Difficult to Treat Hypertension

Medicine Grand Rounds

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Most hypertensive patients are easy to treat and to manage effectively. However, a small number, perhaps 5%, are difficult to manage and an even larger number, averaging 30% in large clinical trials, do not achieve the desired goal of therapy for various reasons (Menard, 1992). The purposes of this presentation are to identify the reasons why some patients are difficult to treat and to provide guidelines to help improve their management.

I. Resistant Hypertension

A. Definition: Most authorities define "resistance" as the persistence of blood pressure above 140/90 mm Hg despite the use of a rational regimen of three or more antihypertensive agents. The definition should be modified by those over age 65, wherein a systolic above 160 is probably a more reasonable limit.

Resistance should also be defined as either primary or secondary (acquired) (Bravo, 1991). If resistance appears after good control has been accomplished, the development of a secondary mechanism (renovascular hypertension, alcohol abuse), should be strongly suspected. Resistance is not synonymous with severe or malignant hypertension: most resistance will be found among patients with fairly mild hypertension.

B. Prevalence: Primary resistance was seen in 2.9% of 1781 hypertensives drawn from employee clinics in New York City (Alderman et al 1988) and in 3.6% of mild hypertensives enrolled in the Australian Therapeutic Trial (Management Committee, 1984).

The prevalence of acquired resistance is unknown but multiple reports from tertiary care clinics report figures from less than 5% to as high as 18% (Setaro and Black, 1992). Obviously, the prevalence depends upon the nature of the patient population, referral patterns and other demographic features (Shea et al, 1992).

C. Causes and Management (Table 1)

Table 1: Causes for Inadequate Responsiveness to Therapy

Pseudo-resistance
- White coat or office elevations
- Pseudohypertension in elderly

Nonadherence to therapy
- Lack of consistent and continuous primary care
- Inconvenient and chaotic dosing schedules
- Side effects of medication
- Cost of medication
- Instructions not understood
- Inadequate patient education
- Organic brain syndrome (e.g., memory deficit)

Drug-related causes
- Doses too low
- Inappropriate combinations (e.g., two centrally acting adrenergic inhibitors)
- Rapid inactivation (e.g., hydralazine)
- Drug interactions
  - Nonsteroidal anti-inflammatory drugs
  - Sympathomimetics
    - Nasal decongestants
    - Appetite suppressants
    - Cocaine
    - Caffeine
  - Antidepressants (MAO inhibitors, tricyclics)
  - Oral contraceptives
  - Adrenal steroids
  - Licorice (e.g., chewing tobacco)
  - Cyclosporine
  - Erythropoietin
  - Cholestyramine
- Excessive volume contraction with stimulation of renin-aldosterone
- Hypokalemia (usually diuretic-induced)
- Rebound after clonidine withdrawal

Associated conditions
- Smoking
- Increasing obesity
- Sleep apnea
- Insulin resistance/hyperinsulinemia
- Ethanol intake more than 1 ounce a day (> 3 portions)
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (Raynaud's, arteritis)

Secondary hypertension
- Renal insufficiency
- Renovascular hypertension
- Pheochromocytoma
- Primary aldosteronism

Volume overload
- Excess sodium intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

(Modified from Joint National Committee. Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-183).

The listing in Table 1 adequately covers the common causes. More relevant to this discussion are analyses reported from clinics which deal with large numbers of resistant patients (Toner et al, 1990; Isaksson et al, 1991; Yakovlevitch and Black, 1991).

A number of cases that I have recently seen will be used to illustrate some of the more important mechanisms.

1. Pseudo-resistance

Case 1: This 73 year old woman has had progressively rising, predominately systolic hypertension over the past few years, with a level of 260/90 recorded by her internist in late 1992. Despite taking a multitude of medications (including agents from every class of antihypertensive drugs), her office readings remained elevated, from 200/90 to 250/110.

Despite these readings, she remains physically and mentally active, has only Grade I retinopathy, no cardiomegaly and her serum creatinine = 1.6 mg/dl.

Her home blood pressures range from 150-170/75-90, with rare systolic readings as high as 200 mm Hg.

As many as half of patients whose office recordings were repeatedly above 140/90 despite intake of 3 or more medications have been found to have normal home recordings (office hypertension) and/or normal intra-arterial measurements (pseudohypertension) (Waeber et al, 1987; Mejia et al, 1990) (Figure 1).

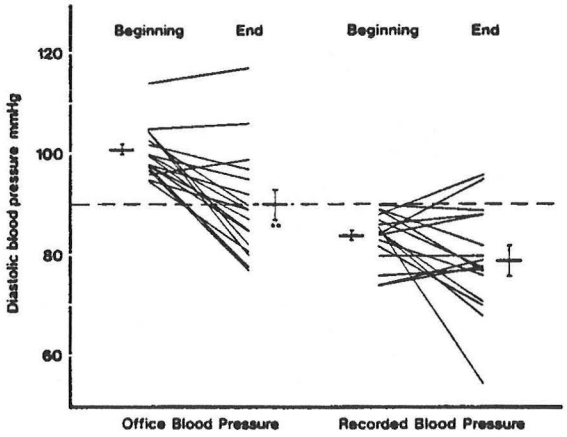

Figure 1: Office and ambulatory diastolic blood pressures at the beginning and the end of the study (n=17). Recorded blood pressures are the average of 24 readings obtained during the daytime by ambulatory monitoring. (From Waeber et al, 1987.)

The elderly with predominantly systolic hypertension have as much or more "office hypertension" as the non-elderly (Cox et al, 1993). Fortunately, they may not have much of a fall in their ambulatory readings when additional therapy is given on the basis of higher office readings (Raccaud et al, 1992). Nonetheless, the potential for overtreatment is present and there is certainly no reason to give drugs that are neither effective nor indicated.

Pickering (1988) has provided a sensible scheme for the evaluation of patients with apparently resistant hypertension (Figure 2). Most patients are willing and able to take home blood pressures with one of the easy to use semi-automatic devices now available (Sunbeam #7601, sold at Service Merchandise for $29). Most of their readings will be lower than those obtained in the office

(Bobrie et al, 1993). Even though most of the risk data are based on office readings, home readings do correlate closely to degrees of target organ damage and should be used to monitor the effectiveness of therapy.

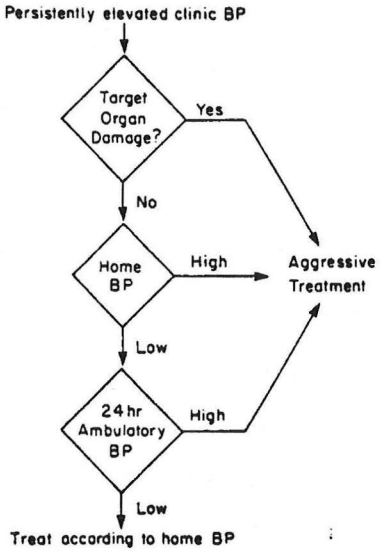

Figure 2: Proposed schema of blood pressure measurement for patients with apparently resistant hypertension. (From Pickering TG, 1988.)

2. Nonadherence to Therapy

Most physicians would pick this as the most common cause for resistance. However, among 91 patients referred to a tertiary care clinic who had been previously dealt with by their primary providers, nonadherence was found to be the primary cause of resistance in only 10% (Table 2).

Table 2: Primary Cause of Resistant Hypertension (From Yakovlevitch & Black, 1991)

Primary Cause of Resistance	No. of Patients	No. Ultimately Controlled	No. Significantly Improved
Noncompliance (without medication intolerance)	9	3	1
Drug related			
Suboptimal medical regimen	39	29	6
Drug interaction	1	0	1
Objective medication intolerance	13	4	1
Interfering substances			
Alcohol abuse	2	2	0
Secondary hypertension			
Renal artery stenosis	6	2	1
Primary aldosteronism	4	4	0
Psychological causes			
Subjective medication intolerance	7	2	0
Office resistance	2	2	0
Cause undetermined	8	0	0

Nonetheless, among an inner-city minority population, in many ways comparable to that seen at Parkland, nonadherence to prescribed therapy was more common, often in association with other obvious causes for poor control of hypertension (Shea et al, 1992) (Table 3).

Table 3: Adjusted Odds Ratios for Severe, Uncontrolled Hypertension According to Various Risk Factors.*

Risk Factor	No. of Patients with Complete Data	Adjusted Odds Ratio (95% CI)	P Value
No primary care physicians	204	4.4 (2.2-8.9)	<0.001
No medical insurance	204	2.2 (1.0-4.6)	0.04
Noncompliance with antihypertensive regimen	199	2.0 (1.5-2.7)	<0.001
One or more alcohol-related problems	204	2.2 (0.8-6.3)	0.14
Illicit drug use in the past year	204	1.3 (0.5-3.6)	0.60

*Adjustment was made in each model for age, sex, race or ethnic group, educational level, and current smoking status, but not for other risk factors. Odds ratios are expressed as the risk of severe, uncontrolled hypertension for a patient with the risk factor listed, as compared with the risk for a patient without it. CI denotes confidence interval. (From Shea et al, 1992.)

When nonadherence is involved, problems with the prescribed medications may be responsible rather than the unwillingness of patients to take them. When cost is a problem (as with many of the non-insured, non-charity patients seen at Parkland), less expensive generic diuretics, beta-blockers, reserpine and calcium channel blockers should be used. However, the cost of the tablets is only a small part of the total cost of therapy and the use of more expensive drugs may be little more expensive overall (Hilleman et al, 1994) (Table 4). Moreover, at some pharmacies, the charges for generic drugs may be even higher than for brand names. Further savings can be gained by breaking larger doses into half with efficient pill cutters costing $3.

Table 4: Mean Costs per Drug per Cost Category for One Year of Use

	Acquisition Cost	Supplemental Drug Cost	Laboratory Cost	Clinic Visit Cost	Side Effect Cost	Total Cost
Diuretics	$133±107	$232±203	$117±32	$298±102	$263±480	$1043±667
Beta-blockers	$334±170	$115±192	$56±32	$187±87	$203±418	$895±545
Alpha blockers	$401±151	$290±290	$114±30	$227±69	$256±485	$1288±697
Centrally Acting Alpha Agonists	$285±224	$295±338	$125±52	$267±114	$193±390	$1165±658
Ace Inhibitors	$444±301	$291±315	$95±33	$218±87	$195±400	$1243±800
Calcium Entry Blockers	$540±219	$278±398	$87±29	$214±81	$306±642	$1425±962

Side effects: In multiple clinical trials involving volunteers who were carefully followed, side effects from antihypertensive medications have caused about 10% to stop therapy (Curb et al, 1988). Although side-effects are reported in about one third of patients in these trials, multiple studies on Quality of Life (QOL) as measured by various questionnaires show that patients who remain on therapy have little or no decrease in their QOL and in fact may have improvements (Beto and Bansal, 1992). But these studies usually do not include the drop-outs and therefore may underestimate the problem.

Nonetheless, data from QOL studies do reveal some interesting facts such as the greater interference with sexual function by centrally acting alpha-agonists, e.g., clonidine, than with other classes (Beto and Bansal, 1992). Moreover, they show that simply asking about adverse reactions may give an incomplete measure of how well a drug is being tolerated (Testa et al, 1991). Therefore, to avoid drop-outs from interferences with QOL, a more detailed questionnaire given to the patient and his or her spouse may be useful. One such questionnaire is provided by Bulpitt and Fletcher (Br J Clin Pharmacol 1990;30:353-364). Others are identified by Guyatt et al (Ann Intern Med 1993;118:622-629).

Note that 7 of the 91 patients described in Table 2 had "subjective medication intolerance" as their primary cause of resistance. These patients were described as having "anxiety (severe and often disabling anxiety and symptoms of panic disorder with episodic elevations in BP) and subjective medication intolerance (misinterpretation of psychological and/or physical stimuli as side effects of drugs, resulting in medication intolerance)." This group will be given special attention later since they comprise many more patients than those who are resistant to therapy in the usual context.

Dosing schedules: Among the other obvious factors listed in Table 1, inconvenient and chaotic dosing schedules should be emphasized. With the availability of once-a-day formulations of every class of antihypertensive drug, there is no excuse for patients being prescribed some drugs on a once-a-day schedule and others on a 2, 3, or 4 times a day schedule. It is possible to treat the majority of even resistant hypertensives with multiple drugs all given once a day (Spitalewitz et al, 1986) (Figure 3).

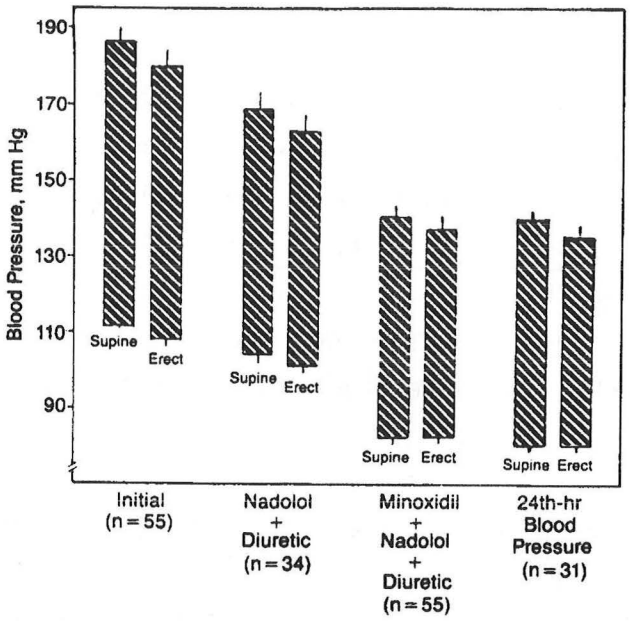

Figure 3: Effect of once-daily drug therapy on blood pressure. (From Spitalewitz et al, 1986.)

3. Drug-related Causes

Case 2: This 60 year old woman, hypertensive for 30+ years and diabetic for 2 years, had office readings around 180/100 despite this regimen:

Clonidine	0.3 mg tid
Diltiazem CD	300 mg q a.m.
Atenolol	50 mg q a.m.
Furosemide	40 mg q a.m.
KC1 tablets	10 mmol q a.m.

Her home BPs were usually about 210/100 in the early morning, falling to about 140/75 in the afternoon.

She took an oral hypoglycemic daily and NSAIDs frequently for arthritis in her hips.

This patient had a combination of inadequate diuretic, inappropriate agents and interference by NSAIDs. When her regimen was changed to include an ACE inhibitor, indapamide 2.5 mg q a.m. instead of furosemide, discontinuation of the beta-blocker and NSAIDs (with acetaminophen in its place) and reduction of the clonidine dose, her morning BP levels were rarely above 170/90 and the afternoon levels averaged 150/70. Her FBS and serum cholesterol levels fell about 25% form their initially high readings.

Doses too low: Some physicians remain insecure about pushing doses of medication to a high enough level. This seems particularly true with alpha-blockers, perhaps because of unnecessary concern about postural hypotension, which is rarely seen after the initial dose of agents from the second generation (terazosin and doxazosin) and even more rarely when doses are raised.

Drug interactions: Of the drug interactions listed, those induced by NSAIDs and various over-the-counter or illicit sympathomimetics are most common (Pope et al, 1993). Since arthritis is the only disease more common than hypertension, the use of NSAIDs is extremely widespread. Since many hypertensives are obese, sympathomimetic agents posing as appetite suppressants are frequently taken.

Excessive volume contraction: A very small number of patients have been described whose resistance is caused by excessive volume contraction that markedly stimulates the renin-angiotensin and sympathetic nervous systems. The involvement of this mechanism is supported by a controlled study of 16 patients with resistant hypertension who were vigorously volume depleted by a 10 mmol/d sodium diet plus large doses of diuretic (Gavras et al, 1981). Although the BPs fell from an average of 176/116 to 155/109, despite marked rises in plasma renin and norepinephrine, the addition of an ACE inhibitor normalized the BP. Therefore, the reactive hyperreninemia must have been blunting the fall in BP that should have occurred with volume contraction.

Most appropriate combinations: Few controlled trials have been done to compare different agents in resistant patients. A number of studies attest to the superiority of calcium blockers and ACE inhibitors over hydralazine and minoxidil, particularly to overcome the extreme volume retention that accompanies the use of the latter drug (Heagerty et al, 1987). Perhaps the best controlled study is that of Bevan et al (1993) who randomly assigned 160 patients inadequately controlled by atenolol 100 mg plus bendrofluazide 5 mg daily to placebo, captopril, hydralazine or nifedipine (Table 5). The three drugs differed little in efficacy and tolerability but the ACE inhibitor seemed to be the "best option."

Table 5: Results from 160 patients with essential hypertension randomised to placebo, captopril, hydralazine or nifedipine (From Bevan et al, 1993.)

Patient Status at Final Visit (%)	Placebo n=38	Captopril n=40	Hydralazine n=41	Nifedipine n=41
Controlled (supine BP <140/95)	10	33	29	17
Not controlled	74	47	39	61
Withdrawn	16	20	32	22
Mean changes in those who completed therapy:	n=32	n=32	n=28	n=32
Mean dose of active drugs (mg/day)	-	119	135	68
Supine Systolic (mm Hg)	-8.0	-21.4	-23.0	-24.8
Supine Diastolic (mm Hg)	-1.8	-12.2	-11.9	-9.9

4. Associated Conditions

> Case 3: This 56 year old attorney had poorly controlled hypertension (180/115) despite clonidine 0.2 mg bid and accupril 20 mg q d. He had gained about 25 pounds in the last 3 years, drank about 1.5 bottles of red wine nightly and smoked one pack per day.
>
> In addition to some changes in his antihypertensive regimen, I asked him to cut way back on his wine consumption (even abstaining for a few days as a test) and to lose weight by caloric restriction and increased physical activity.
>
> In view of the Freedom of Information Act, I will be truthful: The patient did not do what I asked of him. He remains poorly controlled on 3 antihypertensive agents.

The common sins of our society - smoking, obesity, and heavy alcohol intake - may markedly raise the blood pressure and make hypertension resistant to usually effective therapy.

Smoking: Until recently, smokers (while not smoking) were said to have lower pressures because they weighted less on average than non-smokers. However, since BP has been measured during smoking, a significant acute pressor effect has been seen (Groppelli et al, 1992) (Figure 4). Smoking was more prevalent among resistant hypertensives (42%) than controlled patients (25%) from a tertiary clinic in England (Toner et al, 1990).

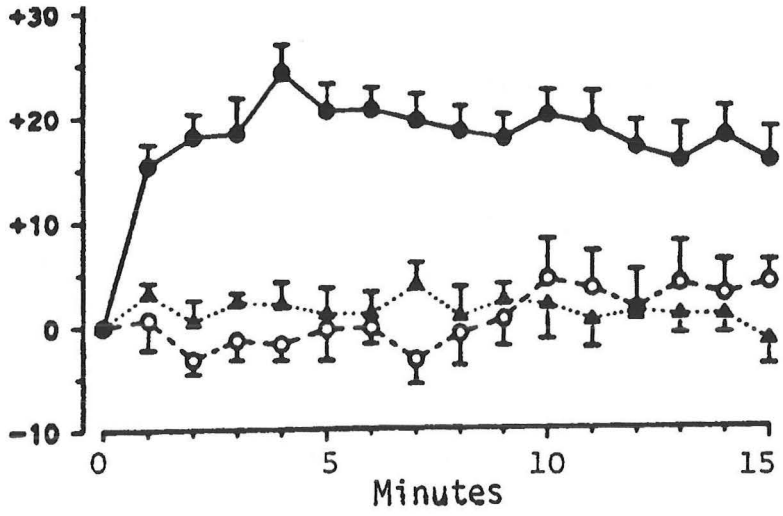

Figure 4: Changes in systolic blood pressure during the first cigarette (●), the correspondent time of non-smoking (o) and during sham-smoking (▲). (From Groppelli et al, 1992.)

Smoking will also decrease the effectiveness of non-selective beta-blockers (propranolol) both by accelerating their metabolism through the hepatic P-450 enzyme system and by potentiating the alpha-mediated vasoconstriction of nicotine by blocking the vasodilatory $beta_2$-receptors (Sleight, 1993).

Obesity: Obese patients are often resistant to therapy, which in turn may

be related to their insulin resistance and resultant hyperinsulinemia. In a study of 7 resistant and 7 controlled male hypertensives matched for age and body mass index (BMI), the resistant patients had more abdominal fat and were more insulin resistant (Isaksson et al, 1993). Modan et al (1991) ranked the dosages of antihypertensive drugs needed to control hypertension in 559 subjects and found a progressive increase in score with increase in BMI. Those with glucose intolerance and hyperinsulinemia required higher doses, irrespective of the BMI.

If obesity is accompanied by sleep apnea, hypertension is usual and it may be resistant to drug therapy (Isaksson and Svanborg 1991).

Alcohol abuse: Those who consume more than 3 usual portions of alcohol containing drinks per day have more hypertension and are more resistant to its treatment (Puddey et al, 1987).

In addition to these aggravating factors, chronic musculoskeletal pain was reported in 39% of resistant patients but in only 7% of controlled patients in a Stockholm hypertension clinic (Isaksson et al, 1991).

5. Secondary hypertension

Case 4: This 35 year old white man has been admitted to Parkland 7 times over the past 20 months with hypertensive crises usually characterized by increasing headache, nausea and vomiting and BP around 240/150, sometimes with papilledema. After parenteral antihypertensives overcome the crisis, he is maintained on varying regimens but, so far, nothing has kept him out of trouble. His serum creatinine runs around 2.4 and he has nephrocalcinosis presumably with medullary sponge kidneys.

On his first admission, a DTPA renal flow study after a single dose of captopril was normal as was a CT scan of the abdomen. Urine metanephrines were elevated (6.19 mg/24 hour) but the specimen was collected the day after intravenous and then oral labetalol was started. A repeat metanephrine 3 days later was normal (0.39 mg/24 hr).

On his 5th admission in August, 1993, renal arteriography revealed a marked stenosis of the mid-portion of the right renal artery. A repeat DTPA renal flow study after captopril showed 34% flow to the right kidney, which increased to 43% without captopril. Angioplasty was performed and one week later the renal flow study showed 47% flow to the right kidney with and without captopril, documenting that there was no longer obstruction of blood flow to the right kidney that had been dependent on increased levels of renin-angiotensin.

Despite the apparently successful angioplasty, his hypertension persisted and required multiple drugs for control. Despite his apparent adherence to therapy, another hypertensive crisis occurred in January, 1994.

This patient demonstrates a number of interesting problems relative to the role of secondary causes of resistant hypertension:

- renal insufficiency from whatever mechanism is the most common cause of secondary hypertension; in a few patients, the driving force is excess renin (this patient's only peripheral PRA was 2.5 ng/ml/hr, a high normal level); in most, volume retention is responsible. The use of moderate doses of metolazone (2.5 mg/d) did not prevent the 6th episode.

- renovascular hypertension is the most difficult to diagnose and should be ruled out in every patient with resistance that is not explained by an obvious cause. The extent of the workup is logically based upon an index of clinical suspicion as nicely delineated by Mann and Pickering (1992) (Table 6 and Figure 5).

Table 6: Testing for Renovascular Hypertension

Index of Clinical Suspicion
Low (should not be tested) Borderline, mild or moderate hypertension, in the absence of clinical clues
Moderate (noninvasive tests recommended) Severe hypertension (diastolic blood pressure greater than 120 mm Hg) Hypertension refractory to standard therapy Abrupt onset of sustained, moderate to severe hypertension at age < 20 or > 50 years Hypertension with a suggestive abdominal bruit (long, high-pitched and localized to the region of the renal artery) Moderate hypertension (diastolic blood pressure exceeding 105 mm Hg) in a smoker, a patient with evidence of occlusive vascular disease (cerebrovascular, coronary, peripheral vascular), or a patient with unexplained but stable elevation of serum creatinine Normalization of blood pressure by an angiotensin-converting enzyme inhibitor in a patient with moderate or severe hypertension (particularly in a smoker or patient with recent onset of hypertension)
High (may consider proceeding directly to arteriography) Severe hypertension (diastolic blood pressure greater than 120 mm Hg) with either progressive renal insufficiency or refractoriness to aggressive treatment (particularly in a patient who has been a smoker or has other evidence of occlusive arterial disease) Accelerated or malignant hypertension (grade III or IV retinopathy) Hypertension with recent elevation of serum creatinine, either unexplained or reversibly induced by an angiotensin-converting enzyme inhibitor. Moderate to severe hypertension with incidentally detected asymmetry of renal size

(From Mann and Pickering 1992.

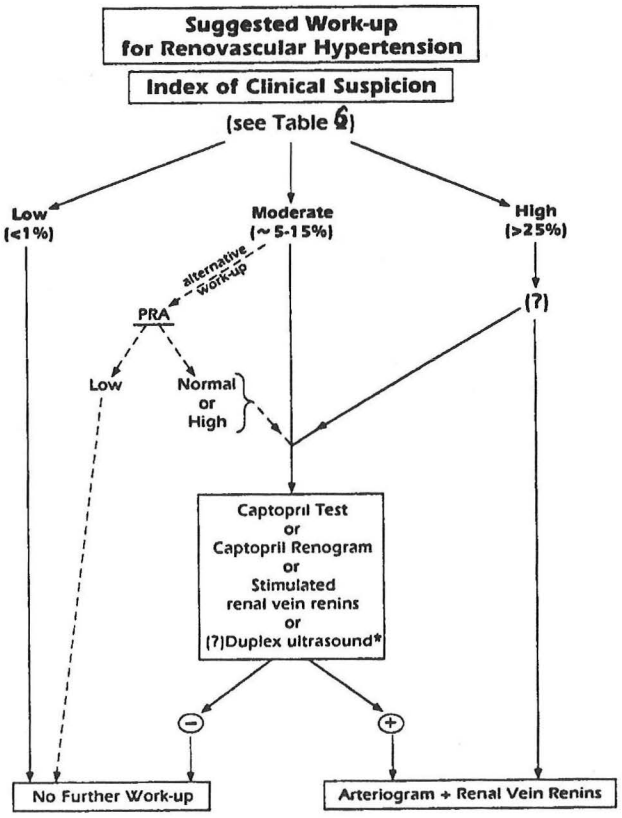

Figure 5: Suggested work-up for patients with suspected renovascular hypertensin. *Clinical usefulness of duplex ultrasound has not been firmly established. (From Mann & Pickering, 1992.)

This patient either had a falsely negative captopril challenge test a year before the recognition of renovascular stenosis or developed the stenosis subsequently. The captopril test remains the best screening study but, even with concomitant measurement of plasma renin (which always should be done with the renogram), there are both false negatives and false positives (Wilcox, 1993).

Of particular concern is evidence that these studies are even less reliable in screening for renovascular hypertension in blacks (Svetkey et al, 1991). Although blacks have renovascular disease less than half as often as do nonblacks with equal degrees of hypertension, blacks more often have severe hypertension that is associated with renal insufficiency wherein it is vital to exclude renovascular hypertension. Therefore, a renal arteriogram likely should be done in all black hypertensives in whom renovascular hypertension needs to be excluded until easier, reliable screening studies (such as ultrasound) become available.

- pheochromocytoma can usually be ruled out by measuring metanephrines in a spot urine (expressed per mg creatinine). However, almost all blood and urine catechol tests are falsely elevated by metabolites of labetalol (Feldman, 1987). The labetalol metabolites do not interfere with measurements of urine VMA or plasma catechols by radioenzymatic assay.

- primary aldosteronism often presents as resistant hypertension but should fairly easily be ruled out by simultaneous measurement of plasma aldosterone and renin levels; a ratio of greater than 30:1 is strongly suggestive of primary aldosteronism.

6. Volume overload

> Case 5: This 35 year old woman was first found to have hypertension at the end of her first pregnancy. Her BP was easily controlled with Dyazide and she was asymptomatic. She quit smoking in March 1993 and rather quickly gained about 25 pounds. Since October, 1993, her BP has become much more severe and is accompanied by left temporal throbbing headaches, despite the following regimen:
>
> Clonidine - 0.3 mg tid
> Labetalol - 300 mg bid
> Enalapril - 10 mg bid
> Spironolactone - 50 mg bid
> Furosemide - 40 mg q a.m.
> Nifedipine - 10 mg prn

Her physical exam shows generalized obesity with trunkal predominance, benign fundi, no tenderness over the temporal artery and a trace of pedal edema.

An extensive evaluation has ruled out renovascular disease, pheochromocytoma, primary aldosteronism and Cushing's disease. Her serum creatinine = 0.6 and the remainder of her routine lab work is normal except for an elevated serum cholesterol (262) and triglyceride (438).

Her regimen was changed to:

Benazepril 20 mg q a.m.
Amlodipine 5 mg q a.m.
Indapamide 2.5 mg q a.m.

The outcome of this patient's resistant hypertension is not yet known but she undoubtedly has volume expansion secondary to inadequate diuretic therapy.

As in Yakovlevitch and Black's series, the most common cause for resistant hypertension is volume expansion, usually related to multiple factors but almost always associated with inadequate diuretic therapy. The most common change in therapy that eventuated in ultimate control of the resistant hypertension in 34 of their patients was the addition of a diuretic (Table 7).

Table 7: Medication Changes in 34 Patients with Initially Suboptimal Regimens Who Were Ultimately Controlled

	Change: Number of Patients			
Agent	Added	Increased	Removed	Decreased
Thiazide	16	1	3	2
Loop diuretic	7	1	2	1
Beta-blocker	0	5	7	3
Central alpha-agonist	0	0	5	1
Minoxidil	3	0	0	0
ACE inhibitor	4	3	4	3
Calcium blocker	13	5	0	3

From Yakovlevitch & Black 1991.

Excess sodium intake: A strong case has been built for a necessary but not sufficient role for excess sodium intake in the pathogenesis of primary (essential) hypertension (Kaplan, 1994). Regardless of how essential is the role for excess sodium in pathogenesis, the continued intake of large amounts of sodium will overwhelm the antihypertensive action of diuretics (Winer, 1961).

A particular problem may appear after patients have been discharged from a hospital where a moderately sodium restricted diet has been appropriately given

and control of hypertension achieved. When the patient goes home, unless carefully instructed in following a diet moderately restricted in sodium, extra sodium may be ingested, overwhelming the antihypertensive regimen constructed in hospital. In a series of 32 patients discharged with hypertension controlled while on a 120 mmol/d (7g NaCl, 2.8 g Na) sodium intake, 18 experienced a rise in BP after discharge averaging 17% (Hirata et al, 1990). Their 24 hour urine sodium excretion had risen more than 2-fold from the in-hospital level. Such data should not be used against the use of moderate sodium restriction in hospital but rather argues for the more aggressive application of dietary sodium restriction in the outpatient management of hypertension. It can be accomplished even among indigent, elderly, uneducated patients (Kaplan et al, 1982).

Progressive renal damage: Sodium retention likely depends upon an impairment of the kidneys to excrete the excess sodium, both in pathogenesis and in the course of therapy. Brenner's construct of an inherited deficiency of nephrons for the pathogenesis of hypertension has received additional support from the growing evidence that low birth weight babies (with fewer nephrons) develop more hypertension later in life (Law et al, 1993).

Once hypertension is present, progressive nephrosclerosis often develops, with a striking predilection for blacks in whom hypertension is by far the leading cause for end stage renal disease. A vicious cycle is established: hypertension destroys nephrons, the subsequent loss of filtering capacity leads to more sodium and volume retention, further accentuating the hypertension.

Fluid retention from reduction of blood pressure: The preceding scenario is exaggerated when the blood pressure is lowered by medications. As shown by Guyton, the hypertensive kidney must have a reset pressure-natriuresis relationship, so that sodium excretion is curtailed in the presence of high pressure, in that sense allowing the pressure to remain high. But, when the pressure is reduced, the reset kidneys perceive the lower pressure to be too low and they respond by reducing sodium excretion (Omvik et al, 1980) (Figure 6). This "inappropriate" sodium retention may be further enhanced by the activation of the renin-angiotensin and sympathetic systems by the hypotensive action of vasodilators (Figure 7). Such compensatory sodium retention is most apparent with minoxidil, wherein marked volume expansion may immediately appear but it has been nicely demonstrated after chronic use of milder agents such as methyldopa (Finnerty et al, 1970).

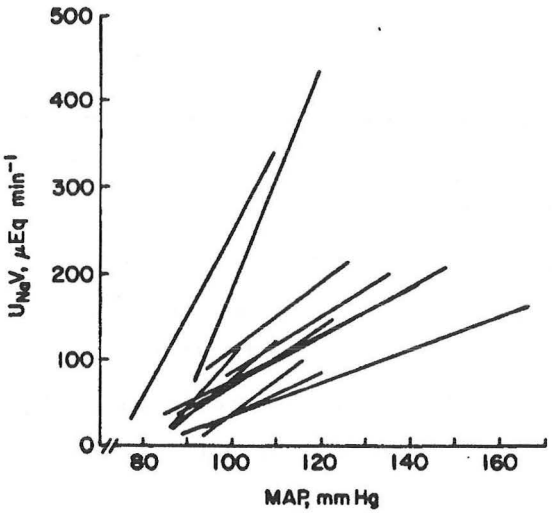

Figure 6: Relationship between sodium excretion ($U_{Na}V$) and mean arterial pressure (MAP) during nitroprusside infusion is illustrated for each patient investigated. (From Omvik et al 1980).

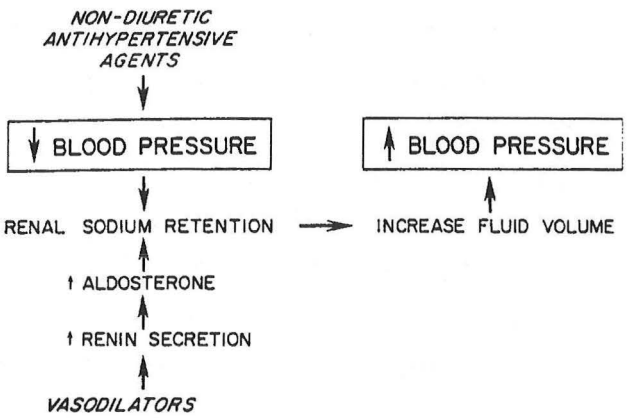

Figure 7: Manner by which nondiuretic antihypertensive agents may lose their effectiveness by reactive renal sodium retention.

The lower intravascular hydrostatic pressure may also lead to fluid retention by altering the Starling forces, within both the systemic and renal circulation. In whatever manner it develops, volume retention is a common feature of hypertension that remains resistant to therapy (Dustan et al, 1972; Graves et al, 1989).

Fortunately such reactive volume retention may be less of a problem with agents that inhibit the renin-aldosterone system (ACE inhibitors) or that have an intrinsic natriuretic action (dihydropyridine calcium blockers). Nonetheless, this process likely explains the potentiation of every other class of antihypertensive agents by the addition of a diuretic. Otherwise the patient may have a dilated vasculature from the action of the other agents but no lower pressure because the vascular bed has been refilled with retained volume.

Inadequate diuretic therapy: All of the above three factors indicate the need for a diuretic in virtually every resistant hypertensive and for most more responsive ones as well. The current common inadequacy of diuretic therapy reflects two practices: 1) The widespread use of once daily furosemide and 2) the increasing avoidance of diuretics because of concerns over their metabolic mischiefs.

- furosemide has a duration of diuretic action of less than 6 hours (the supposed source of the name Lasix). Therefore, all of the volume excreted while

it works is retained during the remaining 18 or more hours, leaving the patient no better off, other than for having to void an extra 2 or 3 times (Kelly et al, 1983) (Figure 8).

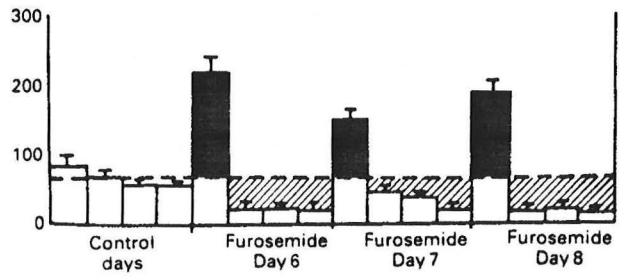

Figure 8: Values for 6 hourly rates of sodium excretion for the control days and the 3 days when furosemide was given. The dashed horizontal line represents the average rate of Na+ excretion determined during the control days, and the solid and diagonal shading represent the differences between the measured Na+ excretion and this basal rate of excretion. (From Kelly et al, 1983).

If a loop diuretic is needed because of renal insufficiency, the recently introduced longer acting torasemide (Demadex) may be an even better choice than either 2 or 3 doses of furosemide a day or once a day metolazone (Rose, 1991; Baumgart, 1993).

The combination of a thiazide and a loop diuretic may be needed to overcome diuretic resistance (Ellison, 1991; Knauf and Mutschler, 1993).

- Many hypertension experts (including the presenter) have decried the metabolic problems induced by diuretics, blaming them for the shortfall in protection from coronary mortality in the multiple clinical trials. However, such criticisms should be aimed at the relatively high doses (50 to 200 mg equivalent of hydrochlorothiazide) used in those trials. There is strong evidence that lower doses are usually equipotent in lowering the pressure than higher doses but less likely to alter potassium, glucose/insulin, and lipid levels (Carlsen et al, 1990) (Table 8).

Table 8: Effect of varying doses of the diuretic bendrofluazide (mg/day)

Change from 0 to 10 weeks	0	1.25	2.5	5.0	10.0
Blood Pressure mm Hg	-3/3	-13/10	-14/11	-13/10	-17/11
Potassium mmol/L	+.09	-0.16	-0.20	-0.33	-0.45
Glucose mg/dl	-1.4	-3.4	+2.5	+0.7	+4.97
Cholesterol mg/dl	-2.2	-1.1	.0	+4.6	+9.5

(From Carlsen et al, 1990)

The 1.25 mg of bendrofluazide shown by Carlsen to possess all of the antihypertensive efficacy of 10.0 mg would be equivalent to 12.5 mg of

hydrochlorothiazide. That is a reasonable beginning dose for a diuretic. More may be needed in more resistant hypertensives, particularly in the presence of the previously noted factors that may mandate more diuretic action. The appropriate use of low doses of diuretics has received appropriate recognition, countering the blanket criticisms that many have covered them with (O'Donovan et al, 1992; Ramsay et al, 1992; Dupont, 1993).

II. Sensitive Hypertension

This term connotes the opposite picture of the resistant patient about whom so much more has been written. I believe as many patients have been exposed to the dangers of poorly controlled hypertension because they are overly sensitive to the effects of usual doses of antihypertensive drugs as from resistance to their effects. The problem is visualized in Figure 9 which shows the idealized dose-response curve (Johnston, 1992). Most doses used clinically are near or beyond the desirable dose range, which varies with individual patients. Therefore, patients who are more responsive will receive excessive doses and thereby be exposed to more adverse effects.

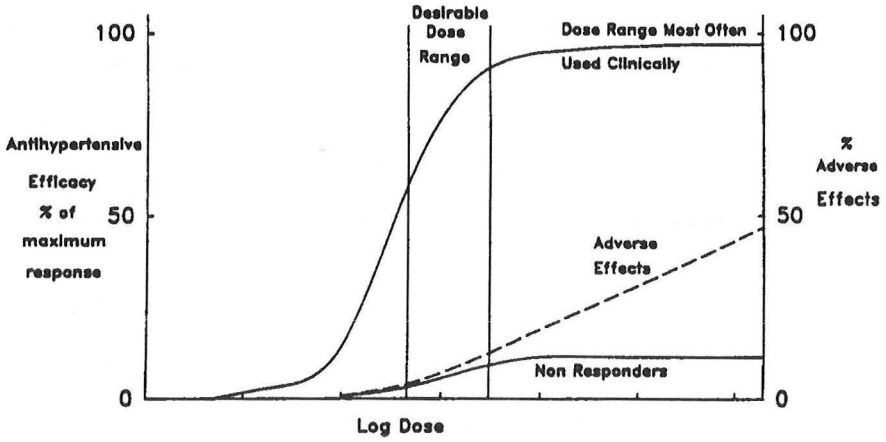

Figure 9: A stylized diagram of the relationship between the efficacy, adverse effects and the dose of an antihypertensive agent plotted on a logarithmic scale. (From Johnston GD, 1989.)

Case 6: This 60 year old woman had taken virtually every available antihypertensive medication in usual doses over the past 10 years but was unable to continue on any of them because of various side effects. When first seen, she was taking minoxidil 2.5 mg daily and her BP in the office was 180/110. Her home BPs were lower, averaging 175/90 in the morning, 140/90 in the afternoon. She described herself as "a wreck" with instability, a tremor and swollen feet. Her recent workup and lab work were all normal.

She was started on doxazosin, 0.5 mg q a.m., because it was the only medication she had not previously taken. Her home BP one week later averaged 160/80. The dose was increased to 1 mg and one week later her home BP averaged 140/80. Subsequently she has been switched to 0.5 mg bid since pressures as low as 125/75 were noted after the 1 mg morning dose.

This patient is obviously exquisitely sensitive to very small doses of an antihypertensive drug and I assume that may be true for all drugs. The problem has been nicely described by Andrew Herxheimer (1991):

"For a new drug to penetrate the market quickly, it should be rapidly effective in a high proportion of patients and simple to use. To achieve this, the dosage of the first prescription is therefore commonly set at about the ED_{90} level - i.e., the dose which the early clinical (phase II) studies have shown to be effective in 90% of the target population, provided that the unwanted effects at this dose are considered acceptable. In 25% of patients a smaller, perhaps much smaller, dose (the ED_{25}) will be effective. The patients in this quartile are the most sensitive to the drug and are liable to receive far more than they need if they are given the ED_{90}. They are also likely to be more sensitive to the dose-related side-effects of the drug."

As I have written (Kaplan, 1992): "Herxheimer goes on to recommend a logical solution: Tablets containing less than the usual maximal effective dose should be marketed. For this to be effective, however, physicians must be willing to start most patients with a dose of medication that will not be fully effective. As Herxheimer states, 'The disadvantage from the marketing standpoint is that for the majority of patients the dose must be titrated. That is time-consuming for doctors and patients and more difficult to explain to them. A drug requiring dose titration cannot be presented as the quick fix, the instant good news that marketing departments love.'

"The 'quick fix' is inappropriate for most hypertensive patients. To allow for autoregulation of blood flow to maintain perfusion to vital organs when perfusion pressure is lowered, the fall in pressure should be relatively small and gradual. More precipitous falls in pressure as frequently seen with larger starting doses may induce considerable hypoperfusion that results in symptoms that are at least bothersome (fatigue, impotence) and that may be potentially hazardous (postural hypotension, coronary ischemia)."

It is far better to "start low and go slow."

III. Psychosomatic Hypertension

The last type of difficult to treat hypertensive is one who carries a great

deal of psychosomatic baggage that is often filled with anxiety over the "silent killer." Such patients may have their BP control markedly perturbed by the physiological reactions to stress-induced sympathetic activation.

> Case 7: This 50 year old woman had been asymptomatic with mild hypertension for abut 5 years but in the last 4 months has had a "rocky" course with markedly high BP (210/110) recorded, at least three times in an E.R. where she went after "being acutely frightened by a big surge in my head, similar to a balloon being blown up." She recognized that she was hyperventilating and on the verge of panic attacks, but she interpreted these as following, not preceding or accompanying the rise in BP. Her physician obtained a 24 hour metanephrine (normal) and prescribed Buspar along with verapamil.
>
> Her major symptoms (band-like pressure in the head, blurry vision, paresthesias, tachycardia) were easily reproduced in the office by a brief series of deep breaths. After a lengthy discussion of hyperventilation she was sent home with a number 6 paper sack to use prn.
>
> One week later, she called to say that she had been able to return to work for the first time in a month and her home BP was quite stable around 140/90.

This patient had considerable insight into her problem but couldn't identify just what precipitated her increasing anxiety nor connect the anxiety-induced hyperventilation with her marked episodic rises in BP. Acute hyperventilation can raise the BP (Todd et al, 1993) (Figure 10) and panic attacks are often accompanied with markedly elevated pressures (White and Baker, 1987).

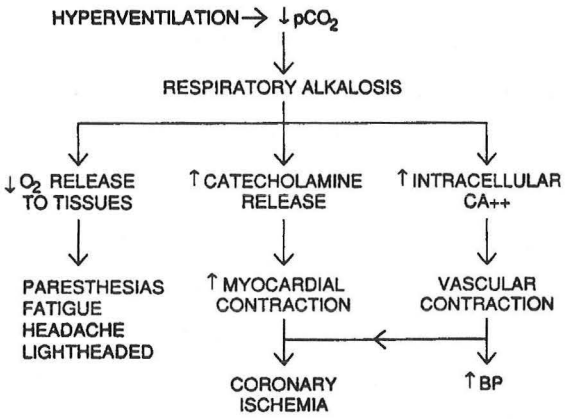

Figure 10: The mechanisms by which acute hyperventilation may induce various symptoms, coronary ischemia, and a rise in blood pressure.

Not all symptoms that bother hypertensives are induced by anxiety-induced hyperventilation. But it is a common problem and a number 6 paper sack can do wonders and should be used (along with some office psychotherapy) before Valium, Xanax, and Buspar. Breathing retraining also helps (DeGuire et al, 1992)

The preceding coverage is intended to help clinicians who deal daily with hypertensives to more effectively manage the relatively few who seem difficult to treat. Truly "untreatable" hypertensives are extremely rare and we can improve the care of almost every difficult patient.

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