

REFRACTORY HYPERTENSION: PATIENT TYPES, SPECIAL PROBLEMS, AND APPROACHES TO THERAPY

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Webster's Dictionary defines refractory as *resisting control or authority; stubborn, unmanageable; resistant to treatment or cure; unresponsive*. These terms adequately describe the issues under discussion in this portion of the symposium. I would describe refractory hypertension as high blood pressure of moderate to severe degree that is not easily controlled or managed; in other words, a hypertensive patient who is resistant to treatment.

But, actually, who is this patient? Is it the patient with a grade IV hypertensive retinopathy or with accelerated hypertension? To be sure this patient is often refractory to treatment, but represents a relatively small portion of the hypertensive population at risk. I think we are talking about a much larger group of refractory patients. Is it the patient with moderate to severe hypertension who needs multiple drugs and is noncompliant because of side effects? Or is it the patient with mild hypertension who should have his blood pressure controlled with monotherapy but fails to achieve control for a variety of reasons?

All of these groups of patients may be defined as "refractory." In regard to those with mild hypertension, most will do well on single-drug therapy if compliance is maintained. This dictates that the drug prescribed should have a convenient dosage schedule with a minimum of side effects, or at least, side effects that can be easily tolerated.

One of the major causes of refractory disease in

patients with mild to moderate hypertension is non-compliance. A study, published approximately ten years ago by Aronow,¹ examined 1,800 patients with the diagnosis of hypertension and identified two major factors affecting blood pressure control.

The first factor, patient compliance, was evident from findings in these 1,800 patients that revealed that 20 percent of patients did not return for follow-up. Additionally, one half did not take the medication prescribed and almost 80 percent did not follow the advice given for reducing risk factors. The second factor was physicians' contribution to noncompliance. Almost one half of the physicians studied were found to have dismissed test results as normal and one third did not prescribe therapy when hypertension was suspected. Only 25 percent of the physicians in this 1975 study actually prescribed appropriate medications for control of blood pressure. It is hoped that these problems have improved greatly since the Aronow study.

PATIENT TYPES

Still, we have not identified the refractory hypertensive patients deserving of our special attention in this symposium. Three types of patient fall into this category and will be discussed at length by various speakers:

1. *The black hypertensive with early development of end-organ damage, particularly in the kidney or heart.* This type of patient tends to develop more severe hypertension. The goals of therapy for this group

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include not only reduction of blood pressure to normal levels, but also reduction of the risk factors causing acceleration of renal failure or enhancement of left ventricular hypertrophy. Improved kidney function should be an additional goal.

2. *The patient, generally with hypertension in the moderate to severe range, who requires multiple medications.* Multiple drug regimens often lead to non-compliance because of adverse effects caused by inappropriate combinations, economic problems, such as increased costs, and the metabolic consequences of this type of therapy.

3. *The elderly patient, with mild to moderate hypertensive disease, at risk of end-organ damage.* These patients generally become noncompliant because of the side effects of commonly prescribed medications, for example, orthostatic hypotension following thiazide diuretics and methyldopa, and/or cold extremities and worsening of peripheral vascular disease due to conventional beta-blocker therapy. These patients are also prone to the development of biochemical alterations such as hypokalemia and hyperlipidemia.

SPECIAL PROBLEMS

The prevalence of hypertension in the black population has been adequately demonstrated for almost 25 years. The National Health Survey in addition to independent studies conducted over a 20-year period have revealed that 20 percent of blacks have blood pressures greater than 160/95 mm Hg, and that mean blood pressure level in black patients was 5.6/5 mm Hg greater than the mean in white patients.² This increased incidence of hypertension was present at all age levels, from teenagers through the elderly, and resulted in a greatly increased mortality rate due to complications.

In 1967, vital statistics issued by the National Center for Health Statistics indicated that death from all causes was approximately four-fold greater among black men than white men.³ Even after correcting for an increased prevalence for hypertension in black patients, the mortality risks from cardiovascular disease were double in black patients. In black men aged less than 50 years, the death rate from hypertension-related disease was six to seven times greater than in white men of the same age.

Perhaps, for the first time, these dramatic findings clearly identified hypertension as a major cause of cardiovascular disease. Subsequently, investigators

began to look for reasons. One theory suggested that plasma volume was higher in black than in white hypertensive patients. Because of the impact of this possibility on therapy, namely, that a diuretic should be the initial drug of choice, additional studies were conducted that have raised questions regarding the accuracy of this theory. Current data indicate that hypertensive white patients have significantly lower plasma volumes than normotensive controls, while black hypertensives appear to have the same plasma volume as normotensive controls. Therefore, the exact reason why black patients appear to respond better to diuretic therapy than white patients is still not clearly understood.

Renal function is one area in which there are real differences between black and white hypertensive patients that can have an impact on therapy. Messerli and co-workers⁴ at the Ochsner Clinic demonstrated conclusively that there is an early development of decreased renal blood flow and increased renal vascular resistance in black hypertensive patients. At all levels of mean arterial pressure, renal vascular resistance was higher and renal blood flow lower in black patients. Similar findings had been reported earlier by Levy et al⁵ using selective arteriography. It appears from these findings that renal vascular disease develops early in black hypertensive patients and is responsible for the low renin measurements found by many investigators.

Findings from one study⁶ that compared the relationships between mean arterial pressure and renal vascular resistance in white and black patients are displayed in Figure 1. Significant correlations are evident in the black patient group, while there is no correlation in the comparative group of white patients. These findings and their clinical significance were supported by the study of Rostand et al⁷ in 1982, who reported that the risk of end-stage renal disease was 18 times greater in black than white hypertensives. Evidence that this renal disease is progressive can be found in the preponderance of black patients on dialysis, and the fact that 80 to 90 percent have end-stage renal disease as a consequence of hypertension.

In summary, studies over the years have revealed the special problems of this refractory population of black hypertensives with mild, moderate, and severe disease to be:

1. The development of early renal disease, requiring therapy that does not significantly affect renal function

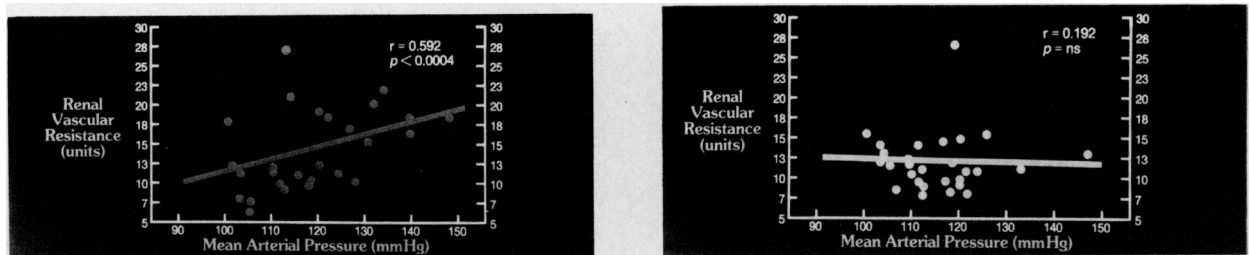


Figure 1. Relationship between mean arterial pressure and mean vascular resistance in black (left) and white (right) patients. Relationship determined using covariant analysis. From Frohlich E et al.⁸ With permission, S. Karger AG, Basel

2. A high incidence of renal and other target organ damage plus an increased risk of stroke and heart attack

3. The need for expensive multiple drug therapy that often leads to economic problems and uncomfortable side effects that ultimately result in noncompliance

THERAPEUTIC APPROACHES

When single-drug therapy is desired, labetalol is an excellent choice for treatment of refractory hypertension in the black patient. The combined vasodilating (selective α_1 -blockade) and nonselective beta-adrenergic blocking properties of labetalol make therapy with this agent extremely successful. Labetalol is also effective, when administered intravenously, for treating the emergency hypertensive patient because of its alpha-blocking activity.

On the other hand, monotherapy with conventional beta-blockers, both selective and nonselective, as well as with angiotensin-converting enzyme inhibitors has not proven effective for the treatment of patients with refractory hypertension. When used as initial therapy, these drugs result in failure in more than one half of the patients and necessitate the addition of diuretic therapy or, preferably, the shifting of the patient to another medication. Multiple drug regimens are often required for black patients presenting with early development of target organ damage, particularly in the kidney and heart.

Calcium channel blockers may prove to be popular therapy for hypertension in the future. Currently, however, they must be taken three to four times daily to be effective—a dosage regimen that encourages noncompliance. Selective and nonselective beta blockers decrease renal blood flow, glomerular filtration rate, and probably should not be used in patients with a propensity for renal disease.

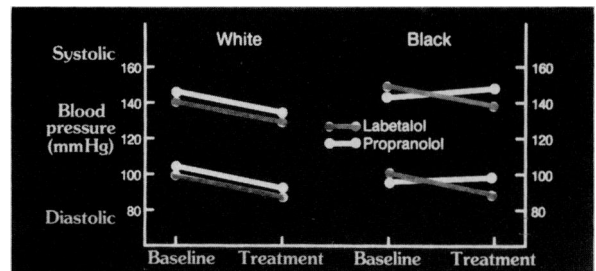


Figure 2. Effects of labetalol and propranolol treatment in black and white patients. From Flamenbaum et al.⁹ With permission, Elsevier Science Publishing Co, Inc

Finally, a multicenter cooperative study by one of our panelists, Dr. Flamenbaum, compared the use of propranolol and labetalol in 140 white and black hypertensive patients. Propranolol was found to lower blood pressure in white patients, but proved totally ineffective in the corresponding group of black patients. Labetalol, with its concomitant α_1 - and nonselective beta-blocking action, lowered blood pressure equally well in both groups (Figure 2). Added to other findings indicating that treatment with labetalol lowers peripheral resistance without significantly altering cardiac output, this agent appears to be an excellent choice for treating the refractory hypertensive black patient.⁹

TREATMENT CONSIDERATIONS IN THE ELDERLY PATIENT

Special problems affect the elderly hypertensive patient. These include hemodynamic abnormalities that worsen with age, cardiac output that decreases progressively, peripheral vascular resistance that increases progressively, a constant deterioration of the microcirculation, an altered response to therapy, and a propensity to orthostatic hypertension. Also, elderly patients can develop hypokalemia and lipid abnormalities, which contribute to coronary artery disease.

TABLE 1. THERAPEUTIC APPROACHES IN THE ELDERLY HYPERTENSIVE PATIENT

Use agents that reduce peripheral vascular resistance, ie, labetalol, calcium channel blockers, angiotensin-converting enzyme inhibitors, alpha antagonists
 Use diuretics with caution
 Avoid conventional beta-blocking agents
 Use appropriate dose of drug

Often, they have peripheral vascular disease that affects the type of therapy that can be administered, or they have an altered drug metabolism that results in control at lower doses than are required by younger patients (Table 1).

These important differences necessitate appropriate prescription and use of antihypertensive medication in the elderly hypertensive patient. Drugs, such as labetalol, that do not reduce peripheral vascular resistance should be prescribed. Conversely, other beta blockers that increase peripheral vascular resistance should be avoided.

Diuretics should be used with caution in the elderly patient because of their effect on peripheral circulation, lipids, uric acid, and potassium. Conventional beta blockers should also be avoided because of their adverse effects on lipids, peripheral resistance, and cardiac output. Here again, labetalol is the exception, as it does not appear to significantly alter the plasma lipid profile when used as monotherapy.^{10,11} And,

lastly, physicians treating these patients should be aware that the elderly may respond to lower doses of antihypertensive drugs and prescribe accordingly.

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