Management of Difficult to Control Hypertension

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Hypertension is a primary risk factor for heart disease and stroke, the first and third most common causes of death in the United States. The National Health and Nutrition Examination Survey (NHANES) revealed an increase in awareness of hypertension from 51% to 73%, and, among persons with hypertension, the treatment rate has increased from 31% to 55% (from 1976-1980 vs 1988-1991). Of importance, the rate of those achieving goal blood pressure (<140/90 mm Hg) has only improved from 10% in NHANES-II (1976-1980) to 29% in NHANES-III (1988-1991). Thus, more than 70% of persons with hypertension in whom good blood pressure control has not been achieved are termed “difficult hypertensives.” Failure to achieve treatment blood pressure goals of less than 140/90 mm Hg is usually attributed to the presence of resistant hypertension, a resistant physician, secondary causes of hypertension such as renovascular disease, medication adverse effects, or a nonadherent patient. A practical understanding of the pathophysiology of resistant hypertension, appropriate screening techniques for secondary forms of hypertension, and alternative management strategies for a chronic disease such as hypertension can result in treatment goals being achieved in most difficult hypertensives.

In the second half of the 20th century, cardiovascular mortality continued to decrease in the United States. Age-adjusted death rates from stroke and coronary heart disease, the first and third most common causes of death in the United States, declined by 60% and 53%, respectively. These reductions in cardiovascular disease occurred despite the Third National Health and Nutrition Examination Survey (NHANES-III) (1988-1991) showing that only 55% of persons with hypertension are being treated (up from 31% in NHANES-II [1976-1980]) and only 29% have reached a goal blood pressure of less than 140/90 mm Hg (up from 10% in NHANES-II). Awareness of hypertension increased from 51% to 73%. This demonstrates that, while any blood pressure reduction dramatically reduces cardiovascular disease, a considerably greater benefit may be achieved if most persons with hypertension can be successfully treated. Despite more than 40 years of advancement in the development of many effective antihypertensive medications, 70% of patients with hypertension are “difficult hypertensives,” i.e., they have not achieved maximal cardiovascular benefit by reaching a goal blood pressure level. Understanding the pathophysiology of resistant hypertension, recognition of secondary forms of hypertension, and alternative management strategies for chronic disease in contrast to acute illness can substantially improve the number of patients who achieve their goal blood pressure.

GOALS OF HYPERTENSION MANAGEMENT

Goal blood pressure according to the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) for the patient with uncomplicated hypertension is a systolic blood pressure lower than 140 mm Hg and a diastolic pressure lower than 90 mm Hg, based on the mean of 3 blood pressure levels determined in the traditional setting of the physician’s office. There is a linear relationship between blood pressure and both risk of stroke and rate of decline in renal function due to all forms of renal disease. Optimal blood pressure is less than 120/80 mm Hg. The “white coat effect” or office pressor effect is well known to the lay public and is often voiced by patients as skepticism of whether they
actually have hypertension or whether their treatment is adequate. Most patients with white coat effect record appreciably lower out-of-office blood pressures; however, most of these determinations will not reach the out-of-office normal of 125/85 mm Hg. Thus, patients with white coat effect have hypertension. An out-of-office blood pressure of less than 135/85 mm Hg is the goal for successful treatment of blood pressure. Recognition of these different goals for office and out-of-office blood pressure determinations is important because out-of-office blood pressure monitoring is an increasingly important tool in the successful management of hypertension. The JNC-VI also identified subsets of hypertensives (Table 1) in whom aggressive therapy is warranted.

Regarding goal blood pressure, the next issue is how often, in the best of circumstances such as treatment trials of hypertension, are these goals achieved. Reviews of recent trials show starkly different results for systolic and diastolic blood pressure. A goal diastolic blood pressure of less than 90 mm Hg was reached in 72% of subjects in the Treatment of Mild Hypertension Study (TOMHS) and in 92% of hypertensive subjects in the Hypertension Optimal Treatment (HOT) trial. Reduction of systolic blood pressure to a goal of less than 140 mm Hg is achieved substantially less often. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 28% of hypertensives had blood pressures lower than 140/90 mm Hg at entry into the study. Two years later, 60% of patients had blood pressures lower than 140/90 mm Hg. In the recent Systolic Hypertension in Europe (Syst-Eur) trial of hypertension therapy, only 43.5% of patients reached a systolic blood pressure of less than 140 mm Hg. These data suggest that new treatment paradigms may be needed to achieve higher control rates for systolic blood pressure.

**SECONDARY CAUSES OF HYPERTENSION**

Identifiable diseases causing hypertension represent less than 5% of all cases of hypertension. Thus, screening all hypertensives for these conditions is inappropriate. A patient’s prior response to antihypertensive therapy may be one of the most helpful screening techniques for secondary hypertension. Pronounced hypokalemia due to low-dose diuretic therapy is highly suggestive of the presence of primary aldosteronism. Renal failure or an exaggerated reduction of blood pressure after treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers may indicate renal artery stenosis. Failure of 2 or more antihypertensive medications to help a patient achieve a goal blood pressure may also suggest the presence of renal artery stenosis. A paradoxical increase in blood pressure with the use of β-blockers may suggest the presence of a pheochromocytoma.

**RESISTANT HYPERTENSION**

“Resistant hypertensives” are an important subset of the difficult hypertensives. Resistant hypertension is defined as failure to decrease blood pressure to less than 140/90 mm Hg while the patient is taking 3 or more appropriate antihypertensive agents; previously, the definition was 2 or more agents. Recent treatment trials have shown that one of the myths of hypertension treatment is that most patients achieve control with only a single agent. The HOT and Syst-Eur trials showed that, at most, one half of patients achieve goal blood pressure with a single agent. Another third of patients require 2 agents, and the rest need 3 or more agents to control hypertension. Characterization of the pathophysiology of the resistant hypertensive allows modification of therapy to achieve a goal blood pressure. A prospective study of the plasma volume in 32 consecutive patients...
Table 2. Testing for Common Secondary Forms of Hypertension

<table>
<thead>
<tr>
<th>Secondary form</th>
<th>Suggested</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal artery stenosis</td>
<td>Doppler ultrasonography</td>
<td>Renogram with and without captopril, captopril challenge test, digital subtraction arteriography, magnetic resonance arteriography, fast spiral computed tomography</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>24-h urinary collections for vanillylmandelic acid, metanephrine, and fractionated catecholamines</td>
<td>Plasma catecholamines, clonidine suppression test</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>24-h urinary collections for vanillylmandelic acid, metanephrine, and fractionated catecholamines</td>
<td>24-h urinary aldosterone excretion rate, saline suppression test, serum 18 hydroxycorticosterone (18-OHB)</td>
</tr>
</tbody>
</table>

patients with resistant hypertension lends important insight into the mechanism of resistance. None of these patients had any clinical signs of volume expansion (increased jugular venous distention, rales, or edema), and all received diuretic therapy and a mean of 2.3 other agents, with a mean ± SD blood pressure of 183±30/107±18 mm Hg. Of these 32 patients, 23 had elevated plasma volumes, 5 had normal plasma volumes, and only 4 had low plasma volumes. Of importance, the plasma volume was evaluated again in 9 patients whose blood pressure was controlled after modification of blood pressure therapy based on the status of the plasma volume. Patients with plasma volume expansion received intensified diuretic therapy and those with plasma volume constriction received vasodilator therapy (Table 3). The plasma volume predicted how to modify blood pressure therapy to achieve goal blood pressure (Figure 1). Not only was blood pressure control achieved but also the number of agents required to accomplish this was reduced substantially after aggressive diuresis (Table 3). Reducing the plasma volume expansion required large doses of diuretics, often loop diuretics (furosemide), even in patients with normal renal function. In resistant hypertensives, attention to sodium intake and basing the antihypertensive regimen on aggressive diuretic therapy (hydrochlorothiazide, 50 mg/d; metolazone, 2.5-5 mg/d; furosemide, 40-120 mg/d; bumetanide, 1-4 mg/d) often lead to success in reaching goal blood pressure.

PATIENT HABITS

Difficult to control hypertension may occur because of patient habits that antagonize antihypertensive therapy (Table 4). The adverse effect of sodium and alcohol on hypertension is well known and was reviewed in JNC-VI. Less appreciated substances that affect blood pressure are cigarettes, caffeine, and over-the-counter medications such as nonsteroidal anti-inflammatory drugs (NSAIDs). Freestone and Ramsay illustrated the effect of caffeine and smoking on hypertension. In their study of 16 patients with hypertension, the equivalent of smoking 2 cigarettes and drinking 2 cups of coffee increased systolic and diastolic blood pressure a mean of 16 mm Hg and 9 mm Hg, respectively. These investigators calculated that smoking 2 packs of cigarettes and drinking 6 to 8 cups of coffee elevate blood pressure throughout the waking day. Whether nicotine and caffeine can cause hypertension is unclear. The pressor effect of these habits may explain why a patient has good blood pressure levels in the physician’s office (waiting to see the doctor is forced abstinence from these habits) and elevated or labile blood pressure when determined out of office. Encouraging cessation of or refraining from these habits for at least 1 hour before blood pressure is measured in or out of the office is important to avoid their effect on evaluation of blood pressure control. Alternatively, if patients are unable to discontinue nicotine and caffeine use, determining their blood pressure at home and using a blood pressure goal of less than 135/85 mm Hg are acceptable.

Use of NSAIDs in the United States is ubiquitous, varying from occasionally to daily. Among hypertensives, 20% or more have concomitant arthritic complaints; thus, awareness of the effect of these agents on antihypertensive therapy is important. Information about NSAIDs and hypertension is from a study by Radack et al who assessed 45 hypertensives receiving a stable regimen of drug therapy. They were randomized to a 3-week course of ibuprofen, acetaminophen, or placebo. Significant elevations in mean systolic (7 mm Hg) and diastolic (6 mm Hg) blood pressure were seen in those taking ibuprofen, whereas acetaminophen and placebo had no pronounced effect on blood pressure. This effect is thought to be mediated by NSAIDs’ interference of renal sodium excretion,
even in the setting of diuretic therapy. An additional concern in hypertensives taking NSAIDs is the development of hyperkalemia. Elderly patients who already have an age-related decrease in aldosterone-mediated potassium homeostasis and are often taking other antihypertensive agents that impair potassium homeostasis, such as ACE inhibitors, angiotensin II receptor blockers, and β-blockers, may develop clinically important hyperkalemia if they also take NSAIDs. A carefully elicited history with attention to the patient’s habits (Table 4) may identify the reason for difficult to control hypertension, and patient education about these habits will increase the ability to achieve goal blood pressure. Of note, low-dose aspirin therapy (81 mg/d) does not affect blood pressure.

### PATIENT ADHERENCE

Successful treatment of hypertension requires patient adherence to the regimen that has been agreed on by the patient and the physician. Achieving adherence has relied on education of the hypertensive patient regarding issues of

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#### Table 3. Antihypertensive Drugs Used at Presentation of Patient and After Blood Pressure Has Been Controlled

<table>
<thead>
<tr>
<th>Patient</th>
<th>Uncontrolled blood pressure (mm Hg)</th>
<th>Controlled blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180/110</td>
<td>160/90</td>
</tr>
<tr>
<td>2</td>
<td>184/114</td>
<td>146/92</td>
</tr>
<tr>
<td>3</td>
<td>142/88</td>
<td>120/80</td>
</tr>
<tr>
<td>4</td>
<td>182/106</td>
<td>134/90</td>
</tr>
<tr>
<td>5</td>
<td>170/110</td>
<td>122/78</td>
</tr>
<tr>
<td>6§</td>
<td>185/94</td>
<td>155/80</td>
</tr>
<tr>
<td>7/§</td>
<td>180/100</td>
<td>135/95</td>
</tr>
<tr>
<td>8/§</td>
<td>168/108</td>
<td>160/80</td>
</tr>
<tr>
<td>9/§</td>
<td>180/120</td>
<td>140/92</td>
</tr>
</tbody>
</table>

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*From Graves et al* with permission.

**bid** = twice a day; **tid** = three times a day.

§Give first dose in the morning and second at noon.

§Plasma volume contracted.

§Abnormal renal function.
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Figure 1. Plasma volume (cc/kg) at patient presentation and after blood pressure has been controlled (from Graves et al16 with permission).

Figure

- Normal Renal Function
- Abnormal Renal Function

Uncontrolled Blood Pressure Controlled Blood Pressure

Outcome of poorly controlled hypertension as well as risks and benefits of therapy. Education alone is ineffective since success rates of blood pressure control remain low despite more than 20 years of educational efforts on hypertension by the National Heart, Lung, and Blood Institute. Education increases awareness but seemingly does not affect behavior. Alternative efforts are necessary to improve blood pressure control rates. Failure of patients to achieve compliance with long-term antihypertensive regimens and the effect of failed compliance on resultant blood pressure control have been documented. Winickoff and Murphy13 demonstrated that only one half to two thirds of patients took 75% of their prescribed antihypertensive medication. Of those who took less than 75% of their antihypertensive medication, only 37% achieved goal blood pressure. Of patients who took 75% or more of their antihypertensive medication, 81% reached goal blood pressure of less than 140/90 mm Hg. The primary correlate with taking more than 75% of the prescribed antihypertensive regimen was the number of pills required. The fewer the pills, the more likely patients were to take them. Thus, the first suggestion to improve adherence is combination therapy for hypertension.

Combination therapy not only improves adherence but also corresponds well with the number of antihypertensive drugs likely needed to control blood pressure in the average patient. The Syst-Eur study7 showed that only one half of patients with hypertension achieved blood pressure control while receiving monotherapy. Therefore, at least half of all hypertensives will require 2 or more agents to achieve blood pressure control. Rational combination therapy, 2 antihypertensive medications in a single pill that complement each other, was an early concept in hypertension therapy, as demonstrated by Ser-Ap-Es (reserpine, hydralazine hydrochloride, and hydrochlorothiazide) and Aldoril (methyldopa and hydrochlorothiazide). Now, there are many different effective combination agents. First, there is the use of diuretics plus ACE inhibitors, angiotensin II blockers, or β-blockers. The second combination therapy, which is increasingly available, is calcium channel blockers with ACE inhibitors, eg, felodipine and enalapril (Lexxel), amlodipine and benazepril (Lotrel), diltiazem and enalapril (Teczem), and verapamil and trandolopril (Tarka). All these combination drugs offer synergy of action and enhanced compliance to a 2-drug regimen, improving the patient’s ability to achieve goal blood pressure. Preliminary studies of a new class of agents, vasopeptidase inhibitors ( omapatrilat), which block ACE and neutral endopeptidase, have shown enhanced effectiveness as a single agent to achieve goal blood pressure.14

The second technique to improve patient adherence and blood pressure control is the frequency of visits for hypertension. An analysis of the clinical trials of hypertension therapy shows how frequency of visits affects the achievement of goal blood pressure. In the HOT trial,9 92% of patients achieved a diastolic blood pressure goal of less than 90 mm Hg; these patients were seen monthly for 2 to 3 months, then at 3, 6, and 12 months, and then at 6-month intervals until study completion. In the Syst-Eur study,7 43.5% of patients achieved a blood pressure of less than 140/90 mm Hg; these patients were seen monthly until goal blood pressure was achieved and then every 3 months thereafter. These results suggest that, for successful blood pressure control, frequent visits with aggressive titration of blood pressure therapy are essential to achieve goal blood pressure. Maintenance of blood pressure control requires frequent patient visits, at least every 3 months. One of the most important aspects of frequent patient visits is frequent measurement of blood pressure. Issues of cost control and limiting of patient-physician visits have increased the use of out-of-office blood pressure monitoring. This type of monitoring provides important information about blood pressure, including evaluation of adverse effects, such as orthostatic hypotension, and monitoring the effects of antihypertensive therapy. A study by Zarnke et al15 showed that home monitoring can result in substantial improvement in blood pressure control. Rapid titration of blood pressure medications may also be a useful method for improving the rates of blood pressure control. Canzanello

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Table 4. Patient Habits Antagonizing Antihypertensive Therapy

<table>
<thead>
<tr>
<th>Dietary sodium</th>
<th>Excessive water consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol consumption</td>
<td>Caffeine consumption</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>Nonsteroidal anti-inflammatory drug use</td>
</tr>
</tbody>
</table>

et al showed that rapid nurse-managed alterations in blood pressure medications are well tolerated and result in a sustained improvement in blood pressure. In their study, 44 patients (mean age, 65 years) had 1 to 3 visits daily for an average of 4 consecutive days; the blood pressure was recorded, and medications were rapidly adjusted to achieve goal blood pressure. After sudden titration, mean dismissal blood pressure was 139/75 mm Hg, and after 1 year, blood pressure was well maintained at a mean of 133/74 mm Hg.

Finally, the integration of the team approach to hypertension management offers the new paradigm for achieving blood pressure goals in difficult hypertensives. The Mayo Clinic Division of Hypertension has been using a team composed of the patient, physician, nurse educator, and dietitian to optimize blood pressure control. Individual hypertension management programs are devised by the team and managed by nurse educators. Nurse educators provide a high frequency of patient contact, increased and continued patient education on the importance of modification of habits that affect blood pressure control, and surveillance of adverse effects. The physician supervises the nurse educators at regular intervals as they pursue goal blood pressure. This strategy enables the physician to focus on management problems and decisions regarding design of therapeutic regimens and delegates maintenance blood pressure control to nurse educators, potentially improving the efficiency of antihypertensive therapy. This approach has been used successfully for short-term alterations of antihypertensive therapy, in special treatment groups such as liver transplant recipients, and in maintenance therapy for hypertensives. The patient is an important part of the team. Identifying goals of treatment and expected outcomes, detecting and managing problems of therapy such as cost and adverse effects, and a willingness to engage in a long-term relationship with the medical members of the team require direct and continuous patient input. Technology may further enhance this relationship. Menard et al used out-of-office blood pressure monitoring with a modem link (Omron HEM 705C) to download out-of-office blood pressures to a central clinic. This improvement in data transfer allows real-time evaluation of blood pressure control. Electronic data transfer and management may increase efficiency by reducing the amount of time the nurse educator needs to collect blood pressures and by allowing more time with the difficult hypertensive.

Currently, the number of difficult hypertensives is too large. Many important clues exist to identify the reasons for inadequate control of blood pressure. The initial history and physical examination findings and the patient’s subsequent response to antihypertensive therapy can easily be used to screen for secondary causes of hypertension. Patient habits that can adversely affect blood pressure control can be identified and can be modified to improve blood pressure control with patient education. Important therapeutic strategies exist to improve adherence. Both the patient to the physician must be aware of the scientific basis that justifies an aggressive pursuit of an individual patient’s blood pressure goals. Physicians must encourage the patient to remember the disability and the mortality that will result if reduction in blood pressure is unsuccessful. Through the use of new combination therapy, enhanced patient contact, and new paradigms of disease management that improve adherence, the number of difficult hypertensives will decrease.

REFERENCES


Questions About Achieving Blood Pressure Control in Difficult Hypertensives

1. Which one of the following percentages is true concerning the known US hypertensives who had a treated blood pressure of less than 140/90 mm Hg in 1991?
   a. 9
   b. 29
   c. 49
   d. 75
   e. Greater than 90

2. Which one of the following is true regarding goal blood pressure?
   a. Is equal to patient age plus 100 for systolic blood pressure
   b. Increases with age for systolic blood pressure but not for diastolic blood pressure
   c. Is less than 140/90 mm Hg for all patients
   d. Is the same for both office and out-of-office blood pressure measurement
   e. Is less than 140/90 mm Hg in the office for the patient with uncomplicated hypertension

3. Which one of the following is not a clue to secondary forms of hypertension?
   a. Flushing, bounding pulses, and headache
   b. Abdominal bruit
   c. Diminished lower extremity pulses
   d. Abdominal striae
   e. Profound hypokalemia while patient is receiving diuretic treatment

4. Which one of the following is true regarding resistant hypertension?
   a. Can commonly be overcome with the 1 correct antihypertensive agent for each given patient
   b. Is defined as failure to reach a blood pressure level lower than 140/90 mm Hg after patient has taken 3 or more single antihypertensive agents
   c. Is commonly mediated by plasma volume contraction
   d. Is commonly caused by vasoconstriction
   e. Occurs more commonly in women than in men

5. Which one of the following strategies is not used to improve blood pressure control?
   a. Diagnosing and treating secondary causes of hypertension
   b. Encouraging patients to drink 2 glasses of red wine daily
   c. Decreasing or discontinuing caffeine and nicotine use
   d. Using a team approach to hypertension management
   e. Using a combination of antihypertensive agents

Correct answers: 1. b, 2. e, 3. a, 4. b, 5. b