An Algorithm for the Management of Resistant Hypertension

RAY W. GIFFORD, JR.

SUMMARY Before hypertension can be considered resistant to a rational triple drug regimen in maximal doses, the physician should rule out poor adherence to the regimen (including diet), adverse drug interactions, pseudotolerance (due to fluid retention), office hypertension, pseudohypertension, and an unrecognized secondary cause (e.g., renovascular disease, primary aldosteronism, and pheochromocytoma). When these have been excluded, hemodynamic measurements are indicated to identify the mechanism(s) at fault so that the therapeutic regimen can be modified appropriately.

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KEY WORDS • resistant hypertension • adherence • pseudohypertension • office hypertension • pseudotolerance

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in an accompanying communication, resistant hypertension was defined as follows: "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 mm Hg by a rational triple drug regimen, including a diuretic, prescribed in nearly maximal doses and if the pretreatment blood pressure was ≥ 180/115 mm Hg. If the pretreatment blood pressure was < 180/115 mm Hg, resistance should be defined as failure to achieve normotension (< 140/90 mm Hg) on a rational triple drug regimen in close to maximal doses."

According to this definition, there are even fewer patients with resistant hypertension than when the late Robert Tarazi* and I, in 1978, stated that "fortunately, hypertension resistant to a good drug regimen is rare." Since that paper was published, angiotensin converting enzyme (ACE) inhibitors, calcium channel blocking agents, and newer β-blockers, including an α- and β-blocker, have become available. The vast majority of patients who are referred to specialists in hypertension because of "resistant hypertension" do not have it according to the above criteria.

Management Steps

Confronted with a patient whose hypertension is not responding to treatment, the first step for a physician is to assess the patient's compliance and the adequacy of the regimen (Figure 1).

Compliance

Frequently, it is not easy to be sure that a patient is adhering to the prescribed regimen. If the patient admits that he or she is not taking medications regularly, find out why. Is it too expensive? Are there side effects? Is he or she unconvinced that treatment is beneficial? Is a friend or family member chiding him or her for taking too much medicine? Is the patient afraid of drugs because of adverse publicity in the media? Answers to these questions may provide the physician with clues as to how to persuade the patient to be more adherent. In this type of discussion, the physician must avoid being angry, threatening, judgmental, or accusatory and should convey sympathy and understanding. Often a nurse clinician or physician's assistant can obtain information about noncompliance that a physician cannot, perhaps because patients are too embarrassed or even frightened to admit to a physician their failure to comply.

It is a well-known fact that patients who claim steadfast adherence to a regimen are not always truthful. Indirect evidence of noncompliance includes failure to keep appointments regularly, failure to renew prescriptions on time, failure to know what medications they are taking and at what intervals ("I just take whatever my wife lays out for me"), frequent complaints about side effects or cost of medication, and evasive answers to questions about how faithful they are in taking medication ("usually," "most of the time," and "I have trouble when I'm busy"). Sometimes, useful information can be gleaned in a private conversation.

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with a spouse or other persons who live with the patient.

There are some subtle, more objective clues to non-compliance that are occasionally helpful. These include a resting pulse rate $\geq 80$ beats/min in a patient who is supposedly taking a $\beta$-blocker, a serum uric acid level that doesn't increase, or a serum potassium level that doesn't decrease in a patient who is supposedly taking a thiazide diuretic.

Finally, the more complicated the regimen, the more the tablets, and the more frequently they are prescribed, the less the compliance.

There are other ways, besides not taking medication regularly, that a patient can thwart an otherwise good regimen, knowingly or unknowingly. These include excessive sodium or alcohol intake and obesity. Sooner or later, a determination of 24-hour urinary excretion of sodium should be made for patients who are not responding optimally to a good regimen. Dustan et al.,3 Finnerty et al.,4 and Finnerty5 have demonstrated the importance of controlling plasma and extracellular fluid volumes during treatment of hypertension. Expansion of fluid volume is a frequent cause for refractoriness to antihypertensive drugs, and this usually occurs because an oral diuretic has been omitted from the regimen or has been prescribed in suboptimal doses or because the patient is ingesting so much sodium that even an average dose of diuretic is ineffective. When used as monotherapy, reserpine, guanethidine, guanadrel, the $\alpha_2$-agonists, $\alpha$-blocking agents, and the vasodilators hydralazine and minoxidil can cause enough sodium and water retention to counteract their antihypertensive action, leading to pseudotolerance.

Adequacy of Regimen

Before hypertension should be considered resistant, the patient should be on a triple drug regimen that includes a diuretic plus an adrenergic inhibitor (or ACE inhibitor) and a direct vasodilator. Doses of each should be maximal or nearly maximal. It is much easier for a physician to evaluate the adequacy of a regimen than to evaluate the level of compliance.

Often patients are referred as resistant hypertensives because their hypertension has not responded satisfactorily to a series of antihypertensive drugs, all prescribed sequentially as monotherapy, sometimes in suboptimal doses, with no attempt made to follow a stepped-care regimen.

For these patients, resistance disappears when two or more antihypertensive drugs are prescribed in rational combinations. In my experience, omission of a diuretic is a frequent reason why hypertension doesn’t respond as anticipated.

Pseudohypertension

When it has been ascertained that the patient is compliant and the regimen adequate, the physician should rule out pseudohypertension due to medial sclerosis of the brachial arteries that leads to spuriously high readings by the indirect method because calcified arteries are difficult to compress. This should be suspected when the systolic pressure is inordinately high and when there are no signs of chronic hypertensive changes in the retinal arterioles and no evidence of left ventricular hypertrophy in the electrocardiogram or cardiomegaly on chest radiograph. The brachial artery is tortuous, readily palpable, and noncompressible and can be seen to pulsate with each heart beat. The radial artery is usually palpable even between heart beats and after a sphygmomanometer cuff has been inflated high enough to compress the brachial artery (Osler’s maneuver).6 If intra-arterial pressures are normal, no treatment is necessary.

Office Hypertension

Office hypertension should also be ruled out by having the patient’s blood pressure measured at home over a period of time or by using an ambulatory blood
pressure monitor for 24 hours. If blood pressure at home is normal, further attempts to reduce office pressure may result in unacceptable side effects or even hypotension at home. Ibrahim et al. have reported that regression or progression of electrocardiographic evidence of left ventricular hypertrophy correlates better with home blood pressure than with office blood pressure when there is a disparity between the two.

**Drug Interactions**

Physicians should appreciate that certain drugs can interfere with the action of antihypertensive agents even when given in appropriate combinations and doses (Table 1). Notorious for this are the oral contraceptives and the nonsteroidal anti-inflammatory drugs, especially indomethacin, ibuprofen, and piroxicam, but any of them can interfere with hypertension control with the possible exception of sulindac. Physicians should inquire specifically about use of these drugs since many patients forget to report that they are taking medication for reasons unrelated to hypertension. Furthermore, some nonsteroidal anti-inflammatory drugs are now available over the counter. Amphetamines, ephedrine, chlorpromazine, cocaine, and tricyclic antidepressants interfere with the action of guanethidine and guanadrel and perhaps also with the action of central α-agonists. It is unlikely that conjugated estrogens in the doses usually prescribed for controlling menopausal symptoms will have an adverse effect on well-treated hypertension. Ingestion of sympathomimetic amines in over-the-counter cold remedies, in appetite suppressants, or in nasal sprays can sometimes elevate blood pressure in spite of an otherwise effective regimen, especially if excessive doses are taken.

**Secondary Hypertension**

When inadequacy of the regimen has been assured and when noncompliance, pseudohypertension, office hypertension, and drug interactions have been ruled out, the physician should consider the possibility that hypertension may be secondary to a definable cause that has been overlooked or that has developed since the initial evaluation. These include pheochromocytoma, primary aldosteronism, and renovascular disease. Thirty percent of patients who were ultimately found to have primary aldosteronism were originally referred to The Cleveland Clinic for resistant hypertension.

Acquired resistance to a previously effective regimen in a middle-aged or elderly patient so strongly suggests atherothrombotic renovascular disease that only a normal renal arteriogram performed by the Seldinger technique should be accepted to rule it out. Atherosclerotic renal vascular disease is not a rare cause for refractory hypertension in patients older than 55 years, and renal revascularization is sometimes the only way to reduce the blood pressure. Even for patients with primary resistance to a triple drug regimen, a renal arteriogram is indicated, as are determinations of plasma catecholamines and urinary metanephrines and determinations of plasma or urinary aldosterone on high and low sodium diets.

**Alteration of Regimen and Measurement of Hemodynamic Parameters**

After a remediable cause has been ruled out, the hypertension can be considered drug resistant. At this point, the physician has the option of altering the regimen, usually by adding a fourth agent, increasing the doses of present agents, substituting other drugs for ones that are in the regimen, or combinations of these. Such modifications of the regimen can be made empirically or can be guided by the results of measurements of hemodynamic parameters while the patient is receiving the ineffective regimen to identify the mechanism or mechanisms for the resistance (Table 2).

Guanethidine has traditionally been considered the

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**Table 1. Some Drug Interactions That Might Lead to Resistant Hypertension**

<table>
<thead>
<tr>
<th>Nonsteroidal anti-inflammatory drugs*</th>
<th>vs</th>
<th>any antihypertensive drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>vs</td>
<td>any antihypertensive drugs</td>
</tr>
<tr>
<td>Symptomatic amines</td>
<td>vs</td>
<td>any antihypertensive drugs</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>vs</td>
<td>diuretics</td>
</tr>
<tr>
<td>Rifampin</td>
<td>vs</td>
<td>propranolol</td>
</tr>
<tr>
<td>Smoking</td>
<td>vs</td>
<td>propranolol</td>
</tr>
<tr>
<td>Aspirin</td>
<td>vs</td>
<td>captopril</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
<td>guanethidine</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>vs</td>
<td>guanadrel</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
<td>? methyldopa</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td>? clonidine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*With the possible exception of sulindac.

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**Table 2. Hemodynamic Aberrations Responsible for Resistant Hypertension and Their Appropriate Management**

<table>
<thead>
<tr>
<th>Hemodynamic measurement</th>
<th>Management*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output ↑</td>
<td>β-Blocker</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td>Peripheral resistance ↑</td>
<td>Hydralazine</td>
</tr>
<tr>
<td></td>
<td>Minoxidil</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Plasma volume ↑</td>
<td>Diuretic (loop)</td>
</tr>
<tr>
<td></td>
<td>Dietary sodium restriction</td>
</tr>
<tr>
<td>24-Hour urinary sodium ↑</td>
<td>Diuretic</td>
</tr>
<tr>
<td></td>
<td>Dietary sodium restriction</td>
</tr>
<tr>
<td>Plasma catecholamines ↑</td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Methylldopa</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
</tr>
<tr>
<td>Plasma renin activity ↑</td>
<td>β-Blocker</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Plasma or urinary aldosterone ↑</td>
<td>Spironolactone</td>
</tr>
</tbody>
</table>

*If patient is already taking drugs listed in this column consider increasing dose.
agent of choice to add as the fourth step when hypertension is resistant to a three drug regimen, but clonidine seems to be more effective and is better tolerated.

In a series of 16 patients whose hypertension remained resistant to triple drug therapy (a diuretic, β-blocker, and vasodilator), clonidine was added as a fourth agent, starting with a dosage of 0.2 mg once daily at bedtime (C. Acker, R.W. Gifford, Jr., K. Bolen, and D.G. Vidt, unpublished data). The dosage was increased to as much as 1.2 mg daily. After 5 months to 8 years of quadruple drug therapy, average supine blood pressure was reduced from 166/99 to 151/87 mm Hg, and average standing blood pressure was reduced from 162/98 to 137/84 mm Hg. The supine and standing diastolic blood pressures were reduced to <90 mm Hg in 12 of the 16 patients. Obviously, if an α2-agonist is already in the regimen, this would not be an appropriate approach.

Minoxidil can be substituted for hydralazine.16-18 This is probably as effective as adding clonidine as a fourth agent but is not as acceptable to many patients, especially women who almost invariably discontinue the drug after 3 to 6 months because of hirsutism. Minoxidil often causes sodium and water retention that leads to marked edema unless large doses of furosemide or bumetanide are prescribed simultaneously. To avoid the undesirable adverse effects of minoxidil, a calcium channel blocking agent could be substituted for hydralazine or even added to a triple drug regimen that includes hydralazine.19

If a converting enzyme (ACE) inhibitor is not already in the regimen, it can be added,20-22 and if it is in the regimen, an adrenergic inhibitor can be added. One of the most potent regimens available consists of a diuretic, β-blocker, ACE inhibitor, and minoxidil. To this regimen, clonidine or a calcium slow channel blocking agent (nifedipine, diltiazem, or verapamil) could be added.

Sometimes, combining two adrenergic inhibitors in a multi-drug regimen is helpful (e.g., a β-blocker plus an α2-agonist or prazosin, an α1-blocker).

Finnerty and associates23 have proposed “resetting the barostats” for patients with resistant hypertension by administering diazoxide intravenously repeatedly for 7 to 10 days to keep the diastolic blood pressure ≤110 mm Hg after which it was found that the hypertension could be controlled with a combination of oral medications. This, of course, requires hospitalization, but it is justified if hypertension is truly resistant. Hospitalization also provides the opportunity to monitor compliance with diet and drugs. Occasionally, patients with what appears to be resistant hypertension can be controlled in the hospital on a rigid dietary sodium restriction (0.5 g sodium/day) and an enforced taking of medications.

With the variety of antihypertensive drugs that are available today, it is usually possible to find a combination that is both effective and that can be tolerated even though four or five drugs of different classes have to be included in the regimen. Only rarely is it justified to resort to lumbo-dorsal sympathectomy or, for patients with bilateral renal parenchymal disease, bilateral nephrectomy16 to control resistant hypertension.

Discussion

Probably less than 1% of hypertensive patients have truly drug resistant hypertension as previously defined. The most common causes for what appears to be resistant hypertension are poor compliance with drug and dietary regimens and inadequate regimens. Less frequently, patients with so-called resistant hypertension have office hypertension, pseudohypertension, or unrecognized secondary hypertension. Drug interactions are being recognized more often because nonsteroidal anti-inflammatory drugs are being widely prescribed and are now available over the counter. When these causes for resistance to antihypertensive therapy have been ruled out, it is appropriate to modify the regimen by adding additional drugs and by substituting drugs that have not been tried before for ones that have not been effective. This can be done more intelligently if the abnormal hemodynamic mechanisms sustaining the hypertension have been identified.

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