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# A different approach to resistant hypertension

## ■ ABSTRACT

Prescription audits document that patients with resistant hypertension are often treated with several vasodilators, with less emphasis on diuretics and beta-blockers. Patients who do not respond to several vasodilators appear to be vasodilator-insensitive; they may be a selected-out cohort who require diuresis or catecholamine suppression for further blood pressure control.

## ■ KEY POINTS

Resistant hypertension is often characterized by resistance to aggressive vasodilator therapy.

An individualized hemodynamic approach in which volume, cardiac output, and systemic vascular resistance are measured has proven effective in treating patients with resistant hypertension.

This strategy may be adapted for routine office use by using a physical examination to estimate the hemodynamic measurements.

The examination will focus physicians on patients in need of diuresis or beta-blockade, emphasize that these are processes that require time and adjustments to reach optimal outcomes, and provide an alternative approach to patients with resistant hypertension.

**A**LTHOUGH a host of antihypertensive agents of different classes are available, many patients cannot reduce their blood pressure to their goals. One problem may not be in the drugs per se but in the way they are prescribed, with too much emphasis on vasodilators and not enough on diuretics and beta-blockers.

More patients with resistant hypertension may be able to control their blood pressure if their physicians would perform a physical examination to try to determine the hemodynamic mechanism driving the hypertension and rationally apply drugs to address the problem in the individual patient. As a result of this approach, more patients would receive diuretics and beta-blockers, and in higher doses.

In this paper I discuss the scope of the problem of resistant hypertension, a reason for this widespread failure, and evidence that a hemodynamic-based approach would be a useful complement to the current stepped-care approach.

## ■ THE 40% WALL OF FAILURE

Resistant hypertension is commonly defined as hypertension that persists despite reasonable doses of three or more medicines, including a diuretic.

Though the precise prevalence of resistant hypertension is unknown, in recent clinical trials<sup>1,2</sup> and in tertiary hypertension clinics,<sup>3-5</sup> 35% or more of patients did not reach their goals for systolic blood pressure. Blood pressure control is often worse in patients with chronic kidney disease,<sup>6-8</sup> including those treated in renal clinics.<sup>9-13</sup> Renal experts in clinical trials also often do not obtain blood pressure targets.<sup>14-16</sup> Even in the African

TABLE 1

## Prescription patterns in resistant and difficult-to-treat hypertension

AUTHORS	COHORT	NO. OF PATIENTS	% OF PATIENTS RECEIVING DRUGS				
			RENIN-ANGIO-TENSIN SYSTEM INHIBITOR <sup>a</sup>	CALCIUM CHANNEL BLOCKER	OTHER VASO-DILATOR	DIURETIC	BETA-BLOCKER
<b>Resistant hypertension</b> (3 or more medicines)							
Yakovlevitch and Black <sup>3</sup>	Tertiary hypertension clinic	91	48	33	34	57	56
Garg et al <sup>5</sup>	Tertiary hypertension clinic	141	89	69	54	84	50
Taler et al <sup>18</sup>	Tertiary hypertension clinic	104	82	59	50	94	70
Ouzan et al <sup>19</sup>	Medical clinic in France	25	68	56	52	64	76
<b>Difficult-to-treat hypertension</b> (typically 2 or more medicines)							
Schwenger and Ritz <sup>9</sup>	Renal clinic in Germany	201	64	58	47	77	40
Minutolo et al <sup>11</sup>	Renal clinic in Italy	186	84	50	~31	54	29
De Nicola et al <sup>12</sup>	Renal clinics in Italy	1,058	81	47	~26	43	17
Sharabi et al <sup>20</sup>	Hypertension clinic in Israel	340	~60	~65	~15	~35	~55
Brenner et al <sup>14</sup>	Chronic kidney disease study	1,513	51	71	35	58	18
Wright et al <sup>17</sup>	Chronic kidney disease study	1,094	38	64	49	62	28

<sup>a</sup>Angiotensin-converting enzyme inhibitors or angiotensin 2 type 1 receptor blockers

Even under ideal conditions, about 40% of patients with resistant hypertension do not get their blood pressure to their target goal

American Study of Kidney Disease and Hypertension (AASK),<sup>17</sup> which was touted for achieving relatively successful blood pressure control, 40% of patients in the low blood pressure goal group did not achieve their goal.

The failures of experts in tertiary clinics and clinical studies bear special emphasis. The treatments were applied in near-optimal conditions by physicians keenly aware of the nuances of therapy. The failures did not result from poorly motivated patients or physicians, lack of access to care, or undiagnosed causes of secondary hypertension. Results obtained by

experts in near-optimal conditions are the best we can realistically expect at present; they characterize the upper limit of success using current medicines and strategies.

The persistence of resistant hypertension as a major clinical problem over the last half-century suggests that we will not break through the approximately 40% “wall of failure” by continuing traditional strategies. Instead, we should consider whether the group for whom traditional therapy fails has defining characteristics that might effectively guide a change in approach. Why do these patients

not respond to the same medicines and strategies that are successful in other patients?

### ■ IS RESISTANT HYPERTENSION TYPICALLY RESISTANCE TO VASODILATORS?

The most comprehensive information available regarding prescription patterns for patients with resistant hypertension comes from audits from tertiary hypertension clinics to which these patients were referred (TABLE 1).<sup>3,5,18–20</sup>

These audits document a heavy use of vasodilators. For example, in two large centers,<sup>5,18</sup> more than 80% of patients with resistant hypertension were prescribed a renin-angiotensin system inhibitor, ie, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). An additional 60% to 70% were prescribed a calcium channel blocker, and about 50% were prescribed yet another vasodilator. Clearly, many patients were prescribed two or more vasodilators without achieving blood pressure control.

These findings are buttressed by audits from renal and medical clinics and large clinical studies in which patients with difficult-to-treat hypertension were generally prescribed two or more drugs (TABLE 1).<sup>9,11,12,14,17,20</sup>

#### Diuretics (and beta-blockers) are underused

In contrast to multiple vasodilator prescription, diuretics and beta-blockers were used more erratically, with significant numbers of patients not prescribed one or the other (TABLE 1). Fewer than 50% of 1,058 patients treated in 26 renal clinics in Italy were prescribed a diuretic, even though almost 90% remained hypertensive.<sup>12</sup> Only 60% of 2,607 patients referred to the AASK study<sup>17</sup> and the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL)<sup>14</sup> study were taking a diuretic.

Failure to prescribe any diuretic is only one aspect of underprescription; inappropriately weak diuretics (eg, thiazides given to patients with chronic kidney disease)<sup>3,11</sup> and inappropriately low dosages<sup>3,5,11,12,18</sup> have also been described and are important. Although larger doses of loop diuretics are required for patients with advanced kidney disease, De Nicola et al<sup>12</sup> found that 69% of patients with stage 3 chronic kidney disease

were given 25 mg or less per day of furosemide (Lasix), and in both of the studies that reported the highest rates of diuretic prescription (84% and 94%),<sup>5,18</sup> blood pressure control improved with increasing diuretic doses.

The reliance on vasodilators may distinguish the 40% of patients who do not respond to antihypertensive therapy from those who do. In other words, by preferentially prescribing vasodilators we may identify, by their lack of response to vasodilators, patients who are or who will become vasodilator-insensitive. For these patients, it follows that excess volume or catecholamines may be maintaining the hypertension, and further manipulation of vasodilators will not likely be helpful. As Finnerty warned in 1971, referring to vasodilators: “Increasing the dose of antihypertensive agents in the presence of an expanded extracellular fluid volume has no effect on the arterial pressure.”<sup>21</sup>

#### Treatment can elicit maladaptive responses

The importance of excess volume in resistant hypertension is well known and has been cited in review articles<sup>21–33</sup> and renal<sup>34</sup> and cardiology<sup>35</sup> textbooks. It has been demonstrated in patients with resistant hypertension in all five studies (with more than 150 patients) that have reported volume measurements.<sup>18,36–39</sup> Diuresis in these patients has typically decreased systolic pressure by 20 to 35 mm Hg, whether guided by volume measurements or applied clinically as “add-on” therapy.<sup>19,20,40–43</sup> Successful results have been reported in patients with high or low renin levels<sup>41,42</sup> and with the addition or increase of thiazides,<sup>3,5,18</sup> loop diuretics,<sup>18,36,37,39,40</sup> epithelial sodium channel blockers,<sup>43</sup> or aldosterone-receptor blockers.<sup>19,20,41,42</sup>

Several mechanisms may contribute to excess volume. Treatment of hypertension with vasodilators often induces secondary volume retention.<sup>18,30,36,40</sup> Secondary sodium retention may also result from blood pressure-lowering in hypertensive patients with an underlying abnormal pressure-natriuresis relationship.<sup>32</sup> These features may lead to excess volume (and vasodilator insensitivity) that was not initially present. In addition, elevated levels of aldosterone<sup>44</sup> are common in patients with resistant hypertension. Excess volume is

**Excess volume is often important in maintaining resistant hypertension**

particularly important in the pathogenesis of resistant hypertension in patients with chronic kidney disease.<sup>30</sup>

Diuretics and direct vasodilators may also stimulate catecholamine secretion, as evidenced by secondary sinus tachycardia. Therefore, as patients with resistant hypertension are selected out by their requirement for multiple medicines, the medicines themselves may elicit maladaptive responses, ie, increased volume and increased catecholamine secretion, which maintain hypertension despite increased therapy. Importantly, the interactions between multiple medicines and the magnitude of the secondary changes in an individual patient's hemodynamic status are not predictable a priori.

#### ■ DIURESIS AND BETA-BLOCKADE ARE PROCESSES, NOT STEPS

If the failure to respond to aggressive vasodilation selects out patients in need of diuresis or beta-blockade, then addition or up-titration of diuretics and beta-blockers becomes more important.

However, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)<sup>45,46</sup> does not emphasize that diuresis and beta-blockade are processes rather than steps. In this stepped-care approach, diuretics and beta-blockers are prescribed at a certain step before moving on to subsequent steps of adding other types of medicines. De Nicola et al,<sup>12</sup> as mentioned, documented that many patients were prescribed furosemide only at its lowest dose, with further therapy characterized solely by adding different medicines.

As a process, diuresis in particular often requires time, adjustments, and increasing doses to reach fruition. Even prescription of a diuretic at maximal doses does not ensure effective diuresis. The latter requires salt restriction, divided doses to compensate for short half-lives, and continually increasing diuretics until excess volume has been removed. If diuresis is incomplete at a large dose of one diuretic, a complementary diuretic should be added, rather than a medicine from a different class of antihypertensives.

Similarly, effective beta-blockade requires continually increasing the dose of beta-blocker until the target heart rate is reached.

#### ■ AN ALTERNATE APPROACH TO RESISTANT HYPERTENSION

The individualized pathophysiologic approach that intensivists take to *low* blood pressure provides a model for a different strategy that may be applied towards resistant hypertension. These physicians identify (and often measure) the mechanism of the hypotension—low volume, cardiac output, or systemic vascular resistance—and provide directed, empiric therapy. Medicines from other classes are not added without evidence that they are addressing an ongoing contributor to hypotension. Medicines are also applied as part of a therapeutic process rather than as an end in themselves; for example, the dose of a pressor agent is titrated upwards, or an additional pressor agent is added, until systemic vascular resistance reaches a target value.

An individualized, hemodynamic-based approach to resistant hypertension, akin to the intensivists' approach to hypotension, was suggested by Gifford<sup>23</sup> and Graves et al,<sup>39</sup> and then tested in a clinical study by Taler et al.<sup>18</sup>

#### Taler et al: Hemodynamic-based care beats specialist care

The study by Taler et al<sup>18</sup> was important because it established the success of the individualized, hemodynamic-based approach.

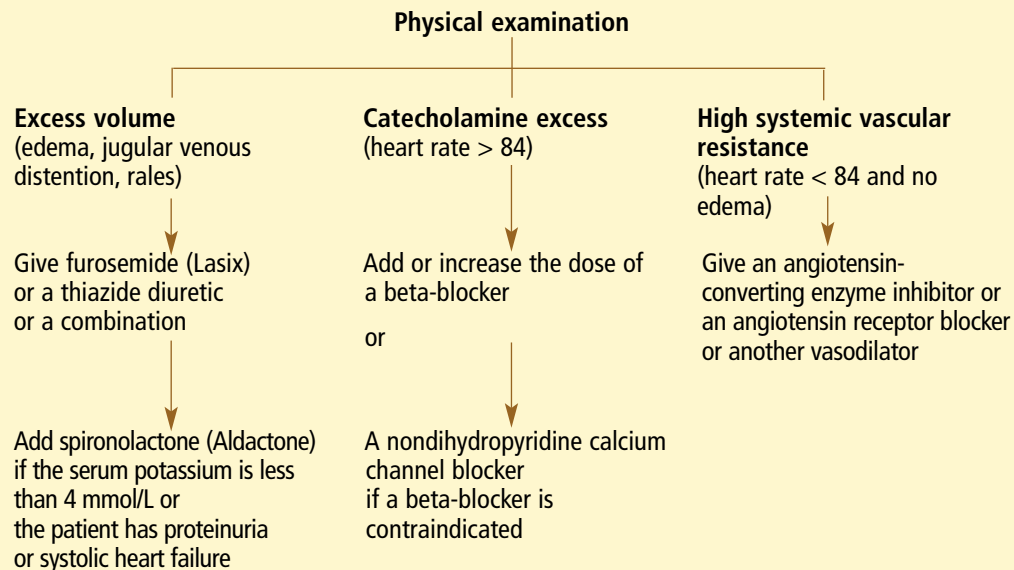
In this trial, the investigators randomly assigned 104 patients with resistant hypertension to undergo treatment either according to an algorithm guided by hemodynamic measurements performed at every visit or as prescribed by specialists who did not have access to these measurements.

The measurements were obtained noninvasively, by impedance plethysmography. If patients had increased systemic vascular resistance, they underwent vasodilation; if they had an elevated cardiac index, they were prescribed beta-blockade; and if they had excess volume, they were prescribed diuresis.

Hemodynamics-guided treatment was more effective than specialist care. After 3

**A patient's hemodynamic profile may change with every visit, necessitating examinations at every visit**

## An alternate approach to resistant hypertension



**FIGURE 1.** An alternate approach to resistant hypertension. See text for detailed discussion. Each patient encounter begins with a new physical examination.

months of treatment, 28 (56%) of the 50 patients in the hemodynamic care group had their blood pressure at 140/90 mm Hg or lower, compared with 18 (33%) of the 54 patients in the specialist care group ( $P < .05$ ).

A major difference in the two treatment groups was that the quantitative measurements led to more aggressive diuretic therapy than prescribed by the expert physicians in the control group. This result was particularly impressive, given that the control group was treated by experts who were attuned to the role of excess volume.

### Estimating hemodynamic variables in a physical examination

At present, we do not have an inexpensive means to routinely duplicate the hemodynamic measurements used by Taler et al. However, the demonstrated success of the quantitative hemodynamic approach to resistant hypertension<sup>18,39</sup> has prompted its adaptation for clinical purposes, emphasizing the role of the physical examination in estimating hemodynamic variables.<sup>47</sup>

The physical examination, applied to resistant hypertension, seeks (in the absence

of actual measurements) to distinguish between catecholamine excess, volume excess, and vasoconstriction as ongoing determinants of hypertension (FIGURE 1).

Hypertensive patients with heart rates greater than 84, suggesting increased sympathetic tone, should be treated with the addition or increase of a beta-blocker.<sup>48</sup> Patients with edema or other signs of excess volume should be treated with diuresis. Patients with both excess volume and tachycardia may be treated with diuresis and beta-blockade. In the absence of edema and tachycardia, elevated systemic vascular resistance is more likely and would suggest that vasodilators should be increased.

Volume excess, however, is often covert in resistant hypertension and is not always evidenced by edema.<sup>18,39,40</sup> It is particularly common with underlying chronic kidney disease. The hemodynamic approach should maintain the flexibility required to address covert volume excess.

When the physical examination suggests high systemic vascular resistance (ie, neither excess volume nor tachycardia is found), the need for vasodilation is suggested (FIGURE 1).

**Volume excess is often covert in resistant hypertension, without edema**

However, when such patients have chronic kidney disease, a physician may suspect covert volume excess and should maintain the option of increasing diuretics in addition to, or in lieu of, a vasodilator.

### Perform a new examination at every visit

A patient's hemodynamic profile may change with every visit, as the previous alteration in therapy may have introduced new perturbations. Therefore, a physical examination must be done at each patient visit. At different times, the findings may suggest that a patient requires diuresis, catecholamine suppression, or vasodilation.

Importantly, serial examinations will emphasize that diuresis and beta-blockade are processes; examinations will identify patients with persistent excess volume (or persistent tachycardia), so that their diuretic (or beta-blocker) regimen will be continually increased until the process of diuresis (or beta-blockade) is complete. Even when patients are prescribed a "maximal" dose of a diuretic, diuresis may be augmented by adding complementary diuretics, ie, combinations of thiazide, loop, and distal-acting diuretics that act at different nephron sites. Aldosterone-receptor antagonists may be particularly effective additions to loop or thiazide diuretics, not only to facilitate diuresis, but also to counteract the effects of the loop and thiazide diuretics on potassium and acid-base homeostasis. In addition, aldosterone-receptor antagonists aid in the treatment of concomitant systolic heart failure and proteinuric renal disease, and may have additional antihypertensive effects independent of volume reduction.<sup>44</sup>

Intensification of both diuresis (particularly with complementary diuretics) and beta-blockade requires careful follow-up to avoid side effects. Diuresis should proceed slowly. Diuretics should be added or increased in small increments only, and weight loss should be no greater than 0.5 kg/day. Weekly visits may be required initially to monitor weight loss, blood pressure, and electrolytes. Heart rate should be monitored, and additional antihypertensives with potential sinus node depressant effects (ie, clonidine [Catapres] and nondihydropyridine calcium channel block-

ers) should generally be avoided when beta-blockade is increased.

The emphasis on physical examination marks a significant change in strategy. The JNC reports do not discuss the physical examination.<sup>45,46</sup> Instead, current emphasis is on studying a patient's medical prescription, looking for a dose to increase or a medicine from a different class to add. By contrast, with the examination-centered approach, physicians will approach a patient without any preconceived preference for the next therapeutic intervention.

### ■ WHEN STEPPED-CARE FAILS, A NEW APPROACH IS NEEDED

Resistant hypertension persists as a major clinical problem despite the development of powerful medicines. Prescription audits suggest that patients are often treated with several vasodilators and not with aggressive diuresis or beta-blockade. The patients who do not respond to aggressive vasodilator therapy may constitute a group selected out by our current strategy: they may be vasodilator-resistant and in need of diuresis or catecholamine suppression. In that event, continued efforts at vasodilation will not succeed and may account for persistent failures.

The basic motif of our standard stepped-care approach to hypertension may prompt physicians to prescribe additional vasodilators. This suggests that physicians should consider a different approach for patients for whom stepped-care and aggressive vasodilation have failed. An alternative strategy, using quantitative measurements to assess hemodynamic determinants has proven effective in a clinical study.<sup>18</sup> In the absence of a means to routinely measure hemodynamic variables in clinical practice, use of the physical examination to estimate these measurements has been described.

The examination-guided strategy is intended as a complement to stepped-care for patients in whom the stepped-care approach has failed. The examination-based approach has not been subjected to rigorous clinical study. It does, however, follow logically from the principles of the hemodynamic approach to hypertension. Based on our knowledge of the pathophysiology of hypertension and results of studies that used individual quantita-

**Diuretics should be added or increased in small increments only, and weight loss should be no greater than 0.5 kg/day**



tive hemodynamic measurements, diuresis and beta-blockade for patients with obvious volume excess and tachycardia, respectively, will be more successful than nondirected therapy.

The prognosis of persistent hypertension is poor, and any strategy that successfully treats previously resistant hypertension is likely to improve a patient's prognosis, with resolution of hypertension serving as a surrogate end point for long-term outcomes. The studies that quantified excess volume or demonstrated

favorable results with diuresis, and the Taler et al study,<sup>18</sup> suggest that a significant proportion of patients with resistant hypertension will respond to the examination-based strategy. Moreover, one could reasonably argue that any proportion of patients who respond constitute a therapeutic success compared with continued hypertension. Therefore, the examination-based approach should be an option for patients whom treating physicians deem resistant to the traditional approach. ■

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