Resistant Hypertension
Introduction and Definitions
RAY W. GIFFORD, JR.

SUMMARY The following definition of resistant hypertension is proposed: Provided that adherence to the regimen can be assured, hypertension should be considered resistant if the blood pressure cannot be reduced to \(<150/100 \text{ mm Hg}\) by a rational triple drug regimen, including a diuretic, prescribed in nearly maximal doses and if the pretreatment blood pressure was \(\geq 180/115 \text{ mm Hg}\). If the pretreatment blood pressure was \(<180/115 \text{ mm Hg}\), resistance should be defined as failure to achieve normotension (\(<140/90 \text{ mm Hg}\)) on a rational triple drug regimen in nearly maximal doses. (Hypertension 11 [Suppl II]: II-65–II-66, 1988)

KEY WORDS • resistant hypertension • refractory hypertension • severe hypertension

The term resistant hypertension is frequently and glibly used because there is no generally accepted definition. For instance, how many antihypertensive drugs should be tried, and in what combinations, before hypertension should be labeled resistant? Is hypertension resistant simply because the patient does not comply with the prescribed regimen? Is resistant hypertension the failure to achieve normotension no matter what antihypertensive drugs are prescribed in rational combinations and in accepted maximal doses? This definition of resistant hypertension automatically excludes any satisfactory pharmacological approach to its management.

If one accepts the definition that the diastolic blood pressure cannot be reduced to \(<100 \text{ mm Hg}\), then, by definition, mild hypertension (diastolic blood pressure 90–100 mm Hg) can never be resistant. On the other hand, is it fair to label hypertension resistant simply because an initial diastolic blood pressure of 140 mm Hg can be reduced to \(<100 \text{ mm Hg}\) but not to \(<90 \text{ mm Hg}\)? And what about systolic hypertension? Should a systolic/diastolic hypertension of 210/130 mm Hg be considered resistant if diastolic blood pressure can be normalized while the systolic is less responsive (e.g., 175/85 mm Hg), and at what level of systolic blood pressure should isolated systolic hypertension (when diastolic blood pressure is \(<90 \text{ mm Hg}\)) be considered resistant to treatment?

Given all the variables that are involved, not the least of which is individual physician opinion and bias, it is doubtful that a consensus can be reached on a definition of resistant hypertension. For many physicians, the definition is subjective: any hypertension that has not been controlled adequately by the regimen that they themselves have prescribed.

Provided that adherence to the regimen can be assured (and frequently this is not easy), hypertension should be considered resistant if the blood pressure cannot be reduced to \(<150/100 \text{ mm Hg}\) by a rational triple drug regimen, including a diuretic prescribed in nearly maximal doses (Appendix, Table A) and if the pretreatment blood pressure was \(\geq 180/115 \text{ mm Hg}\). If the pretreatment blood pressure was \(<180/115 \text{ mm Hg}\), resistance should be defined as failure to achieve normotension (\(<140/90 \text{ mm Hg}\)) on a rational triple drug regimen in nearly maximal doses.

For elderly patients with isolated systolic hypertension, resistance in an adherent patient is defined as failure of a rational triple drug regimen to reduce the systolic blood pressure to \(<170 \text{ mm Hg}\) if pretreatment systolic blood pressure was \(>200 \text{ mm Hg}\) or to \(<160 \text{ mm Hg}\) and by at least 10 mm Hg if pretreatment systolic blood pressure was 160 to 200 mm Hg.

Hypertension may be partially or totally resistant. The latter is uncommon. Usually a rational triple drug regimen will reduce blood pressure by at least 20 mm Hg systolic and by 10 mm Hg diastolic. A lesser reduction should be considered as total resistance, especially if the pretreatment blood pressure was \(>200/130 \text{ mm Hg}\).

Resistance can be primary or acquired, and this distinction has important diagnostic implications. If hypertension becomes resistant to a previously effective regimen (acquired resistance), renovascular hypertension or some other form of secondary hypertension should be strongly suspected. Secondary hypertension may also be primarily resistant to treatment, but so can essential hypertension.

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Finally, it should be emphasized that severe hypertension, malignant hypertension, and resistant hypertension are not synonymous. Severe hypertension (diastolic blood pressure >115 mm Hg) can on occasion be malignant (group IV changes in optic fundi including papilledema by Keith-Wagener-Barker criteria) but is usually not. The diagnosis of malignant hypertension depends on findings in the retina and not the level of blood pressure per se. While severe or malignant hypertension is more likely to be resistant than mild hypertension is, mild hypertension can occasionally be resistant to a triple drug regimen, and severe or malignant hypertension can usually be well controlled with a conventional two or three drug regimen.

**Comment**

The definition of resistant hypertension offered above does not differ substantially from that first proposed by the late Robert C. Tarazi* and me in 1978, except that the level of pretreatment blood pressure is taken into consideration in the present definition.

It is useful to have consensus on a definition of resistant hypertension if it can be achieved. This would provide guidelines to the primary physician with respect to appropriateness of referral, but more importantly, it would be a basis for more precise communications within the community of physicians who specialize in hypertension.

While the definition suggested here may seem arbitrary and unnecessarily rigid, it is offered as a starting point from which to modify and build.

**Appendix**

**TABLE A. Minimal Regimens That Should Be Tried Before Labeling Hypertension Resistant**

<table>
<thead>
<tr>
<th>Regimen</th>
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<tbody>
<tr>
<td>1. Oral diuretic — equivalent to 50 mg hydrochlorothiazide or chlorthalidone*</td>
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<td>plus</td>
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<td>2. Sympathetic inhibitor — β-blocker equivalent to propranolol 320 mg or atenolol 100 mg daily, or methyldopa† 2 g daily, or clonidine† 1 mg daily or prazosin 20 mg daily, or an ACE inhibitor† (e.g., captopril 100 mg three times daily or enalapril 40 mg daily), or a calcium channel blocker (e.g., verapamil SR 480 mg daily, diltiazem 120 mg three times daily, or nifedipine 20 mg four times daily)</td>
</tr>
<tr>
<td>plus</td>
</tr>
<tr>
<td>3. Direct vasodilator — hydralazine 300 mg daily</td>
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</table>

Hypertension should not be considered resistant unless a diuretic is included in the triple drug regimen. *If serum creatinine >3.0 mg/dl, furosemide 320 mg daily, bumetanide 5 mg daily, or metolazone 10 mg daily should be used for the diuretic. †Preferred Step 2 drug in isolated systolic hypertension. ‡ACE inhibitor or calcium channel blocker can also be used as a substitute for a direct vasodilator in Step 3.

**References**


*Co-organizer of this symposium.
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