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Sandra J. Taler, Stephen C. Textor and Jo Ellen Augustine

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# Resistant Hypertension

## Comparing Hemodynamic Management to Specialist Care

Sandra J. Taler, Stephen C. Textor, Jo Ellen Augustine

**Abstract**—Although resistant hypertension affects a minority of all hypertensives, this group continues to experience disproportionately high cardiovascular event rates despite newer antihypertensive agents. Hypertension represents an imbalance of hemodynamic forces within the circulation, usually characterized by elevated systemic vascular resistance. We studied the utility of serial hemodynamic parameters in the selection and titration of antihypertensive medication in resistant hypertensive patients using highly reproducible noninvasive measurements by thoracic bioimpedance. Resistant hypertension patients (n=104) were randomized to drug selection based either on serial hemodynamic (HD) measurements and a predefined algorithm or on drug selection directed by a hypertension specialist (SC) in a 3-month intensive treatment program. Blood pressure was lowered by intensified drug therapy in both treatment groups ( $169 \pm 3/87 \pm 2$  to  $139 \pm 2/72 \pm 1$  mm Hg HD versus  $173 \pm 3/91 \pm 2$  to  $147 \pm 2/79 \pm 1$  mm Hg SC,  $P < 0.01$  for systolic and diastolic BP), using similar numbers and intensity of antihypertensive medications. Blood pressures were reduced further for those treated according to hemodynamic measurements, resulting in improved control rates (56% HD versus 33% SC controlled to  $\leq 140/90$  mm Hg,  $P < 0.05$ ) and incremental reduction in systemic vascular resistance measurements. Although the number of patients taking diuretics did not differ between groups, final diuretic dosage was higher in the hemodynamic cohort. Our results demonstrate superior blood pressure control using a treatment algorithm and serial hemodynamic measurements compared with clinical judgment alone in a randomized prospective study. Our measurements of thoracic fluid volume support occult volume expansion as a mediator of antihypertensive drug resistance and use of impedance measurements to guide advancing diuretic dose and adjustment of multidrug antihypertensive treatment. (*Hypertension*. 2002;39:982-988.)

**Key Words:** hypertension, resistant ■ hemodynamics ■ drug therapy ■ cardiography

Achieving normal blood pressure with antihypertensive medications remains an elusive goal for many hypertensive patients. Hypertension control rates are low, with only 17% to 27% of hypertensives reaching goal levels of  $\leq 140/90$  mm Hg.<sup>1,2</sup> Although reasons for limited control rates are complex, the subset of “treatment resistant” hypertensives poses special concern. Resistant hypertension is defined as the failure to control blood pressure to normal levels ( $< 140/90$  mm Hg) using multiple antihypertensive medications, including a diuretic. Refractory hypertension is a more inclusive term for treatment failure using  $\geq 2$  agents; the terms are sometimes used interchangeably. Reported prevalence rates for resistant hypertension vary from  $< 1\%$  at a hypertension job site clinic to 11% to 13% in hypertension referral clinics.<sup>3,4</sup> Although resistant hypertension affects a minority of treated hypertensive patients, the resulting target organ damage causes a disproportionately high risk of cardiovascular events.<sup>5</sup>

Despite introduction of several new classes of antihypertensive agents over the past 2 decades, suboptimal selection of drug therapy remains among the most common causes for

treatment failures, identified in 43% of a series of 91 patients.<sup>6</sup> Results from recent randomized clinical trials indicate that 19% to 47% of enrolled hypertensive subjects require  $\geq 2$  antihypertensive agents to achieve treatment goals.<sup>7-10</sup> For patients with manifest target organ damage, diabetes mellitus, or renal disease in whom treatment goals are lower ( $< 130/80$  mm Hg), 78% to 93% require  $\geq 2$  medications.<sup>11</sup> Although diuretics potentiate the effectiveness of ACE inhibitors, angiotensin receptor blockers and other agents, the effects of other combinations are not known. When  $\geq 2$  agents are used, few data address the hemodynamic effects of complex multidrug regimens, despite the potential for additive or opposing effects.

Although the use of hemodynamic measurements to characterize blood pressure disorders is not new,<sup>12</sup> application to guide therapy has been limited by a lack of methods to obtain reproducible measurements noninvasively. Recent developments have improved measurement of systemic hemodynamics by use of thoracic bioimpedance.<sup>13</sup> This instrument detects changes in thoracic fluid volume during electrical systole by use of skin electrodes and a low voltage current to derive

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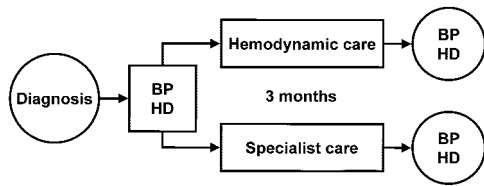
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**Figure 1.** Study design. Resistant hypertensive patients without a secondary cause or who were to be treated medically underwent blood pressure (BP) and hemodynamic measurements (HD) and then were randomized to hemodynamic-based drug selection or hypertension specialist-directed drug selection for 3 months. All subjects returned monthly for BP measurements and drug titration as indicated. Hemodynamic measurements were repeated after 3 months treatment in all subjects; additional monthly measurements were obtained in those randomized to hemodynamic care.

stroke volume. Coupled with heart rate and blood pressure measurements, thoracic impedance offers real-time measurement of cardiac output and systemic vascular resistance. Although the technique has been validated by comparison with other methods<sup>14,15</sup> and is highly reproducible,<sup>16,17</sup> the clinical value of such measurements for management of resistant hypertension is not known. We hypothesized that delineating the specific hemodynamic mechanisms active in the individual with resistant hypertension may provide a means to adjust antihypertensive therapy and, by correcting the hemodynamic abnormalities, to achieve blood pressure goals. We conducted a randomized clinical trial to compare the utility of serial noninvasive hemodynamic measurements by thoracic bioimpedance coupled with a treatment algorithm, to clinical specialist expertise in the selection and titration of antihypertensive therapy for resistant hypertensives.

**Methods**

Patients referred to the Mayo Clinic Division of Hypertension with refractory hypertension, defined as blood pressure >140/90 mm Hg while they were taking ≥2 antihypertensive agents in adequate doses, were evaluated by an American Society of Hypertension-certified specialist in clinical hypertension, with attention to correctable secondary causes and medication compliance. Those who were to be treated medically were invited to participate in a 3-month intensive treatment program. Subjects were excluded from participation if they were unable to return monthly during the trial or if the physician or study nurse identified noncompliance with medications as the cause for treatment resistance. The procedures and protocol for this study were approved by the institutional review board of the Mayo Clinic. Informed written consent was obtained.

Between March 1998 and September 2000, 117 subjects were randomized to drug selection based either on serial hemodynamic measurements and a predefined algorithm (hemodynamic care) or on drug selection directed by a hypertension specialist (specialist care) (Figure 1). A registered nurse, certified by American Heart Association standards<sup>18</sup> and annual audiologic testing, measured blood pressure (mercury sphygmomanometer or calibrated aneroid sphygmomanometer) and heart rate after the patient sat for 5 minutes, in a quiet office with back support and with the arm supported at heart level. Values were reported as the average of 2 readings taken 2 minutes apart. Hemodynamic measurements were obtained from all subjects at entry by use of thoracic bioimpedance and concurrent oscillometric blood pressure measurement (Datascopie Accutorr 4, Datascopie Corporation). For those subjects randomized to specialist care, a technician obtained the hemodynamic measurements, which were then stored, unavailable to the study nurse or treating clinician.

All subjects returned at least monthly for additional blood pressure measurements and medication titration. A single nurse saw all subjects in both treatment arms. Hemodynamic measurements were repeated monthly for hemodynamic care subjects and for all subjects at the conclusion of the 3-month treatment period.

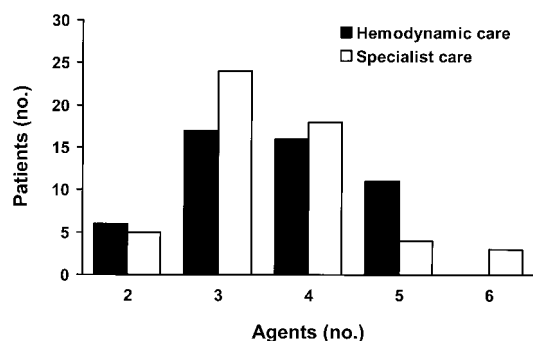
Hemodynamic measurements were obtained by thoracic electrical bioimpedance (Bioz, CardioDynamics International Corporation). This instrument uses surface electrocardiographic electrodes applied at the base of the neck and at the base of the thorax. A low-voltage high-amplitude alternating current is introduced through the outermost sensors and sensed through the innermost sensors. The difference between voltage introduced and that sensed indicates the level of impedance in the thorax and is inversely proportional to the amount of thoracic blood volume.<sup>19</sup> Stroke volume was derived from change in impedance/time measured during electrical systole, calculated using the Z MARC (Modulating Aortic Compliance) algorithm. Cardiac output was determined as the product of stroke volume and heart rate. Systemic vascular resistance index was calculated from measurements of cardiac index and blood pressure. Absolute impedance measurements and change in impedance with posture change from supine to standing positions were utilized as markers of cardiopulmonary volume, standardized to a group of normal subjects placed on controlled sodium intake.<sup>20</sup> Repeated measurements demonstrate high levels of reproducibility for the primary variables (stroke volume correlation, 0.99; thoracic fluid impedance [TBI], 0.99 on 2 consecutive days) in our hands and others (stroke volume, 0.84; TBI 0.66 at 1 week interval).<sup>16</sup>

Subjects in the hemodynamic care group were treated according to a predefined algorithm (Table 1) with medication and dose selections made by a single physician (S.J.T.). In brief, if cardiac output was less than normal and/or systemic vascular resistance higher than normal, an agent with vasodilatory properties was added or the dosage was increased. Agents that reduce cardiac output were reduced in dosage or discontinued. Alternatively, if cardiac output was above normal and/or systemic vascular resistance was below normal, a β-blocker or central sympathetic agonist was added or increased in dosage, or vasodilatory agents were reduced in dosage or withdrawn. In all cases, attention was addressed to impedance change with posture (ΔTBI). Reduced change in impedance with posture (<3 ohms) in association with an elevated blood pressure was interpreted to suggest excess cardiopulmonary volume. In such instances, the diuretic dosage was increased, a more potent diuretic was prescribed, or a second diuretic was started. For the small number of subjects (9%) who were not receiving a diuretic at entry, a separate randomization scheme was used to assure equal distribution of these subjects to both study arms.

Data were recorded in a computer database using Excel software. Statistical analysis was performed using Systat (SPSS) statistical

**TABLE 1. Hemodynamic Care Algorithm**

Cardiac Index	Systemic Vascular Resistance Index		Medication Choices
	Low	High	
Low	High		1. Add or increase dihydropyridine calcium channel blocker, ACE inhibitor, angiotensin receptor blocker, or direct vasodilator 2. Reduce β-blocker 3. Evaluate ΔTBI; if reduced, add or intensify diuretic dose
High	Low		1. Add β-blocker or central agonist 2. Reduce vasodilators 3. Evaluate ΔTBI; if reduced, add or intensify diuretic dose
Normal	Normal		Evaluate ΔTBI; if reduced, add or intensify diuretic dose



**Figure 2.** Number of antihypertensive agents prescribed at study entry. The majority of subjects were receiving 3 or 4 medications at entry, with a range of 2 to 6 medications.

programs.<sup>21</sup> Data were expressed as mean $\pm$ SEM unless otherwise indicated. Comparisons between groups were performed by unpaired *t* tests and between values at different time points by paired *t* tests, with Bonferroni correction as appropriate. Comparison of specific medication usage between groups was examined by  $\chi^2$  analysis. Intensity of drug treatment was quantified by the number of agents prescribed and by a system of dosage equivalents, the Defined Daily Dose (DDD) developed by the World Health Organization for use in drug utilization studies.<sup>22</sup> Total dosage of diuretics was analyzed separately using the DDD system to facilitate comparison of treatment intensity relative to markers of cardiopulmonary volume by thoracic bioimpedance between groups and within the hemodynamic care group.

## Results

One hundred seventeen patients were enrolled in the trial. Results from 104 patients are reported. Thirteen patients were excluded from analysis for the following reasons: 7 were noncompliant with medications (direct observation of drug ingestion causing hypotension in 3) or follow-up, 1 died of metastatic carcinoma, 1 had extreme office hypertension with normal out of office pressures, 2 had normal blood pressure at entry, and 2 were referred for surgery (1 renovascular, 1 aldosterone-producing adenoma). The mean age was 66 $\pm$ 1 years, with 48% male. Office blood pressure obtained by the study nurse at entry was 171 $\pm$ 2/89 $\pm$ 1 mm Hg while the patient was seated and was taking an average of 3.6 $\pm$ 0.1 different antihypertensive medications (range, 2 to 6) (Figure 2), including a diuretic in 91%. There were no differences in age, gender distribution, blood pressure, or renal function at entry between treatment groups (Table 2).

Patient characteristics and comorbid conditions are listed in Table 2. Diabetes mellitus was present in 33% and hyperlipidemia in 50%. Forty-seven percent had manifestations of target organ damage including stroke or TIA, coronary artery disease, peripheral vascular disease, or abdominal aortic aneurysm. Obesity was present in 50% based on body mass index  $>30$  kg/m<sup>2</sup>. One third (37%) had initial creatinine values of  $\geq 124$   $\mu$ mol/L. A secondary cause deemed responsible for a component of their hypertension was identified in 34% of subjects (Table 2). For those subjects, the clinical decision had been made to treat medically and not address the secondary cause at this time. The prevalence of these conditions did not differ between those assigned to hemodynamic or specialist treatment groups.

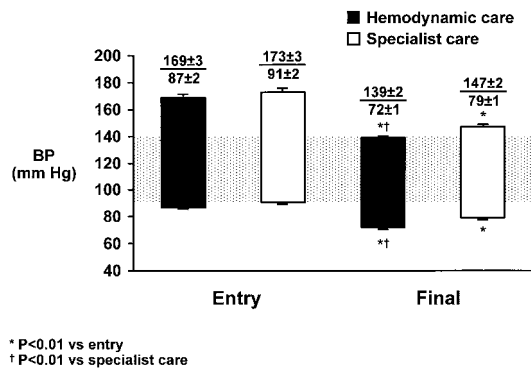
**TABLE 2.** Characteristics Before and After Treatment

Characteristics	Hemodynamic Care (n=50)	Specialist Care (n=54)
Before treatment		
Age, y	67 $\pm$ 2	64 $\pm$ 2
Weight, kg	91.5 $\pm$ 3.2	95.9 $\pm$ 4.0
Body mass index, kg/m <sup>2</sup>	31.4 $\pm$ 1.0	32.7 $\pm$ 1.2
Office blood pressure sitting, mm Hg	169 $\pm$ 3/87 $\pm$ 2	173 $\pm$ 3/91 $\pm$ 2
Heart rate sitting, bpm	66 $\pm$ 1*	72 $\pm$ 2
Serum creatinine, $\mu$ mol/L	115 $\pm$ 9	115 $\pm$ 9
No. of medications	3.6 $\pm$ 0.1	3.6 $\pm$ 0.1
Total medications DDD	5.3 $\pm$ 0.3	5.2 $\pm$ 0.3
Diuretic DDD	1.1 $\pm$ 0.1	1.2 $\pm$ 0.2
Cardiovascular comorbidities		
Diabetes mellitus	16 (32)	18 (33)
Hyperlipidemia	27 (54)	25 (46)
Target organ damage		
Stroke or TIA	5 (10)	5 (9)
Coronary artery disease	15 (30)	10 (19)
Congestive heart failure	3 (6)	3 (6)
Left ventricular hypertrophy	9 (18)	10 (19)
Peripheral vascular disease	9 (18)†	3 (6)
Abdominal aortic aneurysm	4 (8)	2 (4)
Secondary/contributing causes		
Renal artery stenosis	6 (12)	8 (15)
Primary aldosteronism	3 (6)	4 (7)
Obstructive sleep apnea	9 (18)	11 (20)
After 3 months of treatment		
Office blood pressure sitting, mm Hg	139 $\pm$ 2/72 $\pm$ 1‡*	147 $\pm$ 2/79 $\pm$ 1‡
Heart rate sitting, bpm	68 $\pm$ 1†	72 $\pm$ 2
Serum creatinine, $\mu$ mol/L	141 $\pm$ 9‡	133 $\pm$ 9§
No. of medications	4.3 $\pm$ 0.1‡	4.1 $\pm$ 0.1‡
No. of nurse visits	6.2 $\pm$ 0.2	6.2 $\pm$ 0.3
Total medications DDD	6.1 $\pm$ 0.4§	5.7 $\pm$ 0.3§
Diuretic DDD	2.1 $\pm$ 0.2‡*	1.4 $\pm$ 0.1§
Control to $\leq$ 140/90 mm Hg	28/50 (56)†	18/54 (33)
Control to $\leq$ 150/90 mm Hg	40/50 (80)†	33/54 (61)

Values are mean $\pm$ SEM or n (%).

\**P*<0.01 vs specialist care; †*P*<0.05 vs specialist care; ‡*P*<0.01 vs entry; and §*P*<0.05 vs entry.

Results of hemodynamic and specialist care treatment after 3 months are presented in Table 2. Blood pressure was reduced by intensified drug therapy in both treatment groups. The final number of antihypertensive medications, the total number of defined daily doses, and the number of visits did not differ. Achieved blood pressure levels, however, were lower for those treated according to hemodynamic measurements than for those treated by specialists alone (139 $\pm$ 2/

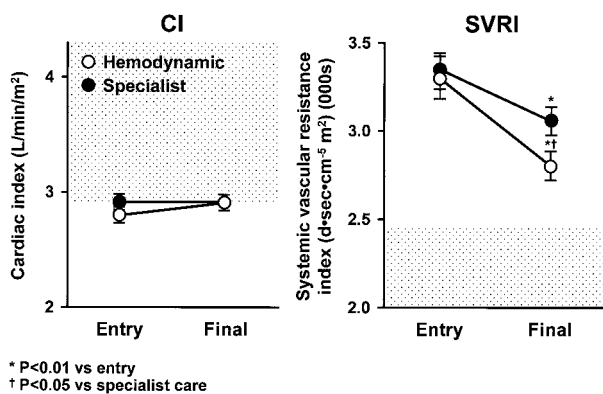


**Figure 3.** Treatment of resistant hypertension. Entry and final blood pressure measurements in hemodynamic and specialist care groups. Blood pressure was reduced by both treatment methods, but to lower levels in those treated according to hemodynamic measurements. Shading indicates limits of normal range.

72 ± 1 versus 147 ± 2/79 ± 1 mm Hg,  $P < 0.01$  for systolic and diastolic pressures) (Figure 3). This difference produced improved control rates in the hemodynamic treatment group compared with the specialist care group (56% versus 33% controlled to 140/90 mm Hg,  $P < 0.05$ ).

Hemodynamic measurements are shown in Figure 4. Mean cardiac index did not change during the trial in either group. At entry, systemic vascular resistance was elevated above normal levels in both groups. Intensive drug treatment reduced systemic vascular resistance, with greater incremental reduction in the hemodynamic group.

Urinary sodium excretion and measurements of thoracic bioimpedance are summarized in Table 3. Supine and standing measures of thoracic impedance were higher at the conclusion of the trial in both groups. These changes were associated with more intensive diuretic use (higher DDD) and a rise in serum creatinine. Thoracic impedance values and postural changes did not differ between treatment groups. Urinary sodium excretion did not differ between treatment



**Figure 4.** Hemodynamic parameters in resistant hypertension before and after intensive treatment. At entry, systemic vascular resistance was elevated in both groups. Mean cardiac index did not change. Although intensive treatment reduced systemic vascular resistance, with further reductions in those treated by hemodynamic measurements, systemic vascular resistance remained above normal levels. Shading indicates normal range for cardiac index and upper boundaries of normal range for systemic vascular resistance index.

**TABLE 3.** Volume Indicators in Resistant Hypertension

	Hemodynamic Care	Specialist Care
Entry		
Supine TBI, ohms	33.4 ± 1.1	34.3 ± 1.1
Standing TBI, ohms	36.5 ± 1.2	36.4 ± 1.1
ΔTBI, ohms	3.4 ± 0.3*	2.5 ± 0.3
24-hr urine sodium, mmol	171 ± 13	160 ± 12
Serum creatinine, μmol/L	115 ± 9	115 ± 9
Diuretic DDD	1.1 ± 0.1	1.2 ± 0.2
Final Results		
Supine TBI, ohms	36.0 ± 1.0†	36.6 ± 1.2†
Standing TBI, ohms	39.0 ± 1.2‡	38.4 ± 1.2‡
ΔTBI, ohms	3.1 ± 0.3	2.4 ± 0.3
24-hr urine sodium, mmol	179 ± 13	194 ± 15
Serum creatinine, μmol/L	141 ± 9†	133 ± 9‡
Diuretic DDD	2.1 ± 0.2†§	1.4 ± 0.1‡

Values are mean ± SEM.

\*  $P < 0.05$  vs specialist care; †  $P < 0.01$  vs entry; ‡  $P < 0.05$  vs entry; §  $P < 0.01$  vs specialist care.

groups at entry or termination of the trial. Although the number of patients taking thiazide diuretics, loop diuretics, or a combination of diuretics did not differ between groups, final diuretic dosage was higher in the hemodynamic cohort (diuretic DDD 2.1 ± 0.2 versus 1.4 ± 0.1,  $P < 0.01$ ) (Table 3).

Other antihypertensive medication use was quantified by drug class and compared between treatment groups (Table 4). There were more frequent changes in medications and dosages in the hemodynamic care group (5.8 ± 0.4 versus 4.6 ± 0.5 for specialist care,  $P < 0.05$ ). More patients were treated with β-blockers and direct vasodilators in the hemodynamic care group and α-β-blockers in the specialist care group. Total DDD rose from entry to the final visit in both groups, but only the intensity of diuretic DDD differed between groups.

## Discussion

The availability of multiple effective antihypertensive medications in recent years offers greater choice in antihypertensive therapy than ever before. Hypertension resistant to treatment with ≥ 2 agents continues to present complex challenges to the clinician. Results from the present study indicated that despite taking 3 or 4 potent antihypertensive medications, our patients demonstrated persistently elevated arterial pressures with high systemic vascular resistance at entry. Reduced thoracic impedance and impaired renal function suggested volume expansion, despite diuretic administration to > 90% of these patients. Our results indicate that more intensive therapy with an emphasis on targeted control of volume using diuretic therapy achieved blood pressure control superior to that attained by empiric selection of drugs. In the present study, experienced clinicians in a hypertension unit in fact did achieve considerable blood pressure reduction. Drug therapy based on a treatment algorithm and repeated noninvasive hemodynamic measurements, however, produced superior blood pressure control in a randomized

**TABLE 4. Medication Usage in Resistant Hypertension**

Drug Treatment	Hemodynamic Care		Specialist Care	
Total No. of medication or dose changes	5.8±0.4*		4.6±0.5	
No. of treatment increases	3.8±0.3		3.0±0.3	
No. of treatment reductions	2.1±0.2		1.6±0.3	
	Entry, %	Final, %	Entry, %	Final, %
Thiazide diuretic	60	66	56	76
Loop diuretic	32	58	41	48
Beta blocker	66	80†	57	52
Adrenergic inhibitor	26	14	20	20
α-Blocker	24	24	22	26
α-β-Blocker	6	2†	13	19
Calcium blocker	58	78	61	80
ACE inhibitor	52	46	54	48
A <sub>2</sub> receptor blocker	28	38	30	35
Vasodilator	4	20*	4	6

Values are mean±SEM.

\* $P<0.05$  vs specialist care; † $P<0.01$  vs specialist care.

prospective fashion. Improved blood pressure control at the final visit correlated with an incremental reduction in systemic vascular resistance in those treated according to hemodynamic values. Our results are supported by previous hemodynamic measurements by use of other methods.<sup>12,23,24</sup> Regardless of the primary etiology, elevated pressures are associated with high peripheral resistance.<sup>25</sup> Although it is recognized that effective blood pressure control requires a reduction in vascular resistance, the effects of specific drugs can be heterogeneous and can lead to both volume retention and reflex changes that offset the desired result.<sup>26–28</sup> Hence, selection of an optimal combination of medications for the patient with resistant hypertension is often empiric. The present study design was based on nurse-supervised visits at least monthly, with review of progress by the treating physician at each visit. This treatment model was applied to both groups, but control rates were incrementally higher when drug selection and adjustment was based on serial hemodynamic measurements, compared with hypertension specialist expertise alone. Better blood pressure control rates did not correlate with greater total numbers of medications, more frequent visits, or selection of any particular drug class. There were, however, more changes in medication choices and treatment intensity in the hemodynamic care group, including both increases and reductions in drug treatment. Although nearly all subjects were taking a diuretic at entry (91%) and all were taking  $\geq 1$  diuretic agents at the final visit, more intensive diuretic therapy was prescribed in the hemodynamic treatment group than in the specialist care group.

Low thoracic impedance levels and the response to intensified diuretic therapy support occult volume expansion in our patients. The issue of unidentified volume expansion is well recognized as a cause for resistance to antihypertensive therapy.<sup>28,29</sup> Plasma volume is normal in untreated essential hypertensives but increased in renal parenchymal disease.<sup>30</sup> Studies in resistant hypertensives support a positive correlation between measured blood volume and systolic and dia-

stolic blood pressure in patients treated with sympatholytic agents or vasodilators.<sup>28</sup> Intensified diuretic treatment effects improve blood pressure control by a reduction in plasma volume.<sup>28,29,31,32</sup> Practical assessment of effective cardiopulmonary volume is particularly difficult in the setting of arterial vasodilating agents, such as calcium channel blocking agents, in which edema formation may not reflect accurately total body sodium.<sup>33</sup> Other markers of volume expansion, such as plasma renin activity, can be affected by numerous drugs and other conditions. Hence, titration of diuretic dose in a specific patient can be difficult.

Use of impedance measurements to guide prescription of diuretic therapy is a novel concept. In the setting of a high sodium diet so common in our society, most patients show no outward signs of excess cardiopulmonary volume. Recent trends to use of microdose diuretic therapy or avoidance of diuretics are based on marketing strategies that emphasize potential metabolic interactions and sometimes weaken the practitioner's resolve to advance diuretic therapy. The availability of impedance change as a volume indicator provides needed guidance to volume control. Low absolute impedance values and diminished impedance change with posture at entry indicated expanded cardiopulmonary volume in our patients. Impedance levels rose with more intensive diuretic dosage in both treatment groups suggesting a reduction in cardiopulmonary volume, although we did not see an incremental rise with the higher doses used in the hemodynamic treatment group. The decision to increase diuretic dosage was based on posture change in impedance and concurrent blood pressure measurements; thus, if blood pressure was at goal levels, diuretic treatment was not further intensified based on impedance values alone. The degree of cardiopulmonary expansion was not fully challenged by this treatment strategy and our patients may still have had expanded volume compared with normotensive individuals. We interpret these observations to suggest that a major contribution of bioimpedance measurements in this study was to guide advancing

diuretic dosage, despite rising serum creatinine (Table 4). We believe it was the availability of a volume indicator that led to use of higher diuretic doses in the hemodynamic treatment group.

Previous treatment trials in the 1980s for resistant hypertensives used standardized multidrug regimens with agents added in stepwise fashion, starting with a diuretic or  $\beta$ -adrenergic blocker then adding peripheral vasodilatory agents. These trials were not randomized, with the more potent agents reserved for those most refractory and more intensive treatment limited by an increase in side effects.<sup>4,34</sup> More recently, Yakovlevitch and Black<sup>6</sup> controlled blood pressure in 34 and improved blood pressure in another 8 of 46 patients with resistant hypertension attributed to a suboptimal treatment regimen. For half of these patients, diuretic therapy was started or intensified. In another 17, the addition of a newer agent or the reduction of sympatholytic medications led to improved blood pressure. There were no specific guidelines or clinical features used to guide treatment changes.

Remarkably, the total number of agents used in both treatment groups in the present trial was similar both at entry and at the end of the trial. Thus, it was not the total number of agents that differed between groups but the choice of specific agents. In the case of diuretic treatment, the dosage was more intense in the hemodynamic group. Efforts to quantify antihypertensive treatment intensity have been limited by narrow, usually nonlinear ranges of effective doses, which are not directly comparable within or between drug classes. We used the DDD classification developed by the World Health Organization as a mechanism to compare intensity of medication utilization between treatment groups and over time.<sup>22,35</sup> Use of drug equivalents for comparison of diuretic doses may be more acceptable, as dose responses are more linear in the usual dose ranges used. We believe it was not the intensity of total treatment but the choice of agents used in combination in individual patients that led to higher control rates in the hemodynamic care group. Diuretic treatment intensity was also higher in the hemodynamic care group based on thoracic impedance measurements.

Our results demonstrate incremental treatment benefit from the use of serial noninvasive hemodynamic measurements in an intensive treatment setting for the adjustment and titration of complex antihypertensive medication regimens in resistant hypertensive patients. The results in this trial may underestimate the value of hemodynamic measurements in the selection and adjustment of multidrug programs. Our specialist care group was comprised of nationally certified hypertension specialists who are expert in the treatment of resistant hypertension, including the need for intensified diuretic therapy. Although total number of medications and total defined daily doses increased to similar extent in both groups, the use of hemodynamic measurements apparently provided more precise dose titration for the hemodynamic care group. These results argue that measurement of hemodynamic and impedance parameters guide selection of antihypertensive therapy more effectively than clinical judgment alone for patients resistant to empiric therapy. Whether such measurements may be of even greater utility in community practice

with treatment decisions made by generalists is not yet known.

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