Attending Rounds: A Patient with Drug-Resistant Hypertension

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Summary

Drug-resistant hypertension is present in about one in eight patients with high BP. It can be a frustrating and expensive condition to pursue from an office-based perspective. In this review, utilizing the American Heart Association scientific statement on drug-resistant hypertension as a guide, a case of drug-resistant hypertension is presented and walked through exactly as encountered by the author. Woven into the discussion is a combination of insights from the literature on this topic, blended with the experience of the author. This is not intended as an exhaustive review of each step in the evaluation and management process but, rather, as an overview incorporating a few carefully chosen references and, hopefully, a logical and useful approach to a common clinical challenge.

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Introduction

A 51-year-old man is referred for further evaluation of his BP. He is a robotics engineer and has a past history of type 2 diabetes for 5 years and high BP for 12 years. His somatic complaints include fatigue and dry mouth. He has no known history of hypertension target-organ damage, and his medications are listed in Table 1. He has no remarkable family history other than hypertension in both parents. His examination was otherwise unremarkable (including normal heart sounds and no peripheral edema), aside from mild arteriolar narrowing in the fundus. His seated BP was 156/90 mmHg and 158/90 mmHg in the right arm (similar to the left arm), with a regular heart rate of 70 beats/min. His BP did not change on standing. His urinalysis showed an unremarkable dipstick evaluation.

The diagnosis of "drug-resistant hypertension" is present when a person takes three or more antihypertensive drugs, one of which is a diuretic (1), and has a BP of more than 140/90 mmHg. Technically speaking, even if the patient's BP was 128/80 mmHg, he would still qualify for the diagnosis of drug-resistant hypertension because he takes five medications. Moreover, because of his diabetes, the definition of "resistant hypertension" could arguably use a target level of 130/80 mmHg. Thus, there is little doubt that his 156 to 158/90–mmHg BP qualifies him as a candidate for drug resistance. Drug-resistant hypertension is present in about one in eight hypertensives (2). Using the American Heart Association (AHA) summary statement (3), the intent herein is to walk the reader through the seven office-based steps (Figure 1) used to evaluate and manage people who present similar to our patient. Additional details pertinent to address each step are discussed later in the paper.

Step 1: Confirm Treatment Resistance

One fortunate privilege of reading ambulatory BP monitor reports is that it provides perspective on the frequent discrepancy between office-based BP and what happens to BP when the patient leaves the office. When BPs taken at home or obtained through ambulatory recordings are compared with office-based values, one of four categories will pertain (see Figure 2). Of particular importance in our patient is the category wherein ambulatory (or home) BP is less than 135/85 mmHg, while office-based values are >140/90 mmHg. This situation is known as "white coat" or "office" hypertension. When a group of patients (n = 118) referred to a hypertension center for uncontrolled BP on three drugs was studied by ambulatory BP monitoring, 28% had ambulatory readings <135/85 mmHg and were classified as "white coat" (and therefore not treatment resistant) (4). Thus, confirming that a patient is really drug resistant is a logical first step and could potentially avoid needless drug therapy adjustments.

In the case of our patient, an engineer, when queried, produced detailed reports of home BP readings that confirmed that out-of-the-office BPs were in a range slightly lower than the office values but above 150 mmHg systolic, indicating true resistance. As an aside, the fatigue and dry mouth were attributed to the β-blocker and the alpha$_2$-agonist, supporting the adherence he claimed to his BP regimen.

Step 2: Pseudoresistance

Poorly obtained BP, whether done at home or in the office, can mislead a clinician into aggressively pursuing drug resistance, when the problem really resides in the technique realm. One common error is to use a cuff that is inadequately matched to the arm size of the patient. A properly done BP is predicated on

Table 1. List of medications taken by the patient

Name	Dose	Frequency
Hydrochlorothiazide	25 mg	Daily
Valsartan	160 mg	Daily
Diltiazem, long acting	300 mg	Daily
Clonidine	0.2 mg	Twice daily
Metoprolol, long acting	100 mg	Daily
Simvastatin	40 mg	Daily
TriCor	145 mg	Daily
Metformin	1000 mg	Twice daily

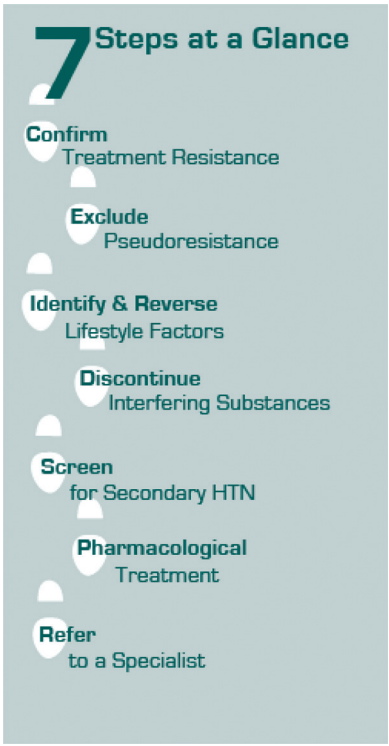

Figure 1. | An overview of the seven basic steps used to pursue drug-resistant hypertension in an office setting.

using a cuff whose bladder (the inflatable part) encircles at least 80% of the arm circumference (5). If the bladder fails to encompass at least that much of the arm circumference, then the pressure used to collapse the brachial artery sufficiently to stop flow (and thus Korotkof sound production) is artifactually increased and reads BP values higher than those obtained when a larger cuff is used. A second technical problem has to do with not allowing an adequate period of rest to elapse before taking a BP. Virtually all of the data obtained on the benefits of treating high BP are based on treating the value of the BP obtained in the sitting position after a minimum of 5 minutes of rest in a quiet environment with an empty bladder, feet on the floor, and back supported. Our patient brought his home BP monitor with him and demonstrated how he takes his BP at home. It is very important when evaluating a home BP monitor to have *the patient* apply the monitor to himself or herself and to do the BP reading while *you observe*. Otherwise, you will

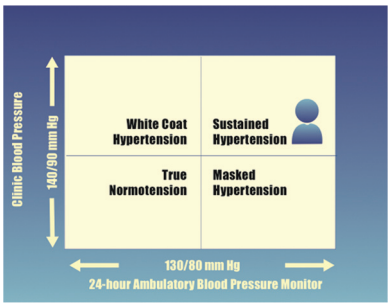

Figure 2. | This grid helps to integrate ambulatory BP monitor (ABPM) data with office BP results. Some debate remains about the optimal 24-hour BP value (the text cites a study where 135/85 mmHg was used; this figure shows 130/80 mmHg). The upper half of a person shows the quadrant location of our patient. If either office value, systolic or diastolic, is >140/90 mmHg, then the upper half of the figure pertains to using the vertical axis dividing value of 140/90 mmHg. To find which of the two upper quadrants a patient's data occupies, use the 24-hour average of the ABPM to place them in either the upper right (Sustained Hypertension, as in our patient) or upper left (White Coat Hypertension).

not know whether even a properly calibrated monitor with an appropriate sized cuff is being used in a haphazard fashion to obtain the BP data. There are two clues to poor home technique. The first is extreme variability in BP readings performed at a similar time of day on different days, which suggests that no rest period was used. The second is digit bias. When you note a majority of BP values ending in 0 or 5, instead of a random assortment of numbers ending about equally in digits 0 through 9, this is digit bias.

In the case of our patient, he had actually read the directions that came with his home monitor and performed the BP measurement flawlessly. He was not "pseudoresistant."

Step 3: Lifestyle Factors

This evaluation step is easy to write about but perhaps the most difficult to execute in practice. The main lifestyle factors contributing to drug-resistant hypertension are dietary sodium exposure and excess body weight. A remarkably informative study, albeit in a small number of patients, was undertaken in 12 people referred for typical drug-resistant hypertension to a hypertension clinic (6). The patients agreed to eat a diet dispensed at the hypertension clinic for a week at a time. One week was a low-salt (50 mEq Na+/d) diet and the other week was a high-salt (250 mEq Na+/d) diet, achieved with supplemental salt tablets, with a 2-week washout between diets. Ambulatory BP monitoring performed the day before, and then on the last day of each diet, was used to capture the differences in the effects of the diet, since medications were unchanged. The low-salt diet had a 23/9-mmHg (systolic over diastolic) difference, an amount remarkably similar to (if not better than) the effectiveness of most antihypertensive drugs when used as monotherapy in hypertension-treatment registration trials.

The benefits of weight loss on BP are well documented, typically in the range of around 6 to 10 mmHg systolic, with an average of 8 kg of weight loss. The problem is that some people do not experience a change in their BP with

weight loss, and it is quite difficult to maintain weight loss, even when participating in carefully monitored clinical trials. Other factors to consider in lifestyle include nonadherence to prescribed therapy or a suboptimally prescribed treatment regimen (tiny doses of medications; in most cases, most of the antihypertensive effect of an agent will require using at least half of the manufacturer's maximum recommended dosage).

Our patient was well aware of sodium content (he carefully read labels). He is 70 in (178 cm) tall and weighed 210 pounds (94.5 kg), yielding a body mass index of 30.1 kg/m^2. He had lost 7 pounds without discernible BP benefit in the last 2 months and took medications faithfully (and, as shown in the table, was on good antihypertensive drug doses).

Step 4: Interfering Substances

A first office encounter with a new patient is greatly aided by asking the prospective patient to bring everything they take (prescription and nonprescription) and, when they have one, their home BP monitoring device. Interfering substances may include prescription drugs (lists of these typically include nonsteroidal anti-inflammatory drugs [NSAIDs]; cyclo-oxygenase 2 inhibitors; corticosteroids; erythropoiesis-stimulating agents; and psychiatric medications including antidepressants, vigilance enhancers, and mood-elevating drugs [both the legal variety and those like cocaine and methylphenidate that may not be used in a medically supervised fashion]). Less obvious to the patient are over-the-counter remedies such as subprescription-strength NSAIDs and a number of cough/cold/allergy preparations and appetite suppressants. Even more occult is the BP-increasing effects of things like alcohol, licorice extract (marketed for dyspepsia), and strength/endurance enhancers like ma-huang, available through Internet sources.

Returning to our patient, he has only one glass of wine (or none) with dinner and does not take prescribed or over-the-counter medications other than those listed previously.

Step 5: Secondary Hypertension

This step requires a combination of a high index of suspicion, tempered with a healthy dose of common sense and plausible pathophysiology. There is an ever-increasing number of impressive imaging procedures and approaches available, and many serum and plasma biomarkers to consider at this step. Most forms of secondary hypertension will fall into one of three categories: adrenal, renal, or the other few possibilities (*i.e.*, the requisite miscellaneous category). Dealing with the miscellaneous category first, there are tabular listings, sometimes spanning two full pages in a journal or a textbook, delineating every conceivable case of BP increase from rare genetic associations with BP to a substantial number of disorders (like lupus, rheumatoid arthritis, Cushing disease, *etc.*) where BP is a known accompaniment. Armed with a reasonable history and examination, and consideration of known comorbidities, the miscellaneous category is usually recognized before the first office visit concludes. Finally, it would be reasonable to mention sleep-disordered breathing at this juncture. Although not a classic "secondary hypertension," apneas and hypopneas are commonly present in the drug-resistant hypertensives, when formally sleep tested. The history may suggest daytime somnolence and fatigue, snoring, and gasping, and times when the patient does not seem to be moving air when breathing, as noted by the bed partner (7,8). Many such patients are obese, and there is often a component of aldosterone excess, which complicates defining what role the sleep disordered breathing has *per se*.

The adrenal forms track to the cortex and the medulla of the gland itself. The adrenal cortex synthesizes a number of steroid hormones, and the most commonly implicated one in hypertension is aldosterone. In our center, we routinely request a serum aldosterone and a plasma renin activity on all new patients referred for drug-resistant hypertension, if their referring clinicians have not already done so. In about 15% to 20% of patients, the aldosterone-to-renin ratio is elevated (more than 25:1), indicating the possibility of aldosterone excess in the pathogenesis of the drug-resistant hypertension. Many caveats about the use of this ratio have been proffered, and the following are useful to recall if you perform this testing on a patient:

- Do the testing after the patient has been awake and walking about for a couple of hours; you want the renin activity to be as stimulated as the usual activities of daily living allow.
- Do not use the ratio unless the aldosterone exceeds a laboratory-based cutoff value for elevation. We typically reserve applying the ratio until the serum aldosterone concentration exceeds, for example, 15 ng/dl.
- Although it makes most sense to do the testing when off antihypertensive medications, this is impractical, in most cases, as these patients are often on five drugs (like our patient). It is important, however, that caution be used if the patient takes spironolactone or eplerenone before testing, as these mineralocroticoid antagonists greatly limit the utility of the ratio (9).
- Lastly, recognize that renin activity (on which ratio recommendations are based) is measured in units of ng of angiotensin-I generated per milliliter of plasma per hour (ng/ml per hour). In the last decade, it has become possible to measure the concentration of renin (*i.e.*, the units here are in mg/ml), which is a different measure of renin and NOT the one typically used in clinical papers addressing the aldosterone-renin ratio (to use the direct renin concentration, see Funder *et al.* [10]).

Most patients with drug-resistant hypertension have suppressed renin activity, despite taking diuretics, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocking (ARB) drugs, which usually increase renin activity (11). Pathophysiologically, it makes sense that the elevated BP and/or a component of sodium or volume excess reduce renin activity. Since renin (through angiotensin II) is a potent stimulus to aldosterone production and release, it should naturally follow that volume excess would be associated with suppressed aldosterone in conjunction with the suppressed renin. Therein lies the value of the ratio. Although cortisol is also an adrenal cortex hormone, it is far less often implicated in drug-resistant hypertension.

The adrenal medulla generates the catecholamines epinephrine and norepinephrine. Patients with drug-resistant hypertension associated with catecholamine excess often have symptoms related to the episodic catecholamine release, such as pounding headaches, spontaneous sweating, and heart racing. However, headaches, sweating, and tachycardia are common symptoms for disorders like hypoglycemia, migraines, menopause, and so on. Genuine catecholamine excess from the adrenal medulla (or a paraganglionoma) is relatively uncommon, as there are fewer than 1000 new cases of pheochromocytomas and paraganglionomas per year in the United States. These tumors have protean manifestations and are clear examples of the oft-cited need for "clinical suspicion." Fortunately, the pursuit of these has been greatly aided by the wide availability of plasma metanephrine assays, which have largely replaced the cumbersome 24-hour urine collections in acidified containers (12).

Impaired kidney function and impaired kidney circulation are additional secondary hypertension considerations. Most drug-resistant hypertensive patients have had a creatinine or GFR estimation, the usual methods that reflect impaired kidney function, when present. Suspicion for the presence of renovascular disease is more tenable when a smoking history, known coronary artery disease, evidence of vascular disease in the neck (bruits) or the legs (claudication), and, often, a subtle reduction in estimated GFR are present in any combination. The presence of abdominal and mid-epigastric bruits further supports this.

Our patient is a nonsmoker, with no bruits noted on examination. His records indicated that he had a plasma metanephrine assay, where values were in the normal range, and also that a computed tomography angiogram of the abdominal vessels was negative (both for renal vascular disease and for abnormalities in the adrenal glands). He had daytime fatigue, as noted, but I attributed it to the clonidine/β-blocker. He has no nocturnal symptoms, although a formal sleep study was not done. I would not have ordered the computed tomography angiography or the plasma metanephrine. I did request a serum aldosterone and a plasma renin activity. These returned the following values: (*1*) renin: 0.10 ng/ml per h (normal 1.5 to 3.5 ng/ml per h), and (2) aldosterone: 8 ng/dl (normal 3 to 15 ng/dl). The renin activity was suppressed, but the aldosterone concentration was in the middle of the normal range, so I did not apply the ratio.

Step 6: Pharmacologic Treatment

We now come to a difficult point in this journey. A useful approach to understanding the physiologic control of BP and a convenient model for approaching drug therapy is shown in Figure 3 (adapted from Townsend and Cirigliano [13]). This figure is not unlike the "Birmingham Square," popular in the United Kingdom, for approaching complicated antihypertensive regimens (14). The art in building, or altering, a combination antihypertensive regimen is to employ medications with complementary, not overlapping, mechanisms of action, and to pursue minimizing side effects by leveraging known pharmacology. Examples of the latter include the addition of an ACE inhibitor to a diuretic, to reduce hypokalemia occurrence,

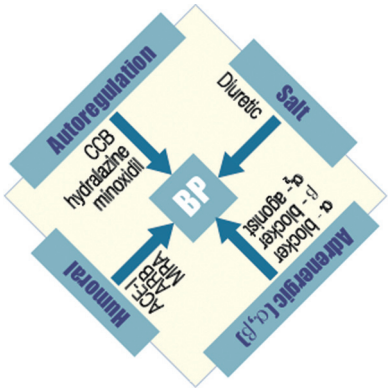

Figure 3. | This diagram emphasizes four basic physiologic processes that regulate BP and situates common antihypertensive drug classes along the side belonging to the process thought to be associated with the drug class's primary antihypertensive effect (adapted from Townsend and Cirigliano [13]). CCB = calcium channel blocker; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

or the use of an ACE inhibitor or an ARB to reduce calcium channel blocker–associated edema.

Evan a quick glance at Figure 3 shows that all four basic processes have at least one drug from that side in current usage in our patient. Returning to the principles in step 3, it is often the case that, even with good diuretic therapy, an element of volume excess may persist in the drug-resistant hypertensive. The low renin activity supports this possibility. It was at this point in his treatment that he was referred to our center.

Step 7: Refer to a Hypertension Specialist

In keeping with the AHA scientific statement, the seventh step involves referral to a specialist with expertise in hypertension, which is how the patient initially made his way to our program (3). Of course, many nephrologists have substantial expertise in the management of patients such as the patient discussed here and will have no difficulty achieving good BP control in even the most complex hypertensive patient. For some patients, however, referral from a nephrologist to another physician who specializes in the care of patients with severe and difficult-to-control hypertension may lead to new diagnoses or treatment changes that improve BP control.

Outcome

With the renin and aldosterone data in hand, the patient and I discussed adding a mineralocorticoid antagonist, reviewing the pros and cons of spironolactone (cheap/generic; gynecomastia) and eplerenone (although generic, not that cheap; far less gynecomastia), acknowledging the need to monitor potassium and creatinine, with either agent, in the coming months, and we settled on adding eplerenone. The reason for this drug choice is based on two findings. First is the low renin activity in the patient despite administration of several drugs that typically increase renin. This suggests a sodium surfeit and the possibility that more aggressive diuresis could be of benefit. Second,

the addition of spironolactone as a fourth-line agent in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) resulted in a substantial improvement (discussed below) in systolic BP (and the choice was an empiric one, not based on hormonal data) (15). As shown in Figure 4, it was possible, in the ensuing months, to taper and withdraw the clonidine and the metoprolol. This was done through a combination of monthly reported home BP recording reviews and scheduled office-based confirmatory checks. This case illustrates two common findings with mineralocorticoid blockade. First, as shown by the experience in ASCOT, the addition of an aldosterone antagonist to an established multidrug regimen produced an additional impressive 22/10-mmHg BP reduction (15); additional antihypertensive benefit often occurs with this agent class. Second, the full antihypertensive effect of aldosterone antagonism may not be evident in the first few weeks of treatment (16), and, not uncommonly, other medications can be titrated down or even discontinued.

Follow-up laboratory values showed a slight increase in creatinine (from 1.3 mg/dl up to 1.5 mg/dl) but no change in potassium values. We continue to monitor the creatinine, aware that it is a concern for the metformin dosage. Blood sugar control was not changed by the added therapy.

The Future

Two ongoing developments in hypertension therapy are worth mentioning here. They both revolve around novel, but not yet FDA-approved, devices for treating drug-resistant hypertension.

The first approach, the Rheos® System (CVRx), utilizes the known effects of baroreceptor stimulation to reduce sympathetic output and lower BP. This requires surgical implantation of a pacemaker-like device that has an electrode tunneled from its subclavicular location to the carotid body on each side of the neck. When the pacemaker is turned on, it activates baroreceptor input into the brainstem, resulting in BP reduction that appears to be sustained for several years (17).

The second approach, the Symplicity® System (Medtronic), uses radiofrequency ablation, delivered by a catheter directly applied to the lumen of both renal arteries (sequentially) through a femoral access procedure that usually takes less than an hour to complete. This procedure reduces sympathetic inflow into (efferent), and out from (afferent), the kidneys. The recent report of the Simplicity HTN-2 trial indicates sustained BP reduction in most patients at 6 months (18).

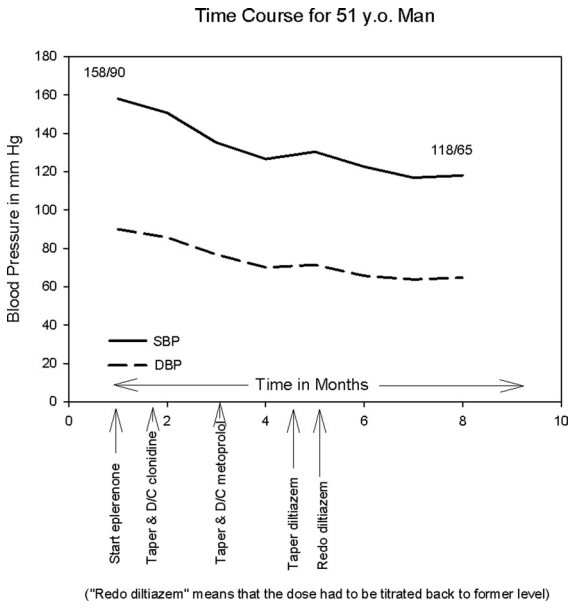

Figure 4. | Course of BP response to patient. "Redo diltiazem" means that the dose had to be titrated back to a former level. D/C, discontinue; SBP, systolic BP; DBP, diastolic BP.

Final Comments

The majority of patients we see at our hypertension center are for drug resistance, typically of the systolic pressure variety. We find this step-based approach useful in the evaluation of such patients, and it has appeared in similar format in earlier reviews of this topic (for example, see Moser and Setaro [19]). If BP is managed exclusively in the office setting, a 2- to 4-week period between drug or dosing adjustments is reasonable. Lastly, the ability to use reliable home BP measurements, which was done in the case of our patient, is beneficial in two ways. It reduces the need for frequent office BP checks and it engages the patient in what can sometimes be a tedious trial-and-error process, wherein support and adherence to our advice is critical to achieving successful BP goals. It is likely that an "e-BP" approach, which leverages home BP values via a secure communication system with the hypertension center, providing feedback and guidance to the patient as they pursue goal BP, will be increasingly applied to drug-resistant hypertensives in the future (20).

Questions:

Dr. Jeffrey Berns:

You describe two investigational treatments for resistant hypertension, baroreceptor stimulation and renal artery neural ablation. For what patient populations do you foresee these therapies being clinically useful and indicated? And a related question, is the radiofrequency ablation procedure one that could be done currently by an experienced interventional radiologist or other interventional physicians?

Dr. Raymond Townsend:

The best patients for these procedures are currently unknown, since the numbers studied so far is modest given the invasive nature of the technologies and the cautions used in subject selection for inclusion so far. As we learn more about the role of the sympathetic nervous system in drug-resistant hypertension it may be that we will be able to "screen" for those most likely to benefit by some manipulation of the sympathetic nervous system, perhaps using an agent like clonidine.

The radiofrequency ablation procedure is already approved in parts of Europe. From what I have seen, and in communications with Ardian (now a part of Medtronic) the procedure is pretty straightforward.

Dr. Paul Palevsky:

One of the major problems in assessing patients with apparent resistant hypertension is medication noncompli-

ance. How do you suggest assessing whether a patient is compliant with his or her medications?

Dr. Raymond Townsend:

I have seen or heard of several methods, including having the patient recite their regimen or describe the pills, and their frequency, and even calling the pharmacy. My experience has been that people who consistently show up for appointments, and who are usually on time, are generally compliant. At the point when they are referred to someone like me they are usually pretty committed to BP control and generally willing to do what we recommend.

Dr. Gary Curhan:

How large of an increase in serum creatinine do you tolerate when adding a new medication to reduce the BP in a patient with resistant hypertension? Does an increase above a certain amount lead you to perform any additional diagnostic studies?

Dr. Raymond Townsend:

I use a 25% increase because it is easy to calculate without an electronic aid, and it has been pretty well accepted by others, for example in the heart failure literature, that it is a "safe" change. When the creatinine doubles, or rises even higher than that, that is when I become concerned. My first thought is that a diuretic dose may be too high. I don't jump to a diagnostic study like pursuing bilateral renal artery stenosis until I am reasonably certain that overt, or even subtle, volume depletion is not the culprit.

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Disclosures

None.

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