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Value of Noninvasive Hemodynamics to Achieve Blood Pressure Control in Hypertensive Subjects

Ronald D. Smith, Pavel Levy, Carlos M. Ferrario; for the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels Study Group

Abstract—Abnormal hemodynamics play a central role in the development and perpetuation of high blood pressure. We hypothesized that hypertension therapy guided by noninvasive hemodynamics with impedance cardiography could aid primary care physicians in reducing blood pressure more effectively. Uncontrolled hypertensive patients on 1 to 3 medications were randomized by 3:2 ratio to either a standard arm or hemodynamic arm that used impedance cardiography (BioZ, CardioDynamics). Each patient completed 5 study visits with a 2-week washout period followed by 3 months of treatment. A total of 164 patients from 11 centers completed the study, 95 in the standard arm and 69 in the hemodynamic arm. At baseline and after washout, there were no differences between arms in number of medications or demographic, blood pressure, or hemodynamic characteristics. Systolic blood pressure reductions in the hemodynamic arm were greater from baseline (19 mm Hg versus 11 mm Hg; $P<0.01$) and after washout (25 mm Hg versus 19 mm Hg; $P<0.05$). Diastolic blood pressure reductions were also greater in the hemodynamic arm from baseline (12 mm Hg versus 5 mm Hg; $P<0.001$) and after washout (17 mm Hg versus 10 mm Hg; $P<0.001$). The hemodynamic arm achieved goal blood pressure ($<140/90$ mm Hg) more frequently (77% versus 57%; $P<0.01$) and a more aggressive blood pressure level ($<130/85$ mm Hg) more frequently (55% versus 27%; $P<0.0001$). These study results indicate that antihypertensive therapy guided by impedance cardiography in uncontrolled hypertensive patients on ≥ 1 medications is more effective than standard care. (*Hypertension*. 2006;47:771-777.)

Key Words: hemodynamics ■ cardiac output ■ vascular resistance ■ hypertension, arterial ■ hypertension, essential ■ blood pressure

Approximately 65 million people in the United States¹ and 1 billion people worldwide² have hypertension; it is the most common reason adults visit US physicians.³ Hypertension is a major public health concern, because it significantly increases risk of coronary artery disease, heart failure, renal disease, and stroke.⁴ In spite of major public health and medical education efforts and availability of effective antihypertensive agents, blood pressure (BP) control rates in the United States remain low, with only 31% of hypertensives and 54% of those actively treated and taking medications achieving BP $<140/90$ mm Hg.⁵ Why is BP control such an elusive goal? The reasons are numerous and complex. However, inadequate pharmacological treatment remains the most common cause of uncontrolled BP in actively treated patients.⁶

Hypertension is a hemodynamic-related disorder. BP rises as the result of increased systemic vascular resistance (SVR), cardiac output (CO), fluid volume, or a combination of these factors.^{7,8} Consequently, antihypertensive agents lower BP by reducing SVR, CO, fluid volume, or combinations thereof.⁹

Previous authors hypothesized that hemodynamic information could help tailor therapy and subsequently improve BP control.¹⁰ Invasive procedures for hemodynamic profiling are not warranted in outpatient clinics, and noninvasive procedures, such as echocardiography, are costly and operator dependent.¹¹

Impedance cardiography (ICG) has emerged as a reliable noninvasive method to measure hemodynamics in physician offices. In a randomized, controlled trial, ICG-guided treatment improved BP control rates in resistant hypertension treated by hypertension specialists.¹² We hypothesized that ICG-guided treatment could aid physicians in reducing BP more effectively than standard care in a population of uncontrolled hypertensive patients receiving 1 to 3 medications in a primary care setting.

Methods

Eligibility

Male and female patients (age range, 18 to 75 years) were eligible if they had a diagnosis of essential hypertension and were currently on

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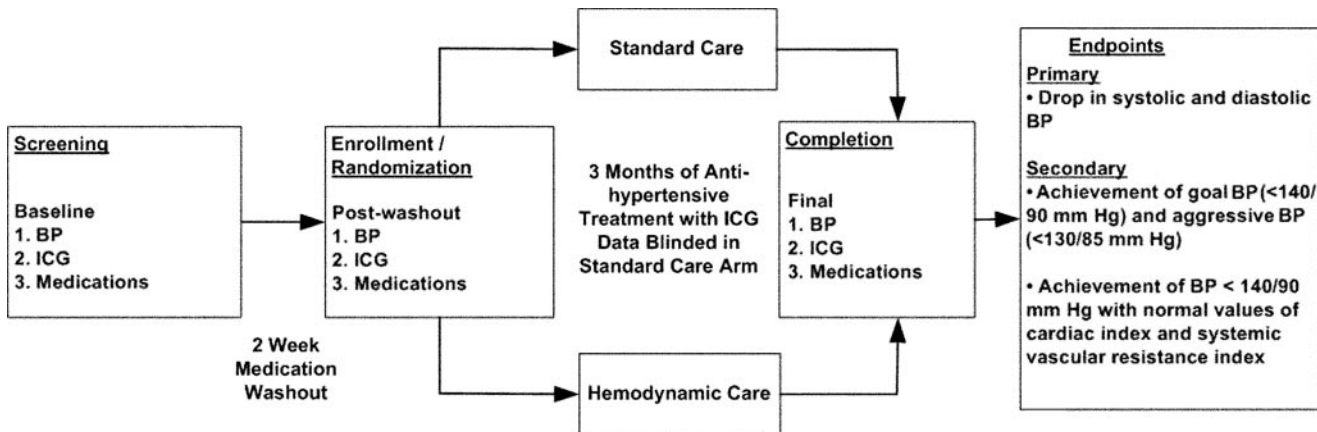


Figure 1. Study design comparing efficacy of standard arm vs hemodynamic arm treatment of high BP.

1 to 3 antihypertensive medications with systolic BP of 140 to 179 mm Hg and/or diastolic BP of 90 to 109 mm Hg. Patients were excluded if they were on >3 antihypertensive agents; had abnormal laboratory findings; or had history of heart failure, left ventricular ejection fraction <40%, atrial fibrillation, severe valvular disease, cerebrovascular event within 3 months, severe renal disease, nephrotic syndrome, or cirrhosis. Patients in whom ICG might be subject to technical limitations were excluded (height <47 or >75 inches or weight <66 or >341 pounds, presence of activated minute-ventilation pacemaker, known hypersensitivity to sensor gel or adhesive, or skin lesion interfering with sensor placement). Patients who were enrolled and subsequently found to have not met the inclusion/exclusion criteria were terminated and excluded from analysis. Therefore, this was not an intention-to-treat analysis. The study was approved by an independent institutional review board, which adheres to the Declaration of Helsinki and US Code of Federal Regulations. These hypertensive outpatients provided written informed consent and had study procedures consistent with the protocol (no. 20021400).

Hemodynamic Evaluation Assignment

Eligible patients (N=164) underwent a 2-week washout period at which time all of the antihypertensive medications were discontinued according to the manufacturer’s recommendations. After screening and medication washout, each patient had 3 monthly office visits

(Figure 1). After the 2-week washout period, patients meeting inclusion/exclusion criteria were randomized in a 3:2 ratio to the standard arm (n=95) or ICG-aided hemodynamic arm (n=69) using a central telephone service and stratified by site. All of the physicians were educated on the hemodynamic treatment strategy illustrated in Figure 2.

Procedures

BP determinations were made in the seated position using the oscillometric technique. ICG data were collected by trained technicians at each visit in all of the patients, but ICG findings were not revealed in the standard arm to treating physicians or patients. ICG was performed with patients in the supine position, resting for 5 minutes before measurement (BioZ ICG Monitor, CardioDynamics). ICG involves the measurement of thoracic impedance through placement of 4 dual sensors, 2 on the neck and 2 on the chest. Electrical impedance changes are digitally processed to calculate CO, SVR, and thoracic fluid content (TFC).¹³ CO and SVR are normalized for body size by indexing to each patient’s body surface area to obtain cardiac index (CI) and SVR index (SVRI). TFC is the inverse of baseline chest impedance, and any changes in TFC are directly proportional to total fluid (intravascular and extravascular) changes.¹⁴ TFC has different normal ranges for each gender that are displayed and printed for reference. The reproducibility of this ICG device in stable outpatients has been established,¹⁵ and accuracy

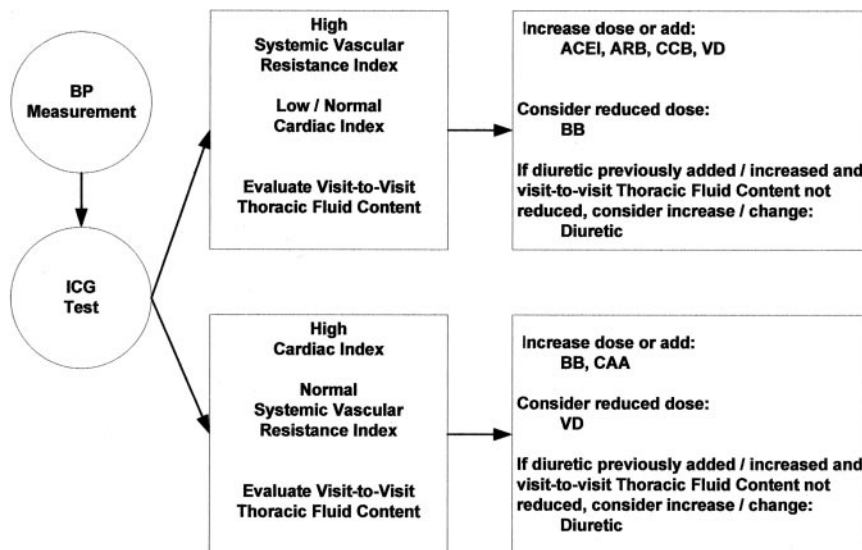


Figure 2. Suggested treatment strategy for hemodynamic arm; BB indicates β blocker; CAA, central acting agent; and VD, vasodilator.

has been validated versus invasive methods in patients with various cardiovascular disorders.^{16,17}

Outcome Measures

Physician investigators were instructed that the treatment goal was to reduce systolic and diastolic BP as low as they believed would be beneficial to the patient and to achieve sustained BP <140/90 mm Hg. The primary study end points were reductions in systolic and diastolic BP from baseline and post-washout visit. Additional study end points were achievement of: (1) goal BP <140/90 mm Hg, (2) more aggressive BP of <130/85 mm Hg, and (3) BP of <140/90 mm Hg with normal values of CI and SVRI. Normal range for CI was defined as 2.5 to 4.2 L/min per m² and for SVRI as 1680 to 2580 dyne \times s \times m²/cm⁵. Isolated systolic hypertension was defined as systolic BP >140 mm Hg and diastolic BP <90 mm Hg.

Interventions

After randomization, therapy was initiated in all of the patients at the post-washout visit, 2 weeks after screening. Physician investigators prescribed medications consistent with published guidelines, their usual practice patterns, and patient clinical characteristics. In the hemodynamic arm, the treating physician was also encouraged to use a hemodynamic treatment strategy to guide therapeutic decisions about pharmacological agents and dosing (Figure 2).

Physicians could share ICG information with patients in the hemodynamic arm, and patients in both arms received education on the importance of medication compliance, which was reinforced with a nurse telephone call midway between each study visit. Compliance was assessed at each visit by asking patients to estimate the percentage of prescribed pills they had taken over the previous month. Patients were considered compliant with the prescribed protocol if pill count was >85% over the prior month.

Statistical Analysis

Data from case report forms were collected by study coordinators and entered into a locked database. Statistical analysis was performed with SAS statistical analysis software, version 8.2. Continuous variables are expressed as mean \pm SD and categorical variables as n (%). Differences in continuous variables between treatment groups were examined by the Student *t* test and by ANOVA and in discrete variables using Fisher's exact tests. Subgroup analysis was performed in subjects with isolated systolic hypertension, age \geq 55 years, and those receiving a thiazide diuretic. Additional evaluation of age-specific results was performed by a 2-way ANOVA for achievement of BP end points, in which treatment arm and dichotomized age (\geq 55 years) were included in the model. In combination agents, each class and dosage was counted separately for analysis. Equivalency of defined daily doses for each class of medication was calculated using World Health Organization criteria.¹⁸ Medication changes were evaluated in visits where such changes affected BP end points (visits 2 versus 1, 3 versus 2, and 4 versus 3). Medication class and dose were compared with the prior study visit, with any change in class or dose counted separately. Sample size was powered using 5 mm Hg as the detectable difference between treatment groups with a type I error of 5% and type II error of 20%. The expected heterogeneity in treatment approach for patients in the standard arm was offset by the greater number of patients randomized to the standard arm. Although this approach increased the probability that the standard arm results would reflect actual practice patterns, it required a larger sample size to power the study.

Results

Eleven primary care centers participated in the study between November 2002 and November 2004. Of 262 patients screened, 184 were randomized. A total of 164 patients (95 in the standard arm and 69 in the hemodynamic arm) completed the study and were analyzed. There were 20 early terminations, including 2 who withdrew and 18 who were randomized but were subsequently found not to have met BP

enrollment criteria (BP >140/90 mm Hg at screening) and were removed as protocol violations. No reported adverse events (minor or serious) were attributable to ICG.

There were no differences in the number of antihypertensive medications, patient demographic, clinical, BP, or ICG variables at baseline or after washout (Table 1). At baseline, there were no differences in the percentage of patients in the standard versus hemodynamic arm on 1 (42% versus 45%; $P>0.05$), 2 (48% versus 44%; $P>0.05$), or 3 (6% versus 10%; $P>0.05$) medications. Baseline medication usage in the

TABLE 1. Patient Characteristics

Variable	Standard Care (n=95)	Hemodynamic Care (n=69)	P Value
Age, y	54.5 \pm 9.4	55.2 \pm 9.2	ns
Body mass index, kg/m ²	30.2 \pm 6.3	30.8 \pm 5.1	ns
Men	51 (53.4)	38 (55.1)	ns
Ethnicity			
White, non-Hispanic	75 (79.0)	53 (76.8)	ns
White, Hispanic	7 (7.4)	5 (7.3)	ns
Black	8 (8.4)	6 (8.7)	ns
Asian	3 (3.2)	3 (4.4)	ns
History			
Type II diabetes mellitus	4 (4.2)	3 (4.4)	ns
Ischemic heart disease	2 (2.1)	5 (7.3)	ns
Hyperlipidemia	14 (14.7)	12 (17.4)	ns
Baseline BP and hemodynamics			
Systolic BP, mm Hg	147 \pm 9	148 \pm 12	ns
Diastolic BP, mm Hg	87 \pm 10	89 \pm 8	ns
Heart rate, bpm	75 \pm 12	74 \pm 13	ns
Cardiac index, L/min/m ²	2.8 \pm 0.5	2.9 \pm 0.6	ns
Systemic vascular resistance index, dyne \times s \times m ² /cm ⁵	2933 \pm 576	2956 \pm 605	ns
Thoracic fluid content, /kOhm	28.6 \pm 4.9	28.0 \pm 4.8	ns
Isolated systolic hypertension at baseline	46 (48.4)	31 (44.9)	ns
Post-washout BP and hemodynamics			
Systolic BP, mm Hg	156 \pm 13	155 \pm 13	ns
Diastolic BP, mm Hg	92 \pm 9	94 \pm 9	ns
Heart rate, bpm	79 \pm 12	78 \pm 14	ns
Cardiac index, L/min/m ²	2.9 \pm 0.5	2.9 \pm 0.5	ns
Systemic vascular resistance index, dyne \times s \times m ² /cm ⁵	3083 \pm 630	3122 \pm 672	ns
Thoracic fluid content, /kOhm	29.1 \pm 5.0	28.4 \pm 4.3	ns
Medications			
Total antihypertensive medications	1.7 \pm 0.8	1.7 \pm 0.7	ns

Categorical variables expressed as n (%), continuous variables as mean \pm SD; ns indicates not significant.

standard versus hemodynamic arm was as follows: α blockers (2.1% versus 1.4%; $P>0.05$), angiotensin converting enzyme inhibitors (ACEI; 53.7% versus 47.8%; $P>0.05$), angiotensin II receptor blockers (ARB; 14.7% versus 29.0%; $P<0.05$), β blockers (23.2% versus 13.0%; $P>0.05$), calcium channel blockers (CCB; 33.7% versus 39.1%; $P>0.05$), central acting agents (0% versus 1.4%; $P>0.05$), diuretics (31.6% versus 26.1%; $P>0.05$), and other vasodilators (0% versus 0%; $P>0.05$).

BP and ICG values at the final visit and their differences from baseline and post-washout visits are shown in Table 2. Systolic BP reductions were greater in the hemodynamic arm from baseline (19 ± 17 versus 11 ± 18 mm Hg; $P<0.01$) and post-washout (25 ± 18 versus 19 ± 17 mm Hg; $P<0.05$). Diastolic BP reductions were also greater in the hemodynamic arm from baseline (12 ± 11 versus 5 ± 12 mm Hg; $P<0.001$) and post-washout (17 ± 12 versus 10 ± 11 mm Hg; $P<0.001$). Final BP was lower in the hemodynamic arm ($129/76\pm 14/11$ versus $136/82\pm 15/10$ mm Hg; $P<0.01$). Figure 3 demonstrates that goal BP ($<140/90$ mm Hg) was achieved more frequently in the hemodynamic arm (77% versus 57%; $P<0.01$), and the more aggressive BP ($<130/85$ mm Hg) was also achieved more often (55% versus 27%; $P<0.0001$).

Patients with isolated systolic hypertension in the hemodynamic arm ($n=31$) had greater systolic BP reductions from

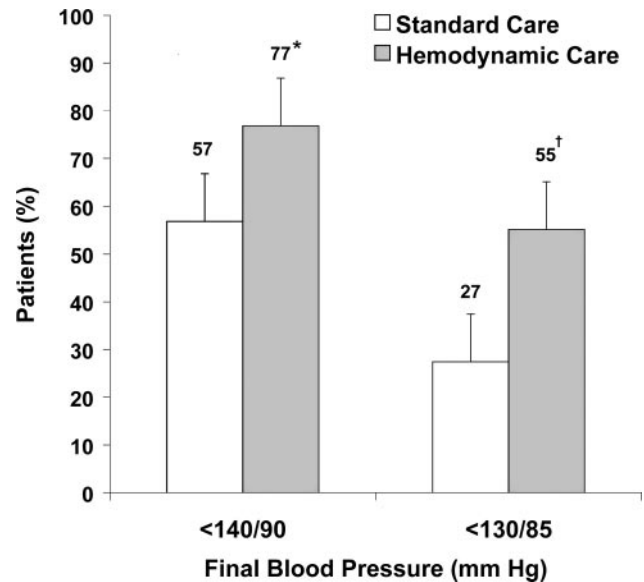


Figure 3. Target BP achievement; with 95% CI; * $P<0.01$ vs standard care, † $P<0.0001$ vs standard care.

TABLE 2. Final BP and Hemodynamic Values

Variable	Standard Care (n=95)	Hemodynamic Care (n=69)	P Value
Systolic BP, mm Hg			
Final	136 \pm 15	129 \pm 14	<0.01
Δ baseline to final	-11 \pm 18	-19 \pm 17	<0.01
Δ post-washout to final	-19 \pm 17	-25 \pm 18	<0.05
Diastolic BP, mm Hg			
Final	82 \pm 10	76 \pm 11	<0.01
Δ baseline to final	-5 \pm 12	-12 \pm 11	<0.001
Δ post-washout to final	-10 \pm 11	-17 \pm 12	<0.001
Heart rate, bpm			
Final	77 \pm 13	76 \pm 11	ns
Δ baseline to final	1 \pm 12	2 \pm 13	ns
Δ post-washout to final	-2 \pm 13	-2 \pm 13	ns
Cardiac index, L/min/m²			
Final	2.9 \pm 0.5	2.9 \pm 0.5	ns
Δ baseline to final	0.1 \pm 0.5	0.0 \pm 0.5	ns
Δ post-washout to final	0.0 \pm 0.5	0.0 \pm 0.5	ns
Systemic vascular resistance index, dyne\timess\timesm²/cm⁵			
Final	2714 \pm 619	2523 \pm 581	<0.05
Δ baseline to final	-219 \pm 667	-433 \pm 660	<0.05
Δ post-washout to final	-369 \pm 642	-599 \pm 738	<0.05
Thoracic fluid content, /kOhm			
Final	27.8 \pm 4.1	28.2 \pm 4.9	ns
Δ baseline to final	-0.8 \pm 3.6	0.1 \pm 3.0	ns
Δ post-washout to final	-1.2 \pm 3.3	-0.2 \pm 2.7	<0.05

Variables expressed as mean \pm SD; ns indicates not significant.

baseline (22 ± 16 versus 11 ± 17 mm Hg; $P<0.01$) and post-washout (28 ± 16 versus 18 ± 16 mm Hg; $P<0.05$) than those in the standard arm ($n=46$). Patients ≥ 55 years in the hemodynamic arm ($n=33$) had greater systolic BP reductions compared with the standard arm ($n=51$) from baseline (21 ± 17 versus 11 ± 20 mm Hg; $P<0.05$) and trended greater from post-washout (26 ± 20 versus 21 ± 19 mm Hg; $P>0.05$). Diastolic BP reductions were also greater in those ≥ 55 years in the hemodynamic arm from baseline (13 ± 11 versus 4 ± 12 mm Hg; $P<0.001$) and post-washout (16 ± 11 versus 10 ± 12 mm Hg; $P<0.05$). In patients ≥ 55 years, goal BP ($<140/90$ mm Hg) was achieved more frequently in the hemodynamic arm (76% versus 53%; $P<0.05$), and the more aggressive BP ($<130/85$ mm Hg) was also achieved more often (58% versus 27%; $P<0.01$). ANOVA also indicated that age ≥ 55 years had no effect on study end points ($P>0.05$).

SVRI was reduced to a greater extent in the hemodynamic arm than in the standard arm from baseline and post-washout. There were no significant differences between arms at the final visit for heart rate, CI, or TFC. However, the standard arm had a small but significant reduction in TFC from post-washout to final. The percentage of patients achieving normal hemodynamic values defined as simultaneously normal values of BP, CI, and SVRI was 52% in the hemodynamic arm and 29% in the standard arm ($P<0.01$). Patients in either arm who achieved BP $<130/85$ mm Hg had lower SVRI (2646 ± 592 versus 2855 ± 606 dyne \times s \times m²/cm⁵; $P<0.05$) and lower CI (2.7 ± 0.5 versus 2.9 ± 0.5 L/min/m²; $P<0.05$) than those who did not achieve BP $<130/85$ mm Hg. Patients in the hemodynamic arm who achieved BP $<130/85$ mm Hg trended toward lower SVRI (2446 ± 580 versus 2573 ± 612 dyne \times s \times m²/cm⁵; $P>0.05$) and higher CI (2.8 ± 0.5 versus 2.6 ± 0.5 L/min/m²; $P>0.05$) than those in the standard care arm who achieved BP $<130/85$ mm Hg.

In the visit after medication washout, patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB, or CCB (92.8% versus 80.0%; $P<0.05$). Over

the course of the study, patients in the hemodynamic arm were more likely to be prescribed an ACEI, ARB, or CCB when their SVRI was high, per the hemodynamic treatment strategy (78.3% versus 67.1%; $P < 0.05$). However, there were no differences in the other 2 treatments encouraged by the hemodynamic treatment strategy, β blocker use based on high CI, or in diuretic use when TFC did not decrease in response to diuretic initiation or increase. Patients in the hemodynamic arm were more likely to avoid β blocker use or to have their β blocker reduced in the presence of low or normal CI (85.4% versus 77.0%; $P < 0.05$) as the hemodynamic strategy suggested. Direct vasodilators were not used, and, therefore, changes in vasodilator use in the presence of normal SVRI were not evaluated. Table 3 lists all of the medications at the final visit. Patients in the standard arm were on 2.0 ± 0.8 medications compared with 2.1 ± 0.9 for the hemodynamic arm ($P > 0.05$). In the hemodynamic arm, ARB use was higher (46.4% versus 30.5%; $P < 0.05$), and ACEI use was similar (49.3% versus 53.7%; $P > 0.05$). However, the percentage of patients in the hemodynamic arm who were prescribed either an ACEI or ARB was not significantly different (87.0% versus 76.8%; $P > 0.05$). There were no differences in the percentage of patients in the hemodynamic care on 1 (25% versus 26%), 2 (48% versus 53%), 3 (19% versus 15%), 4 (9% versus 5%), or 5 (0% versus 1%) medications at the final visit ($P > 0.05$ for all). There were a greater number of medication dose increases in the standard versus hemodynamic arm (3.6 ± 1.3 versus 3.0 ± 1.2 ; $P < 0.001$), as well as a greater number of dose decreases (2.7 ± 1.3 versus 1.7 ± 1.0 ; $P < 0.001$). Medication class changes in the standard and hemodynamic arm were similar in both class initiation (1.0 ± 0.9 versus 1.1 ± 0.9 ; $P > 0.05$) and removal (0.8 ± 0.8 versus 0.7 ± 0.8 ; $P > 0.05$).

Thiazide diuretic use at baseline was similar in the standard versus hemodynamic arm (28.4% versus 24.6%; $P > 0.05$). A similar proportion of patients were prescribed thiazide diuretics at some point during the trial in both the standard and

hemodynamic arms (44.2% versus 40.2%; $P > 0.05$), and use was similar at the final visit (33.7% versus 34.8%; $P > 0.05$). Medication doses were not different between arms except that patients in the standard arm were on higher doses of thiazide diuretics (18.9 ± 8.3 versus 13.0 ± 2.6 mg/day; $P < 0.01$). There were no differences in the hemodynamic arm in the dosing of ACEIs (19.1 versus 19.1 mg/day; $P > 0.05$), ARBs (93.9 versus 87.0 mg/day; $P > 0.05$), β blockers (65.6 versus 80.9 mg/day; $P > 0.05$), or CCBs (7.9 versus 7.9 mg/day; $P > 0.05$). The greater mean dose of thiazide diuretics was because of a higher percentage of patients taking ≥ 25 mg/day versus 12.5 mg/day in the standard arm (40.1% versus 8.3%; $P < 0.05$). When the study end points were analyzed only for patients on a thiazide diuretic in the final visit, patients in hemodynamic arm had greater decreases in systolic BP from baseline (26 ± 19 versus 8 ± 17 mm Hg; $P < 0.001$) and post-washout (36 ± 17 versus 21 ± 20 mm Hg; $P < 0.01$) and greater decreases in diastolic BP from baseline (16 ± 11 versus 3 ± 14 mm Hg; $P < 0.001$) and post-washout (20 ± 12 versus 11 ± 13 mm Hg; $P < 0.01$). There were no differences in patient-reported compliance between the standard and hemodynamic arm in visit 3 (96.8% versus 97.1%; $P > 0.05$), 4 (96.8% versus 98.6%; $P > 0.05$), or 5 (100% versus 100%; $P > 0.05$) or when these visits were combined (97.9% versus 98.6%; $P > 0.05$).

Discussion

Our results demonstrate that ICG-guided antihypertensive treatment was more effective in reducing BP than standard therapy and empiric selection of antihypertensive medications. Patients in the 2 arms of our study were not significantly different at baseline, and each patient underwent a medication washout period to additionally equalize the 2 groups. The 57% BP control rate in the standard arm was substantial and compared favorably to BP control rates of long durations in large antihypertensive trials.^{19,20} However, the 77% BP control rate in the hemodynamic arm was even more impressive with an 8/7 mm Hg greater BP reduction from baseline and a 6/7 mm Hg greater BP reduction from post-washout. As a result, patients in the hemodynamic arm achieved goal BP of $< 140/90$ mm Hg 35% more often (77% versus 57%) and the more aggressive level of BP control ($< 130/85$ mm Hg) 104% more often (55 versus 27%) than those in the standard arm. The hemodynamic arm maintained superiority in 3 key subgroups: patients who were older, on thiazide diuretics, or had isolated systolic hypertension.

Why did the hemodynamic arm achieve greater reductions in BP and higher BP control rates than the standard arm? The fundamental difference between the two arms was that patient treatment in the hemodynamic arm was individualized and targeted at the hemodynamic abnormality associated with the elevated BP. This approach led to greater reductions in SVRI in the hemodynamic arm, which allowed greater decreases in both systolic and diastolic BP. The mechanistic and hemodynamically based improvement in BP was also demonstrated in patients achieving BP $< 130/85$ mm Hg through significantly lower SVRI and higher CI in both arms. In theory, the larger drop in SVRI and BP levels in the hemodynamic arm could have occurred through use of more

TABLE 3. Final Antihypertensive Medications

Antihypertensive Medication	Standard Care (n=95)	Hemodynamic Care (n=69)	P Value
No. at final visit	2.0 ± 0.8	2.1 ± 0.9	ns
α Blocker	1 (1.0)	1 (1.4)	ns
ACEI	51 (53.7)	34 (49.3)	ns
ARB	29 (30.5)	32 (46.4)	< 0.05
β Blocker	18 (19.0)	6 (8.7)	ns
Calcium channel blocker, dihydropyridine	36 (37.9)	28 (40.6)	ns
Calcium channel blocker, nondihydropyridine	6 (6.3)	7 (10.1)	ns
Central acting agent	0 (0.0)	1 (1.4)	ns
Diuretic, thiazide	32 (33.7)	24 (34.8)	ns
Diuretic, loop	1 (1.1)	0 (0.0)	ns
Diuretic, potassium sparing	6 (6.3)	3 (4.3)	ns
Vasodilator	0 (0.0)	0 (0.0)	ns

Categorical variables expressed as n (%); ns indicates not significant.

medications, more effective medications, greater dosing intensity, more effective combination therapy, or better patient compliance. Our study allowed full discretion by the physician in choosing the agents, and a multitude of classes and doses within classes were used. The study was not powered to find small disparities in medication use, and most medication differences did not reach statistical significance.

On the other hand, some differences are worth noting. Patients in the standard arm were more likely to experience both increases and decreases in their medication doses, whereas medication class changes were not different between arms. This result might have been expected, because treatment in the standard arm followed guidelines and usual practice patterns in which a stepped approach to therapy contributes to a "trial-and-error" method of determining whether agents and doses are working. In the hemodynamic arm, the initial selection of antihypertensive medications appears to have been influenced by the hemodynamic data, because these patients were more likely to be prescribed a vasodilating agent to reduce SVRI. Additionally, the hemodynamic treatment strategy influenced medication use when SVRI was considered high, because patients in the hemodynamic arm were more likely to have received an ACEI, ARB, or CCB, as was suggested. The hemodynamic treatment strategy did not influence the prescription of β blockers in the presence of high CI or in diuretic use in response to TFC changes. However, β -blocker use was lower or reduced in the presence of low or normal CI in the hemodynamic arm. Although the final number of antihypertensive medications given to patients in both arms of the study was similar, patients in the hemodynamic arm were more likely to be prescribed an ARB. However, when ACEI and ARB use was combined into a single category (renin-angiotensin-aldosterone system inhibitors), the hemodynamic arm only trended toward greater use at the final visit (87.0% versus 76.8%).

Thiazide diuretic use increased during the study but was lower than in some pharmacological trials and what hypertension guidelines currently suggest. However, the percentage of patients in both arms who were prescribed a thiazide diuretic at the final visit was very similar to the 35.6% usage that was reported in recent analysis of over 25 000 hypertensive patients.²¹ The lower use of diuretics and β blockers also follows the previously recognized physician preference for other antihypertensive agents.²² Some might hypothesize that greater BP reductions could have been achieved in the standard arm if diuretics were used more frequently. However, when patients taking a thiazide diuretic were examined as a subgroup, the hemodynamic arm maintained its superiority. Additionally, although the higher doses of thiazide diuretics in the standard arm may have contributed to a greater drop in TFC from the post-washout visit, they did not lead to better BP control.

Our study was not intended to evaluate whether a particular antihypertensive agent was more effective at reducing BP than another. Rather, it was designed to determine whether providing hemodynamic data to the physician and patient could more effectively reduce BP. Whether hemodynamic data led to a more tailored approach to selection and monitoring of antihypertensive agents or by other factors, it

resulted in greater reduction in BP and SVRI and better BP control. Physicians cannot adequately estimate hemodynamics from routine clinical examination or BP measurements,²³ because at similar levels of BP, SVR and CO can vary widely. Therefore, the addition of accurate, noninvasive, and readily obtainable hemodynamic measurements is clinically relevant.

Importantly, the current study also showed that patients in the hemodynamic arm were almost twice as likely to achieve BP control with normalization of both CI and SVRI. Improvements in vascular resistance may result in greater benefits in reducing cardiovascular risk than improvement in BP alone,²⁴ and differences in SVRI at the same BP may explain poorer prognosis for men versus women²⁵ and black versus nonblack patients.²⁶ Hemodynamics are also known to change with age. In older subjects, decreased arterial compliance and CI lead to increased SVRI, arterial BP, and pulse pressure.²⁷ In spite of the expected differences in the hemodynamics of older patients, this study demonstrated that hemodynamically driven, individualized therapy was similarly effective regardless of age or existence of isolated systolic hypertension.

The use of ICG to achieve greater BP control offers the potential for better short-term use of healthcare resources. In addition, the long-term benefits of even small levels of BP reduction are well known. A sustained BP reduction of 4/3 mm Hg is expected to reduce stroke risk 23%, coronary heart disease events 15%, heart failure 16%, and overall mortality 14%.²⁸ Accordingly, a recent meta-analysis of major hypertension trials reveals that an antihypertensive agent is judged favorably when it produces mean BP improvements versus placebo of only 3 or 4 mm Hg or versus another antihypertensive agent of only 1 or 2 mm Hg.²⁹

Previously, ICG has been used to profile hemodynamic variability across BP values³⁰ and to identify left ventricular dysfunction.³¹ Changes in ICG parameters have demonstrated the hemodynamic effect of antihypertensive agents^{32,33} and dietary sodium.³⁴ ICG-guided therapy has shown benefit in a case series,³⁵ observational study,³⁶ and a randomized trial in resistant hypertensive patients.¹² In the randomized trial, ICG-guided therapy resulted in better final BP and greater BP control. Similar to our study, that study showed no differences in the number of medications between arms. In contrast to our study with lower diuretic doses and fewer medication changes in the hemodynamic arm, resistant hypertension patients receiving ICG-guided therapy had higher diuretic doses and more medication changes. The differences between the studies might be expected because of the difference in patients (severe hypertension on more medications versus milder hypertension on fewer medications) and setting (specialist versus generalist). However, in both studies, ICG-guided therapy led to more effective treatment as evidenced by better BP outcomes.

The conclusions of this study may be limited to its duration of 3 months. However, in pharmacological trials, short-term reductions in BP are typically sustained over longer periods.³⁷ Another limitation may be in our use of patient-reported medication compliance. Without using automatic counting procedures, our goal was to educate both arms equally and to reinforce patient compliance with follow-up phone calls.

Lastly, treatment differences in the hemodynamic arm do not imply superiority of one medication over another, because the study was not designed to evaluate this question.

Perspectives

The results of this study indicate that ICG-guided antihypertensive therapy in uncontrolled hypertensive patients on 1 to 3 antihypertensive medications is more effective than standard care. This was evident by greater reductions in systolic and diastolic BP and by achieving a better level of BP control. Our study showed that, in clinical practice, inclusion of ICG hemodynamic assessment may improve BP control rates in patients who are not controlled on initial therapy.

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References

- Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension*. 2004;44:398–404.
- Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223.
- Chery DK, Woodwell DA. National Ambulatory Care Medical Survey: 2000 summary. *Advance Data*. 2002;328:1–32.
- American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, Texas: American Heart Association; 2003.
- Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. *Arch Intern Med*. 2004;164:2126–2134.
- Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. *Arch Intern Med*. 1991;151:1786–1792.
- Ferrario CM, Page IH. Current views concerning cardiac output in the genesis of experimental hypertension. *Circ Res*. 1978;43:821–831.
- Davidson RC, Ahmad S. Hemodynamic profiles in essential and secondary hypertension. In: Izzo JL, Black HR, eds. *Hypertension Primer*. 3rd ed. Dallas, TX: Council on High Blood Pressure Research, American Heart Association; 2003:349–351.
- Sullivan JM, Schoeneberger TE, Ratts ET, Palmer ET, Samaha JK, Mance CJ, Muirhead EE. Short-term therapy of severe hypertension. Hemodynamic correlates of the antihypertensive response in man. *Arch Intern Med*. 1979;139:1233–1239.
- Egan B, Schmouder R. The importance of hemodynamic considerations in essential hypertension. *Am Heart J*. 1988;116:594–599.
- Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Noninvasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. *Br Heart J*. 1990;63:93–97.
- Taler SJ, Textor SC, Augustine JE. Resistant hypertension: Comparing hemodynamic management to specialist care. *Hypertension*. 2002;39:982–988.
- Ventura HO, Taler SJ, Strobeck JE. Hypertension as a hemodynamic disease: the role of impedance cardiography in diagnostic, prognostic, and therapeutic decision making. *Am J Hypertens*. 2005;18:265–435.
- Van De Water JM, Mount BE, Chandra KM, Mitchell BP, Woodruff TA, Dalton ML. TFC (thoracic fluid content): a new parameter for assessment of changes in chest fluid volume. *Am Surg*. 2005;71:81–86.
- Treister N, Wagner K, Jansen PR. Reproducibility of impedance cardiography parameters in outpatients with clinically stable coronary artery disease. *Am J Hypertens*. 2005;18:445–505.
- Van De Water JM, Miller TW. Impedance cardiography: the next vital sign technology? *Chest*. 2003;123:2028–2033.
- Yung G, Fedullo P, Kinninger K, Johnson W, Channick R. Comparison of impedance cardiography to direct fick and thermodilution cardiac output determination in pulmonary arterial hypertension. *Congest Heart Fail*. 2004;10(2 suppl 2):7–10.
- Defined Daily Dose (DDD) developed by the World Health Organization for use in drug utilization studies. *WHO Collaborating Centre for Drug Statistics Methodology*. Anatomical Therapeutic Chemical (ATC) Classification Index With Defined Daily Doses (DDDs). Oslo, Norway: WHO Collaborating Centre; 2000.
- Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998–3007.
- Singh H, Johnson ML. Prescribing patterns of diuretics in multi-drug antihypertensive regimens. *J Clin Hypertens*. 2005;7:81–87.
- Ubel PA, Jepsen C, Asch DA. Misperceptions about β -blockers and diuretics: a national survey of primary care physicians. *J Gen Intern Med*. 2003;18:1060–1061.
- Connors AF, Dawson NV, Shaw PK, Montenegro HD, Nara AR, Martin L. Hemodynamic status in critically ill patients with and without acute heart disease. *Chest*. 1990;98:1200–1206.
- Fagard RH, Pardaens K, Staessen JA, Thijs L. Prognostic value of invasive hemodynamic measurements at rest and during exercise in hypertensive men. *Hypertension*. 1996;28:31–36.
- Messerli FH, Garavaglia GE, Schmieder RE, Sundgaard-Riise K, Nunez BD, Amodeo C. Disparate cardiovascular findings in men and women with essential hypertension. *Ann Intern Med*. 1987;107:158–161.
- Hinderliter A, Blumenthal J, Waugh R, Chilukuri M, Sherwood A. Ethnic differences in left ventricular structure: Relations to hemodynamics and diurnal blood pressure variation. *Am J Hypertens*. 2004;17:43–49.
- Alfie J, Galarza C, Waisman G. Noninvasive hemodynamic assessment of the effect of mean arterial pressure on the amplitude of pulse pressure. *Am J Hypertens*. 2005;18:60S–64S.
- Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet*. 2003;362:1527–1545.
- Williams B. Recent hypertension trials: implications and controversies. *J Am Coll Cardiol*. 2005;45:813–827.
- Abdelhammed AI, Smith RD, Levy P, Smits GJ, Ferrario CM. Noninvasive hemodynamic profiles in hypertensive subjects. *Am J Hypertens*. 2005;18:51S–59S.
- Bhalla V, Isakson S, Bhalla MA, Lin JP, Clopton P, Gardetto N, Maisel AS. Diagnostic ability of B-type natriuretic peptide and impedance cardiography: testing to identify left ventricular dysfunction in hypertensive patients. *Am J Hypertens*. 2005;18:73S–81S.
- Mitchell A, Buhrmann S, Saez AO, Rushentsova U, Schafers RF, Philipp T, Nurnberger J. Clonidine lowers blood pressure by reducing vascular resistance and cardiac output in young, healthy males. *Cardiovasc Drugs Ther*. 2005;19:49–55.
- Breithaupt-Grogler K, Gerhardt G, Lehmann G, Notter T, Belz GG. Blood pressure and aortic elastic properties—verapamil SR/trandolapril compared to a metoprolol/hydrochlorothiazide combination therapy. *Int J Clin Pharmacol Ther*. 1998;36:425–431.
- Ashida T, Nishioeda Y, Kimura G, Kojima S, Kawamura M, Imanishi M, Abe H, Kawano Y, Yoshimi H, Yoshida K, Kuramochi M, Omae T. Effects of salt, prostaglandin, and captopril on vascular responsiveness in essential hypertension. *Amer J Hypertens*. 1989;2:640–642.
- Sharman DL, Gomes CP, Rutherford JP. Improvement in blood pressure control with impedance cardiograph-guided pharmacologic decision making. *Congest Heart Fail*. 2004;10:54–58.
- Sramek BB, Tichy JA, Hojerova M, Cervenka V. Normohemodynamic goal-oriented antihypertensive therapy improves the outcome (abstract). *Amer J Hypertens*. 1996;9:141A.
- Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.