxidil plus propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index (L/min/M²)</td>
<td>2.8</td>
<td>5.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>192</td>
<td>159</td>
<td>116</td>
</tr>
<tr>
<td>PAP</td>
<td>28/15</td>
<td>40/20</td>
<td>23/13</td>
</tr>
<tr>
<td>PWP</td>
<td>10</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Resistance (µM²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>72</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3.1</td>
<td>1.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; PAP = pulmonary artery pressure; PWP = pulmonary wedge pressure.

R.C. Tarazi, unpublished observations.
ic stimulation. If this were true, the reflex tachycardia would not occur, and at least two related counterbalancing mechanisms would be abolished, namely, the increased cardiac output and the generation of ischemic myocardial foci as sources of pressor cardiogenic reflexes. However, we do not know the distribution of β-receptors in the sinoatrial node, so the reflex tachycardia may still occur in presence of LVH.

Role of Cardiogenic Reflexes in Resistant Hypertension

Cardiogenic hypertension is not limited to high cardiac output states. Increased blood pressure due to elevation of TPR may result from pressor reflexes originating from the heart and large vessels in the cardiopulmonary area. These cardiogenic reflexes could conceivably not only initiate but also perpetuate peripheral vasoconstriction.

Powerful pressor reflexes have been described as originating from the heart. They have been found to be triggered by distension of coronary vessels, myocardial ischemia, or specific chemoreceptors as well as by rhythmic stretch of the aortic wall. Although usually described as paroxysmal, the rise in blood pressure resulting from such positive cardiogenic pressor reflexes has been made to persist for 7 days during chronic stellate stimulation in conscious dogs.

The situation in humans is influenced by the major role of low pressure receptors and the importance of postural changes on the reflexes originating from the cardiopulmonary area. In this respect, the heart may have influence on reflex cardiopulmonary constrictor mechanisms through inhibitory reflexes to the medullary vasomotor center. Thus, Mark and Kerber demonstrated that the response of the forearm vascular resistance to different grades of lower-body negative pressure has been consistently higher in patients with borderline hypertension compared with normal volunteers. Similarly, Frohlich et al. had shown in 1967 that the degree of vasoconstriction in response to head-up tilt in hypertensive patients was inversely proportional to their baseline peripheral resistance. The studies by Mark and Kerber and Frohlich et al. could be integrated in a construct based on the interaction between reflexes from the cardiopulmonary area and the high-pressure baroreceptors. In borderline hypertension, the cardiopulmonary receptors are thought to be hyperactive to compensate for the diminished sensitivity of the high-pressure receptors so that the net sympathetic activity is close to normal at rest. In the advanced stages of hypertension, however, the cardiopulmonary reflexes seem to be also blunted so that the net sympathetic activity is increased at rest. In the first case, unloading of the cardiopulmonary area leads to marked increases in sympathetic tone, whereas in more advanced hypertension, there is little to deactiv (Copyright 2000, Elsevier)


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