AJH 2005; 18:23S–25S

Introduction

New Approaches to Hypertension Management: Always Reasonable But Now Necessary

Carlos M. Ferrario

"The sphygmomanometer would not be welcomed by the overworked and underpaid general practitioner already loaded with thermometer and stethoscope." — Blake E: Recent British researches on arterial tension. Med Times Gaz 1895;23:29.

In the late 1800s and early 1900s, most physicians practiced medicine without the availability of blood pressure (BP) measurements. Stephen Hale first measured arterial pressure in a horse in 1733, but it was not until Scipone Riva Rocci invented the BP cuff and Harvey Cushing introduced the concept in the United States that it was considered for clinical medicine.[1] At that time, the concept of BP measurement was met with a large degree of skepticism.[2] Physicians asked questions about BP such as: "Is it important clinically?" "Is it accurate?" "What is the best method to measure it?" and "Is its benefit worth the time and expense to obtain it?"

Acceptance of BP measurement was slow over time, but measuring BP for the diagnosis and management of hypertension was even slower. In 1913, Janeway first reported the fatal complications of hypertension.[3] Actuarial reports provided additional evidence in 1925 and 1940.[4] As recounted by Page,[5] it was not until the availability of oral medications in the 1950s and 1960s that physicians recognized the risks and actively treated high BP.[6] During that time, most physicians still focused on the benefits of reducing diastolic BP because of its known benefit in reducing mortality risk in younger patients.[7,8] In 1971, data from the Framingham Study provided compelling evidence of the risks of high systolic BP,[9] but recognition and treatment of systolic BP was not fully embraced until additional studies were published in the 1980s.[10,11] The equal importance of systolic and diastolic BP was finally asserted in the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) in 1993.[12] Today, we recognize that reduction of systolic BP is critically important in reducing the risk for target-organ damage and clinical events.

It is not surprising that physicians are skeptical about new methods. Rigor is warranted when evaluating new medical technologies, but when we look back it is still surprising how slowly the measurement and treatment of high BP has evolved. Today, of course, none of us would treat patients without the routine use of BP measurements. We know much more about the pathophysiology, risks, and treatment of hypertension than ever before. Public health initiatives to increase awareness in the general population and among physicians have been widespread. Multiple classes of antihypertensive medications have been identified, and more than 100 medications are available for the treatment of high BP.[13] New antihypertensive drugs continue to be introduced to the market, at an estimated development cost approaching 1 billion dollars per drug.[14]

However, improved BP control has remained an elusive target despite greater public and physician awareness and a large armament of antihypertensive medications with proven benefit. Data from the National Health and Nutrition Examination Survey, published in the JNC-7,[15] reveals the general lack of progress of BP control rates in the United States (Fig. 1). In the year 2000, only 59% of the hypertensive population were being diagnosed and treated, with only 34% at treatment goal, equating to a 58% control rate among actively treated hypertensive patients. Thus, despite the large number of medications that have become available, both the overall and active treatment BP control rates have increased only 5% in 15 years.

Hypertension management has become increasingly complex. The number of available drugs and comorbidities creates difficult management decisions, especially in the patient with long-standing disease. Many look to newer antihypertensive drugs recently released or under investigation, but suboptimal pharmacologic management with currently available medications is probably the most significant factor in our lack of treatment success.[16] For most physicians, the only diagnostic tool that they rely upon to manage BP is their stethoscope for auscultation, or potentially an oscillometric-based BP device. Measurement of BP has been our focus, largely because it has been

Received November 19, 2004. First decision November 19, 2004. Accepted November 24, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.042

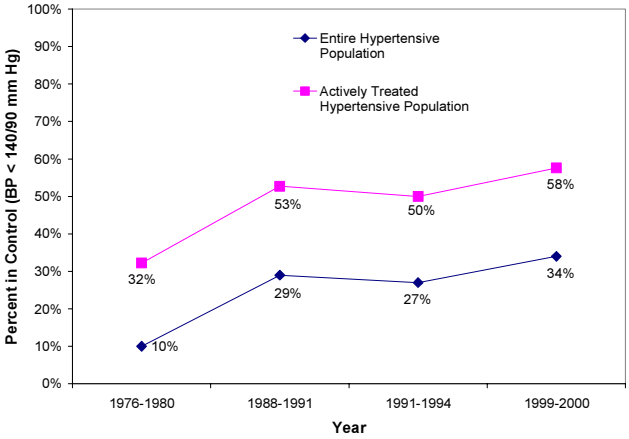

FIG. 1. Trends in blood pressure control in hypertensive persons 18 to 75 years of age in the United States. Data computed from the seventh report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure/National Health and Nutrition Examination Survey (NHANES).

readily available, simple to perform, and reproducible. However, elevated mean arterial pressure is caused by a variety of mechanisms that ultimately exert their influence through increase cardiac output, systemic vascular resistance, or both. Elevated pulse pressure results from decreased vascular compliance or increased stroke volume. Unfortunately, cardiac output, systemic vascular resistance, and vascular compliance cannot be assessed by physical examination. Such hemodynamic information can only be obtained reliably using invasive or noninvasive measurement techniques. The use of invasive hemodynamic monitoring is not practical in the office management of hypertension, as it requires placement of catheters into the central venous circulation or the heart in a hospital setting.

Recently, the noninvasive technology of impedance cardiography (ICG) has emerged as a valuable new tool for diagnostic and prognostic assessment in hypertensive patients to aid therapeutic decision making. The ICG approach provides a quick, painless, noninvasive method to determine a patient's blood flow (stroke volume and cardiac output), systemic vascular resistance, arterial compliance, and thoracic fluid levels. The applicability of hemodynamic data obtained noninvasively has gained popularity among physicians treating hypertension, including cardiologists, nephrologists, internists, and general practitioners.

The series of articles presented in this issue of the *American Journal of Hypertension* add to the existing body of evidence supporting the use of ICG in hypertension. Ventura et al provide a comprehensive review of the rationale to consider hemodynamic factors in hypertension and the evidence supporting the use of ICG. Treister et al profile the normal variability of ICG hemodynamic parameters in stable patients, providing a basis to determine whether therapeutic interventions or disease progression have significantly altered underlying hemodynamics. Abdelhammed et al describe the hemodynamic differences between and within normotensive and hypertensive subjects. Alfie et al explore the hemodynamic mechanisms leading to elevated pulse pressure. Ramirez et al illustrate significant prognostic value of hemodynamics in hypertensive stroke patients. Bhalla et al identify the diagnostic roles of ICG compared with B-type natriuretic peptide levels in determining the presence of left ventricular dysfunction. Quale et al provide further evidence that measurements of BP alone do not constitute a complete picture of the underlying vascular state of the patient with chronic heart failure. Lastly, Sanford et al report several cases in which the use of ICG provided important therapeutic decision-making support. Altogether, the experiences gathered by these investigators provide compelling evidence for the introduction of new approaches for assessment of the hemodynamic characteristics of hypertensive stages and the applicability of these measures to the management of their therapies.

Some have suggested that only evidence-based medicine[17] should define the role of new therapies and diagnostic tools. Despite a number of evidenced-based strategies in cardiovascular medicine, most of what we do today in everyday practice is still normative; that is, it is driven by the clinical judgment and practice of experienced physicians. Clearly, there must be a balance of both evidence-based and normative factors when considering new technologies. Such balance requires an assessment of how well the current standard of care is achieving its desired results and whether restricting access to new technologies might prevent progress in patient care.[18] It is fair to question whether any diagnostic technology, including ICG, should be held to the standard that a therapeutic agent must achieve in randomized clinical trials to obtain regulatory approvals. Diagnostic tests are truly different from therapeutic medications—if only because their value to improve outcomes is only as good as the clinician using the information. Nonetheless, and as Ventura et al describe in detail, ICG met criteria of evidence base medicine, including a randomized trial showing a 70% improvement in BP control rates in those with resistant hypertension.[19]

Further evidence of the value of ICG in mild-to-moderate hypertension is currently under investigation in the multicenter trial called Efficacy of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL). The CONTROL trial is being conducted in a primary care setting in uncontrolled hypertensive patients on one to three antihypertensive drugs. After randomization to either a standard-care or an ICG-guided arm, each patient discontinues medications for a 2-week washout period. These patients then undergo active treatment with office visits once per month for 3 months. Hemodynamic measurements from ICG are taken in both arms but are only provided to the physician in the ICG-guided arm. The primary endpoints of the study are the reduction in systolic and diastolic BP and the percentage of patients in each arm of the study who achieve BP

control (defined as <140/90 mm Hg). Results are expected in mid-to-late 2005.

Today, physicians and payors evaluating ICG are asking questions similar to those asked about BP more than 100 years ago. Similar to BP measurements and treatment of hypertension, the inability to recognize a new paradigm of using more advanced testing for hypertension management could lead to missed opportunities to improve patient care. When ICG is incorporated into hypertension assessment, it has the strong potential 1) to improve BP control rates, and 2) to profile which patients are at the highest long-term risk. Both of these outcomes would result in a more efficient use of health care resources. It is estimated that the costs of treating hypertension in 2003 will be more than 50 billion dollars, with almost 18 billion directly related to drug costs.[20]

It is also possible that a broader implementation of hemodynamic measures in hypertensive individuals will further the paradigm that reduction in BP levels should not be the only target toward the prevention and treatment of hypertensive cardiovascular disease. This possibility has been underscored in recently published, large clinical trials[21,22] and associated commentaries.[23] Hemodynamic and vascular compliance measures—the physiologic causes of high BP—may be even better targets of therapy.[24] Additionally, ICG may provide a tool with which to identify those patients categorized as prehypertensive, who are at greatest risk for clinical events. Such risk assessment in this important population might allow earlier treatment that could prevent the progression to overt hypertension and other cardiovascular diseases, along with efficient use of health care resources.

There continues to be a substantial need to improve our treatment of hypertension. History tells us that we are slow to adopt new tools that can have a significant impact on patient outcomes. It is time for a reappraisal of whether we are using all of the tools available to profile risk and to treat our hypertensive patients effectively. Many physicians and health care policy makers continue to hold out hope for improvement in hypertension management through better application of existing methods. Both the recent and not-so-recent past tell us that to truly advance, we must look at new methods. A new approach is not only reasonable but is now necessary, given our current lack of success and the known challenges that physicians treating hypertension will face in the future.

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AJH 2005; 18:26S–43S

Featured Review Article

Hypertension as a Hemodynamic Disease: The Role of Impedance Cardiography in Diagnostic, Prognostic, and Therapeutic Decision Making

Hector O. Ventura, Sandra J. Taler, and John E. Strobeck

Hypertension is the most common cardiovascular disease, affecting approximately 60 million Americans. Despite the importance of this condition, only the minority of patients are appropriately identified and treated to reach recommended blood pressure (BP) goals. Although historically defined as an elevation of BP alone, hypertension is characterized by abnormalities of cardiac output, systemic vascular resistance, and arterial compliance. These hemodynamic aspects of hypertension have implications for diagnosis, risk stratification, and treatment. Impedance cardiography (ICG) has emerged as a unique and highly accurate noninvasive tool that is used to assess hemodynamic parameters. Measurement of the various hemodynamic components using ICG in those with hypertension allows more complete characterization of the condition, a greater ability to identify those at highest risk, and allows more effectively targeted drug management. This article reviews the importance of hemodynamic factors in hypertension and the evolving role of ICG technology in the assessment and management of this important cardiovascular condition. Am J Hypertens 2005;18:26S–43S

Key Words: Hypertension, hemodynamics, impedance cardiography.

When functioning properly, the cardiovascular system provides normal blood flow to the various tissues of the body under normal arterial blood pressure (BP). Historically, BP is the most commonly measured parameter of cardiovascular function. Hypertension–typically defined by BP levels of 140/90 mm Hg and higher—leads to increased rates of coronary artery disease, heart failure, renal disease, and stroke. Therefore, BP control is of paramount importance for both individual and public health considerations.

Blood pressure by itself is an incomplete indicator of the status of the cardiovascular system. Mean arterial pressure (MAP) is the product of two hemodynamic components: cardiac output (CO), the flow of blood pumped by the heart each minute; and systemic vascular resistance (SVR), the force the left ventricle must overcome to expel blood into the systemic vasculature, also called total peripheral resistance. Hypertension results from elevations of CO, SVR, or both. Because "hemodynamics" literally refers to blood flow–related parameters of the arterial system, CO and SVR are fundamental to obtaining greater insight into the pathophysiology of hypertension, and they can help to guide diagnostic, prognostic, and therapeutic management decisions. Thus, the hemodynamic model of hypertension has intrigued scientists and clinicians since the early part of the last century[1] and has been reviewed extensively by leaders in the field.[2–7]

The hemodynamic components of BP, CO, and SVR, and other related parameters such as arterial compliance provide insight into mechanisms of hypertension[8] and have implications for management of patients with this condition. Historically, most hemodynamic information used in research has been obtained using invasive techniques, including arterial cannulation and placement of a pulmonary artery catheter for the measurement of cardiac output and determination of SVR. However, invasive procedures are not feasible in the routine care of patients with hypertension. Echocardiography provided early noninvasive measurement of cardiac output, but it is costly and highly operator dependent, and it is therefore impractical for frequent serial measurements in the clinical setting. Recent advancements in noninvasive hemodynamic monitoring with impedance cardiography (ICG) have been achieved, elevating its role as a unique and valuable noninvasive tool for the assessment of hemodynamic status in patients with hypertension.

This review describes the historical use of hemodynamics in hypertension and reveals the growing body of evi-

Received October 29, 2004. Accepted November 4, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.002

Table 1. JNC 7 Classification of blood pressure for adults ≥18 years of age

BP classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

JNC = Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

dence using noninvasive monitoring of hemodynamics with ICG. The specific role of hemodynamics in diagnostic, prognostic, and therapeutic decision making in the patient with hypertension is reviewed in detail.

Hypertension: Definition and Clinical Presentation

Hypertension is most commonly defined as a systolic BP (SBP) of ≥140 mm Hg or a diastolic BP (DBP) of ≥90 mm Hg. In patients at high risk for complications from elevated BP levels, such as those with diabetes or chronic renal disease, lower levels of BP (eg, <130/80 mm Hg) are recommended. Between BP levels of 115/75 mm Hg and 185/115 mm Hg, each 20–mm Hg increase in SBP or 10–mm Hg increase in DBP doubles the risk of a cardiovascular event.[9] In recognition of this increase in risk from levels as low as 115/75 mm Hg, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[9] recently identified "prehypertension" (defined as a BP of 120 to 139 / 80 to 89 mm Hg) as a significant potential health problem associated with "increased risk for progression to hypertension." The JNC 7 recommended lifestyle modification for the management of prehypertension. Table 1 lists the stages of hypertension as defined in the JNC 7 classification.

Secondary hypertension results from an identifiable cause such as renal, adrenal, or vascular pathology. In contrast, 90% of patients have no specific identifiable cause of their BP elevation[10] and are thus diagnosed with essential hypertension. Most patients with hypertension are asymptomatic and do not show evidence of acute pathologic changes; their clinical presentation has been termed "benign," although their long-term risk of cardiovascular complications is significantly greater than in normotensive persons without so-called benign hypertension. Severe elevation of BP, associated with papilledema on fundoscopic examination, is termed "malignant hypertension." Similar levels of BP elevation with congestive heart failure, anginal symptoms, or other evidence for accelerated end-organ injury (but without papilledema) are termed "hypertensive urgencies" or "hypertensive emergencies." The etiologies of hypertension (essential versus secondary) and the various clinical presentations (benign, malignant, unspecified, and with or without associated co-morbidities) are reflected in the World Health Organization's International Classification of Diseases, Ninth Revision (ICD-9), coding for hypertension (Table 2).

Hypertension: Magnitude of the Problem

Hypertension affects up to 60 million Americans and as many as 1 billion persons worldwide; and it is the most common reason that patients in the United States visit their physicians.[9,11] The incidence of hypertension increases significantly with advancing age (Fig. 1), such that a normotensive adult in the United States 55 years of age still has a 90% lifetime risk of developing hypertension.[9] In fact, the most common group with hypertension is comprised of elderly patients with systolic hypertension.[12]

Although controlling BP levels reduces the incidence of stroke and other cardiovascular complications, BP control in the US is well below stated goals. For an individual patient, this may be due to the lack of recognition of the condition, failure to institute effective treatment, or the result of a suboptimal long-term medical regimen (Table 3). There remains a substantial need for improvement in the effectiveness of hypertension treatment. As reported in JNC 7, only 34% of adults aged 18 to 74 years with hypertension have achieved BP control, despite a published goal of 50%. In the elderly population, BP control is even less successful: fewer than 20% of treated patients 70 years or more of age attain BP levels of <140/90 mm Hg.[9]

Hypertension treatment commonly requires multiple medications. "Refractory hypertension" has been defined as hypertension that is not controlled on two or more antihypertensive medications.[13] "Resistant hypertension" has been defined by some as BP readings of ≥140/90 mm Hg "despite an optimal two-drug regimen that has had adequate time to work (at least 1 month since last drug or dosage adjustment)."[14] As defined by Gifford, resistant hypertension is the failure to reach goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic.[15] The JNC 7 recommends a goal BP of <140/90 mm Hg for the general population, with the tighter goal of <130/80 mm Hg for persons with chronic renal disease or diabetes mellitus.

Hypertension substantially increases the incidence of cardiovascular events, especially the risk of stroke. Wilking et al,[16] in data from the Framingham study, reported on the prognostic significance of systolic hypertension. They found that for men and women, the relative risk of cardiovascular disease event adjusted for age was approximately 2.5 times greater for persons with isolated systolic hypertension compared with those with BP levels <140/95 mm Hg. Lower BP levels are thus associated with improved prognosis and decreased incidence of morbidity and mortality. From pooled data of more than 60

Table 2. International Classification of Diseases codes for hypertension

Essential hypertension	
401.0	Essential hypertension; Malignant
401.1	Benign essential hypertension
401.9	Unspecified essential hypertension
Hypertensive heart disease	
402.00	Hypertensive heart disease; malignant; without congestive heart failure
402.01	Hypertensive heart disease; malignant; with congestive heart failure
402.10	Hypertensive heart disease; benign; without congestive heart failure
402.11	Hypertensive heart disease; benign; with congestive heart failure
402.90	Hypertensive heart disease; unspecified; without congestive heart failure
402.91	Hypertensive heart disease; unspecified; with congestive heart failure
Hypertensive renal disease	
403.00	Hypertensive renal disease; malignant; without mention of renal failure
403.01	Hypertensive renal disease; malignant; with renal failure
403.10	Hypertensive renal disease; benign; without mention of renal failure
403.11	Hypertensive renal disease; benign; with renal failure
403.90	Hypertensive renal disease; unspecified; without mention of renal failure
403.91	Hypertensive renal disease; unspecified; with renal failure
Hypertensive heart and renal disease	
404.00	Hypertensive heart and renal disease; malignant; w/o mention of congestive heart failure or renal failure
404.01	Hypertensive heart and renal disease; malignant; with congestive heart failure
404.02	Hypertensive heart and renal disease; malignant; with renal failure
404.03	Hypertensive heart and renal disease; malignant; with congestive heart failure and renal failure
404.10	Hypertensive heart and renal disease; benign; w/o mention of congestive heart failure and renal failure
404.11	Hypertensive heart and renal disease; benign; with congestive heart failure
404.12	Hypertensive heart and renal disease; benign; with renal failure
404.13	Hypertensive heart and renal disease; benign; with congestive heart failure and renal failure
404.90	Hypertensive heart and renal disease; unspecified; w/o mention of congestive heart failure or renal failure
404.91	Hypertensive heart and renal disease; unspecified; with congestive heart failure
404.92	Hypertensive heart and renal disease; unspecified; with renal failure
404.93	Hypertensive heart and renal disease; unspecified; with congestive heart failure and renal failure
Secondary hypertension	
405.01	Secondary hypertension; malignant; renovascular
405.09	Secondary hypertension; malignant; other
405.11	Secondary hypertension; benign; renovascular
405.09	Secondary hypertension; benign; other
405.91	Secondary hypertension; unspecified; renovascular
405.99	Secondary hypertension; unspecified; other

prospective studies and 1 million patients, Lewington et al[17] report that 10–mm Hg reductions in systolic BP would be expected to reduce stroke mortality by as much as 40%. Importantly, the authors note that even a 2–mm Hg reduction in systolic BP is associated with a 10% lower death rate from stroke. These reductions in risk apply all the way to BP levels of 115/75 mm Hg. Thus, the failure to lower BP even modestly in patients with hypertension is responsible for a significant number of preventable cardiovascular events each year.

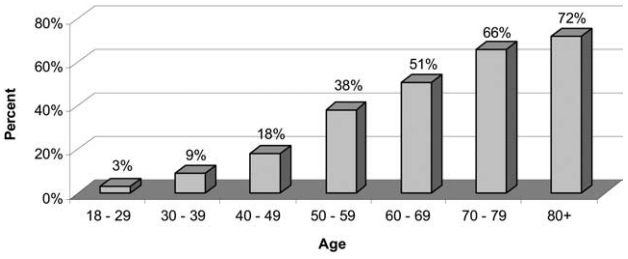


FIG. 1 Prevalence of hypertension by age.

The financial implications of hypertension and hypertension management are substantial.[18] The direct costs of treating hypertension exceeded $37 billion in the year 2003, and additional costs due to loss of productivity were more than $13 billion (Table 4). Of the ten medical conditions evaluated for their effects on absenteeism from work and loss of productivity, hypertension was the most

Table 3. Trends in awareness, treatment, and control of high blood pressure in adults with hypertension 18 to 74 years of age

NHANES	II (1976–1980)	III-1 (1988–1991)	III-2 (1991–1994)	1999–2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control	10	29	27	34

NHANES = National Health and Nutrition Examination Survey.
All numbers expressed as percentages.

expensive—costing businesses an average of $392 per eligible employee per year.[19] Improving the efficiency and effectiveness of drug management in the hypertensive population would likely reduce these costs in addition to decreasing morbidity and mortality associated with the condition.

Hemodynamic Measurements Using ICG

The historical use of BP without CO or SVR is, in part, because it has been impractical to estimate or measure these parameters in most clinical settings. The assessment of the hemodynamic components of hypertension from clinical evaluation alone is unreliable. Even in patients with acute conditions such as those requiring the emergency department or patients with decompensated congestive heart failure (in whom hemodynamic derangements are greater than those in patients with essential hypertension), clinicians are generally unable to estimate CO or SVR with accuracy.[20,21]

Echocardiography has been used to measure cardiac output and in some studies has demonstrated acceptable correlation with invasive techniques.[22] However, in a comparison with ICG, echocardiography is considerably more time consuming and technically demanding.[23] In the office setting, CO is not generally reported by most physicians interpreting echocardiograms in clinical practice. Thus, until recently, CO and SVR were commonly measured only in the intensive care setting or catheterization laboratory setting using invasive means such as a pulmonary artery catheter.

In recent years, ICG has emerged as an accurate, safe, and inexpensive tool with which to measure hemodynamic parameters by noninvasive means. The procedure is most commonly performed in the physician office setting by medical assistants or nurses, requiring about 5 min to complete the test. Using four sets of paired sensors on the neck and chest, ICG measures the instantaneous change of an electrical signal across the thoracic cavity (Fig. 2). As the changes of thoracic impedance during the cardiac cycle are most dependent on the changes in the size and the blood volume of the thoracic aorta, ICG is able to calculate the amount of blood ejected from the left ventricle (that is, the stroke volume [SV]). The product of heart rate (HR) and SV yields CO. In addition, ICG-derived parameters related to the changes of thoracic impedance are indicative of aortic blood velocity and acceleration, and they correlate with measures of inotropic state and cardiac performance. As fluid is the best conductor of the electrical signal through the chest (when

Table 4. Direct and indirect costs attributable to hypertension

Type of cost	Cost (in $ billion)
Direct costs	
Inpatient	8.7
Professional services	9.2
Drugs and medical durables	17.8
Home health care	1.5
Total direct costs	37.2
Indirect costs of lost productivity	
Related to morbidity	7.0
Related to mortality	6.1
Total indirect costs	13.1
Total costs	50.3

Data are from Heart Disease and Stroke Statistics—2003 Update. American Heart Association; 2002.

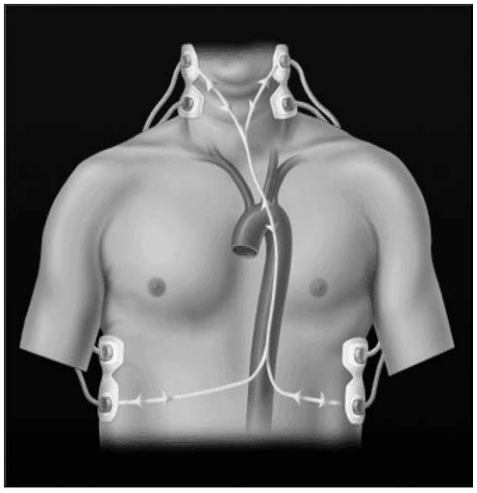


FIG. 2 Measurement of impedance signal using four sets of paired sensors. Sensors transmit and record electrical signal from which multiple hemodynamic parameters are derived.

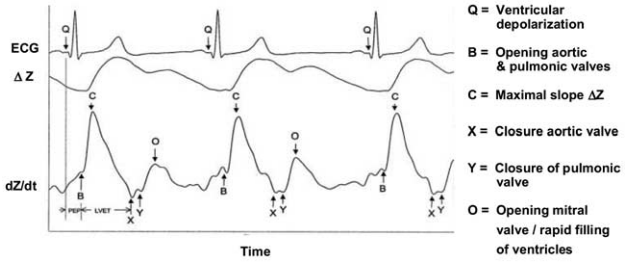


FIG. 3 Representative simultaneous tracings of electrocardiogram (ECG), thoracic impedance (ΔZ), and first-time derivative of impedance (dZ/dt), and dZ/dt waveforms. Fiducial points are identified on the dZ/dt tracing from which various hemodynamic and parameters and timing intervals are derived.

compared with bone, air and fat, in particular), the total thoracic impedance is inversely related to an index of fluid termed the "thoracic fluid content" (TFC). Finally, using a simultaneous electrocardiographic recording, ICG measures the pre-ejection period and LV ejection time—timing intervals that relate to cardiac performance.

Representative simultaneous tracings of an electrocardiogram, change in thoracic impedance (ΔZ), and first derivative of impedance (dZ/dt) are shown in Fig. 3. From the measured variables and from HR and mean BP determined by oscillometry, SVR and other parameters are calculated and displayed. An ICG test report is shown in Fig. 4. A more detailed description of selected parameters is provided in Table 5.

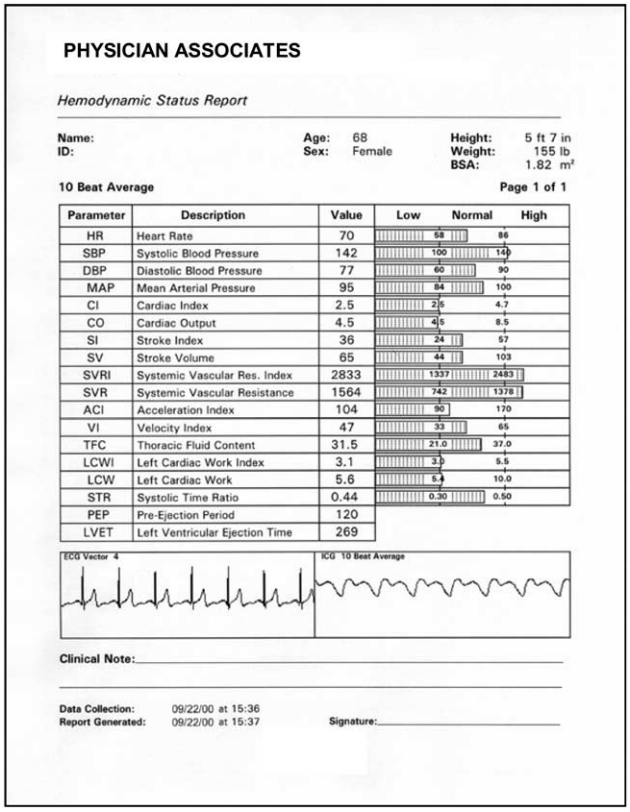
Validation of Current ICG Technology

Placement of a pulmonary artery catheter is a costly procedure requiring special training and expertise; and it is associated with risks of bleeding, infection, and damage to vascular and other structures. Because of the risks inherent in invasive methods for measuring hemodynamics, studies comparing ICG to invasive techniques of hemodynamic measurement are only available from populations with significant underlying cardiovascular conditions or situations that justify the risks associated with pulmonary artery catheter placement. In such clinical settings and patient populations, multiple studies have shown that current ICG technology, using advanced data processing and modeling techniques, yields data that are significantly more accurate than those obtained with prior generations of ICG devices.[24] Five additional validation studies of ICG presented since 1998, [25–29] using refined ICG technology (BioZ ICG Monitor, CardioDynamics, San Diego, CA), demonstrate the high correlation and accuracy available with ICG when compared with invasive techniques (Table 6).

The ability to measure changes in hemodynamic parameters reliably in a given patient is critically important from a clinical perspective, as the changes in serial measurements are the basis for evaluating patients' disease progression, response to therapy, and need for further intervention. Thermodilution, using a pulmonary artery catheter, has traditionally been the standard to which ICG has been compared. Van De Water et al[24] assessed the relative reproducibility of ICG and thermodilution cardiac outputs in hospitalized patients in whom a pulmonary artery catheter was placed for hemodynamic monitoring after bypass surgery. Serial ICG measurements in a given patient showed better reproducibility than serial CO measurements using thermodilution technique (Table 7). The investigators concluded that current ICG technology has advanced such that ICG provides "a level of agreement that is equivalent to thermodilution." Their findings support the clinical utility of ICG for serial measurements in patients with cardiovascular disease.

In a stable group of patients in the outpatient setting, Verhoeve et al[30] demonstrated a high reproducibility of measurements performed on the same day and appropriate sensitivity for the physiologic variations expected from day to day. The variation in the average of readings for CO, SVR, and thoracic fluid content (TFC) ranged between 3% and 7% for serial measurements 1 week apart. Figure 5 illustrates the high degree of correlation between stroke index measured on day 1 and then 1 week later in 96 patients who were clinically stable.

The ICG technique is widely applicable, and reliable information can be obtained in minutes at virtually no


PHYSICIAN ASSOCIATES

Hemodynamic Status Report

Name:
ID:
Age: 68
Sex: Female
Height: 5 ft 7 in
Weight: 155 lb
BSA: 1.82 m²

10 Beat Average — Page 1 of 1

Parameter	Description	Value	Low	Normal	High
HR	Heart Rate	70	58		86
SBP	Systolic Blood Pressure	142	100		140
DBP	Diastolic Blood Pressure	77	60		90
MAP	Mean Arterial Pressure	95	84		100
CI	Cardiac Index	2.5	2.5		4.7
CO	Cardiac Output	4.5	4.5		8.5
SI	Stroke Index	36	24		57
SV	Stroke Volume	65	44		103
SVRI	Systemic Vascular Res. Index	2833	1337		2483
SVR	Systemic Vascular Resistance	1564	742		1378
ACI	Acceleration Index	104	90		170
VI	Velocity Index	47	33		65
TFC	Thoracic Fluid Content	31.5	21.0		37.0
LCWI	Left Cardiac Work Index	3.1	3.0		5.5
LCW	Left Cardiac Work	5.6	5.4		10.0
STR	Systolic Time Ratio	0.44	0.30		0.50
PEP	Pre-Ejection Period	120			
LVET	Left Ventricular Ejection Time	269			

ECG Vector 4 — ICG 10 Beat Average

Clinical Note:

Data Collection: 09/22/00 at 15:36
Report Generated: 09/22/00 at 15:37
Signature:

FIG. 4 Hemodynamic status report.

Table 5. Impedance cardiography variables

Impedance Cardiography Variable	Units	Measurement/Calculation
Blood flow		
Stroke volume	mL	VI × LVET × VEPT (Z MARC algorithm)
Stroke index	mL/m^2	SV/BSA
Cardiac output	L/min	SV × HR
Cardiac index	$L/min/m^2$	CO/BSA
Resistance		
Systemic vascular resistance	$dyne \cdot sec \cdot cm^{-5}$	[(MAP - CVP)/CO] × 80
Systemic vascular resistance index	$dyne \cdot sec \cdot cm^{-5} \cdot m^2$	[(MAP - CVP)/CI] × 80
Contractility		
Velocity index	/1000/sec	1000 × first-time derivative of ΔZ_{max}/ baseline impedance
Acceleration index	$/100/sec^2$	100 × second-time derivative of ΔZ_{max}/baseline impedance
Pre ejection period	msec	ECG Q wave to aortic valve opening
Left ventricular ejection time	msec	Aortic valve opening to closing
Systolic time ratio	-	PEP/LVET
Cardiac work		
Left cardiac work index	$kg \cdot m/m^2$	(MAP - PCWP) × CI × 0.0144
Fluid status		
Thoracic fluid content	/kOhm	1000 × 1/baseline impedance

BSA = body surface area; cm = centimeter; CVP = central venous pressure (estimated value of 6 mmHg); ECG = electrocardiography; HR = heart rate; ICG = impedance cardiography; MAP = mean arterial pressure; PCWP = pulmonary capilary wedge pressure (estimated value of 10 mmHg); R to R interval = 60/ heart rate: VEPT = volume of electrically participating tissue; Z MARC = impedance modulating aortic compliance.

risk to the patient. However, ICG has some limitations related to the technology and patient factors. Although ICG equations have demonstrated accuracy over a wide range of conditions and patient populations, ICG has not been evaluated extensively in patients <66 pounds or >342 pounds. Severe aortic insufficiency may affect ICG reliability, but it has not been fully studied and validated in such patients. In addition, a few models of permanent pacemakers use impedance technology to measure minute ventilation. If the minute ventilation function is activated, the paced rate may increase because of ICG signals[31]; therefore, patients with such pacemakers must have the minute ventilation sensor function inactivated before ICG testing. In patients with atrial fibrillation or frequent premature ventricular contractions, marked irregularity in heart rhythm can affect data collection and analysis of wave forms.

Hemodynamic Parameters in Hypertension

Hypertension is the result of complex cardiac, renal, neurohormonal, and vascular mechanisms that are modulated by both genetic and environmental factors.[10,32] The interactions of these many factors result in endothelial dysfunction and hemodynamic derangements of arterial compliance, CO, and SVR. As noted earlier, MAP is the product of CO and SVR, and elevations of BP can result

Table 6. Validation studies of impedance cardiography (ICG)

Population	Author[Ref]	Parameter	Comparison	*r* Value	Bias	Precision
HF in ICU	Albert et al[25]	CO	ICG-TD	0.89	0.08	1.38
HF in catheterization laboratory	Drazner et al[26]	CO	ICG-Fick	0.73	0.74	1.1
			TD-Fick	0.81	0.75	0.95
			ICG-TD	0.76	0.03	1.1
Mechanical ventilation	Ziegler et al[27]	CO	ICG-TD	0.89	−0.45	1.2
Post-CABG	Sageman et al[28]	CI	ICG-TD	0.92	0.07	0.40
Post-CABG	Van De Water et al[24]	CO	ICG-TD	0.81	−0.17	1.09
Pulmonary hypertension	Yung et al[29]	CO	ICG-Fick	0.84	−0.24	0.87
			TD-Fick	0.89	0.19	0.76
			ICG-TD	0.80	−0.43	1.01

CABG = coronary artery bypass surgery; CO = cardiac output; HF = heart failure; ICU = intensive care unit. TD = thermodilution;

Table 7. Reproducibility of serial measurements: impedance cardiography (ICG) versus thermodilution (TD)

Comparison	Correlation (*r* value)	SD (L/min)
TD 2 *v* TD 1	0.83	1.02
TD 3 *v* TD 2	0.84	1.01
TD 3 *v* TD 1	0.83	1.07
ICG 2 *v* ICG 1	0.97	0.44
ICG 3 *v* ICG 2	0.98	0.39
ICG 3 *v* ICG 1	0.97	0.43

Adapted from Van De Water et al.[24]

from elevation of either or both of these hemodynamic parameters. Pulse pressure (PP), that is, the difference between systolic BP and diastolic BP, is determined by SV and total arterial compliance (TAC). Arterial compliance is a complex parameter that is most closely approximated using a complicated and sophisticated model (the three-element Windkessel model) that incorporates the ratio of the decay time constant to peripheral resistance.[33,34] True arterial compliance is thus tedious and time-consuming to measure and is not clinically useful. However, studies have shown that arterial compliance can be reliably estimated as the ratio of SV to PP.[34,35] Relationships among the hemodynamic parameters including PP, SV, MAP, CO, and SVR are shown in Fig. 6. The hemodynamics of hypertension have been studied for decades, and previously various aspects have been extensively reviewed.[3,36–39]

Hemodynamics of Hypertension: Diagnostic Considerations

Numerous studies using either invasive or noninvasive techniques have demonstrated that there are distinct hemodynamic subsets among various groups of patients with hypertension. Hemodynamic measurements allow the differentiation of patients with primarily elevated CO from those in which elevated SVR (signifying a vasoconstricted state) is the primary mechanism of their hypertension.

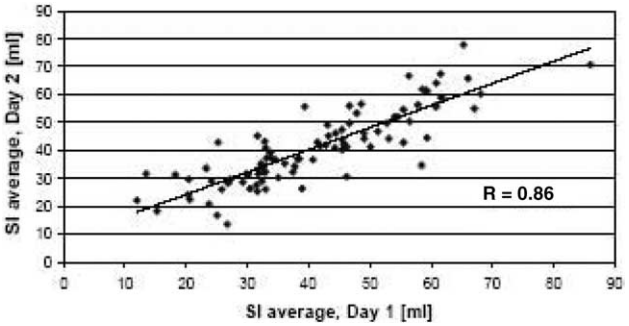


FIG. 5 Reproducibility of stroke index (SI) measurements made 1 week apart. Adapted from Verhoeve et al.[30]

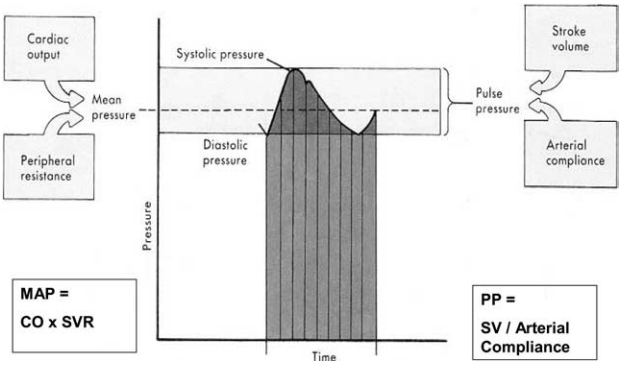


FIG. 6 Components of mean arterial pressure (MAP) and pulse pressure (PP). CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.

Moreover, hemodynamic measurements can elucidate the relative contributions of SV and arterial compliance to elevations in PP.

Invasive Hemodynamic and Echocardiographic Studies

In the Tecumseh, Michigan study, [40] patients were studied using echocardiographic techniques and investigators found that 37% of patients with hypertension were "hyperkinetic," as defined by increased cardiac index, HR, forearm blood flow, and plasma norepinephrine levels. The distribution of cardiac index in this population study is shown in Fig. 7. The wide distribution of cardiac index values in these patients provides corroboration that hypertension represents a heterogeneous mix of various hemodynamic subsets.

In general, aging is associated with decreases in CO and increases in SVR, as shown in Fig. 8. In young adults, hypertension may be more commonly associated with increased CO, whereas in older adults it is more commonly associated with elevated SVR. Lund-Johansen[41] found a change in hemodynamic pattern in patients with borderline hypertension at 10 and 17 years of follow-up. There was a significant and progressive decrease in CO over time, associated with an increase in SVR.

Age-related changes in hemodynamic status, as evidenced by changes in arterial compliance, occur in patients with hypertension even in the absence of changes in CO or SVR. Slotwiner et al[42] used echocardiographic estimates of cardiac output to study hemodynamic parameters in 272 patients who were 25 to 80 years of age and had mild hypertension. These investigators found that in their study group, CO and SVR levels did not vary significantly with age. However, vascular stiffness, as reflected by the ratio of PP to SV (the reciprocal of TAC) increased with age, which is possibly the mechanism for increased rates of cardiovascular events in elderly individuals. Others have noted that arterial stiffness exerts deleterious effects due to increases in central aortic pressure—another hemodynamic mechanism that is key in the pathophysiology of hypertensive cardiovascular disease.[43]

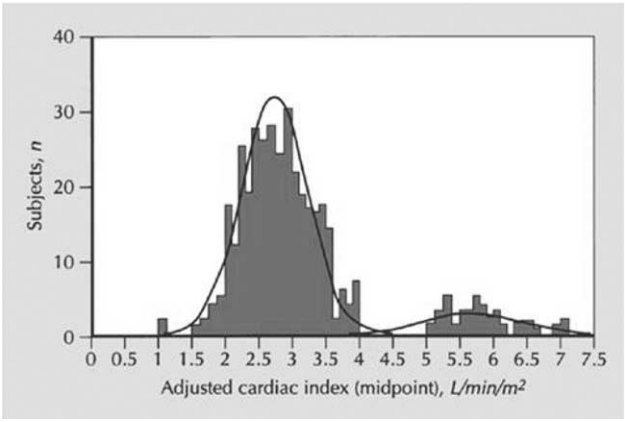


FIG. 7 Distribution of cardiac index values in Tecumseh, Michigan study. Cardiac index values for the hypertensive population show a bimodal distribution. From Julius et al.[40]

Other factors besides age appear to predict general trends in the hemodynamic parameters in hypertensive populations. Hemodynamic parameters differ between hypertensive men and women. Messerli et al[44] measured PP, CO, and SVR using invasive techniques in 200 subjects. Despite equal levels of arterial BP, women had significantly higher CO, PP, and lower SVR compared with men. Isometric exercise was associated with an increase in arterial pressure that was nearly 50% greater in men than in women. The hemodynamic differences between men and women were confined to premenopausal women, suggesting that estrogens play a significant role in the cardiovascular and hemodynamic responses in patients with hypertension. The mechanisms of hypertension seen with acute stressors, such as public speaking or mental arithmetic, also vary based on gender. Studies have shown that men and postmenopausal women have a more significant increase in SVR in response to acute stressors, whereas premenopausal women exhibit a hypertensive response that is due primarily to increases in CO. Some studies have suggested that hypertension early in the course of diabetes and with obesity are associated with increased CO and relatively normal SVR.[45] Others have shown that the earliest hemodynamic abnormalities may be changes in arterial compliance.[46] To a significant degree, hypertension in patients on dialysis results from volume expansion and can be associated with signs of sympathetic stimulation such as increased HR and SV.

Impedance Cardiographic Studies

Impedance cardiography has been used to evaluate the hemodynamic parameters in normotensive individuals at different ages and in various hypertensive populations. In a study of 640 normal subjects evaluated as renal transplant donors, Taler et al[47] found that increasing age was associated with increasing BP, increasing SVR, and decreasing CO due to decreased SV. Hemodynamic changes with age were similar in men and women, although BP and CO were lower and HR and SVR were higher in women. Age-related changes included an increase in total thoracic impedance, equivalent to a decrease in its reciprocal TFC and consistent with decreasing cardiopulmonary volume or muscle mass or both.

In a study comparing hemodynamic variables between pre-menopausal and post-menopausal women, Hinderliter et al[48] showed that post-menopausal women had lower CO and higher SVR for any given BP level compared with pre-menopausal women. Importantly, these significant changes in CO and SVR occurred without significant changes in BP levels, suggesting that the hemodynamic parameters underlying BP provide more information than does MAP alone. This is also seen in data from a study by Galarza et al,[49] in which, despite relatively stable DBP levels in patients from the third to seventh decades of life, the investigators found significant increases in SVRI of nearly 50% and decreases in cardiac index of 27%. Alfie et al[50] used impedance techniques to show that elevations in the difference between SBP and DBP (pulse pressure [PP]) occurred due to different hemodynamic mechanisms in men <30 years of age compared with those middle aged and older. In younger men, increased PP was associated with increases in stroke index, reflecting preserved hemodynamic load with normal arterial compliance. In contrast, after age 50 years, men showed increases in PP associated with decreases in stroke index, reflecting age-related decreases in arterial compliance. Thus, BP readings alone did not reflect the underlying hemodynamic differences in groups with presumably different cardiovascular risk despite similar levels of MAP and PP. Gender differences are seen in impedance studies of the hypertensive response to caffeine: men who show hypertensive responses to caffeine increase their SVR, whereas women primarily increase SV and CO.[51] Yu et al[52] studied hemodynamic parameters in patients with different mood states. Findings of correlation of CO and SVR—but not SBP, DBP, or

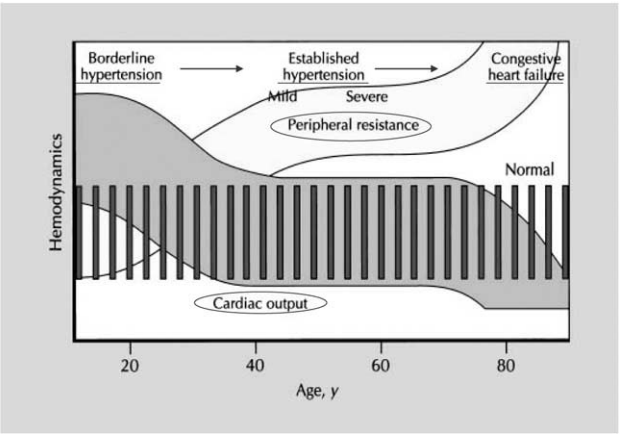


FIG. 8 Age-related changes in cardiac output and peripheral resistance. With increasing age, peripheral resistance rises in the hypertensive population and at higher levels it is associated with decreasing cardiac output and ultimately congestive heart failure.

Table 8. Improved predictive power of pulse pressure (PP) to stroke volume index ratio (SVIR) compared with pulse pressure alone*

	Hazard rate, CV event	Hazard rate, mortality
PP	1.46 (0.91–2.35)†	1.65 (0.83–3.30)†
PP to SVIR	1.79 (1.15–2.80)‡	2.05 (1.15–3.65)‡

CV = cardiovascular.

Values and 95% confidence intervals for 1-SD increase in the variable of interest.

Adapted from Fagard et al.[56]

* Adjusted for age, gender, mean arterial pressure, and heart rate; † P = NS; ‡ $P < .01$.

MAP—with affective state is further evidence of the heterogeneity of hemodynamic subsets within various groups clinically identified.

Hinderliter[53] reported that African American men and women had increased SVR, decreased CO, and associated LV remodeling compared with Caucasian men and women despite similar BP readings. In normotensive African Americans, Calhoun et al[54] postulated that vasoconstrictor responses seen with mental stress and cold presser testing may contribute to elevated SVR and the development of hypertension.

These and other studies using ICG technology show that within any given population SVR, CO, and TAC show significant variation. The heterogeneity of hemodynamic findings within various cohorts is evidence that the specific hemodynamic status of an individual patient cannot reliably be predicted on the basis of age, gender, or ethnic background. Moreover, that hemodynamic values cannot be identified by BP levels or clinical assessment alone supports the need for measurement of hemodynamic parameters in individual patients with hypertension.

Hemodynamics of Hypertension: Prognostic Considerations

The underlying hemodynamic abnormalities in hypertension result in structural and functional changes in the cardiovascular system that adversely affect prognosis, ie, that increase risk of morbidity or mortality. Increases in hemodynamic measures such as SVR and reductions in arterial compliance provide prognostic information in addition to that obtained by BP measurements alone.

Invasive Hemodynamic and Echocardiographic Studies

Elevated arterial BP is the result of increased arterial stiffness and increased SVR. This results in increased LV wall stress, the best measure of LV afterload. Using catheterization techniques, Fagard et al[55] demonstrated that SBP and SVR at rest and during exercise correlated with the risk of cardiovascular events and total mortality at an average of 16.2 years of follow-up. In this study, exercise SVR—but not exercise BP—added prognostic value to parameters measured at rest, suggesting that hemodynamic variables other than BP might have greater prognostic value.

A subsequent article[56] reported the relationship between another hemodynamic parameter, namely, the ratio of PP to stroke index (PP-to-SVi ratio), and outcomes in patients followed for an average of 16.5 years. In this study, the PP-to-SVi ratio, that is, the reciprocal of TAC index, was independently associated with cardiovascular events or death. Each increase in PP-to-SVi ratio of 0.75 mm Hg/(mL/m^2) was associated with a 79% increase in the risk of a cardiovascular event (P = .01) and greater than double the risk of all-cause mortality (P = .01). As shown in Table 8, the increased hazard rates with PP-to-SVi ratio compared with PP alone demonstrates the additional predictive value when the hemodynamic parameter of flow (SVi) is added to the pressure measurement alone.

De Simone et al[57] studied the effects of TAC on cardiovascular events over a 10-year period. They found that risks of fatal and total cardiovascular events were independently correlated with age, LV mass, and lower levels of arterial compliance, defined as decreasing values of the measured ratio of echocardiographic SV to PP (SV/PP) to that predicted from previously developed equations (% SV/PP). Moreover, consistent with the results of Fagard et al,[56] the investigators found that systolic BP, mean BP, or PP alone (without including the flow-related hemodynamic parameter of SV) were not independent predictors of prognosis. After adjustment for age and LVH there remained an independent effect of % SV/PP on cardiovascular endpoints at 10-year follow-up (Fig. 9). These investigators found that hemodynamic parameters such as arterial compliance and percent predicted arterial compliance correlated better with changes in cardiac structure (ie, hypertrophy and remodeling) than did BP levels alone.

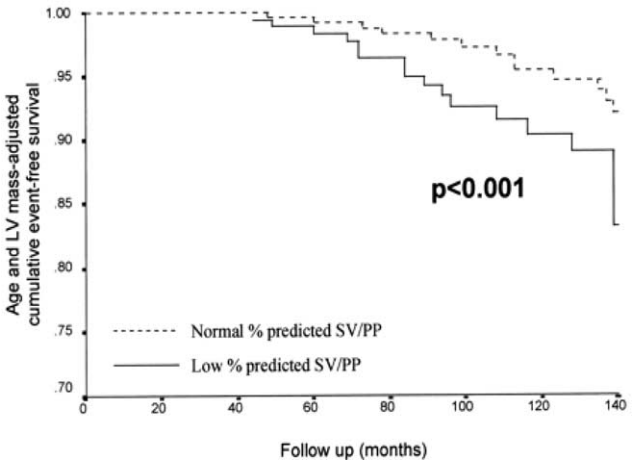


FIG. 9 Event-free survival based on predicted ratio of stroke volume (SV) to pulse pressure (PP). Event-free survival is reduced in hypertensive patients with reduced arterial compliance, as defined as a low predicted SV/PP ratio. From De Simone et al.[57]

Gender has long been known to affect prognosis in patients with hypertension. In 1913, Janeway[58] published the observation that women with hypertension tended to have a better prognosis than men. More recent studies have suggested that this difference may be related to different hemodynamic substrates in men compared to women with elevated BP levels. Messerli et al[44] suggested that the disparate prognosis between men and women might be explained on the basis of differing hemodynamic mechanisms: "For any level of arterial pressure, total peripheral resistance (and therefore the risk of hypertensive cardiovascular disease) was lower in women than in men."

The mechanism of the adverse prognosis from hypertension is in part related to structural changes in the heart that result from elevated wall stress. Prolonged increases in wall stress lead to left ventricular (LV) structural changes with relative increases in wall thickness, overall LV mass or both.[59] In concentric remodeling, there is a relative increase in LV thickness without increase in overall LV mass. This structural change appears to be related to increased pressure load but with relative decrease in volume as evidenced by low normal CO (termed "volume underload"). Concentric left ventricular hypertrophy (LVH) is characterized by an increase in wall thickness with increase in LV mass or mass index and also results from pressure overload caused by long-term hypertension. Eccentric hypertrophy is defined as increased LV mass index with preserved relative wall thickness and is associated with both pressure and volume overload. This pattern, a common result of the afterload and volume excesses in long-standing severe aortic insufficiency, results in spherical remodeling of the LV. Interestingly, in this study of hypertensive individuals,[59] both eccentric hypertrophy and concentric remodeling were more common than the "classic" pattern of hypertensive heart disease, namely, concentric LVH.

Nonetheless, LVH is a powerful predictor of cardiovascular risk and is independently associated with mortality in patients with coronary artery disease.[60–63] For example, Vakili et al[63] reported on the pooled results of 20 published studies of LVH as defined by electrocardiographic or echocardiographic criteria. They demonstrated a weighted mean relative risk of cardiovascular morbidity from LVH of 2.3, independent of all covariates analyzed. As reported by Ichkhan et al,[64] LVH is associated with abnormalities of ventricular repolarization and at least a twofold increase in the risk of serious ventricular arrhythmias.

Hypertension results in abnormalities of endothelial function, affecting hemodynamic factors such as arterial compliance. Gomez-Cerezo et al[65] demonstrated impaired brachial artery flow–mediated dilation, a common test of endothelial function, in patients with sustained or labile hypertension. They found that flow-mediated dilation was abnormal to a similar degree in patients with sustained essential hypertension or "white-coat hypertension" but was normal in individuals with normal BP levels. Others have evaluated measures of arterial compliance (or, alternatively, arterial stiffness) using the measure of pulse wave velocity.[66,67]

Additional structural changes occuring at the level of the heart and blood vessel have prognostic significance in persons with hypertension, including vascular remodeling with changes in lumen to wall thickness.[68,69] Apoptosis, or programmed cell death, contributes to the vascular changes (ie, remodeling) in hypertension. Inflammation and fibrosis similarly contribute with the accumulation of various components in the extracellular matrix such as collagen and fibronectin. Intengan and Schiffrin[69] reviewed the factors that result in arterial remodeling and altered hemodynamic parameters in patients with hypertension.

Importantly, studies have shown that treatment with antihypertensive agents may result in regression of the structural abnormalities caused by long-standing hypertension and may result in improved prognosis.[70–72] Mathew et al,[70] reporting on data from the Heart Outcomes Prevention Evaluation (HOPE) study, demonstrated that treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril was associated with regression of LVH by electrocardiographic criteria compared with placebo control. That BP showed minimal difference between the treatment and control groups is consistent with other studies demonstrating improvement in overall hemodynamics (as shown by significant decreases in SVR and parallel increases in CO) that are not evident from BP levels alone. Ofili et al,[73] in an echocardiographic substudy of the Systolic Hypertension in the Elderly Program (SHEP), demonstrated partial regression of LVH in patients treated with a diuretic-based regimen for a minimum of 3 years. In a meta-analysis of >1000 patients with serial echocardiography during treatment of essential hypertension, Verdecchia et al[74] demonstrated that patients whose LVH regressed during treatment had significantly fewer cardiovascular events compared with those in whom LV mass increased, consistent with the hypothesis that improvements in hemodynamics correlate with improved prognosis in patients with appropriately treated hypertension.

Impedance Cardiographic Studies

The ICG technique has been used to explore age-related changes in hemodynamic variables and their correlation with cardiovascular risk and the adverse prognosis. These studies support previous findings that future risk in patients with hypertension may not be reflected in BP levels alone. Alfie et al[50] demonstrated that despite similar elevations in PP, younger men had preserved stroke index (and arterial compliance) compared with older men. They concluded that preserved arterial compliance and cardiac pump function may explain the lack of prognostic significance of elevated PP in younger men. These findings lend further support to the value of the incremental information

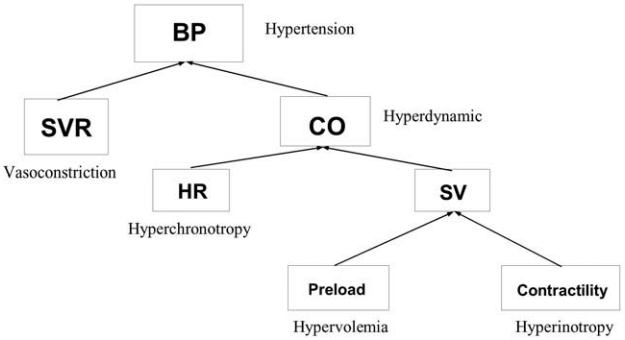


FIG. 10 Hemodynamic components of hypertension. BP = blood pressure; CO = cardiac output; HR = heart rate; SV = stroke volume; SVR = systemic vascular resistance.

provided by the hemodynamic components of BP and PP levels.

Hemodynamic differences have been demonstrated in patients who have experienced complications of hypertension compared with those with hypertension alone. In a study of hemodynamic status in hypertensive patients with and without a history of stroke, Galarza et al[75] found lower cardiac index and higher SVR index in those with history of stroke. These differences occurred in the absence of differences in BP or antihypertensive treatment, providing another example of the unreliability of BP to reflect the severity of underlying hemodynamic abnormalities.

Hemodynamics of Hypertension: Therapeutic Considerations

Hypertension management includes hygienic measures such as sodium restriction and weight loss; and, in most cases, it requires the use of one or more antihypertensive agents. Antihypertensive medications exert their BP-lowering effects by reductions in SVR or CO. Hemodynamic effects can be used to classify antihypertensive agents, predict the response to antihypertensive therapy, and guide both the initiation and titration of these agents.[76–78]

Just as interpretation and treatment of serum cholesterol level improves when its components (HDL-cholesterol and LDL-cholesterol) are measured, hypertension may be better diagnosed and treated by examining its hemodynamic components (CO and SVR). As MAP is the product of CO and SVR, elevated mean BP results from elevated CO, SVR, or both. As shown in Fig. 10, CO is the product of HR and SV. Stroke volume is determined in part by LV filling (preload) and contractile (inotropic) state. Hypertension can thus result from increases in SVR (vasoconstriction), HR (hyperchronotropy), preload (hypervolemia), or contractility (hyperinotropy).

Invasive and Echocardiographic Studies

In a small group of men with severe hypertension, Sullivan et al[79] studied the relationship between baseline hemodynamic status and the response to various antihypertensive agents that were randomly selected. Patients with elevated SVR responded with decreases in SVR, and those with elevated CO had BP control associated with normalization of CO.

Treatment targeted at the specific hemodynamic cause of hypertension has predictable and appropriate results. Easterling et al[80] studied noninvasive hemodynamic parameters using Doppler echocardiography in 19 pregnant hypertensive women. Ten patients had elevated CO, whereas nine patients had elevated SVR, demonstrating hemodynamic heterogeneity within this apparently homogeneous population. Patients with elevated CO were treated with a β-blocker (atenolol) and those with elevated SVR were treated with hydralazine, a vasodilator targeted at elevated SVR. Patients given hydralazine had dramatic improvements in CO in association with decreases in SVR; those given atenolol for elevated CO had improvement in BP and normalization of CO. The investigators suggest that the failure of previous studies to show consistent results in the drug management of hypertension in pregnancy may have resulted from treating a heterogeneous hemodynamic group with a single regimen. The implication of their study is that hemodynamically guided therapy would be expected to show more consistent results in hemodynamically diverse populations.

Differential effects of antihypertensive medications on hemodynamic variables may not be evident from changes in BP alone. Resnick and Lester[81] studied the effects of various BP medications on arterial compliance in patients referred to an outpatient practice specializing in hypertension. The changes in compliance of the large arteries (capacitive compliance) and in smaller arteries (reflective compliance) were evaluated during treatment with ACE inhibitors, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), and β-blockers. The researchers found that despite similar changes in SBP, DBP, and PP during treatment, there were improvements in arterial compliance with ACE inhibitors, ARB, and CCB but not with β-blockers. These researchers suggest that choosing medications that have favorable effects on both BP and arterial compliance "might further enhance the potential clinical benefit of drug therapy in hypertension." Similarly, Zusman[78] reported that despite similar degrees of BP reduction, the hemodynamic effects of the CCB nifedipine were favorable when compared with the β-blocker atenolol, resulting in decreased SVR, increased CO and improved measures of LV contractility and diastolic function. Others have shown significantly different hemodynamic effects between various β-blockers such as between metoprolol and carvedilol due to the α-adrenergic blocking properties of the latter.[82]

Studies suggest that most patients require multiple medications to achieve BP control. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[83] a large randomized trial comparing outcomes in patients treated with different classes of antihypertensive agents, 90% of patients were

on treatment at time of pre-randomization visit, although only 27% had adequate BP control. After 5 years of treatment, 66% had achieved levels of BP <140/90 mm Hg. Of the participants whose hyptertension was controlled, 63% were on two or more medications, indicating that BP control required combination therapy in the majority of cases. Yakovlevitch and Black[84] reviewed 436 charts to identify 91 cases of resistant hypertension referred to their hypertension clinic of a tertiary care center and evaluated for possible causes of resistance, including medication noncompliance, secondary causes of hypertension, drug interactions, and the appropriateness of the medical regimen. They found that the most common cause of inadequate BP control in the 91 patients identified with resistant hypertension was an inappropriate medical regimen.

The hemodynamic responses of various classes of antihypertensive medications have been categorized in an extensive review of hypertension by Houston,[85] and selected hemodynamic effects are summarized in Table 9.

Rationale for an ICG-Guided Approach to Antihypertensive Therapy

The foregoing discussion has presented data on the role of hemodynamic information for diagnostic, prognostic, and therapeutic decision making for patients with hypertension. The use of ICG-derived hemodynamic information to improve BP control requires accurate assessment of baseline hemodynamic state, creation of a therapeutic regimen based on hemodynamic status, and timely measurement of changes in various hemodynamic parameters in response to therapy.[86] Studies have shown that it is very difficult—if not impossible—to make an accurate assessment of CO and SVR at the bedside by physical examination alone.[20,21,87,88] Therefore, it is not likely to be possible to use physical examination to reliably identify baseline hemodynamic subsets or changes in hemodynamic status so as to optimize therapy.

Clinicians have used ICG in various patient care settings to assess its applicability in the assessment and treatment of hypertension.[89–95] As noted earlier here and in Fig. 7, there is significant hemodynamic heterogeneity among individuals with hypertension, suggesting that BP level alone is not adequate to categorize patients into clinically meaningful subgroups. De Divitiis et al[91] used ICG to confirm the presence of distinct hemodynamic profiles in patients with hypertension: 1) elevated CO in association with normal or nearly normal SVR, and 2) predominantly elevated SVR. Margulis et al[96] evaluated other hemodynamic parameters in untreated patients with hypertension. They found impairment of cardiac performance with decreased indices of contractility and evidence for increased thoracic fluid content, suggesting increased water content of the lungs or thoracic wall tissues.

Thoracic fluid content, the reciprocal of total thoracic

Table 9. Selected hemodynamic effects of various antihypertensive agents by class

Effect	Diuretics	β blockers	Calcium channel blockers	ACE inhibitors	Central α-agonists	α-blockers	Direct vasodilators	α- and β-blockers	β-blockers with ISA
SVR	↓ or NC	↔	↓	↓	↓	↓	↓	↓ or NC	↓ or NC
CO	↑	↑	↑ or NC	↑	NC	NC or ↑	↑	↑ or NC	↑ or NC
Stroke volume	↑	↑	↑ or NC	↑	NC	NC or ↑	↑	↑ or NC	↑ or NC
Heart rate	↔	↓	NC or ↓	NC	↓ or NC	NC	↑	↑ or NC	NC or ↑
Intravascular volume	↓	↑ or NC	↓	↓	↓ or NC	NC or ↑	↑	NC or ↑	NC
LVH	↑ or NC	NC	↓	↓	↓	↓	↑	↓	↑

ACE = angiotensin converting enzyme; CO = cardiac output; LVH = left ventricular hypertrophy; NC = no change; SVR = systemic vascular resistance; ↑ = Increase, ↓ = decrease.
Adapted from Houston.[85]

impedance, is strongly correlated with amount of fluid in the chest cavity, whether intravascular or extravascular. In patients undergoing thoracentesis, Petersen et al[97] demonstrated a strong correlation between the volume of pleural fluid removed and the change in total thoracic impedance (correlation coefficient, 0.97). In studies using lower-body negative pressure to create pooling of venous blood in the lower extremities, Ebert et al[98] found a nearly perfect linear correlation with changes in central venous pressure and changes in thoracic impedance. Thus, TFC has been used to monitor changes in fluid volume and guide diuretic therapy in patients with hypertension.

Linb et al[89] reported that BP reductions resulted from improvements in baseline hemodynamic abnormalities; patients with elevated CO responded to targeted therapy with a β-blocker (propranolol), whereas those with elevated SVR responded to treatment with the vasodilating CCB (nifedipine). Mattar et al[99] showed that an intensive regimen of diet and exercise resulted in improvements in hemodynamic parameters with substantial increases in CO and decreases in SVR despite only modest changes in MAP. Moreover, the investigators speculated that failure of some hypertensive patients to show hemodynamic improvement on serial ICG measures resulted from the inappropriate choice of medications that were not targeted toward the underlying hemodynamic abnormalities.

Hemodynamic parameters derived from ICG have been used to evaluate the differential effects of medications in patients with essential hypertension. In a study of the effects of a cardioselective β-blocker compared with a β-blocker with intrinsic sympathomimetic activity, Toth et al[100] studied 57 patients randomized to treatment with either atenolol or pindolol for 12 weeks. Pindolol therapy was associated with a 12% decrease in SVR compared with minimal change with atenolol. Atenolol-related improvement in BP resulted from decrease in HR and cardiac index. Breithaupt-Grogler et al[67] reported on the differential hemodynamic effects of combination therapy with verapamil/trandolapril (Vera/Tran) compared with metoprolol/hydrochlorothiazide (Meto/HCTZ) in 26 patients after 6 months of therapy. In addition to ICG-derived CO and SVR, the authors measured carotidofemoral pulse wave velocity as a measure of arterial stiffness. The combination of CCB and ACE inhibitor (Vera/Tran) reduced diastolic BP to a greater degree than Meto/HCTZ and lowered SVR by about 15% compared with minimal change with the β-blocker/diuretic combination. Treatment with Meto/HCTZ was associated with a significant reduction in CO compared with baseline, which was not seen with Vera/Tran. However, pulse wave velocity decreased with Vera/Tran but not with Meto/HCTZ, suggesting an improvement in the elastic properties of the aorta with the former drug regimen.

The ICG technique has been used to assess the hemodynamic effects of sodium restriction in a small group of subjects with mild hypertension.[101] During sodium restriction, ICG-derived measures of SV decreased in association with fall in diastolic BP. An increase in overall thoracic impedance (the reciprocal of TFC) was consistent with a decrease in extracellular fluid volume. In addition, ICG has been used to explore the mechanisms of responses to ACE inhibitors and prostaglandin inhibitors in patients who are either salt sensitive or salt insensitive.[102] These examples illustrate the use of ICG in assessing the mechanisms of BP elevation and the hemodynamic effects of nonpharmacologic interventions in hypertension.

As noted above, antihypertensive medications ultimately act on one or more of the hemodynamic components that determine BP.[79,80] Once the baseline hemodynamic status is known, an appropriate medical regimen can be designed based on the expected hemodynamic effects of various medications. However, individual patients vary in their responses to antihypertensive drugs such that the actual hemodynamic effects and side effects cannot reliably be predicted. Therefore, empiric selection of drug combinations based on their general hemodynamic actions as a class may not be successful in managing a specific patient, even if the baseline hemodynamic status is known. The ICG technique is unique in that it can provide not only an accurate hemodynamic profile noninvasively but can guide therapy toward a drug regimen that is most appropriate for the specific patient based on serial measurements. Periodic measurements of hemodynamic status allow the physician to monitor therapy when results are suboptimal or unexpected. It is for these reasons that ICG has emerged as a valuable tool in the evaluation and treatment of patients with hypertension.

Outcome Studies Using ICG-Guided Therapy in Hypertension

The observation that hypertension is a hemodynamic disease implies that measurement of hemodynamic parameters can be used to guide medication selection, to titrate dose, and to evaluate efficacy of the medical regimen. Several studies have used ICG to evaluate hemodynamic parameters and demonstrated that ICG-guided therapy improves BP control. Taler et al[103] randomized 104 patients with hypertension uncontrolled on two or more drugs to a 3-month trial of ICG-guided therapy or standard therapy directed by a hypertension specialist. In this study, BP control (defined as achieving BP $<$140/90 mm Hg) occurred 70% more often in the ICG-guided group (Fig. 11). Use of ICG resulted in greater reductions in SVR index and more intensive use of diuretic therapy, guided by levels of TFC. According to the study investigators, measurement of hemodynamic and impedance parameters was more effective than clinical judgment alone in guiding selection of antihypertensive therapy patients resistant to empiric therapy.

Sharman et al[104] studied a cohort of patients in the primary care office setting with drug-resistant hypertension, defined as systolic BP $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg during treatment with two antihypertensive

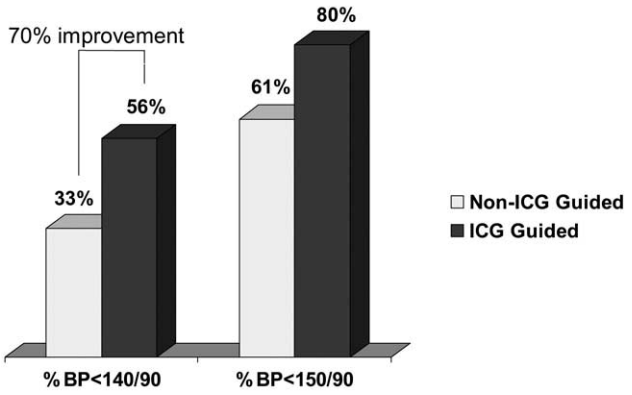


FIG. 11 Percentage of patients achieving blood pressure (BP) control using impedance cardiography (ICG)–guided therapy compared with non–ICG-guided therapy. Adapted from Taler et al.[103]

medications. Patients were treated based on a published ICG-guided treatment algorithm (Fig. 12) for an average of 7 months. In this study, ICG resulted in BP control in 57.1% of patients who were not controlled before the use of ICG-guided therapy. The average number of medications increased from 2.0 at time of entry to 2.5 ± 0.7 at the end of the study period. The observation that hemodynamic information derived from ICG resulted in BP control with two medications in some patients and three or more in others is consistent with both higher intensity and more appropriate medical regimens. The investigators concluded that ICG is safe and cost-effective and could assist community-based physicians in treating uncontrolled hypertension.

Sramek et al[105] reported on a series of 322 patients with hypertension uncontrolled despite previous therapy with two or more antihypertensive agents for periods of 2 years or more. The researchers directed the management of hypertension at both control of BP and improvement in underlying hemodynamic parameters including CO and SVR. At baseline, 16% of subjects had significantly reduced CO (ie, were considered hypodynamic) and approximately 19% were hyperdynamic. In this large series of patients treated using the results of ICG evaluation, so-called normodynamic goal-oriented therapy controlled BP in 203 subjects (63%) within several weeks. The investigators highlight the observation that ICG was able to identify medications that were optimal and specific for the individual patients, resulting in an approach superior to the conventional "trial-and-error" method.

Additional Roles of ICG in Patients With Hypertension

The evidence cited above supports the use of ICG-derived hemodynamic information in guiding the selection, initiation, titration, and evaluation of antihypertensive medication. However, patients and their physicians fail to achieve adequate BP control for reasons other than the responses to specific medications. Common barriers to BP control include lack of awareness of the condition, inability to make necessary dietary and other lifestyle modifications, noncompliance with medications, complicating factors such as drug interactions, secondary causes of hypertension, and comorbidities such as kidney disease.

Testing with ICG using currently available equipment may favorably affect each of these issues. Oscillometric measurements of BP, as with the most widely used ICG equipment, are more reliable and less operator dependent than standard BP techniques. The accurate and reproducible measures of CO and SVR identify patients with abnormal hemodynamic states and may increase clinical suspicion and diagnostic sensitivity for those with borderline or prehypertensive BP readings. The ICG reports are useful teaching tools for patients and may provide motivation for the dietary and other lifestyle changes that assist in BP control.

Changes in hemodynamic parameters may identify instances when patients stop their medications or when there are complicating factors such as worsening renal function or interactions with medications such as over-the-counter nonsteroidal anti-inflammatory drugs. As noted,[103] an increase in one class of hypertensive agents may result in compensatory fluid retention, leading to an increase in TFC as measured by ICG and the need for higher doses of diuretics. Similarly, fluid retention resulting from the renal effects of anti-inflammatory medications may be recognized by changes in TFC. Importantly, ICG-derived measures of cardiac performance, such as velocity index or

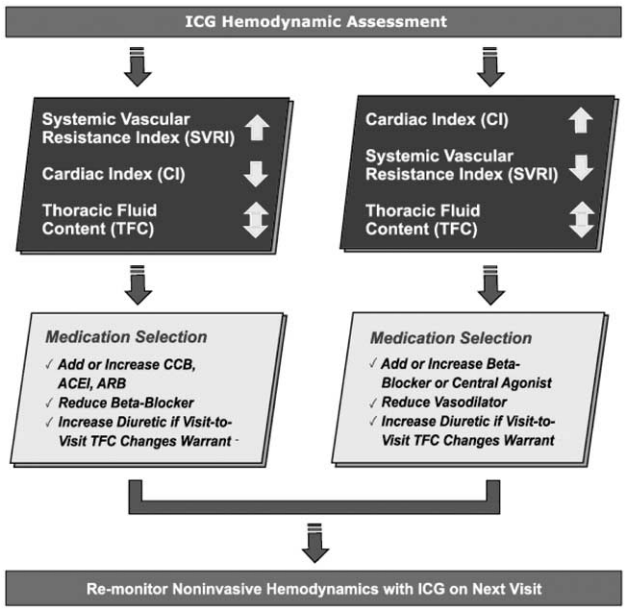


FIG. 12 Algorithm for hemodynamically guided therapy of hypertension. Adapted from Sharman et al[105] and Taler et al.[104] In the latter study, postural changes in total body impedance (TBI), the reciprocal of thoracic fluid content (TFC), were used as the criteria for decisions reguarding fluid status.

systolic time ratio, may be the initial signs of the development of LV dysfunction.[106,107]

Implications of Hemodynamics and Future Considerations

In addition to improving the diagnosis and therapy of hypertension, hemodynamic measurements provide insights into other aspects of cardiovascular function. For example, studies have shown the importance of endothelial function in the development and progression of cardiovascular disease.[108] Endothelial dysfunction, as measured by reduced flow-mediated arterial dilation, is associated with abnormal hemodynamic measures, including elevated SVR.[109] In the HOPE study,[110] an ACE inhibitor—a drug that both lowers SVR and improves endothelial function—reduced mortality from cardiovascular disease despite only minor effects on BP. Future studies will likely examine the significance of elevated SVR and arterial compliance in individuals with hypertension or prehypertension and will correlate ICG-derived hemodynamic parameters with other evolving markers of increased cardiovascular risk such as C-reactive protein, homocysteine level, and the metabolic syndrome.

The studies included in this supplement of the journal add to the growing body of literature that supports the accuracy, reliability, and clinical utility of ICG in diagnostic and prognostic assessment and therapeutic management of patients with hypertension. The use of ICG has added significantly to our understanding of hypertension as a disease with both hemodynamic causes and hemodynamic consequences. Just as congestive heart failure reflects abnormal flow or inappropriate ventricular filling pressures, hypertension occurs when there is abnormal flow or inappropriate vascular resistance or compliance. When hypertension impairs LV performance (either systolic or diastolic), heart failure ensues. Although these conditions often co-exist, in many cases hypertension is a step in a hemodynamic continuum that leads to further hemodynamic derangement and heart failure. It is believed that future studies will confirm recent findings that hemodynamic measurements in individual patients will improve diagnosis, risk assessment, and treatment for these patients. It is also possible that further exploration of the implications of hypertension as a hemodynamic disease will lead to studies demonstrating that earlier detection and treatment of the hemodynamic components of hypertension may change the natural history of this disease process.

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AJH 2005; 18:44S–50S

Original Contributions

Reproducibility of Impedance Cardiography Parameters in Outpatients With Clinically Stable Coronary Artery Disease

Neil Treister, Kevin Wagner, and Paul R. Jansen

Background: Impedance cardiography (ICG) is a noninvasive method of determining hemodynamic parameters. It is clinically important to determine whether any change in ICG parameters occur due to changes in disease status or therapeutic interventions, or due to normal hemodynamic and technology variability. The objective of this study was to establish the intra- and inter-day reproducibility of ICG in a stable population with coronary artery disease (CAD).

Methods: A prospective, time series design was used. The study group consisted of 96 clinically stable CAD patients in an outpatient cardiac rehabilitation program. Measurements of ICG hemodynamic parameters were obtained at four points in time: after 5 and 10 min of rest on the first day and after 5 and 10 min of rest on a second day, 1 week later.

Results: There were small but significant intra-day changes between the 5- and 10-min hemodynamic measures. Mean absolute percent changes in intra-day hemodynamic measures were <8%. High intra-day correlation was observed, ranging from 0.85 for mean arterial pressure to 0.99 for thoracic fluid content. There were expectedly larger inter-day hemodynamic variation of up to 18% and lower inter-day correlation for all ICG parameters ranging from 0.66 to 0.88.

Conclusions: Impedance cardiography measurements demonstrate both intra- and inter-day reproducibility within clinically acceptable ranges in a clinically stable population of CAD patients. The expected ranges of variation can be used to gauge whether a patient's hemodynamic status has changed because of disease or intervention. Am J Hypertens 2005;18:44S–50S © 2005 American Journal of Hypertension, Ltd.

Key Words: Impedance cardiography, thoracic electrical bioimpedance, hypertension, reproducibility, coronary artery disease, heart failure.

The validity of a diagnostic test or monitoring technology is based on both accuracy and reproducibility. Accuracy is defined as the degree to which a given test provides measurements in agreement with a known reference standard. Reproducibility of a diagnostic test is defined as the ability to achieve the same result when the test is repeated under similar circumstances. Understanding the accuracy and reproducibility of a diagnostic test forms the foundation for determining whether a change in the measure is due to normal physiology or test reproducibility, or due to clinically significant changes as a result of the underlying disease or therapeutic intervention.

Impedance cardiography (ICG) is a noninvasive hemodynamic diagnostic and monitoring technology.[1] Previous generations of ICG devices yielded inconsistent results compared with invasive hemodynamic methodology,[2,3] but the most recent generation of ICG has shown improved accuracy in a broad range of patient populations.[4–8] In recent years, ICG has established a role in the outpatient management of patients with hypertension, heart failure, and other chronic diseases.[9,10] The use of ICG in therapeutic decision making regarding such patients is primarily based on its ability to identify the presence or absence of hemodynamic abnormalities and therefore target hemodynamically active medications to alleviate symptoms, lower patient risk, or better reach a clinical goal such as control of blood pressure (BP) levels.

Establishing the reproducibility of ICG parameters in stable outpatients is important to determine whether a change in any ICG parameter is due to either a significant change in disease status or to an effect of therapy, or whether it is a result of normal physiologic or technologic variation. The aim of this study was to evaluate the intra- and inter-day reproducibility of ICG parameters in a stable population with coronary artery disease (CAD).

Received October 29, 2004.

From CardioDynamics International Corporation, San Diego, California.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.001

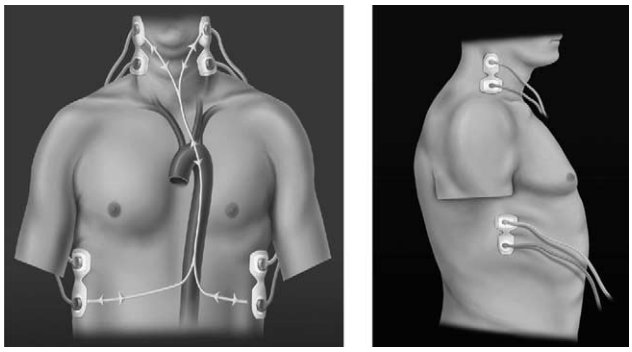

FIG. 1. The impedance cardiography method and sensor placement are shown in front and lateral views.

Methods

Patients

A convenience sample of clinically stable CAD patients participating in an outpatient cardiac rehabilitation program who met inclusion criteria were enrolled in the study. Clinical stability was defined as: 1) the absence of clinically significant changes in symptoms or physical signs as determined by examination by the attending physician, and 2) no changes in medical therapy during the interval between the inter-day studies. Patients were required to be >48 inches but <90 inches in height, and >67 but <341 pounds in weight. All patients provided written informed consent.

Exclusion Criteria

Patients were excluded from the study if they had one or more of the following: a minute ventilation pacemaker, severe aortic valve disease, clinical instability, medication, or clinical changes as determined by an examining physician or reported by the patient.

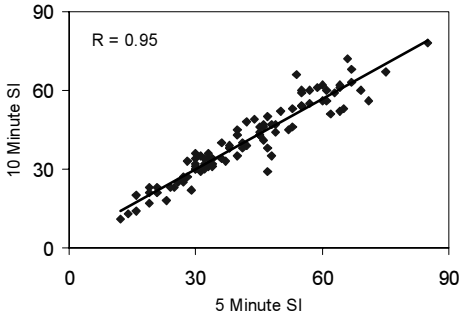

FIG. 4. Intra-day correlation of stroke index.

Impedance Cardiography Method

Impedance cardiography (ICG) devices use baseline and changes in thoracic bioimpedance to determine indices of blood flow (stroke index [SI] and cardiac index [CI]), resistance (systemic vascular resistance index [SVRI]), contractility (velocity index [VI]), and chest fluid volume (thoracic fluid content [TFC]). A total of four dual sensors are placed laterally on the patient's neck and thorax and a high-frequency (70 kHz), low-amplitude (2.5 mA) electrical current is applied to the outer sensors (most superior sensors on the neck and most inferior sensors on the thorax, as depicted in Fig. 1). The inner sensors measure the pulsatile changes in voltage that occur due to pulsatile

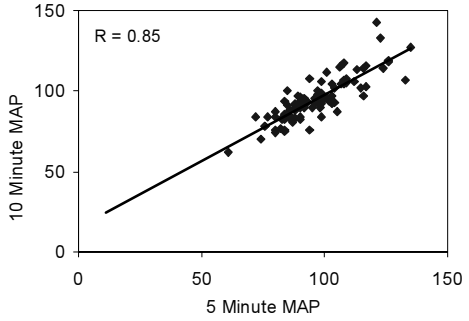

FIG. 2. Intra-day correlation of mean arterial pressure.

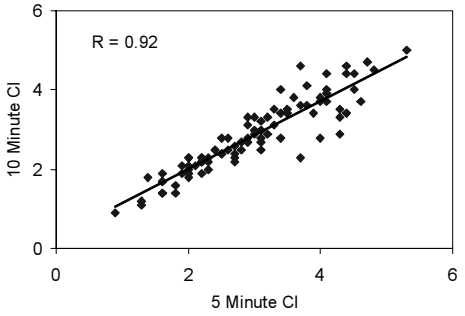

FIG. 5. Intra-day correlation of cardiac index.

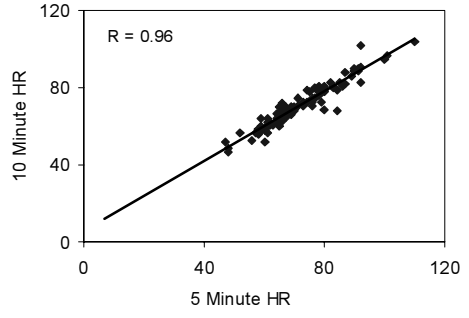

FIG. 3. Intra-day correlation of heart rate.

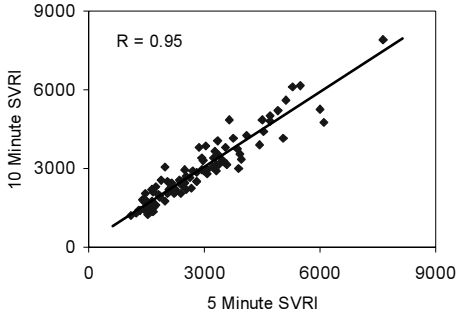

FIG. 6. Intra-day correlation of systemic vascular resistance index.

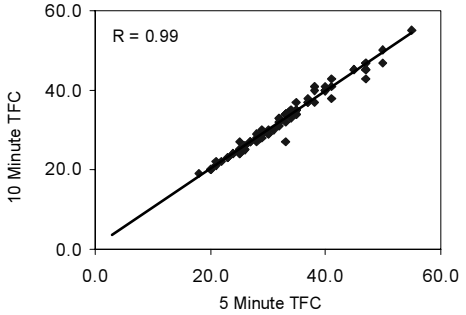

FIG. 7. Intra-day correlation of thoracic fluid content.

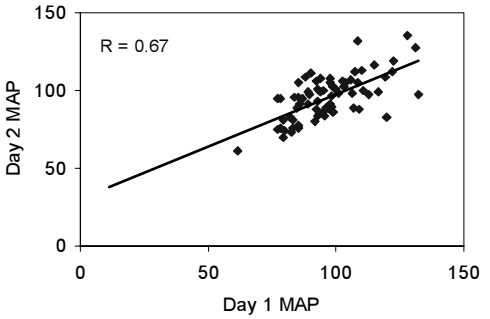

FIG. 10. Inter-day correlation of mean arterial pressure.

changes in thoracic impedance related to the change in the size of the thoracic aorta and reflecting stroke volume.

Data Collection

A nurse trained in the application of ICG obtained all hemodynamic measurements. Height, weight, gender, and BP obtained via a Dinamap 1846 SX Vital Signs monitor (Critikon, Tampa, FL) were entered into the ICG device. Measurements were obtained with the patient in the supine position at rest for 12 min during each of two monitoring sessions, 1 week apart. Blood pressure measurements were entered into the ICG device at four and nine minutes each session. The ICG data were recorded at 5 and 10 minutes of each session. Measurements at the specified time periods were based upon 30 beats of averaged data.

After 1 week, measurements were obtained using the same method as the previous week. Any changes in pacemaker settings, medications, or exercise status were recorded.

Data and Statistical Analysis

Patient data files were transferred from the ICG device and converted to an Excel (Microsoft, Redmond, WA) format. Intra-day comparison was between the 5- and 10-min parameter values. Inter-day comparison was between the average of the 5- and 10-min parameter values on week 1 and week 2. Descriptive statistics were performed to obtain the group mean, standard deviation, and 95% confidence interval for parameter measurements at each time period. The paired *t* test was used to determine significant differences ($P < .05$). Intra-day and inter-day correlation of each parameter was calculated by the Pearson method. The absolute value of the difference between parameter measurements was calculated and was reported for each

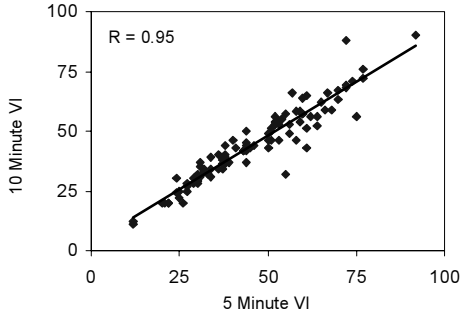

FIG. 8. Intra-day correlation of velocity index.

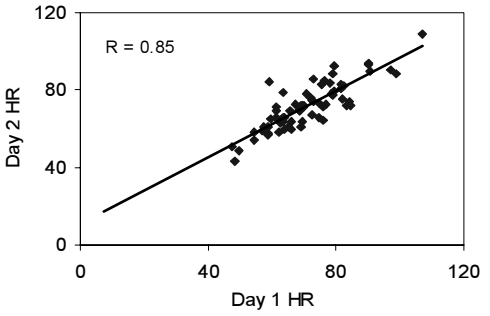

FIG. 11. Inter-day correlation of heart rate.

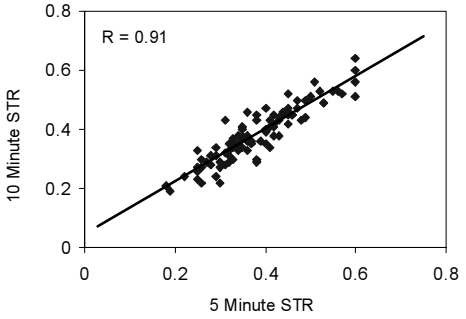

FIG. 9. Inter-day correlation of systolic time ratio.

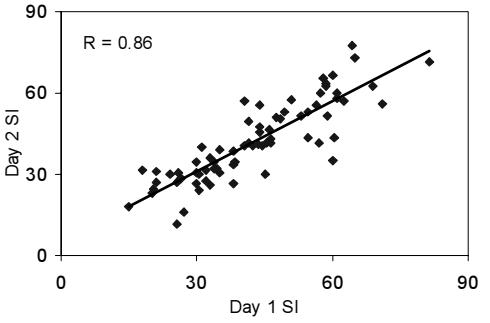

FIG. 12. Inter-day correlation of stroke index.

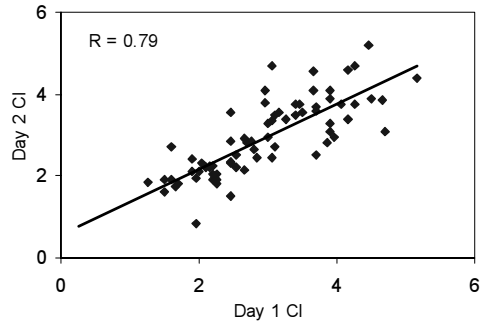

FIG. 13. Inter-day correlation of cardiac index.

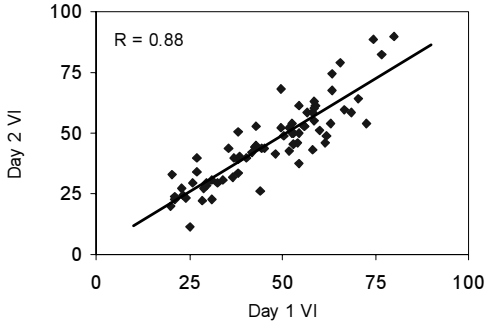

FIG. 16. Inter-day correlation of velocity index.

group as the mean absolute difference and mean absolute percent difference. The mean absolute percent difference was calculated by comparing the absolute difference to the parameter measurement at the prior time (5-min values for intra-day, week 1 values for inter-day) and reported as a percentage. Mean, standard deviation, and 95% confidence interval for the absolute and absolute percent differences are reported.

Results

Patient Characteristics

A total of 96 patients, 55 (57%) female and 41 (43%) male, enrolled in the study and met the inclusion criteria for week 1 intra-day reproducibility measurements. A total of 71 patients, 40 (56%) female and 31 (44%) male, met the inclusion criterion of clinical stability for inter-day reproducibility measurements. Of the 25 patients who were excluded from inter-day measurements, 13 had a change in their exercise status, four had a change in both exercise and medication, four had a change in medication only, three did not return for their second visit, and one had a change in pacemaker setting.

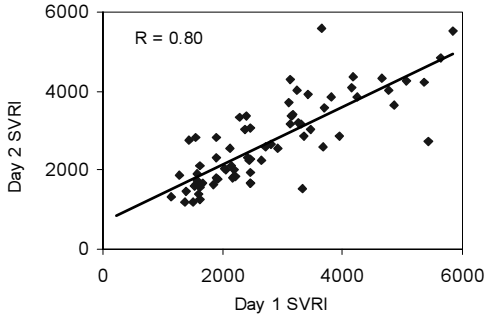

FIG. 14. Inter-day correlation of systemic vascular resistance index.

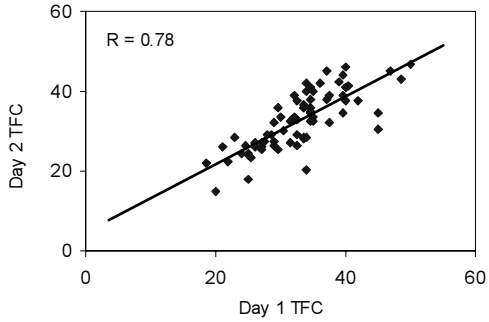

FIG. 15. Inter-day correlation of thoracic fluid content.

Intra-Day Reproducibility

The reproducibility of the 10-min values compared with the 5-min values for mean arterial pressure (MAP), heart rate (HR), stroke index (SI), cardiac index (CI), systemic vascular resistance index (SVRI), thoracic fluid content (TFC), velocity index (VI), and systolic time ratio (STR) are summarized in Tables 1 and 2 and plotted in Figs. 2–9. All parameters exhibited a strong intra-day correlation. Mean arterial pressure had the lowest intra-day correlation ($r = 0.85$), whereas the correlation for the ICG parameters ranged from 0.91 for STR to 0.99 for TFC. The mean absolute percent difference in parameters ranged from 2.0% for TFC to 11.0% for SVRI. For example, the mean absolute difference between MAP at 5 min and 10 min for the patients tested was 5.7 mm Hg, reflecting a 5.8% mean absolute percent difference between the 5- and 10- min measurements. The mean HR, SI, CI, and VI had small but statistically significant decreases in their 10-min values as compared with their 5-min values (all $P < .01$). The MAP also decreased ($P < .05$). The 10-min SVRI was greater than the 5-min SVRI; however, the difference was

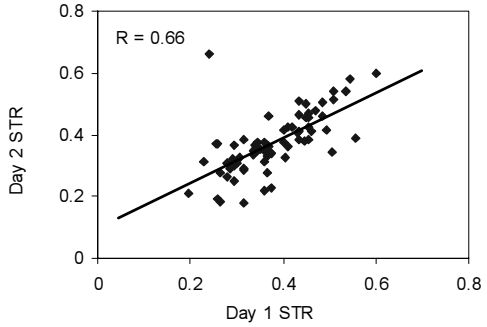

FIG. 17. Inter-day correlation of systolic time ratio.

Table 1. Intra-day mean values and correlation between 5-min and 10-min values (n = 96)

Parameter	Mean 5 min ± SD (95% CI)	Mean 10 min ± SD (95% CI)	Correlation (R)	P value
MAP (mm Hg)	96.5 ± 13.8 (93.7–99.3)	94.9 ± 13.4 (92.2–97.6)	0.85	.04
HR (beats/min)	71.7 ± 12.3 (69.2–74.2)	70.7 ± 11.7 (68.3–73.1)	0.96	<.01
SI (mL/m^2)	42.2 ± 15.5 (39.1–45.4)	40.9 ± 14.6 (38.0–43.9)	0.95	<.02
CI (L/min/m^2)	2.9 ± 0.95 (2.7–3.1)	2.8 ± 0.89 (2.6–3.0)	0.92	<.01
SVRI (dyne · sec · cm^{-5} · m^2)	2816 ± 1257 (2562–3071)	2878 ± 1259 (2623–3133)	0.95	.14
TFC (/kOhm)	32.6 ± 7.6 (31.0–34.1)	32.5 ± 7.5 (31.0–34.0)	0.99	.55
VI (/1000/sec)	46.4 ± 16.6 (43.0–49.7)	44.8 ± 15.8 (41.6–48.0)	0.95	<.01
STR (unitless)	0.38 ± 0.10 (0.36–0.40)	0.38 ± 0.09 (0.37–0.40)	0.91	.52

CI = cardiac index, 95% CI = 95% confidence interval, HR = heart rate, MAP = mean arterial pressure, SD = standard deviation, SI = stroke index, STR = systolic time ratio, SVRI = systemic vascular resistance index, TFC = thoracic fluid content, VI = velocity index.

not statistically significant (P = .14). The TFC and STR were unchanged, with statistically insignificant differences (P = 0.55 and 0.52, respectively).

Inter-Day Reproducibility

The reproducibility of the week 2 values compared with week 1 values is summarized in Tables 3 and 4 and plotted in Figs. 10–17. The mean difference in time of day between the day 1 and day 2 monitoring sessions was 35 min (95% CI, 12 to 59 min). All parameters exhibited a strong correlation, although they were not as high as the intra-day measurements. The STR and MAP had the lowest correlations (0.66 and 0.67, respectively). An outlier significantly affected the STR correlation; removing the outlier resulted in a correlation of 0.80. Correlation for the remaining ICG parameters ranged from 0.78 for TFC to 0.88 for VI. The mean absolute percent change was also greater as compared with the intra-day. The changes ranged from 6.6% for HR to 18.1% for SVRI.

Discussion

The results obtained in this study indicate that in CAD patients, current ICG technology has high intra-day and inter-day reproducibility. Inter-day reproducibility measured by correlation, absolute difference, and absolute percent difference was expectedly greater than intra-day reproducibility. In addition, ICG is responsive to intra-day hemodynamic changes that occur during an initial period of rest. Although changes in 10-min v 5-min values for MAP, HR, SI, CI, and VI were statistically significant, they were not clinically significant. Because there was no gold standard for accuracy used in this study, we cannot determine the exact source of differences between measurements; however, we believe that the differences in the 10-min v the 5-min values can be attributed largely to normal physiologic response to rest that has been shown previously in HR and BP.[11] Other factors that could affect the intra-day reproducibility include operator technique and patient motion.

The parameter with the lowest intra-day variability (that is, the highest correlation and lowest mean absolute percent change) was TFC (2.0%). We suspect that this is due to physiologic factors. The TFC measurement is taken directly from the baseline impedance measured in the chest, which changes only when the net electrical conductivity of the chest changes. The net electrical conductivity of the chest changes due to increases or decreases in intravascular and extravascular fluid, which would not be expected to change within a 10-min period on the same

Table 2. Intra-day mean absolute and absolute percent differences between measurements (n = 96)

Parameter	Intra-day (10 min v 5 min) mean absolute difference ± SD (95% CI)	Intra-day (10 min v 5 min) Mean absolute % difference ± SD (95% CI)
MAP (mm Hg)	5.7 ± 5.2 (4.6–6.7)	5.8% ± 4.9 (4.8–6.8)
HR (beats/min)	2.6 ± 2.6 (2.0–3.1)	3.5% ± 3.4 (2.8–4.2)
SI (mL/m^2)	3.5 ± 3.5 (2.8–4.2)	8.3% ± 7.2 (6.8–9.8)
CI (L/min/m^2)	0.27 ± .29 (0.21–0.33)	8.8% ± 7.9 (7.2–10.4)
SVRI (dyne · sec · cm^{-5} · m^2)	300 ± 284 (242–357)	11.0% ± 10.2 (8.9–13.0)
TFC (/kOhm)	0.7 ± 1.0 (0.5–0.9)	2.0% ± 2.8 (1.5–2.6)
VI (/1000/sec)	3.7 ± 4.2 (2.9–4.6)	7.7% ± 7.4 (6.2–9.2)
STR (unitless)	0.03 ± 0.03 (0.02–0.03)	8.2% ± 7.4 (6.7–9.7)

Abbreviations as in Table 1.

Table 3. Inter-day mean values and correlation between week 1 and week 2 (n = 71)

Parameter	Week 1 mean ± SD (95% CI)	Week 2 mean ± SD (95% CI)	Correlation (*R*)	*P* value
MAP (mm Hg)	96.8 ± 14.1 (93.4–100.1)	95.5 ± 14.3 (92.1–98.9)	0.67	.18
HR (beats/min)	70.7 ± 11.8 (67.9–73.5)	71.5 ± 11.9 (68.7–74.3)	0.85	.13
SI (mL/m^2)	42.9 ± 14.6 (39.4–46.3)	42.1 ± 14.6 (38.6–45.5)	0.86	.02
CI (L/min/m^2)	2.95 ± 0.92 (2.73–3.17)	2.94 ± 0.93 (2.72–3.16)	0.79	.41
SVRI (dyne · sec · cm^{-5} · m^2)	2788 ± 1177 (2510–3067)	2721 ± 1067 (2469–2974)	0.80	.22
TFC (/kOhm)	32.8 ± 6.6 (31.3–34.4)	32.7 ± 7.2 (31.0–34.4)	0.78	.39
VI (/1000/sec)	46.6 ± 15.6 (42.9–50.3)	45.8 ± 16.5 (41.9–49.7)	0.88	.21
STR (unitless)	0.38 ± 0.09 (0.36–0.40)	0.37 ± 0.10 (0.35–0.40)	0.66	.32

Abbreviations as in Table 1.

day. The parameter with the highest intra-day variability was SVRI (11%). The variation in SVRI can be attributed to the combined, known variability of the individual components of SVRI, which include HR, CI, and MAP.

There were no statistically significant differences in the inter-day mean values for any of the hemodynamic parameters in the CAD population. Other than STR (r = 0.66) and MAP (r = 0.67), the correlation between day 2 and day 1 measurements remained high (r = 0.79 to 0.88). There was an expectedly greater mean absolute percent difference in the hemodynamic values for the inter-day as compared with the intra-day results. The inter-day differences are likely due to the same reasons as intra-day variation but are of greater magnitude because of the expectedly greater hemodynamic changes taking place over a 1-week period. It may be possible to generalize our findings to other populations with cardiovascular disease, as our results are consistent with a similar ICG reproducibility study in heart failure patients in whom there was higher variability for inter-day measurements than for intra-day comparisons.[12]

In caring for patients with cardiovascular disease, physicians are called upon to interpret serial hemodynamic measurements obtained by ICG in their patients. To apply the results of this study to patient management decisions, clinicians might consider changes that fall outside of the demonstrated ranges to reflect changes in disease status or as intended or unintended effects of therapeutic interventions. Likewise, the lack of change outside the demonstrated ranges may indicate the underlying hemodynamic status due to disease or intervention has not changed. Of course, changes in ICG parameters alone cannot be used in isolation; they are just one aspect of patient evaluation and should always be used in concert with history, physical examination, and other diagnostic and laboratory tests.

There are several limitations to this study. All of the potential factors that contribute to changes in hemodynamic values (such as when the patient had last eaten) were not collected and thus were not factored into the results. In addition, although changes in mean values were used to estimate physiologic changes, it is not possible to completely separate variability due to factors intrinsic to ICG technology from variation in physiologic state that is likely present in patients with underlying cardiovascular disease. The study design and relatively short interval between inter-day measurements makes variation due to disease progression or response to therapeutic intervention unlikely. Finally, because the study was based on only one group of CAD patients at a single site, the week-to-week variation in hemodynamic values may not be applicable to other patient populations.

In conclusion, managing disease progression and effi-

Table 4. Inter-day mean absolute and absolute percent differences between measurements (n = 71)

Parameter	Inter-day mean absolute difference ± SD (95% CI)	Inter-day mean absolute % difference ± SD (95% CI)
MAP (mm Hg)	8.9 ± 7.5 (7.1–10.7)	9.2% ± 7.3 (7.5–10.9)
HR (beats/min)	4.7 ± 4.5 (3.7–5.8)	6.6% ± 6.0 (5.2–8.0)
SI (mL/m^2)	5.8 ± 5.0 (4.6–7.0)	15.1% ± 14.6 (11.7–18.6)
CI (L/min/m^2)	0.44 ± 0.39 (0.35–0.54)	15.5% ± 14.3 (12.1–18.9)
SVRI (dyne · sec · cm^{-5} · m^2)	500 ± 505 (381–620)	18.1% ± 16.3 (14.3–22.0)
TFC (/kOhm)	3.5 ± 3.0 (2.8–4.2)	10.8% ± 9.5 (8.6–13.0)
VI (/1000/sec)	6.0 ± 5.2 (4.8–7.2)	13.7% ± 13.6 (10.5–16.9)
STR (unitless)	0.05 ± 0.06 (0.03–0.06)	13.4% ± 16.1 (9.6–17.3)

cacy of therapeutic intervention in the outpatient setting relies heavily on patient symptoms and physician examination. However, underlying hemodynamic changes may occur before any changes in symptoms or physical findings. Since most of the therapeutic agents used in treating the CAD patient have hemodynamic effects, accurate and reproducible noninvasive hemodynamic information can aid the clinician in evaluating the efficacy of treatment or the occurrence of disease progression or both. The relatively high degree of intra- and inter-day reproducibility demonstrated in this study suggests that serial ICG measurements provide clinically useful information with which to assess changes in patient status.

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Noninvasive Hemodynamic Profiles in Hypertensive Subjects

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Background: Hypertension is a disease state characterized by increased blood pressure (BP) associated with hemodynamic abnormalities, including elevated systemic vascular resistance index (SVRI); and altered cardiac index (CI). The objective of this study was to use noninvasive impedance cardiography (ICG) to evaluate hemodynamic characteristics of subjects with and without hypertension.

Methods: A total of 19 healthy nonhypertensive and 136 hypertensive subjects were retrospectively evaluated. Hemodynamic parameters were measured with ICG and included CI, SVRI, total arterial compliance index (TACI), and thoracic fluid content (TFC); these were compared with subject type, blood pressure value, demographics, and medications.

Results: The BP levels of healthy and hypertensive subjects were 117/71 and 154/90 mm Hg, respectively ($P < .0001$). Subjects with prehypertension had a lower TACI (0.97 *v* 1.21, $P < .05$) compared with those with a normal BP, ie, <120/80 mm Hg. Hypertensive subjects had significantly lower SI, CI, TACI, and TFC and significantly higher SVRI. Subjects with stage 2 hypertension had higher SVRI (4149 *v* 3418 dyne $\cdot$ sec^2 $\cdot$ cm^{-5} $\cdot$ m^2, $P < .01$) and lower TACI (0.61 *v* 0.53 mm Hg/mL/m^2, $P < .05$) than those with stage 1 hypertension. Compared with subjects with controlled hypertension, normal subjects had significantly lower SVRI (1996 *v* 2746 dyne $\cdot$ sec^2 $\cdot$ cm^{-5} $\cdot$ m^2, $P < .0001$) and significantly higher CI (3.23 *v* 2.63 L/min/m^2, $P < .001$), SI (48.2 *v* 37.4 mL/m^2, $P < .0001$), TACI (1.08 *v* 0.85 mm Hg/mL/m^2, $P < .01$), and TFC (29.1 *v* 24.1/kOhm, $P < .0001$). The parameters of TACI, SVRI, and CI demonstrated modest correlation (-0.75, 0.62, and -0.30), respectively, with SBP. In the 54 subjects with BP <140/90 mm Hg, SVRI values varied significantly, with 32 subjects (39.2%) with SVRI values in the high range (>2483 dyne $\cdot$ sec^2 $\cdot$ cm^{-5} $\cdot$ m^2).

Conclusions: Hemodynamic parameters from ICG displayed significantly different hemodynamic profiles between hypertensive and nonhypertensive subjects. However, significant individual variation of hemodynamic status exists. Hemodynamic measurements with ICG characterize hemodynamic status and may be helpful in diagnostic, prognostic, and therapeutic decision making in hypertensive subjects. Am J Hypertens 2005;18:51S–59S © 2005 American Journal of Hypertension, Ltd.

Key Words: Hypertension, prehypertension, hemodynamics, cardiac output, systemic vascular resistance, arterial compliance.

Although hypertension can result from multiple pathophysiologic conditions,[1] hemodynamic derangements of elevated cardiac output, systemic vascular resistance, or both are the phenotypic characteristics of increased blood pressure (BP). Subjects who are younger or pregnant are more likely to have a high cardiac output as a component of their hypertension.[2,3] In contrast, increased systemic vascular resistance often associated with either normal or reduced cardiac output is the hallmark of hypertensive stages in older subjects.[4] However, significant heterogeneity in cardiac output and systemic vascular resistance exists across all age groups.

The characterization of the specific hemodynamic components of hypertension has implications in the choice of antihypertensive therapy. Reductions in BP are obtained by use of antihypertensive medications that alter cardiac output, fluid volume, or systemic vascular resistance.[5,6] Despite the multitude of pharmacologic options that are available today, a suboptimal medical regimen is a leading cause of failure to control BP.[7]

Received November 5, 2004. Accepted November 9, 2004.

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The work described here was supported in part by CardioDynamics, Inc. (San Diego, CA), which provided technical support; by National Heart, Lung and Blood Institute of the National Institutes of Health grants HL−51952 and HL-068258; and by an unrestricted grant from the Unifi Corporation (Greensboro, NC).

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.043

Recently, impedance cardiography (ICG) has gained popularity as a noninvasive method to measure hemodynamic variables in hypertensive patients.[8–11]

The technology of ICG involves the measurement of thoracic impedance through the placement of four dual sensors on the neck and chest. Changes in electrical impedance are digitally processed and used to calculate parameters of blood flow (cardiac output [CO], cardiac index [CI], stroke volume [SV], and stroke index [SI]), vascular resistance (systemic vascular resistance [SVR], systemic vascular resistance index [SVRI]), and chest fluid level (thoracic fluid content [TFC]). Physiologically, arterial compliance is known to express the relationship between stroke volume and pulse pressure.[12,13] Therefore, a patient's arterial compliance (total arterial compliance index [TACI]) can be easily measured by dividing ICG stroke index by the pulse pressure calculated from the patient's systolic BP (SBP) and diastolic BP (DBP).[13,14] The ability of ICG to provide accurate and reproducible measures of hemodynamic parameters that correlate well with invasive hemodynamic measures has been demonstrated in a wide variety of patients with cardiovascular disease.[15–19] The use of ICG allows identification of the underlying hemodynamic abnormalities in patients with hypertension[20–22] and also in discerning risk that is not apparent from measurements of BP levels alone.[4,22] The use of ICG has been shown to aid therapeutic decision making and to improve BP control.[23,24] Population studies have shown that the risk of cardiovascular morbidity and mortality increases steadily with increasing levels of BP, beginning at levels as low as 115/75 mm Hg.[25] In recognition of the significance of even minor elevations of BP, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[26] elected to define a new BP category called prehypertension. This is characterized as SBP between 120 and 139 mm Hg or DBP between 80 and 89 mm Hg. In addition, JNC-7 combined previously defined stages 2 and 3 hypertension into a single category, stage 2, defined as BP $\geq$160/100 mm Hg.[26]

The goal of this study was to use ICG to characterize the hemodynamic characteristics of the various stages of hypertension to gain insight into whether variations in cardiac output, vascular resistance, or both may provide additional information in tailoring therapies.

Methods

Patients

The sample of subjects retrospectively reviewed in this study included hypertensive patients who presented for consultation at an academic tertiary care clinic and healthy normal subjects $<$30 years of age without known established disease. The study was approved by the institutional review board, and all patients signed a consent form before inclusion in the study.

Data Collection

Demographic and medication information was recorded for each subject. Hypertension was defined as active treatment with any antihypertensive agent or current SBP $\geq$140 mm Hg or DBP $\geq$90 mm Hg. Vascular disease was identified through patient history and was defined by clinical diagnosis of peripheral artery disease, antecedent evidence of a previous stroke, or carotid disease. Blood pressure was taken with the patient seated using the oscillometric method. Hemodynamic measurements were performed using the BioZ ICG Monitor (CardioDynamics, San Diego, CA) by a technician after 5 min of rest in the supine position; these included heart rate, CI, SI, SVRI, TACI, and TFC. In this study, the index values were chosen to help normalize the results by body surface area. The exact calculation of these parameters has been described.[27] Hemodynamic data were transcribed from the printed ICG report to a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA) by a research technician. Total arterial compliance index was calculated as stroke index divided by pulse pressure and expressed in units of mL/m^2 mm Hg.[13,14]

Categorization of BP

For the purpose of this study, normal subjects were categorized into two categories: those with BP $<$120/80 mm Hg and those with prehypertensive levels as defined by JNC-7 guidelines (SBP between 120 and 139 mm Hg or DBP between 80 and 89 mm Hg). Hypertensive patients were categorized as controlled or uncontrolled based on the traditional values of BP being $<$140/90 mm Hg; subjects with hypertension classified as controlled were further defined as having BP either $<$120/80 mm Hg or $>$120/80 mmHg; those whose hypertension was uncontrolled BP were further defined as having stage 1 (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg) or stage 2 (SBP $\geq$160 mm Hg or DBP $\geq$100 mm Hg) hypertension.

Statistical Analysis

Data analysis was performed by an independent statistician using the Statistical Analysis Software program (SAS Institute, Cary, NC). Discreet variables such as gender, race, BP category, and medications were summarized as *N* (%). Continuous variables were summarized as mean $\pm$ SD. Differences in ICG hemodynamic parameters among BP categories were examined for differences using the Student *t* test. The relationships of demographic and baseline variables to ICG hemodynamic parameters were evaluated by linear regression modeling.

Results

Patients

A total of 155 subjects were evaluated, including 19 subjects with BP $<$140/90 mm Hg and 136 subjects with established hypertension. Demographic, BP, and medica-

tion data for all study subjects are shown in Table 1. Of the 19 normal subjects, nine (47.4%) had BP levels below 120/80 mm Hg, and the other ten (52.6%) had BP levels that could be categorized within the prehypertensive range. Normal subjects were significantly younger (23 ± 1 years of age) than the hypertensive subjects (55 ± 14 years; $P < .0001$). Of the 136 hypertensive subjects, 30 (22.2%) had BP at the control level and 106 (78.5%) did not. Of the 30 hypertensive patients with controlled BP, only seven (5.1% of the hypertensive subjects) had their BP within optimal levels, defined as <120/80 mm Hg. Of the 106 patients without controlled BP, 44 (41.5%) had stage 1 and 62 (58.5%) had stage 2 hypertension. Hypertensive subjects took an average of 2.35 ± 1.52 antihypertensive medications. Those with stage 2 hypertension took 2.56 medications, whereas those with stage 1 took 2.18 medications. Differences in numbers of medications among the three groups were not statistically significant ($P > .05$). Diuretics were the most commonly used antihypertensive medications and were prescribed to 52.2% of the hypertensive subjects. This was followed by β-blockers (49.3), calcium channel blockers (43.4%), angiotensin-converting enzyme inhibitors (37.5%), angiotensin receptor blockers (30.1%), and centrally acting agents (17.6%).

Hemodynamic Characterization

Hemodynamic parameters for nonhypertensive subjects are shown in Table 2. Prehypertensive subjects had significantly higher SBP (124 *v* 110 mm Hg, $P < .001$) and pulse pressure (51.2 *v* 40.9 mm Hg, $P < .01$) and lower TACI (0.97 *v* 1.21 mm Hg/mL/m^2, $P < .05$) than those without prehypertensive BP levels. Heart rate and CI trended to be higher and stroke index trended to be lower in the prehypertensive group, but these differences did not reach statistical significance ($P = .20$ and 0.13, respectively).

Hemodynamic parameters for hypertensive subjects are shown in Table 3. Compared with all nonhypertensive subjects, patients with stage 1 and stage 2 hypertension had significantly lower stroke index (35 *v* 45 mL/m^2), CI (2.56 *v* 3.23 L/min/m^2, TACI (0.63 *v* 1.08 mm Hg/mL/m^2), and TFC (23.6 *v* 29.1 kOhm) whereas, pulse pressure (63.7 *v* 46.3 mm Hg, $P < .0001$) and SVRI (3603 *v* 1996 dyne · sec · cm^{-5} · m^2, $P < .0001$) were significantly higher. The only variable that was not significantly different was heart rate (71 *v* 68 beats/min). As BP increased, SVRI increased and TACI decreased. Accordingly, subjects with controlled BP had lower SVRI (2763 *v* 3846 dyne · sec · cm^{-5} · m^2, $P < .0001$) and higher TACI (0.85 *v* 0.56 mm Hg/mL/m^2, $P < .0001$) than those without controlled BP. Cardiac index trended higher (2.63 *v* 2.53 L/min/m^2) in those with controlled BP versus uncontrolled BP but the difference was not statistically significant ($P = .37$). Subjects with stage 2 hypertension had higher systemic vascular resistance (4149 *v* 3418 dyne · sec · cm^{-5} · m^2, $P < .01$) and higher TACI (0.61 *v* 0.53 mm Hg/mL/m^2, $P < .05$) than those with stage 1 hypertension.

The hemodynamic parameters of the 19 untreated nonhypertensive and 30 treated hypertensive subjects with BP <140/90 mm Hg were also compared. Normal subjects had significantly lower SBP (118 *v* 124, $P = .02$), DBP (71 *v* 79, $P < .01$), and SVRI (1995 *v* 2746 dyne · sec · cm^{-5} · m^2, $P < .0001$), and significantly higher CI (3.22 *v* 2.63 L/min/m^2, $P < .001$), stroke index (48.2 *v* 37.4 mL/m^2, $P < .0001$), TACI (1.08 *v* 0.85 mm Hg/mL/m^2, $P < .01$), and TFC (29.1 *v* 24.1 kOhm, $P < .0001$). Pulse pressure in normal subjects versus controlled hypertensive subjects was not significantly different (46.3 *v* 45.2 mm Hg).

Scatter plots comparing SBP with SVRI, TACI, and CI in all study subjects is shown in Figs. 1, 2, and 3, respectively. Total arterial compliance index had a strong negative correlation with SBP ($R = -0.75$, $P < .0001$), and SVRI had a lower positive correlation ($R = 0.62$, $P < .0001$). Cardiac index had a low negative correlation with SBP ($R = -0.30$, $P < .001$); however, when evaluated solely in nonhypertensive subjects, CI and SBP trended to be positively correlated ($R = 0.44$, $P > .05$).

Although there was a modest and statistically significant correlation between SVRI and SBP, a significant variation was observed at various SBP levels, as illustrated in Table 4. The normal range for SVRI is 1337 to 2483 dyne · sec · cm^{-5} · m^2.[28] A total of 22.2% of subjects with BP <120/80 mm Hg and 50.0% of subjects with SBP between 120 and 139 mm Hg and DBP between 80 and 89 mm Hg showed vasoconstriction, as evidenced by high SVRI values. In subjects with BP >140/90 mm Hg, 8.9% of subjects had SVRI in the normal range.

Correlations of various hemodynamic parameters and demographic variables are shown in Table 5. The highest correlations were found between TACI and age ($R = -0.54$, $P < .0001$) and TFC with male gender ($R = 0.48$, $P < .0001$). The number of antihypertensive medications had a negative association with CI ($R = -0.34$, $P < .0001$) and TACI ($R = -0.44$, $P < .0001$) and a positive association with SVRI ($R = 0.40$, $P < .0001$).

Discussion

Characterization of hemodynamic correlates of hypertension by a noninvasive method documents the nonhomogeneous nature of the mechanisms that contribute to the elevation in arterial pressure and underscores important differences between nonhypertensive and hypertensive subjects. Moreover, our findings document for the first time significant differences between ICG hemodynamic parameters in subjects with controlled versus uncontrolled hypertension and in subjects with controlled hypertension versus normotension. Subjects with prehypertension had a higher TACI than those with BP <120/80 mm Hg, a finding that substantiates the

Table 1. Subject characteristics ($N = 155$)

Characteristic	Normal Subjects			Hypertensive Subjects				
					BP Controlled, <140/90 mm Hg		BP Not Controlled, ≥140/90 mm Hg	
	All	SBP <120 and DBP <80 mm Hg	Prehypertensive, SBP ≥120 or DBP ≥80 mm Hg	All	SBP <120 and DBP <80 mm Hg	SBP ≥120 or DBP ≥80 mm Hg	Stage I: SBP 140–159 or DBP 90–99 mm Hg	Stage II: SBP ≥160 or DBP ≥100 mm Hg
Demographic								
Number of subjects (%)	19 (100%)	9 (47.4%)	10 (52.6%)	136 (100%)	7 (5.1%)	23 (16.9%)	44 (32.4%)	62 (45.6%)
Age (y)	23.4 ± 1.1	23.6 ± 1.2	23.3 ± 1.1	55.1 ± 13.8	50.3 ± 13.0	52.9 ± 13.9	53.5 ± 13.1	57.6 ± 14.1
Male gender	12 (63.2%)	4 (44.4%)	8 (80.0%)	64 (47.1%)	5 (71.4%)	14 (60.9%)	21 (47.7%)	24 (38.7%)
White race	15 (78.9%)	8 (88.9%)	7 (70.0%)	105 (77.2%)	6 (85.7%)	20 (87.0%)	33 (75.0%)	46 (74.2%)
Body surface area (m^2)	1.89 ± 0.24	1.93 ± 0.25	1.88 ± 0.19	1.93 ± 0.24	1.98 ± 0.36	1.95 ± .39	1.91 ± 0.20	1.93 ± 0.24
Disease								
Hypertension only	—	—	—	100 (73.5%)	4 (57.1%)	14 (60.9%)	33 (75.0%)	49 (79.0%)
Hypertension and vascular disease	—	—	—	36 (26.5%)	3 (42.9%)	9 (39.1%)	11 (25.0%)	13 (21.0%)
Medications								
All medications	—	—	—	2.35 ± 1.52	2.14 ± 1.52	2.17 ± 1.52	2.18 ± 1.50	2.56 ± 1.69
Angiotensin-converting enzyme inhibitor	—	—	—	51 (37.5%)	2 (18.2%)	8 (33.3%)	15 (33.3%)	26 (41.9%)
Angiotensin receptor blocker	—	—	—	41 (30.1%)	2 (18.2%)	11 (45.8%)	8 (17.8%)	20 (32.3%)
β-Blocker	—	—	—	67 (49.3%)	6 (54.5%)	9 (37.5%)	23 (51.1%)	29 (46.8%)
Calcium channel blocker	—	—	—	59 (43.4%)	2 (18.2%)	9 (37.5%)	19 (42.2%)	29 (46.8%)
Central acting	—	—	—	24 (17.6%)	0 (0.0%)	1 (4.2%)	6 (13.3%)	17 (27.4%)
Diuretic	—	—	—	71 (52.2%)	3 (27.3%)	12 (50.0%)	21 (46.7%)	35 (56.5%)
Nitrates	—	—	—	7 (5.1%)	0 (0.0%)	0 (0.0%)	4 (8.9%)	3 (4.8%)

DBP = diastolic blood pressure; SBP = systolic blood pressure.
Data are mean ± SD.

Table 2. Hemodynamic values for normal subjects, continuous variables (N = 19)

Variable	All Normal Subjects (N = 19)	Subjects With SBP <120 and DBP <80 mm Hg (N = 9)	Prehypertensive Subjects, SBP >120 or DBP >80 mm Hg (N = 10)
Systolic blood pressure (mm Hg)	118 ± 9	110 ± 6	124 ± 6*
Diastolic blood pressure (mm Hg)	71 ± 7	69 ± 4	73 ± 9
Mean arterial pressure (mm Hg)	85 ± 7	82 ± 3	88 ± 8
Pulse pressure (mm Hg)	46 ± 9	41 ± 6	51 ± 8†
Heart rate (beats/min)	68 ± 12	64 ± 13	72 ± 10
Stroke index (mL/m^2)	48.2 ± 8.1	48.8 ± 8.1	45.5 ± 5.6
Cardiac index (L/min/m^2)	3.23 ± 0.47	3.06 ± 0.38	3.38 ± 0.50
Systemic vascular resistance index (dyne · sec · cm^{-5} · m^2)	1996 ± 258	2015 ± 244	1978 ± 283
Total arterial compliance index (mm Hg/mL/m^2)	1.08 ± 0.27	1.21 ± 0.21	0.97 ± 0.28*‡
Thoracic fluid content (/kOhm)	29.1 ± 3.5	30.2 ± 3.9	28.1 ± 2.8

Abbreviations as in Table 1.
Data are mean ± SD.
Compared with normal subjects with SBP < 120/80 mm Hg: * $P < .001$; † $P < .01$; ‡ $P < .05$.

risk for progression of vascular disease in this group of individuals.

In this study, we chose to use the indexed values of the more commonly referenced variables of cardiac output, systemic vascular resistance, and total arterial compliance by normalizing each of these to body surface area. The effects of gender and body mass index in determining parameter differences may be minimized. This approach may also allow the results to be generalized to populations with different gender and body mass index values, although this possibility will require additional studies in a larger population of subjects.

An important observation derived from determinations of ICG hemodynamic variables across BP levels appears

Table 3. Hemodynamic values for hypertensive subjects (N = 136)

Parameter	All Hypertensive Subjects (N = 136)	BP Controlled: <140/90 mm Hg		BP Not Controlled: ≥140/90 mm Hg	
		SBP <120 and DBP <80 mm Hg (N = 7)	SBP >120 or DBP >80 mm Hg (N = 23)	Stage I: SBP 140–159 or DBP 90–99 mm Hg (N = 44)	Stage II: SBP >160 or DBP >100 mm Hg (N = 62)
Systolic blood pressure (mm Hg)	154 ± 25*	107 ± 34*	130 ± 35*	146.3 ± 7.3*	174 ± 21*
Diastolic blood pressure (mm Hg)	90 ± 14*	72 ± 19	82 ± 20*	88 ± 10*	98 ± 14*
Mean arterial pressure (mm Hg)	112 ± 18*	83 ± 25	96 ± 26*	109 ± 9*	124 ± 18*
Pulse pressure (mm Hg)	64 ± 23*	35 ± 24†	48 ± 24	59 ± 12*	76 ± 25*
Heart rate (beats/min)	71.2 ± 11.7	69.3 ± 14.9	71.9 ± 15.7	70.6 ± 10.6	71.6 ± 13.1
Stroke index (mL/m^2)	35.8 ± 9.4*	35.1 ± 10.4†	38.2 ± 10.6*	34.4 ± 9.0*	35.9 ± 10.4*
Cardiac index (L/min/m^2)	2.56 ± 0.61*	2.39 ± 0.69†	2.70 ± 0.71*	2.53 ± 0.51*	2.54 ± 0.70*
Systemic vascular resistance index (dyne · sec · cm^{-5} · m^2)	3603 ± 1469*	2756 ± 1527‡	2743 ± 1547*	3418 ± 921*	4149 ± 1818*
Total arterial compliance index (mm Hg/mL/m^2)	0.63 ± 0.25*	0.99 ± 0.26	0.81 ± 0.25*	0.61 ± 0.19*	0.53 ± 0.24*
Thoracic fluid content (/kOhm)	23.6 ± 4.6*	25.3 ± 5.6‡	23.7 ± 5.8*	23.9 ± 5.4*	23.2 ± 4.6*

Abbreviations as in Table 1.
Data are mean ± SD.
Compared with all normal subjects (N = 19): * $P < .001$; † $P < .01$; ‡ $P < .05$.

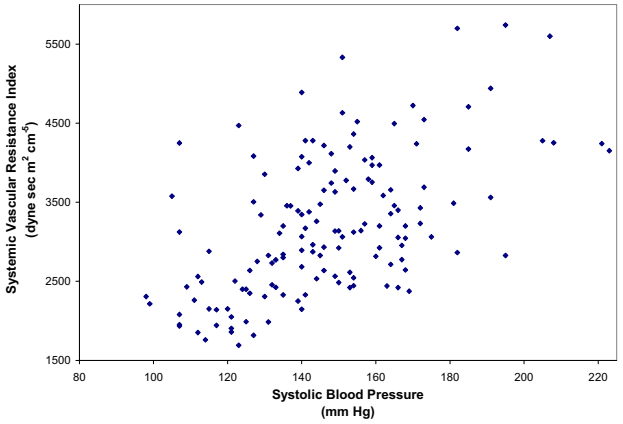

FIG. 1. Scatter plot of systemic vascular resistance index (SVRI) versus systolic blood pressure (SBP) ($N = 155$, $R = 0.62$, $P < .0001$).

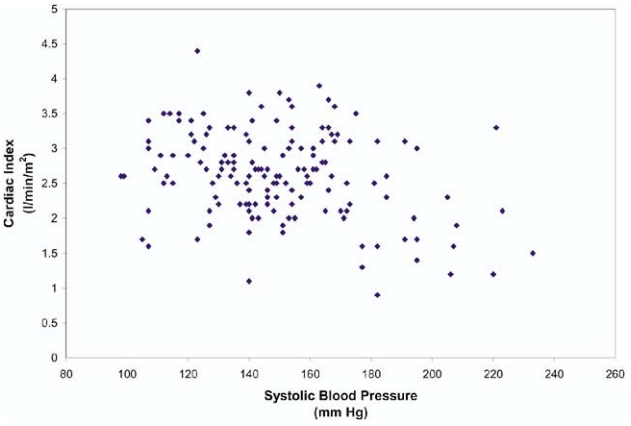

FIG. 3. Scatter plot of cardiac index (CI) versus systolic blood pressure (SBP) ($N = 155$, $R = -0.30$, $P < .001$).

to be those of SVRI and TACI. A higher BP was associated with higher SVRI and lower TACI in both controlled and uncontrolled hypertension and stage 1 and stage 2 hypertension. These results are in alignment with the known pathophysiology of hypertension, which initially results from decreased arterial compliance and is often followed by an associated increased systemic vascular resistance.[29] Systemic vascular resistance index was not different in prehypertensive normal subjects and those with controlled BP <120/80 mm Hg. The observation that total vascular resistance index did not reach normal values in subjects with SBP between 120 and 140 mm Hg is another important finding in this study, as it substantiates the possibility that the choice of medication used in these subjects may be an important element in guiding therapeutic decisions.[30] The transition from the normal state to the hypertensive state is heterogeneous and may be bimodal among individuals with prehypertension—a group in which some individuals have elevated cardiac output with low-to-normal systemic vascular resistance, whereas others have elevated vascular resistance with low or normal cardiac output.

Higher arterial stiffness has proved to be a BP-independent predictor of cardiovascular morbidity and mortality.[31–36] In this study, a reduced TACI was associated with increasing age, a finding that is consistent with known age-related changes in arterial elastic tissue. Despite an age-related association, TACI readily separated not only hypertensive subjects from the normal group but also differentiated truly normal subjects from those with prehypertension. The validity of the TACI will need to be correlated with the anatomical changes of small resistance arteries in future studies. This parameter could then prove to be of great significance in the clinical evaluation of hypertensive patients.

Within the nonhypertensive subjects, CI trended higher as BP increased, as has been shown previously,[2] although the numbers were small and the correlation was not strong. Cardiac index was significantly lower in the hypertensive subjects than in the normal subjects, a known effect of aging that is caused by decreased aortic and vascular compliance, decreased myocardial contractility, increased systemic vascular resistance, and decreased intravascular volume.[37,38]

The TFC was also significantly different between hypertensive and nonhypertensive individuals, although it did not differ according to different BP levels in both groups. Paradoxically, TFC was lower in the hypertensive patients than in the normotensive subjects. These data may be interpreted to suggest that thoracic fluid volume was controlled to a greater degree in the hypertensive patients, possibly by diuretics and salt restriction. In previous studies, TFC has been shown to accurately reflect changes in extravascular and intravascular volume changes.[39,40] In this study, higher values were correlated with male gender (Table 5), consistent with the published normal ranges for the parameter of 30 to 50/kOhm for men and 21 to 37/kOhm for women.[30] Evidence of decreased intravascular volume in older subjects may also be supported by the significantly lower TFC in the hypertensive subjects, who were significantly older but who had similar body surface area values.

The significant differences in hemodynamic parameters

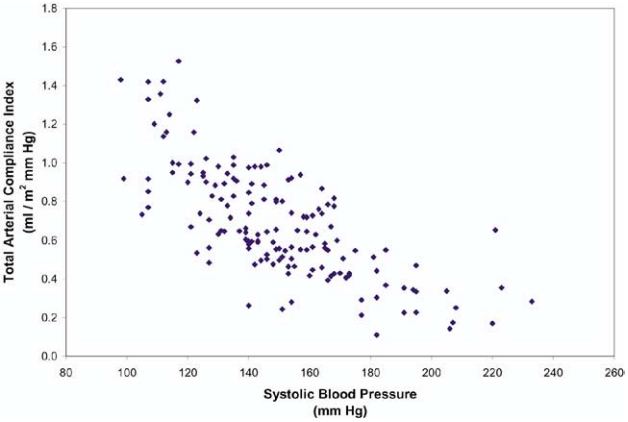

FIG. 2. Scatter plot of total arterial compliance index (TACI) versus systolic blood pressure (SBP) ($N = 155$, $R = -0.75$, $P < .0001$).

Table 4. Descriptive characteristics of systemic vascular resistance index by systolic blood pressure category

Systemic Vascular Resistance Index Characteristic (dyne · sec · cm^{-5} · m^2)	Systolic Blood Pressure Category				
	All (*N* = 155)	<120 mm Hg (*N* = 18)	120–139 mm Hg (*N* = 36)	140–159 mm Hg (*N* = 52)	≥160 mm Hg (*N* = 49)
Mean	3,406	2,348	2,639	3,438	4,323
Median	3,052	2,151	2,486	3,262	3,571
Standard deviation	1,477	627	684	907	1,980
Minimum	1,636	1,691	1,636	2,259	2,300
Maximum	10,000	4,100	4,329	7,564	10,000
% Low (<1337)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
% Normal (1337–2483)	41 (26.4%)	14 (77.8%)	18 (50.0%)	6 (11.5%)	3 (6.1%)
% High (>2483)	114 (73.5%)	4 (22.2%)	18 (50.0%)	46 (88.5%)	46 (93.9%)

across the different BP levels illustrate the progression of hemodynamic characteristics with the severity of hypertension. However, it is important to note the significant inter-subject variation in hemodynamic parameters that exists within a BP category. There can be significant individual patient variation when SBP is compared with SVRI, CI, or TACI. In the clinic, there is a limited ability to determine vascular resistance using measurement of BP alone. At all levels of BP, vascular resistance may be high or normal.

Various investigators have evaluated the ability of physicians to accurately estimate cardiac output and vascular resistance from clinical examination alone in critically ill patients. The accuracy of predicting the underlying hemodynamic parameters by clinical evaluation alone is low.[39–41] In patients with hypertension, it may be even less likely that physical examination can reveal hemodynamic status than in more severely ill patients who present with symptomatic heart disease. This analysis shows that various demographic factors and the number of medications used have a modest correlation with underlying hemodynamic parameters. It therefore appears that there is no substitute for direct measurement of hemodynamic parameters, as clinicians are not likely to reliably estimate specific hemodynamic values in an individual hypertensive patient from the physical examination or other clinically readily available factors.

It is tempting to suggest that our findings provide some insight into the relatively low levels of BP control in patients with hypertension. As estimated by data from the National Heart, Lung, and Blood Institute, only 34% of hypertensive adults <75 years of age have their hypertension controlled at the level of 140/90 mm Hg. In addition, hypertension management is even less successful for the elderly population.[26] Because precise measures of hemodynamic variables are outside the scope of the clinical office work-up, the choice of antihypertensive therapy is more often empirical and less likely to target and monitor the hemodynamic abnormalities for the particular patient. The ICG method was used in a randomized controlled trial to identify the initial and ongoing hemodynamic parameters of patients with resistant hypertension. The efficacy of antihypertensive therapy was improved by 70% in that study.[11] Because the success of antihypertensive therapy may be improved when medications target the appropriate hemodynamic characteristic, the findings of this study may provide support for future studies linking the use of ICG-guided therapy to improvement in BP control.

This study was limited by the inclusion of a selected patient population comprised of those referred to an academic, tertiary hypertension clinic. Patients were receiving therapy at the time of their evaluation, and medications were not stopped before hemodynamic assessment. Thus, hemodynamic parameters may reflect not only the underlying hemodynamic derangements associated with the hypertension but may also be influenced to varying degrees by the choice and intensity of antihypertensive medications. Although antihypertensive medication classes were recorded, the specific agent and dose were not, thereby preventing a medication analysis. In addition, there were a limited number of truly normal subjects, which limited the statistical power to determine differences within that group. The normal group consisted of subjects who were significantly younger than the hypertensive subjects. Finally, this study did not perform serial hemodynamic assessments and therefore did not assess the ability of the various ICG variables to characterize changes over time due to disease progression or therapy.

In conclusion, the categories of BP defined by JNC-7 are characterized by significantly different hemodynamic values, but significant variation in hemodynamic values among BP categories exists. Hemodynamic findings in an individual patient cannot be predicted by BP values, demographic information, or medications. Noninvasive ICG can help to characterize hemodynamic values and to identify variance at similar BP levels, which may improve BP management.

Table 5. Correlation of hemodynamic parameters with patient characteristics

Comparison (*N* = 155)	Correlation (*R*)	*P* value
Cardiac index versus:		
Sex (male)	0.29	< .001
Race (white)	0.16	< .05
Age	−0.28	< .001
Body surface area	−0.24	< .01
Number of antihypertensive medications	−0.34	< .0001
Stroke index versus:		
Sex (male)	0.20	< .05
Race (white)	0.22	< .01
Age	−0.18	< .05
Body surface area	−0.34	< .0001
Number of antihypertensive medications	−0.25	< .01
Systemic vascular resistance index versus:		
Sex (male)	−0.21	< .01
Race (white)	−0.20	< .05
Age	0.25	< .01
Body surface area	0.30	< .001
Number of antihypertensive medications	0.40	< .0001
Total arterial compliance index versus:		
Sex (male)	0.22	< .01
Race (white)	0.13	.09
Age	−0.54	< .0001
Body surface area	−0.31	< .001
Number of antihypertensive medications	−0.44	< .0001
Thoracic fluid content versus:		
Sex (male)	0.48	< .0001
Race (white)	−0.36	< .0001
Age	−0.31	< .001
Body surface area	−0.14	.07
Number of antihypertensive medications	−0.11	.17

Acknowledgments

We acknowledge the assistance of CardioDynamics International Corporation (San Diego, CA) in compiling and analyzing these data, and we thank Kevin Wagner and Kelly Stamper for their assistance in creating the figures and tables.

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Noninvasive Hemodynamic Assessment of the Effect of Mean Arterial Pressure on the Amplitude of Pulse Pressure

José Alfie, Carlos Galarza, and Gabriel Waisman

Background: The present study compares the relationships between mean arterial pressure (MAP) and pulse pressure (PP) in young and older men and whether MAP determines age-related changes in PP.

Methods: Impedance cardiography was used to evaluate systemic hemodynamics noninvasively in 189 unmedicated men referred to our hypertension unit. Patients were divided by age according to the median value ($<$ and $\geq$40 years).

Results: In younger patients, increasing supine MAP was associated with a transition in the blood pressure pattern from systolic to diastolic, whereas in older patients, increasing MAP was associated with change from diastolic to systolic hypertension. In young patients elevation in MAP was associated with a parallel decrease in PP ($P < .001$) and stroke volume index (SVI) ($P < .001$), whereas in older patients higher MAP was associated with higher PP ($P < .001$) and PP/SVI ratio ($P < .001$), a measure of arterial stiffness. When the sample was divided according to the median value of MAP ($<$ and $\geq$101 mm Hg), differences in the age-related change in PP and SVI became apparent. With a lower MAP, changes in PP and SVI remained parallel until the sixth decade, after which they began a progressive dissociation. In contrast, at higher MAP, the dissociation between PP and SVI began two decades earlier, indicating an acceleration of the age-related increase in arterial stiffness. Therefore, the relationship between MAP and PP was negative in younger men at the expense of a decrease in SVI, and positive in older men due to increasing arterial stiffness.

Conclusions: Noninvasive hemodynamic parameters from impedance cardiography provide a useful method to characterize the mechanism of increased blood pressure. Am J Hypertens 2005;18:60S–64S

Key Words: Mean arterial pressure, pulse pressure, impedance cardiography, hypertension.

The amplitude of blood pressure (BP) oscillation during the cardiac cycle, represented as pulse pressure (PP), is determined by stroke volume (SV, the amount of blood pumped with each heart beat) and the buffering capacity or compliance of the arterial tree. It has been shown that the ratio of SV to PP is a useful estimate of arterial compliance that can be obtained using noninvasive hemodynamic assessments.[1] Arterial stiffness, the hallmark of vascular aging, magnifies the increase in BP during systole and its decrease during diastole.[2,3] On the basis of the relationship between arterial stiffness, SV, and PP, it is apparent that elevated PP can be due to increased arterial stiffness, increased SV, or both. In hypertensive patients more than 50 years, increased PP is classically attributed to increased arterial stiffness, whereas before that age it predominantly represents a manifestation of high SV.[3–5] Knowledge of the mechanism underlying the increase in PP has clinical implications, as shown by a number of prospective studies demonstrating that the lower the SV for a given PP the higher the rate of cardiovascular events and deaths.[1,6,7] This suggests that the hemodynamic mechanism underlying high PP influences prognosis beyond its amplitude per se.

Arterial hypertension also promotes arterial stiffness, leading to a steeper age-related widening of PP.[8] On the other hand, high peripheral resistance, the hallmark of arterial hypertension, exerts hemodynamic changes that could counteract the expected effect of the increase in mean arterial pressure (MAP) on PP. In this regard, peripheral resistance maintains a reciprocal relationship with SV and PP.[9] We hypothesize that the latter effect could be more evident in young individuals because of the greater contribution of SV to PP in younger than in older adults. To test this hypothesis, we evaluated the hemodynamic

Received October 25, 2004. Accepted November 4, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.026

mechanisms underlying the relationship between MAP and PP in younger and older men. In addition, we investigated whether differences in MAP modify the age-related change in PP and its relationship with SV.

Methods

Study Population

We evaluated otherwise healthy men referred to a hypertension unit because of transient or sustained increases in BP. Patients included in the study were free of antihypertensive medication for at least 2 weeks at the time of hemodynamic measurements. Exclusion criteria were secondary or severe hypertension, coronary or valvular heart disease, previous stroke, anemia, diabetes, thyroid disease, body mass index (BMI) more than 35 kg/m^2, abnormal waveform morphology on thoracic impedance tracing, or suboptimal ambulatory BP monitoring, defined as having fewer than 80% valid readings.

Blood pressure and tracings of the first derivative of thoracic impedance were obtained in duplicate after 10 min of supine rest. Patients were instructed to avoid smoking or drinking tea or coffee the morning of the hemodynamic evaluation. Blood pressure was determined with a mercury sphygmomanometer on the right arm using cuffs of adequate size. Stroke volume was estimated noninvasively by impedance cardiography (Minnesota model 304B, SURCOM, Inc., Minneapolis, MN) using the technique and formula previously describe.[10] Heart rate (HR) and SV were calculated from tracings of consecutive cardiac cycles recorded at a paper speed of 50 mm/sec. Stroke volume index (SVI) was obtained by dividing SV by body surface area in meters squared. Systemic vascular resistance (SVR) was calculated as (MAP − CVP/CO) × 80, where CO is cardiac output and CVP is the central venous pressure, which was assumed to be 4 mm Hg.

Several reports have shown the accuracy of impedance cardiography for estimating SV and CO.[10–13] Pulse pressure was calculated as the difference between systolic BP and diastolic BP, with diastolic BP defined using the phase V of Korotkoff. The ratio of brachial PP to SVI (PP/SVI) was used as an indirect measure of arterial stiffness.[14]

Ambulatory BP was recorded in the nondominant arm, every 10 min from 7 AM to 11 PM, and every 20 min from 11 PM to 7 AM using a SpaceLabs 90207 monitor (SpaceLabs, Redmond, WA). Readings of systolic BP >260 or <70 mm Hg, diastolic BP >150 or <40 mm Hg, and PP >150 or <20 mm Hg were automatically discarded.

Statistical Analysis

Data are expressed as mean ± standard deviation. Patients were divided in two groups according to mean age (< and ≥40 years) and compared by Student *t* test. The strength of correlation between MAP and other parameters was assessed separately in younger and older groups by Pearson correlation coefficients. Because MAP showed a progressive increase with age, multiple regression analysis was used to evaluate whether MAP influences PP independently of age. The contribution of MAP to the age-related change in PP and SVI was evaluated comparing groups below and above the median MAP value (≤ and >101 mm Hg).

Table 1. Demographic and hemodynamic characteristics according to age

Variables	Age Groups, Years	
	<40 (*n* = 89)	≥40 (*n* = 100)
Age (years)	27.7 ± 6.2	54.1 ± 11 &
Height (cm)	175.4 ± 6.5	172.3 ± 7.5†
Weight (kg)	81.2 ± 10.7	80.4 ± 12.2
Corporal surface (m^2)	1.97 ± 0.14	1.96 ± 0.21
BMI (kg/m^2)	26.3 ± 2.9	27 ± 3.2
Supine SBP (mm Hg)	134.4 ± 10.4	141.5 ± 16*
Supine DBP (mm Hg)	77.7 ± 12.9	86.8 ± 8.7*
Supine MAP (mm Hg)	96.6 ± 10.1	104.8 ± 9.5*
24-h MAP (mm Hg)	97.9 ± 7.5	105.3 ± 9.6*
Supine PP (mm Hg)	56.7 ± 14.3	54.7 ± 14.4
24-h PP (mm Hg)	51.9 ± 7.4	49.3 ± 8.6‡
CI (mL/min/m^2)	3930 ± 976	3136 ± 840*
HR (beats/min)	70.2 ± 10.7	69.8 ± 11.6
SVI (mL/m^2)	56.9 ± 15.3	45.8 ± 12.1*
SVRI	2020 ± 618	2731 ± 739*
PP/SVI (mm Hg/mL/m^2)	1.04 ± 0.30	1.27 ± 0.49*

CI = cardiac index; DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; PP = pulse pressure; PP/SVI = pulse pressure to stroke volume index ratio; SBP = systolic blood pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index.

Values are mean ± standard deviation.

* $P < .001$; † $P < .01$; ‡ $P < .05$; and age was a selection criteria and therefore not subject to statistical analysis.

Results

One hundred eighty-nine men were included in the study, with median age of 40 years (17 to 78 years) and median MAP of 101 mm Hg (77 to 129 mm Hg. As shown in Table 1, older age was associated with higher supine systoilic BP, diastolic BP, and MAP (all $P < .001$ *v* younger age), but comparable PP. Pulse pressure was slightly but significantly lower in older than in younger patients ($P < .05$) when ambulatory measurements were used. Cardiac index (CI) and SVI were approximately 20% lower, whereas systemic vascular resistance index (SVRI) was approximately 35% higher in older compared to younger patients ($P < .001$ for all). Older men had a

Table 2. Hemodynamic correlates of supine MAP in young and older patients

Variables	Age, Years	
	<40	≥40
Supine SBP (mm Hg)	0.57*	0.85*
Supine DBP (mm Hg)	0.94*	0.84*
Supine PP (mm Hg)	−0.44*	0.49*
CI (mL/min/m^2)	−0.28†	0.06
HR (beats/min)	0.12	0.10
SVI (mL/m^2)	−0.30†	−0.04
SVRI (dyn · sec · cm^{-5} · m^2)	0.59*	0.30†
PP/SVI (mm Hg/mL/m^2)	−0.05	0.31†

Abbreviations as in Table 1.
* $P < .001$; † $P < .01$.

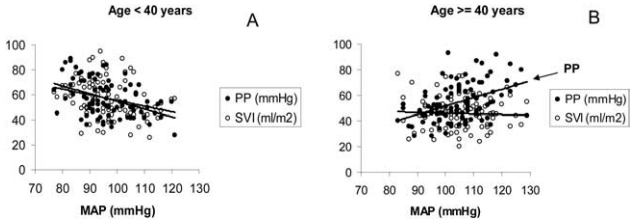

FIG. 2. The relationship between supine MAP, PP and SVI in young (A) and older patients (B). Younger men exhibited parallel and negative relationships of PP and SVI with increasing MAP, resulting in a constant PP/SVI ratio. In men 40 years of age and older, PP and SVI showed diverging relationships with MAP such that PP was positively correlated and SVI showed an insignificant negative correlation. In the older group, the ratio of PP to SVI, an index of arterial stiffness, increases with increasing MAP. MAP = mean arterial pressure, PP = pulse pressure, SVI = stoke volume index.

22% higher PP/SVI ratio compared to younger men ($P <$ .001).

Hemodynamic Correlates of MAP According to Age

Supine MAP correlated positively with systolic and diastolic BP in both age groups (Table 2); however, the relationship was steeper for diastolic BP in young, and steeper for systolic BP in older patients (Fig. 1). As a result, the correlation between supine MAP and PP was negative in younger ($R = -0.44$, $P < .001$), and positive in older patients ($R = 0.43$, $P < .001$). Similar results were obtained between 24-h MAP and PP ($R = -0.27$, $P < .02$ in younger men, and $R = 0.21$, $P < .05$ in older men).

As shown in Fig. 2, the younger group exhibited parallel and negative relationships of PP and SVI with MAP, resulting in a constant PP/SVI ratio. In contrast, in the older group, PP and SVI showed diverging relationships with MAP: PP was positively correlated and SVI showed an insignificant negative correlation. Thus, the ratio PP/SVI showed a positive change with increasing MAP ($P = .31$, $P < .01$).

The MAP correlated negatively with CI in younger patients ($P < .01$), whereas there was no statistically significant relationship in older patients The correlation between MAP and SVRI was positive in both younger and older patients, but the relationship was stronger in the former group ($P < .001$ and $< .01$, respectively). There was no significant relationship between MAP and HR in either age group.

In younger men, both age and MAP were independent predictors of PP ($\beta = -0.38$ and -0.33, respectively; $P = .001$ for both) and SVI ($\beta = -0.33$, $P = .001$ and $\beta = -0.21$, $P = .04$, respectively), without significant relationship with the PP/SVI ratio. In older men, both age and MAP were independent predictors of PP ($\beta = 0.42$ and 0.34 for MAP, $P < .001$ for both) and PP/SVI ratio ($\beta = 0.48$, $P < .001$ and $\beta = 0.21$, $P < .05$, respectively), whereas only age predicted SVI ($\beta = -0.26$, $P = .01$).

Age-related Change in PP According to MAP Level

In the whole sample, supine PP exhibited a curvilinear change with age ($R^2 = 0.22$ for supine and $R^2 = 0.32$ for 24-h PP; $P < .001$ for both), with a nadir at the fifth decade. Supine PP and SVI exhibited a parallel decrease up to the fifth decade, and a progressive dissociation thereafter. When viewed according to MAP, the relation

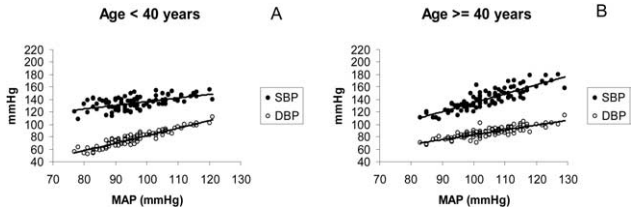

FIG. 1. The relationship between supine MAP, SBP and DBP in young and older patients. In younger men (panel A), the relationship between DBP and MAP is steeper than between SBP and MAP, resulting in a decrease in PP with increasing MAP. In older men (panel B), SBP increases more steeply with MAP than does DBP, resulting in higher PP with increasing MAP, MAP = mean arterial pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure.

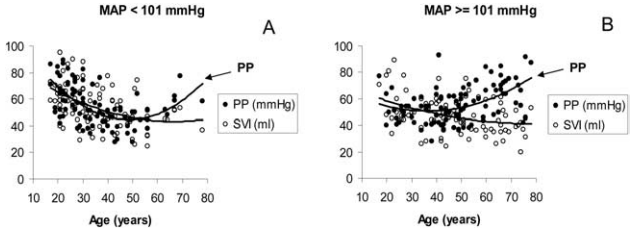

FIG. 3. Relationship of PP and SVI to age, for MAP below and above median value. The relation between PP and age was ″U″ shaped below 100 mmHg (panel A) and ″J″ shaped when MAP was greater than 100 (panel B). Higher MAP was associated with an earlier dissociation between PP and SVI, occurring in the fourth decade for MAP≥101 compared to the sixth decade for MAP<100 consistent with accelerated arterial stiffness in those with elevated MAP, PP = pulse pressure, SVI = stroke volume index, MAP = mean arterial pressure.

between PP and age was U-shaped below 100 mm Hg, and J-shaped above this value. Higher MAP was associated with an earlier dissociation between PP and SVI, occurring in the fourth decade for MAP ≥101 mm Hg compared to the sixth decade for MAP <100 mm Hg—a finding indicating an accelerated arterial stiffening (Fig. 3).

Discussion

The present study shows that MAP influences PP differently in younger and older individuals. Higher MAP was associated with a lower PP in young, and a higher PP in older individuals, causing a shift in the relation between PP and age, from U- to J-shaped. Narrowing of PP associated with increasing MAP seen in young individuals accompanied a decrease in SV. In contrast, increasing MAP in older subjects was associated with a steeper dissociation between PP and SV, most consistent with a decrease in arterial compliance.

The mechanical consequence of a given pressure load is conditioned by the elastin and collagen content of the arterial wall. At a low distending pressure, wall stress is mostly borne by elastic fibers, whereas less extensible collagen fibers become progressively recruited as pressure increases. Accordingly, increasing MAP in older subjects was associated with a higher PP/SVI ratio, indicating an expected decrease in arterial compliance. In contrast, the lack of such a finding before age 40 years could indicate that a greater content of elastic fibers in the arterial wall is able to buffer the negative effect of increasing MAP on arterial function. Nevertheless, the anticipated dissociation between PP and SVI in patients at higher MAP suggests that this apparent refractoriness of arterial capacitance to the pressor overload is lost around the fourth decade of life.

It is generally accepted that MAP and PP are positively correlated. However, our data demonstrate that decreasing SV and CO associated with increasing MAP could indirectly counteract the expected increase in PP. High SVRI, the hallmark of arterial hypertension, is associated in young men with a reciprocal decrease in SV, CO, and PP. Although the reciprocal relationship between peripheral resistance to venous return and CO was described by Guyton et al[15] several decades ago, the corresponding change in PP has not been emphasized. Experimental data using simulated models of the circulation showed that an increase in resistance not only lowers SV but also narrows PP,[9] similar to our finding in young men.

Although not generally recognized, high PP and even systolic hypertension are relatively common among men in their twenties.[16] Our data support the hypothesis that this early peak in PP is secondary to high SV. The parallelism between PP and SV shown here in young men using impedance cardiography resembles previous data using dye dilution[17] or Doppler-echocardiography.[4] Our findings additionally showed that a high MAP blunts the juvenile peak in PP at the expense of a negative effect of SV.

One limitation of the present study is that the analysis was based on brachial rather than central PP. It is known that conventional measurements overestimate aortic systolic BP, and that the difference is greatest in youth.[18] However, widening of PP in our young patients was more commonly associated with lower diastolic BP rather than higher systolic BP. On the other hand, we have recently shown in young men that, despite the numerical difference, brachial PP and the corresponding aortic value are closely related, and both parameters correlate with SV.[19]

On the other hand, the inverse correlation between MAP and PP observed in young subjects could represent an artifact due to an auscultatory overestimation of diastolic BP.[20] This appears unlikely as our finding was reproduced by oscillometric measurements in ambulatory conditions, and, secondly, the concomitant decrease in PP and SVI associated with increasing MAP provides a pathophysiologic support to our observation.

In conclusion, the study showed that age and MAP exerted opposite effects on PP in younger and older men. In young adult men (<40 years of age), higher MAP decreased PP in parallel with SV. In contrast, in older men (≥40 years), increasing MAP was linked to increasing PP. In addition, higher MAP anticipated the age-related increase in PP, most likely explained by an accelerated arterial stiffening. Impedance cardiography-derived stroke volume, systemic vascular resistance, and total arterial compliance are useful methods to assess the mechanism of changes in BP and PP.

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Prognostic Value of Hemodynamic Findings from Impedance Cardiography in Hypertensive Stroke

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Background: Impedance cardiography (ICG), a noninvasive method of hemodynamic monitoring, is a useful tool in the care of critically ill patients. Use of this technology shows promise in the hemodynamic assessment of hypertensive stroke patients. This study describes the different ICG findings of patients with hypertensive stroke and correlates parameters with patient outcome.

Methods: Adult patients with stroke admitted to the intensive care unit (ICU) who were on antihypertensive medications or had hypertensive blood pressure (BP) levels at the time of admission were included. Patients were classified as having ischemic or hemorrhagic stroke on the basis of imaging studies. The ICG was done in the initial 24 h of admission using the BioZ Cardiac Output Monitor (CardioDynamics, Inc., San Diego, CA) and 18 hemodynamic parameters were analyzed. Statistical analysis was performed to assess correlation of hemodynamic findings with the type of stroke and survival to hospital discharge.

Results: Fifty-two adult patients with a mean age of 60.5 ± 12.4 years were included. Of this population, 29 had ischemic stroke and 23 had hemorrhagic stroke. Seventeen patients died during hospital stay. Overall, noninvasive hemodynamic parameters of stroke patients showed a high systemic vascular resistance index (SVRI) and systemic vascular resistance (SVR), and decreased cardiac output (CO), stroke index (SI), and stroke volume (SV). Among the ischemic stroke group, nonsurvivors had a significantly higher mean SVRI and mean SVR compared to the survivors. In contrast, among the hemorrhagic stroke patients, nonsurvivors had a significantly lower mean SVRI and SVR compared to survivors. Except for SI and BP, there was no difference in the noninvasive hemodynamic parameters between the ischemic stroke group and the hemorrhagic stroke group.

Conclusions: In this population of hypertensive stroke patients admitted to the ICU, ICG showed an elevated SVRI and SVR and depressed CO, SV, and SI. In the ischemic stroke group, higher SVR and SVRI were associated with in-hospital death, whereas in the hemorrhagic stroke group, lower SVR and SVRI were associated with in-hospital death. The ICG may provide significant prognostic information in patients admitted with hypertensive stroke. Am J Hypertens 2005;18:65S–72S © 2005 American Journal of Hypertension, Ltd.

Key Words: Thoracic electrical bioimpedance, impedance cardiography, hypertension, stroke, noninvasive, hemodynamic.

Reliable hemodynamic measurements help clinicians make appropriate decisions regarding diagnosis and treatment of various cardiovascular and noncardiovascular diseases. For many years, the pulmonary artery catheter (PAC) has been the only hemodynamic monitoring device in the intensive care unit (ICU).[1] Due to the associated risks and cost, invasive hemodynamic monitoring has been restricted to only the most critically ill patients in the most acute level of care. Some studies have suggested an association between PAC usage and increased morbidity and mortality[2] due to insertion and infection risks. Therefore, measurement of hemodynamic variables in critically ill patients without invasive catheterization is highly desirable.

In recent years, a noninvasive method of hemodynamic monitoring called impedance cardiography (ICG) has been evaluated[3–9] and validated with PAC in prospective controlled trials.[2,10–17] In a recent meta-analysis reviewing 154 studies, Chaney and Derdak[3] concluded that ICG was useful for trend analysis and diagnostic interpreta-

Received October 25, 2004. Accepted November 4, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.027

tion. Drazner and associates[10] demonstrated good correlation of cardiac output (CO) by ICG with CO by thermodilution (TD) in patients with heart failure. Recently, Van De Water and Miller[18] showed that current ICG signal processing and measurement techniques have achieved significantly greater correlation with CO by TD compared to prior generations of devices. In addition, they showed that ICG had better correlation and precision in serial measurements in individual patients when compared to TD.

Impedance cardiography uses change in impedance of an alternating current applied across the thorax to determine various hemodynamic parameters, including stroke volume, CO, and thoracic fluid content.[3–10] During ICG monitoring, a low amplitude (4 mA), high frequency (70 kHz) electrical signal is transmitted from sensors placed on both sides of the neck and thorax, each of which has a transmitter and a receiver. A microprocessor then interprets and displays data on the monitor in numeric and graphic formats.[4] Second-generation ICG products capitalize on improved computer technology with faster signal processing, filtering, and improved electrocardiographic triggering as compared to previous models.[11] The newest devices are portable and can be used in all health care settings. They provide accurate values for 14 different hemodynamic parameters, which include measures of flow dynamics (CO, cardiac index [CI], stroke index [SI], and stroke volume [SV]); measures of resistance or afterload (systemic vascular resistance [SVR] and systemic vascular resistance index [SVRI]); indices of contractility or performance (acceleration index [ACI], velocity index [VI], pre-ejection period [PEP], left ventricular ejection time [LVET], and systolic time ratio [STR]); and a measure of fluid status (thoracic fluid content [TFC]).

Hypertension (HTN) has been a major problem in nearly all countries around the world as increasing proportions of people develop elevated BP.[19–26] It is quantitatively the largest single risk factor for premature death and disability, because of the large number of people afflicted and the consequences of uncontrolled HTN. Hypertension is the single most important risk factor for stroke and is present in approximately 70% of stroke patients. It is associated with high incidences of both stroke and mortality.[20]

Early recognition of cardiovascular and cerebrovascular complications related to HTN has been of prime importance in the management of HTN and preventing its complications. Recently, determination of systemic hemodynamics of hypertensive patients using noninvasive hemodynamic monitoring in the critical care setting is being used by clinicians to assist in the management of patients.[27] Abdelhamed et al[27] noted that hypertensive patients had lower SV and CO, and increased SVR when studied by ICG. In their study, they noted that noninvasive hemodynamic monitoring can provide a reproducible way to detect functional changes in hemodynamic variables, which may be important in guiding therapeutic approaches to the management of these patients.[27]

The aims of the present study were to determine the systemic hemodynamics of hypertensive stroke patients (ischemic and hemorrhagic) using ICG and whether noninvasive hemodynamic monitoring can provide prognostic information for these patients.

Methods

We retrospectively studied adult patients (more than 18 years old) admitted to the ICU at our institution with a diagnosis of hypertensive stroke (ischemic infarct or hemorrhage) from January 2002 to November 2003. Medical records were reviewed for demographic information (eg, age, sex, smoking history), neurologic evaluation (including Glasgow Coma Scale [GCS]), and diagnostic imaging studies performed. A history of each of the following comorbid factors was recorded: previous stroke, coronary artery disease (CAD), and diabetes mellitus (DM). All hemodynamic data was obtained by ICG using the BioZ ICG Monitor (CardioDynamics, San Diego, CA).

The diagnosis of stroke was based on history and neurologic examination: presence of rapidly developing clinical symptoms or signs of focal, or at times global, loss of cerebral function, with symptoms lasting more than 24 h. The stroke category was classified as either ischemic infarct or hemorrhage based on neuroimaging studies (brain computed tomography [CT] or magnetic resonance imaging [MRI]). Outcome was classified as death or survival.

Hypertension was defined, based on the Joint National Committee (JNC 7) Report, as BP $\geq$140/90 mm Hg on two or more determinations or use of antihypertensive drugs at any time.[28] The BP status was categorized on the basis of measurements obtained at physical examination during baseline clinical evaluation in the ICU.

Patients with the following conditions were excluded: 1) cardiorespiratory arrest and resuscitation; 2) postcraniotomy; 3) sepsis, as defined by the criteria of the American Thoracic Society (ATS); 4) acute coronary syndrome; 5) pleural effusion or pulmonary edema; 6) weight $<$66 lbs or $>$342 lbs; and 7) presence of significant aortic regurgitation.

Differences in ICG variables between survivors and nonsurvivors were determined by the Student t test. The χ^2 test was used to assess for any statistically significant differences among patients' demographic profile, GCS, and outcome.

Results

The study population consisted of 52 adult patients with acute hypertensive stroke (hemorrhagic or ischemic) confirmed by brain imaging studies. Hemodynamic parameters by ICG were recorded on admission. The patient characteristics are shown in Table 1. Thirty-two patients (61.5%) were men and mean age was 60.5 $\pm$ 12.4 years (range 38 to 81 years).

Table 1. Baseline demographic and clinical profile of the study population

Characteristic	Number (%)
Age	Mean 60.5 ± 12.4
Male gender	32 (61.5%)
Days of hospitalization	17.8 ± 23.2
Ischemic stroke	29 (55.8%)
Hemorrhagic stroke	23 (44.2%)
Diabetic	12 (23.1%)
Previous history of stroke	10 (19.2%)
Previous history of coronary artery disease	14 (26.9%)
Family history of diabetes	13 (25%)
Family history of hypertension	16 (30.8%)
Family history of stroke	6 (11.5%)
Family history of coronary artery disease	10 (19.2%)
Smoker	20 (38.5%)
Alcoholic beverage drinker	17 (32.7%)
Admission GCS	Mean 10.2 ± 4.2
Nonsurvivors	17 (32.7%)
Survivors	35 (67.3%)

Twenty-nine patients (55.8%) had ischemic stroke and 23 (44.2%) patients were diagnosed with hemorrhagic stroke. Twenty-three percent of the population had DM, whereas 26.9% had a history of CAD. Family history of HTN, DM, and coronary artery disease (CAD) was present in 30.8%, 25%, and 19.2%, respectively. More than one-third of the patients were smokers (38.5%) and 32.7% reported history of drinking alcoholic beverages.

The mean hospital stay was 17.8 ± 23.1 days. Seventeen patients (32.7%) died before discharge, whereas 35 patients (67.3%) survived. Average admission GCS was 10.2 ± 4.2.

Among the baseline clinical and demographic characteristics, there was no significant difference between the survivors and nonsurvivors in terms of age, sex distribution, hospital days, or past history and family history of comorbidities. However, the difference in GCS between the two groups almost reached statistical significance at $P = .059$ (Table 2).

Table 3 lists the mean hemodynamic parameters by ICG of all 52 stroke patients. Among the parameters, SVRI and SVR (indices of vascular resistance) were elevated, whereas CO, SI, and SV were decreased. Mean arterial pressure (MAP) was elevated, reflecting the inclusion criteria. Indices of contractility, ACI, VI, and STR were within normal limits, as was the measure of fluid status, TFC. The left cardiac work (LCW) and LCW index were within normal limits. When patients with ischemic stroke and those with hemorrhagic were viewed together, hemodynamics measurements by ICG did not predict death during the hospital admission (Table 4).

Patients with ischemic stroke had lower mean systolic BP compared to those with hemorrhagic stroke (158.9 *v* 181 mm Hg, $P = .02$); the same was true for diastolic BP (ischemic versus hemorrhage, 90.7 *v* 102.6 mm Hg, $P = .04$). Stroke index by ICG was significantly lower in those with ischemic stroke versus those with hemorrhagic stroke (27.3 *v* 32.7, $P = .04$). The hemodynamic values in patients with ischemic stroke versus hemorrhagic stroke were otherwise similar, as shown in Table 5.

When the study population was further analyzed for the association of hemodynamic values with survival based on the mechanism of stroke, significant differences were evident between the two groups. In the ischemic stroke patients, higher values for SVRI and SVR correlated with poor outcome (Table 6). The mean SVRI (4224.8 ± 3050) and SVR (2649.5 ± 1889) of those who died were significantly higher compared to those who survived (mean SVRI of 2905.4 ± 1159 and SVR of 1881.5 ± 791).

In the hemorrhagic stroke group (Table 7), the prog-

Table 2. Comparison of demographic and clinical characteristics between nonsurvivors and survivors

Characteristic	Nonsurvivors *N* = 17	Survivors *N* = 35	*P*
Age	59 ± 11.5	61.3 ± 12.9	.537 (NS)
Sex	12 males 5 females	20 males 15 females	.349 (NS)
Hospital days	10.1 ± 6.7	21.5 ± 27.2	.093 (NS)
Type of stroke	10 ischemic 7 hemorrhagic	19 ischemic 16 hemorrhagic	.757 (NS)
Diabetes	5/17	7/35	.449 (NS)
Previous stroke	3/17	7/35	.839 (NS)
Previous history of CAD	4/17	10/35	.700 (NS)
Family history of diabetes	6/17	7/35	.232 (NS)
Family history of stroke	3/17	3/35	.336 (NS)
Family history of CAD	4/17	6/35	.583 (NS)
Family history of hypertension	5/17	11/35	.882 (NS)
Smoker	9/17	11/35	.134 (NS)
Alcoholic beverage drinker	7/17	10/35	.363 (NS)
Admission GCS	8.6 ± 4.9	11.0 ± 3.6	.059 (NS)

Table 3. Hemodynamic parameters by impedance cardiography of 52 stroke patients

Hemodynamic Parameters	Mean ± Standard Deviation	Normal Value
HR (heart rate)	90.3 ± 21.8	58–86 beats/min
MAP (mean arterial pressure)	119.1 ± 26.2	84–100 mm Hg
CI (cardiac index)	2.6 ± 0.7	2.5–4.7 L/min/m^2
CO (cardiac output)	**3.9 ± 1.1**	4.5–8.5 L/min
SI (stroke index)	**29.7 ± 19.5**	35–65 mL/beat/m^2
SV (stroke volume)	**49.0 ± 19.5**	60–130 mL
SVRI (systemic vascular resistance index)	**3231.7 ± 1730.4**	1337–2483 dynes · sec · m^2/cm^5
SVR (systemic vascular resistance)	**2041.3 ± 1105.9**	742–1378 dynes · sec/cm^5
ACI (acceleration index)	75.4 ± 30.5	Males: 70–150 /100/sec^2 Females: 90–170 /100/sec^2
VI (velocity index)	40.6 ± 17.1	33–65 /1000/sec
TFC (thoracic fluid content)	29.6 ± 6.6	Males: 30–50/kohm Females: 21–37/kohm
LCWI (left cardiac work index)	3.2 ± 1.4	3.0–5.5 kg m/m^2
LCW (left cardiac work)	5.3 ± 3.2	5.4–10 kg m
STR (systolic time ratio)	0.40 ± 0.17	0.3–0.5
PEP (preejection period)	99.3 ± 28.1	Depends on HR, preload and contractility
LVET (left ventricular ejection time)	258.9 ± 45.3	Depends on HR, preload and contractility
Computed indices		
TACI (total arterial compliance index)	0.50 ± 0.26	
SSRI (stroke systemic resistance index)	29,1924.8 ± 16,8887.5	

Bolded values indicate mean outside the normal range.

nostic value of SVR and SVRI was reversed, that is, elevations of SVRI and SVR predicted better prognosis. The mean SVRI and SVR of survivors (3392.4 ± 1281 and 2156.6 ± 807, respectively) were significantly greater than for nonsurvivors (mean SVRI 2271.2 ± 604 and mean SVR 1310 ± 467). Higher CI at time of ICU admission correlated with poorer survival. There were no significant differences between the other ICG parameters.

In addition to the parameters routinely reported by ICG, we also computed total arterial compliance index (TACI),

Table 4. Comparison of impedance cardiography (ICG) values to outcome (combined population)

ICG Parameter	Values* Expired (*n* = 17)	Values* Survived (*n* = 35)	*P*
CI	2.7 ± 1.1 0.8–4.9	2.4 ± 0.7 (2.4) 1.0–4.6	>.05 (NS)
CO	4.0 ± 1.3 1.2–6.0	3.9 ± 1.2 3.1–8.3	>.05 (NS)
SI	27.9 ± 11.3 7–48	30.5 ± 9.8 10–54	>.05 (NS)
SV	50.6 ± 26.2 11–111	48.2 ± 17.0 16–86	>.05 (NS)
SVRI	3420.4 ± 2520.3 1351–8475	3128.1 ± 1223.9 1505–6863	>.05 (NS)
SVR	2098.2 ± 1597.5 742–5000	2007.3 ± 799.2 841–4106	>.05 (NS)
ACI	75.3 ± 36.0 30–150	80.6 ± 38.1 30–217	>.05 (NS)
VI	38.7 ± 19.3 11–77	41.9 ± 17.6 13–89	>.05 (NS)
TFC	30.7 ± 6.0 21.7–42.6	29.0 ± 7.0 19.1–48.4	>.05 (NS)

NS = not significant.
* All values are for mean ± standard deviation.

Table 5. Comparison of ICG parameters in patients with ischemic stroke to those with hemorrhagic stroke

Parameter	Ischemic Stroke	Hemorrhagic Stroke	*P*
Heart rate (HR)	92.1 ± 20.0	87.9 ± 24.3	.5 (NS)
Systolic BP	**159.0 ± 29.8**	**181 ± 35.6**	**.02 (S)**
Diastolic BP	**90.7 ± 17.3**	**102.6 ± 23.1**	**.04 (S)**
Mean arterial pressure (MAP)	113.0 ± 24.3	126.9 ± 27.0	.059 (NS)
CI	2.5 ± 0.8	2.7 ± 0.8	.39 (NS)
CO	3.9 ± 1.2	3.9 ± 0.9	.97 (NS)
SI	**27.3 ± 8.6**	**32.7 ± 10.2**	**.04 (S)**
SV	44.1 ± 15.8	55.1 ± 22.3	.053 (NS)
SVRI	3372.1 ± 2058.4	3054.6 ± 1220.7	.49 (NS)
SVR	2152.2 ± 1296.3	1901.5 ± 812.5	.39 (NS)
ACI	71.9 ± 31.5	79.8 ± 29.5	.35 (NS)
VI	36.5 ± 15.9	45.8 ± 17.6	.055 (NS)
TFC	30.2 ± 6.4	29.0 ± 6.9	.544 (NS)
LCWI	2.9 ± 1.3	3.5 ± 1.5	.16 (NS)
LCW	4.8 ± 2.6	6.0 ± 3.9	.199 (NS)
STR	0.44 ± 0.19	0.36 ± 0.14	.088 (NS)
PEP	103.4 ± 27.5	94.3 ± 28.7	.25 (NS)
LVET	248.8 ± 40.8	271.7 ± 48.3	.07 (NS)
Computed indices			
TACI	0.51 ± 0.28	0.52 ± 0.22	.45 (NS)
SSRI	304,333.2 ± 198,534.8	276,279.3 ± 124,485.8	.26 (NS)

NS = not significant; S = significant.
Bold values indicate statistically significant difference at $P < .05$.

an indirect measure of arterial stiffness,[29,30] and stroke systemic resistance index (SSRI), the systemic vascular resistance indexed to the patient's heart rate.[31] The TACI was computed by dividing stroke index by pulse pressure, whereas SSRI was calculated by multiplying systemic vascular resistance index by heart rate.

Overall, in the 52 hypertensive stroke patients, TACI was 0.50 ± 0.26, and the SSRI was 291,924.8 ±

Table 6. Comparison of ICG findings according to outcome among ischemic stroke patients

	Outcome*		
ICG Parameter	**Expired (*n* = 10)**	**Survived (*n* = 19)**	***P***
CI	2.3 ± 1.0 0.8–3.9	2.5 ± 0.8 1.0–4.6	>.05 (NS)
CO	4.0 ± 1.4 1.2–6.0	4.0 ± 1.5 1.7–8.3	>.05 (NS)
SI	23.3 ± 8.7 20–48	29.5 ± 8.8 10–48	>.05 (NS)
SV	40.1 ± 16.45 11–60	46.5 ± 17.8 16–86	>.05 (NS)
SVRI	**4224.8 ± 3050.0** **1531–8475**	**2905.5 ± 1160.0** **1505–6863**	**<.05** (S)
SVR	**2649.5 ± 1889.7** **916–5000**	**1881.5 ± 791.3** **841–4106**	**<.05** (S)
ACI	58.0 ± 30.9 30–126	82.6 ± 32.8 38–156	>.05 (NS)
VI	29.7 ± 16.68 11–17	41.4 ± 16.9 13–72	>.05 (NS)
TFC	31.9 ± 5.9 21.7–42.6	28.9 ± 6.9 19.1–48.4	>.05 (NS)
Computed indices			
TACI	0.52 ± 0.25	0.48 ± 0.31	>.05 (NS)
SSRI	317253.9 ± 247818.1	298519.0 ± 179203.0	>.05 (NS)

NS = not significant; S = significant.
Bold values indicate statistically significant difference at $P < .05$.
* All values are mean ± standard deviation, followed by range.

Table 7. Comparison of ICG findings according to outcome among hemorrhagic stroke patients

	Outcome*		
ICG Parameter	**Expired (*n* = 7)**	**Survived (*n* = 16)**	***P***
CI	**3.3 ± 0.9** **2.6–4.9**	**2.4 ± 0.5** **1.3–3.1**	**<.01 (S)**
CO	4.1 ± 1.2 2.2–6.0	3.8 ± 0.8 2–5.1	>.05 (NS)
SI	34.6 ± 11.7 20–48	31.8 ± 10.0 18–54	>.05 (NS)
SV	65.6 ± 31.4 33–111	50.3 ± 16.5 30–80	>.05 (NS)
SVRI	**2271.3 ± 604.2** **1351–3192**	**3392.4 ± 1281.9** **1809–6134**	**<.05 (S)**
SVR	**1310.7 ± 467.8** **742–2072**	**2156.7 ± 807.8** **1039–3931**	**<.05 (S)**
ACI	100 ± 28.5 55–150	78.3 ± 44.5 30–217	>.05 (NS)
VI	51.4 ± 15.9 25–77	42.4 ± 19.0 18–89	>.05 (NS)
TFC	29.1 ± 6.2 22.5–37.7	29.0 ± 7.4 20.8–47.6	>.05 (NS)
Computed indices			
TACI	0.64 ± 0.32	0.47 ± 0.15	>.05 (NS)
SSRI	271006 ± 133782.7	278586.4 ± 124702.6	>.05 (NS)

NS = not significant; S = significant.
Bold values indicate statistically significant difference at $P < .05$.
* All values are mean ± standard deviation, followed by range.

168,887.5 (Table 3). When stratified into ischemic and hemorrhagic stroke groups, there was no significant difference in TACI (Table 5). Similarly, there was no significant difference in the TACI and SSRI between survivors and nonsurvivors in the ischemic and hemorrhagic stroke groups (Tables 6 and 7).

Discussion

In this study of 52 hypertensive stroke patients in the ICU, hemodynamic findings using ICG were consistent with those of Abdelhamad et al[27] involving hypertensive patients: elevated MAP, decreased CO, SI and SV, and increased indices of vascular resistance. The decrease in SV and SI might be associated with left ventricular hypertrophy and other structural changes that occur in patients with longstanding HTN. Systolic dysfunction is aggravated by increased peripheral vascular resistance (increased SVR and SVRI) in these patients.[27] This forms a vicious cycle that can eventually lead to severe cardiac decompensation.

In each group of stroke patients, SVRI and SVR might have potential to predict outcome. In the ischemic stroke group, nonsurvivors presented with significantly higher vascular resistance. This may suggest more intense vasoconstriction, which may be either an inappropriate response to this type of stroke with deleterious effects or a marker of more diffuse vasculopathy and peripheral vasoconstriction.

Among hemorrhagic stroke patients, the reverse was true. Nonsurvivors had lower vascular resistance than survivors. This finding may reflect a decrease in systemic vascular resistance secondary to distributive or neurogenic causes or central hypotension due to increased intracranial pressure in the expired group—the presence of which is associated with a decrease in peripheral vascular tone—and may lead to a greater risk of death in these patients.[32] In addition, it may also reflect overaggressive reduction of the BP, which has been shown to be detrimental in this condition. In patients with intracranial bleed and increased intracranial pressure, systemic arterial pressure needs to be maintained high to perfuse the brain and maintain an arteriovenous pressure gradient. Extreme reductions of the arterial pressure in these patients may make their condition worse.[33]

When analysis was performed on all patients (combined hemorrhagic and ischemic stroke), there was no difference between the ICG parameters of survivors and nonsurvivors. This is consistent with a heterogeneous population and suggests that the hemodynamic parameters are most likely to be helpful and specific for prognosis when used in homogeneous groups of patients. In addition, although the hemorrhagic stroke group had a significantly higher systolic BP and diastolic BP than the ischemic stroke group, the other ICG parameters did not differ significantly between patients with ischemic stroke and hemorrhagic stroke, except for the stroke index. This suggests that ICG can detect changes in hemodynamic vari-

ables among hypertensive patients, specifically among hypertensive stroke patients, but it is not able to identify the type of stroke in a particular patient. It also suggests that overall, stroke patients have similar hemodynamic findings regardless of the mechanism of stroke, although the prognostic significance of those findings appears to depend on the type of stroke.

Our findings are similar to those of Galarza et al[34] who investigated hemodynamics in stroke patients and compared them to hypertensives (matched by age, sex, BP, and medications) and normotensives. They found lower CI and higher SVRI in patients with stroke when compared to uncomplicated hypertensives or normals, consistent with our results. When all outcomes were combined, there was no correlation between the hemodynamic findings and type of stroke (ischemic, hemorrhage, or lacunar). They did not report outcome data or compare hemodynamic findings in survivors versus nonsurvivors for stroke type, thus direct comparison to our study is not possible.

The TACI did not show any statistically significant difference between the two populations as well as between the expired and survived groups. Nevertheless, the mean TACI was low compared to the usual values seen in normal individuals in previous studies,[29] which is consistent with underlying cardiovascular disease. Reduced TAC has been shown to correlate with an increased risk of cardiovascular event. Another measure of arterial stiffness, decreased aortic distensibility, has been associated with the presence of cerebrovascular disease.[35]

Although the SSRI, the resistance imposed by the vasculature with each heart beat, has been shown in a previous study to be higher in more severe forms of hypertensive states,[31] this was not shown to be significantly different between the two populations in our study.

In conclusion, in this population of hypertensive stroke patients admitted to the ICU, ICG showed an elevated SVRI and SVR and depressed CO, SV, and SI. There was no difference in the ICG parameters between the ischemic stroke group and hemorrhagic stroke group when all patients were considered. However, in only those with ischemic stroke, higher SVR and SVRI were associated with poor outcome. In the hemorrhagic stroke group, lower SVR and SVRI were associated with a poorer outcome. Prospective studies will further define the predictive value of SVRI and SVR in patients with HTN and acute stroke.

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Diagnostic Ability of B-Type Natriuretic Peptide and Impedance Cardiography: Testing to Identify Left Ventricular Dysfunction in Hypertensive Patients

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Background: Patients with hypertension are at high risk for the development of left ventricular dysfunction (LVD). Echocardiography is considered to be the gold standard for diagnosis of LVD; but its cost, complexity, and availability prevents its use for frequent evaluation. Brain natriuretic peptide (BNP) and N-terminal BNP (NT-BNP) can identify heart failure in dyspneic patients. Impedance cardiography (ICG) is a noninvasive method of measuring hemodynamic and electromechanical timing parameters. The objective of this study was to determine the ability of BNP, NT-BNP, and ICG to detect the presence of LVD in patients with hypertension.

Methods: A convenience sample of subjects undergoing echocardiography who had a history of hypertension or current systolic blood pressure ≥140 mm Hg were enrolled and retrospectively evaluated. Patients with known LVD were excluded. Diagnosis of LVD was determined by the presence of systolic or diastolic dysfunction, valvular or wall motion abnormalities, or left ventricular hypertrophy.

Results: A total of 193 subjects were enrolled: 189 men and four women, age 68.8 ± 11.7 years. Multivariate regression analysis of history and symptoms, BNP, and ICG parameters identified significant predictor variables for LVD including cardiac index ($P = .005$), left cardiac work index ($P = .008$), BNP ($P = .017$), arrhythmia ($P = .023$), angina ($P = .034$), and systemic vascular resistance ($P = .048$). Receiver operating characteristic (ROC) analysis determined the area under the ROC curve (AUC) of BNP (0.60), NT-BNP (0.67), ICG velocity index (0.66), composite ICG (0.66), ICG combined with BNP (0.70), and ICG combined with NT-BNP (0.73).

Conclusions: In this high-risk hypertensive population, BNP, NT-BNP, and ICG were useful to identify the presence of LVD. The use of ICG with natriuretic peptide testing may improve the ability to detect LVD. Am J Hypertens 2005; 18:73S–81S © 2005 American Journal of Hypertension, Ltd.

Key Words: Echocardiography, B-type natriuretic peptide (BNP), impedance cardiography, ventricular dysfunction, hypertension.

Hypertension results in 35 million physician office visits per year and represents the most common primary outpatient diagnosis in the United States.[1] Hypertension is a major cause of left ventricular (LV) dysfunction[2] and of stroke, cardiovascular disease, and heart failure.[3] Lowering blood pressure (BP) significantly reduces the incidence of these conditions,[4] but only 34% of hypertensive patients have their BP controlled to <140/90 mm Hg.[5] Hypertension therefore remains a major public health issue.

The early detection of LV dysfunction is important because aggressive treatment can improve patient quality of life and decrease the costs associated with the development of complications. Although echocardiography is the gold standard for the detection of LV dysfunction, its routine use for diagnostic evaluation of hypertensive patients is limited due to its cost and complexity.[6]

B-natriuretic peptide (BNP) and N-terminal Pro BNP (NT-BNP) are cardiac neurohormones that are released from the ventricles in response to LV volume expansion and pressure overload. Levels of BNP are known to be elevated in patients with LV dysfunction and to correlate with echocardiography findings.[7,8] Impedance cardiogra-

Received November 10, 2004. Accepted November 16, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.044

Table 1. Impedance cardiography (ICG) variables

Abbreviation	Variable	Units	Measurement/Calculation
Blood flow			
SV	Stroke volume	mL	VI × LVET × VEPT (Z MARC algorithm)
SI	Stroke index	mL/m^2	SV/BSA
CO	Cardiac output	L/min	SV × HR
CI	Cardiac index	L/min/m^2	CO/BSA
Vascular resistance			
SVR	Systemic vascular resistance	dyne sec cm^{-5}	[(MAP − CVP)/CO] × 80
SVRI	Systemic vascular resistance index	dyne sec cm^{-5} m^2	[(MAP − CVP)/CI] × 80
SSRI	Stroke systemic resistance index	dyne cm^{-5} m^2	[(MAP − CVP)/SI] × 80
Contractility			
VI	Velocity index	/1000/sec	1000 × first time derivative$_{max}$/ baseline impedance
ACI	Acceleration index	/100/sec^2	100 × second time derivative$_{max}$/ baseline impedance
PEP	Pre-ejection period	msec	ECG Q-wave to aortic valve opening in milliseconds
LVET	Left ventricular ejection time	msec	Aortic valve opening to closing
STR	Systolic time ratio	—	PEP/LVET
Cardiac work			
LCWI	Left cardiac work index	kg m/m^2	(MAP − PCWP) × CI × 0.0144
Fluid status			
TFC	Thoracic fluid content	/kOhm	1000 × 1/baseline impedance
Log transformations to achieve normality			
LTFC	Log thoracic fluid content		Common log (TFC − 15.5)
LACI	Log acceleration index		Common log (ACI − 5)
LSVRI	Log systemic vascular resistance index		Common log (SVRI − 900)
LSVR	Log systemic vascular resistance		Common log (SVR − 400)
LLCWI	Log left cardiac work index		Common log (LCWI + 2)
LSTR	Log systolic time ratio		Common log (STR − 0.04)

BSA = body surface area; CVP = central venous pressure (estimated value of 10 mm Hg); ECG = electrocardiography; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure (estimated value of 10 mm Hg); R-R interval = 60/heart rate; VEPT = volume of electrically participating tissue; Z MARC = impedance modulating aortic compliance.

Table 2. Patient characteristics

Characteristic	Normal (%) (n = 45)	LVD (%) (n = 148)	P Value
Sex	100	97	NS
Race (white)	71	81	NS
Obesity	20	22	NS
History variables			
Coronary artery disease	38	32	NS
Myocardial infarction	18	15	NS
Angina	20	6	.005
Arrythmia	31	20	NS
Coronary artery bypass graft	16	14	NS
Percutaneous transluminal coronary angioplasty	4	6	NS
Acute coronary syndrome	7	8	NS
Stroke	4	9	NS
Chronic obstructive pulmonary disease	9	12	NS
Hyperlipidemia	62	55	NS
Diabetes	36	32	NS
Renal dysfunction	9	9	NS
Medication history			
Angiotensin-converting enzyme inhibitor	44	55	NS
Angiotensin receptor blocker	4	5	NS
Anti-arrythmics	2	5	NS
Anti-coagulant	18	14	NS
Anti-lipidemic	47	51	NS
β-Blocker	40	47	NS
Calcium channel blocker	29	35	NS
Digoxin	11	12	NS
Diuretic	31	45	NS
Hypoglycemic	27	24	NS
Nitrate	18	22	NS

phy (ICG) is a noninvasive method to determine hemodynamic parameters and systolic time intervals, and it has been used to identify patients with low ejection fraction and changes in ejection fraction.[9,10]

Determination of BNP, NT-BNP, and ICG represent potential tools for initial and ongoing diagnostic evaluation in hypertensive patients at high risk for the development of LV dysfunction. The purpose of this study was to collect concurrent echocardiography and BNP, NT-BNP, and ICG data to retrospectively evaluate their individual and joint abilities to detect LV dysfunction.

Methods

Study Sample

The Institutional Review Board of the University of California, San Diego, approved this study, and all patients provided written informed consent. The participants included 193 patients at San Diego Veteran's Healthcare System who were referred for echocardiography between June 2003 and May 2004. Patient referrals were made by clinic physicians, attending physicians, or nurse practitioners. Patients with a history of hypertension or current systolic BP measurement of $\geq$140 mm Hg were included. Patients with a previous history of LV dysfunction or congestive heart failure were excluded.

Echocardiography Data Collection

Echocardiography

M-mode and two-dimensional images and both spectral and color flow Doppler recordings were obtained with commercially available instruments operating at 2.0 to 3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical four- and two-chamber views. Pulsed Doppler spectral recordings were obtained in the apical four-chamber view from a 4 $\times$ 4–mm sample volume positioned at the tips of the mitral leaflets and in the right upper paraseptal pulmonary vein and were adjusted to yield velocity signals of maximal amplitude. All data were hard-copied to 1/2-inch VHS videotape for subsequent playback, analysis, and measurement. Two-dimensional echocardiograms were subjected to systematic visual analysis to detect regional contractile abnormalities. Left ventricular systolic and diastolic volumes and ejection fraction were derived from biplane apical (two- and four-chamber) views with a modified Simpson's rule algorithm. Left atrial and LV dimensions were measured from M-mode images according to standard criteria. The transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: E and A velocities, the peak values

Table 3. Patient characteristics by normal function versus left ventricular (LV) dysfunction

Variable (units)	Normal		LV Dysfunction		*P* Value
	N	Mean ± SD	*N*	Mean ± SD	
Demographic					
Age (y)	45	65.1 ± 11.7	148	69.9 ± 11.5	.016
Weight (lbs)	45	192.7 ± 38.7	148	197.5 ± 49.9	NS
Height (in.)	45	69.2 ± 2.9	148	70.2 ± 9.3	NS
BMI (kg/m^2)	45	28.3 ± 5.5	148	28.5 ± 7.2	NS
Heart rate (beats/min)	45	65.6 ± 13.3	148	67.6 ± 12.1	
Blood pressure					
Systolic BP (mm Hg)	45	145.2 ± 17.1	148	148.4 ± 17.8	NS
Diastolic BP (mm Hg)	45	76.1 ± 8.5	148	79.0 ± 11.3	NS
Mean arterial pressure (mm Hg)	45	94.8 ± 9.6	148	97.8 ± 11.9	NS
ICG					
Cardiac index (L/min/m^2)	45	2.91 ± 0.64	148	2.69 ± 0.66	.052
Cardiac output (L/min)	45	5.88 ± 1.76	148	5.53 ± 1.71	NS
Stroke index (mL/m^2)	45	45.2 ± 8.8	148	40.55 ± 9.96	.005
Stroke volume (mL)	45	91.0 ± 23.19	148	83.1 ± 24.32	.053
Log systemic vascular resistance index (dynes × sec × cm^{-5} × m^2)	45	3.19 ± 0.16	148	3.26 ± 0.19	.017
Log systemic vascular resistance (dynes × sec × cm^{-5})	45	2.92 ± 0.21	148	2.98 ± 0.21	NS
Log acceleration index (/100/sec^2)	45	1.83 ± 0.19	148	1.73 ± 0.18	.002
Velocity index (/1000/sec)	45	42.6 ± 14.2	148	35.0 ± 13.1	.001
Log thoracic fluid content (/kOhm)	45	1.18 ± 0.14	148	1.17 ± 0.16	NS
Left cardiac work index (kg × m/m^2)	45	3.55 ± 0.92	148	3.41 ± 1.01	NS
Log left cardiac work (kg × m)	45	0.95 ± 0.11	148	0.94 ± 0.11	NS
Log systolic time ratio (no units)	45	−0.56 ± 0.14	148	−0.51 ± 0.16	.042
Pre-ejection period (msec)	45	101 ± 21	148	109 ± 25	.043
LVET (msec)	45	317 ± 31	148	306 ± 36	NS
Laboratory					
Log BNP (pg/mL)	45	1.60 ± .45	148	1.77 ± .52	.055
Log NT-BNP (pg/mL)	42	1.99 ± .53	141	2.40 ± .66	< .001
Serum creatinine (units)	44	1.12 ± 0.33	148	1.35 ± 1.12	NS
BUN levels (units)	43	17.86 ± 6.75	148	18.72 ± 9.93	NS

BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; BUN = blood urea nitrogen; ICG = impedance cardiography; LVET = left ventricular ejection time; NT = N-terminal brain natriuretic peptide.

reached in early diastole and after atrial contraction, respectively; and deceleration time (DT), the interval from the E-wave peak to the decline of the velocity to baseline. In those cases in which velocity did not return to baseline, extrapolation of the deceleration signal was performed. In addition, pulmonary venous systolic and diastolic flow velocities were obtained as the maximal value reached during the respective phase of the cardiac cycle, and the pulmonary venous "A" reversal was the maximal velocity of retrograde flow into the vein after the P wave of the ECG. Finally, the LV isovolumetric relaxation time (IVRT) was obtained in the apical five-chamber view with a continuous-wave cursor or, if possible, a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmitral flow. The IVRT was taken as the time in milliseconds from the end of ejection to the onset of LV filling.

Echocardiographic Classifications

Experienced cardiologists who were blinded to the BNP, NT-BNP, and ICG results interpreted all echocardiograms. If classification was deemed difficult, another cardiologist was asked to concur with or offer an alternative classification. The patients were divided into two subgroups based on echocardiogram interpretation: namely, normal LV function and LV dysfunction.

Patients classified as normal LV function had: a) normal LV end-diastolic (3.5 to 5.5 cm) and end-systolic (2.5 to 3.6 cm) dimensions; b) ejection fraction >50%; c) no wall motion abnormalities; d) no evidence of impaired or restrictive diastolic relaxation abnormalities; e) no significant valvular disease (trace or mild allowed); and f) no LV hypertrophy.

Patients classified with LV dysfunction had one or more of the following: a) systolic dysfunction defined by an ejection fraction <50% or any wall motion abnormality (degree of systolic impairment was estimated by the echo-

Table 4. Logistic regression analysis using all variables to predict left ventricular (LV) dysfunction

Variables	β	SE(β)	Wald	P	Exp(β)	(95% CI)
Angina	−1.133	0.533	4.512	.034	0.322	(0.113–0.916)
Arhythmia	−0.993	0.436	5.171	.023	0.371	(0.158–0.872)
Log BNP	0.980	0.411	5.676	.017	2.663	(1.190–5.962)
ICG cardiac index	−3.914	1.386	7.974	.005	0.020	(0.001–0.302)
ICG log systemic vascular resistance	−4.844	2.454	3.898	.048	0.008	(0.000–0.965)
ICG left cardiac work index	1.539	0.581	7.029	.008	4.662	(1.494–14.55)
Constant	19.821	9.205	4.637			

Abbreviations as in Table 3.

cardiogram reader as mild, moderate, or severe dysfunction); b) diastolic dysfunction, classified by echocardiogram readers into three categories (namely mild, moderate, or severe); c) diastolic dysfunction, due to either impaired relaxation or restrictive filling dynamics; d) left atrial enlargement, defined as left atrial size ≥5.0 cm; e) LV hypertrophy, described as moderate or severe (LV hypertrophy was defined as mean LV wall thickness of septum and posterior wall ≥1.2 cm).

Measurement of BNP and NT-BNP Levels

All samples were collected by venipuncture into EDTA tubes at the time of echocardiography. The blood samples were kept at room temperature and analyzed within 4 h of the draw time. Before analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed for BNP (Bayer Diagnostics, Tarrytown, NY) and NT-BNP (Roche, Indianapolis, IN) as previously described.[11,12]

Measurement of ICG

All ICG measurements were collected with the BioZ ICG Monitor (CardioDynamics, San Diego, CA) as previously described.[13] Four dual ICG sensors were placed on the patient, two above the base of the neck and just below each ear and one on either side of the thorax in the mid-axillary line at the level of the xiphoid. A cable with eight ICG lead wires was attached to the individual sensor sites. An integrated oscillometric BP cuff was attached to the patient's left arm and the patient was placed in the supine position. After confirmation of a visible ICG waveform on the ICG monitor screen, the patient was instructed to rest while ICG hemodynamic data was collected. After approximately 3 min, the operator printed an ICG status report. Table 1 describes the ICG variables evaluated in this study.

Statistical Analysis

Multivariate regression analysis was performed to determine association of independent variables associated with LV dysfunction. The log values of continuous variables were used when appropriate. Variables in the first step included: 1) patient history (coronary artery disease, myocardial infarction, angina, arrhythmia, cor pulmonale, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, acute coronary syndrome, hyperten-

Table 5. Logistic regression analysis predicting left ventricular (LV) dysfunction from impedance cardiography (ICG) variables alone and in combination with BNP or NT-BNP brain natriuretic peptide (BNP) or N-terminal brain natriuretic peptide (NT-BNP)

Variable	β	SE(β)	Wald	P	Exp(β)	(95% CI)
Model using ICG variables only						
ICG cardiac index	−4.251	1.364	9.708	.002	0.014	(0.001–0.207)
ICG stroke volume	−0.026	0.013	4.241	.039	0.974	(0.951–0.999)
ICG log systemic vascular resistance	−7.371	2.859	6.649	.010	0.001	(0.000–0.171)
ICG left cardiac work index	1.758	0.582	9.117	.003	5.801	(1.853–18.16)
Constant	30.949	10.994	7.925			
Model using ICG variables and BNP						
Log BNP	0.993	0.414	5.769	.016	2.700	(1.200–6.072)
ICG cardiac index	−3.242	1.302	6.198	.013	0.039	(0.003–0.502)
ICG stroke index	−0.065	0.028	5.643	.018	0.937	(0.888–0.989)
ICG log systemic vascular resistance	−5.699	2.419	5.551	.018	0.003	(0.000–0.384)
ICG left cardiac work index	1.375	0.538	6.534	.011	3.954	(1.378–11.35)
Constant	23.428	9.143	6.566			
Model using ICG variables and NT-BNP						
Log NT-BNP	1.209	0.333	13.172	.000	3.352	(1.744–6.440)
ICG log acceleration index	−3.346	1.072	9.741	.002	0.035	(0.004–0.288)
Constant	4.487	1.949	5.300			

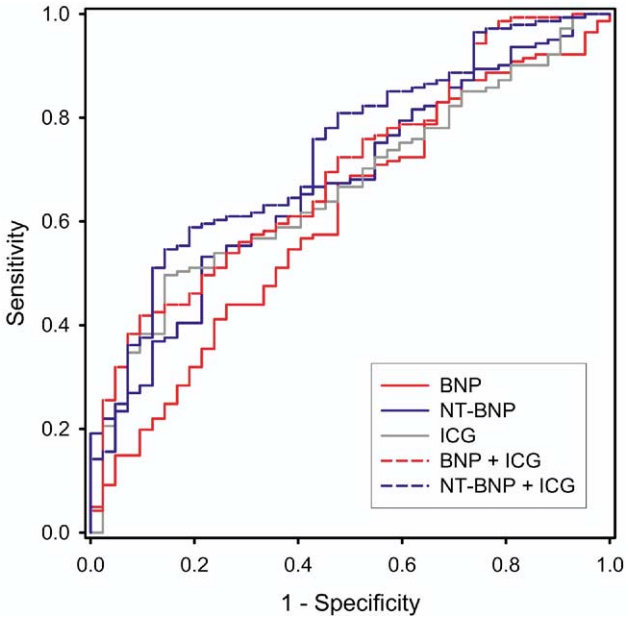

FIG. 1. Receiver operating characteristic (ROC) curve analysis for left ventricular (LV) dysfunction

sion, stroke, chronic obstructive pulmonary disease, hyperlipidemia, diabetes, renal disease, obesity); 2) symptoms (shortness of breath, edema); 3) vital signs (heart rate, systolic BP, diastolic BP; 4) log BNP; 5) all ICG parameters (cardiac index, cardiac output, stroke index, stroke volume, velocity index, log acceleration index, left cardiac work index, log left cardiac work, pre-ejection period, LV ejection time, log thoracic fluid content, log systemic vascular resistance, log systemic vascular resistance index, log systolic time ratio). Variables were removed from the model in a reverse stepwise manner if the LR contribution was not significant at $P < .05$.

Individual BNP, NT-BNP, and ICG parameter were evaluated for their ability to detect LV dysfunction. Additionally, three multivariate regression equations were created to assess the joint ability to detect LV dysfunction of: 1) all ICG variables; 2) all ICG variables and BNP; 3) all ICG variables and NT-BNP. The reverse stepwise approach was used for these models as well. Receiver operating characteristic (ROC) curves were constructed, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated[1] based on the best cutoff for each value. The optimal cutoff for each parameter was determined from the ROC curve as the point nearest the upper left corner. The BNP and NT-BNP cutoff levels are expressed in picograms per milliliter, whereas multivariate regression equation values are unitless.

Results

Patients

Echocardiography, BNP, and ICG data were collected in 193 patients. A total 189 patients (98%) were male and 120 (62%) were white, with age 68.8 ± 11.7 years. In all, 163 patients had a history of hypertension and 30 patients had current systolic BP of ≥140 mm Hg. Left ventricular dysfunction by echocardiography was present in 148 patients, whereas 45 patients had normal echocardiograms. The NT-BNP data was collected in 183 patients. Population prevalence of disease, symptoms, and medications are shown in Table 2.

Patient characteristics, neurohormones, and hemodynamics in those with normal LV function versus those with LV dysfunction are shown in Table 3. Patients with LV dysfunction had fewer symptoms of angina (6% *v* 20%, $P < .01$), but otherwise there were no differences in demographic, history, or medication variables. Patients with LV dysfunction had higher NT-BNP ($P < .001$) values than those with normal LV function, and the BNP difference approached significance ($P = .055$). Patients with LV dysfunction also had lower stroke index ($P = .005$), acceleration index ($P = .002$), and velocity index ($P = .001$) and had higher systolic time ratio ($P = .042$) and systemic vascular resistance index ($P = .017$) than those with normal LV function.

Multivariate Regression Analysis

Table 4 details the results of the reverse stepwise logistic regression analysis for association with the presence of LV dysfunction. The ICG cardiac index and left cardiac work index were the most significant, followed by BNP, history of arrhythmia, history of angina, and ICG systemic vascular resistance index.

Table 5 lists the results of the reverse stepwise logistic regression analyses for LV dysfunction predicted by three models: ICG parameters, ICG parameters with BNP, and ICG parameters with NT-BNP. As might be expected, the specific ICG variables that are retained differ from model to model, but ICG does make a significant contribution, alone or in combination with either BNP or NT-BNP.

Characteristics of ROC

Figure 1 shows the ROC and area under the curve (AUC) for BNP, NT-BNP, ICG, and ICG with BNP and ICG with NT-BNP. The combination of ICG and natriuretic peptides

Table 6. Receiver operating characteristic curve statistics for left ventricular (LV) dysfunction

Category	Area Under the Curve	*P* Value
BNP	0.60 (0.51–0.70)	.047
NT-BNP	0.67 (0.59–0.76)	.001
Multivariate ICG	0.66 (0.58–0.75)	.001
Multivariate ICG + BNP	0.70 (0.61–0.78)	< .001
Multivariate ICG + NT-BNP	0.73 (0.65–0.82)	< .001

Abbreviations as in Table 5.

Table 7. Decision statistics of brain natriuretic peptide (BNP), N-terminal BNP (NT-BNP), and multivariate impedance cardiography (ICG), ICG and BNP, and ICG and NT-BNP

Category	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
BNP (pg/mL)	35	69 (61–76)	49 (34–64)	82 (74–88)	32 (22–45)	64 (57–71)
NT-BNP (pg/mL)	235	53 (44–61)	78 (63–89)	89 (81–95)	33 (24–43)	59 (52–66)
Multivariate ICG	0.776	54 (46–62)	76 (60–86)	88 (79–93)	33 (25–43)	59 (52–66)
Multivariate ICG+BNP	0.780	57 (48–65)	71 (56–83)	87 (78–92)	33 (24–44)	60 (53–67)
Multivariate ICG+NT-BNP	0.803	59 (50–67)	81 (66–91)	91 (83–96)	37 (27–48)	64 (57–71)

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 5.

resulted in increases in the AUC. Table 6 gives the AUC results, and Table 7 shows the sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy of these variables based on the optimal cut point. Both a BNP level of 35 pg/mL and NT-BNP level of 235 pg/mL show a moderately high positive predictive value in this population. A theoretically optimal cut point for the ICG and the combination model also shows the improved specificity and PPV over the use of BNP alone. The univariate optimal cut points for the best ICG variables for LV dysfunction in ROC curve analysis (stroke index, systemic vascular resistance index, acceleration index, and velocity index) and their decision statistics are given in Tables 8 and 9. All of these variables showed high PPV similar to the ICG multivariate models.

Discussion

Echocardiography is the most common diagnostic test to determine LV dysfunction, and under optimal conditions its accuracy for detecting heart disease can exceed 90%.[14] However, its cost and complexity reduce its availability to clinicians looking for simpler, more cost-effective, and more frequent assessment of LV dysfunction. This is especially true in high-risk populations, such as elderly patients with hypertension, in whom symptoms may be mild or absent and diagnosis may be difficult. Despite the degree of equipoise that exists, physicians are often reluctant to obtain echocardiographic measurements; only one-half of patients with a suspected diagnosis of heart failure have the diagnosis confirmed by a cardiologist.[15,16]

Lack of definitive testing in patients with possible LV dysfunction is due to a variety of factors, including physician or diagnostic test access, physician education, and a general reluctance to order an expensive test without a high degree of probability. For the patient in whom the physician is reluctant to order echocardiographic evaluation, there appears to be an opportunity for a simpler, more cost-effective test to indicate the degree of likelihood of LV dysfunction. Additionally, in the patient with established mild to moderate LV dysfunction, there is a potential need for more frequent assessment to gauge disease progression or response to therapeutic interventions. However serial echocardiographic studies are prohibitively expensive and subject to inter- and intra-observer variation.[17]

Over time, our understanding of the development of LV dysfunction and heart failure has evolved, and it is now viewed as a complex syndrome characterized by both hemodynamic and neurohormonal derangements.[18] It then follows that measurements of hemodynamic and neurohormonal levels may be of benefit in establishing both the absolute and relative state of cardiac performance in patients at risk for the development of LV dysfunction. The role of BNP and NT-BNP in the diagnosis of heart failure has been shown in both the outpatient and emergency care settings,[19] and it has been shown that elevated BNP levels correlate with the presence of both systolic and diastolic dysfunction on echocardiography.[20] Evaluation with ICG has been used in dyspneic patients to differentiate diagnosis[21] and to determine therapeutic options.[22] Recently, ICG has also shown independent predictive power from

Table 8. Area-under-the-curve (AUC) of individual impedance cardiography (ICG) variables for determination of left ventricular (LV) dysfunction

ICG Variable	AUC	P Value	95% Confidence Interval	
			Lower Bound	Upper Bound
Stroke index (mL/m^2)	0.63	.009	0.54	0.72
Systemic vascular resistance index (dynes sec m^2 cm^{-5})	0.60	.044	0.51	0.68
Acceleration index (/100/sec^2)	0.66	.001	0.57	0.75
Velocity index (/1000/sec)	0.66	.001	0.58	0.75

Table 9. Decision statistics of individual impedance cardiography (ICG) variables for determination for presence of left ventricular (LV) dysfunction

ICG Variable	Cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
Stroke index (mL/m^2)*	44	59 (51–67)	58 (42–72)	82 (73–88)	30 (21–41)	59 (51–65)
Systemic vascular resistance Index (dynes × sec × cm^{-5} × m^2)†	2602	54 (46–62)	67 (51–80)	84 (75–90)	31 (22–41)	57 (50–64)
Acceleration index (/100/sec^2)*	63	53 (45–61)	73 (58–85)	87 (78–93)	32 (24–42)	58 (51–65)
Velocity index (/sec)*	38	62 (54–70)	62 (46–76)	84 (76–90)	33 (24–44)	62 (55–69)

Abbreviations as in Table 7.
* Lower values predict LV dysfunction; † higher values predict LV dysfunction.

standard clinical variables to identify short-term risk for adverse events in chronic heart-failure patients.[23] The combined use of BNP and ICG has additive diagnostic and prognostic ability in acutely dyspneic patients[24] and a better combined than individual ability to stratify mortality risk in established heart failure.[25]

We have previously shown the ability of BNP at low cut-off values to function as a screening test with strong negative predictive value for the purpose of ruling out the presence of LV dysfunction by echocardiography.[26] In this study, our goal was to characterize the cut points that provided the optimal positive predictive value for LV dysfunction. Systolic, diastolic, and mean arterial BP levels were not different in patients with or without LV dysfunction, but BNP, NT-BNP, and ICG were. Patients with LV dysfunction had higher neurohormonal levels and impaired hemodynamic function, evidenced by lower blood flow, higher vascular resistance, and poorer performance indices. These results are supported by previous studies showing the independence of hemodynamics from BP to predict cardiovascular events.[27–29]

In this group of hypertensive patients, we have shown for the first time the independent association of both ICG variables and neurohormonal levels with BNP to LV dysfunction. In addition, we have shown the ability of BNP, NT-BNP, and ICG to provide a high positive predictive value for the diagnosis of occult LV dysfunction. Although it was not the purpose of this study, visual examination of the ROC curve analysis shows that it is possible to define different cutpoints for each modality to create higher specificity and negative predictive value. When hemodynamic and neurohormonal testing are combined, they may be better than either alone. We do not believe that the use of BNP, NT-BNP, or ICG will preclude the need for an echocardiographic examination. However, we do believe the practical application of this information will be to help physicians suspect abnormal LV function in patients in whom they would have otherwise not ordered an echocardiogram, establish baseline measurements in high-risk patients, and trend changing LV function in patients with established LV dysfunction.

Study Limitations

This study was done at a single Veterans Hospital, so the results may not generalize to the entire population of patients with hypertension. Both the AUC under the ROC curve characteristics are dependent on the patient population studied. We used a broad criterion for LV dysfunction, and it is likely that the decision characteristics for neurohormones and hemodynamic variables would improve if a more narrow definition such as systolic dysfunction were evaluated. Our population generally represents older male veterans with a high prevalence of cardiac disease. We encourage a prospective evaluation of specific cut point values of ICG variables in this and other populations of interest.

In conclusion, if a patient is at high risk for LV dysfunction, an echocardiographic examination should be undertaken regardless of BNP, NT-BNP, or ICG findings. The results of this study suggest that BNP, NT-BNP, and ICG, when used alone or in combination, are useful to identify patients with increased likelihood of LV dysfunction. Hemodynamic and neurohormonal determinations may allow more frequent monitoring of LV function in high-risk patients to gauge disease status and efficacy of therapeutic interventions.

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AJH 2005; 18:82S–86S

Systolic Blood Pressure Does Not Reliably Identify Vasoactive Status in Chronic Heart Failure

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Background: In chronic heart failure (CHF), titration of vasodilating medications is often guided by monitoring of systolic blood pressure (BP). However, systolic BP may not indicate the patient's true vasoactive status—best approximated by systemic vascular resistance—because cardiac output is also a contributing factor. Impedance cardiography (ICG) is a validated noninvasive method of measuring cardiac output and systemic vascular resistance.

Methods: To evaluate the relationship between systolic BP and systemic vascular resistance index (SVRI) in patients with CHF, we retrospectively evaluated the systolic BP and SVRI from 71 consecutive patients during 615 CHF clinic visits. Measurement of systolic BP was through the oscillometric method and SVRI through ICG (BioZ ICG Monitor, CardioDynamics, San Diego, CA). Absolute values and relative changes in systolic BP and SVRI were compared and characterized by systolic BP grouping.

Results: The 71 patients were an average of 69.3 ± 12.2 years, New York Heart Association functional class 2.52 ± 0.6, 46.5% men, and 47.8% ischemic etiology. Frequency by systolic BP grouping was: <100 mm Hg in 67 subjects (10.9%), 100 to 119 mm Hg in 245 subjects (39.8%), and ≥120 mm Hg in 303 subjects (49.3%). The correlation (R^2 value) of systolic BP to SVRI was 0.21 (N = 615), and change in systolic BP to change in SVRI from previous visit was 0.27 (N = 547). In 138 visits in which systolic BP did not change by 5 mm Hg or more, SVRI changed by 20% or more in 41 (29.7%). In the 67 visits in which systolic BP was below 100, only 6 (9.0%) had low SVRI and 57 (85.1%) had normal SVRI. In the 245 visits with systolic BP 100 to 119, 58 (23.7%) had high SVRI.

Conclusions: Measurement of systolic BP alone does not reliably indicate the degree of vasoconstriction or vasodilation that exists in patients with CHF. Measurement of SVRI by ICG may help guide determination of need and tolerance for vasodilating medications in CHF. Am J Hypertens 2005;18:82S–86S © 2005 American Journal of Hypertension, Ltd.

Key Words: Impedance cardiography, thoracic electrical bioimpedance, hemodynamics, heart failure, vasoconstriction, vasodilation, hypertension.

In patients with chronic heart failure (CHF), titration of vasodilating medications is often guided with monitoring of arterial blood pressure (BP). Symptomatic CHF due to volume overload can be treated with diuresis or through afterload reduction with angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or other vasodilating agents. The use of ACEIs has been shown to reduce systemic vascular resistance (SVR) and increase stroke volume and cardiac output in patients with heart failure.[1,2]

Although BP is the pressure exerted on the arterial vessel walls, its level is determined by the degree of vasoconstriction or vasodilation and by the rate of blood flow measured as cardiac output (CO). Thus, BP may not indicate the patient's true vasoactive status because CO is also a contributing factor. Historically, hemodynamic measurement required invasive pulmonary artery catheterization and was therefore not used in routine outpatient CHF care. More recently, noninvasive impedance cardiography (ICG) has become more widespread in the management of patients with CHF.[3] The ICG uses the changes in thoracic impedance during the cardiac cycle to measure hemodynamic parameters such as CO and cardiac index (CI), SVR and systemic vascular resistance index (SVRI), an index of total chest fluid called thoracic fluid content, and electromechanical timing intervals. Measurements of ICG have demonstrated good reproducibility[4] and high correlation when compared to invasive hemodynamic

Received November 12, 2004. Accepted November 16, 2004.
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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.024

Table 1. Patient characteristics at initial measurements (n = 71)

Characteristic	Value
Age	69.3 ± 12.2
Gender—male	33 (46.5%)
Ethnicity—white	49 (69.0%)
Ischemic etiology	34 (47.8%)
New York heart association class	2.52 ± 0.6
Number on β blocker (%)	56 (78.9%)
Number on ACEI or ARB (%)	61 (87.3%)

measurements in patients with heart failure in both chronic[5] and acutely decompensated[6] heart failure.

The objective of this study was to evaluate the diagnostic relationship between systolic BP and SVRI in patients with CHF to determine whether systolic BP indicate a patient's absolute or relative change in vasoactive status.

Methods

Patient Selection

A retrospective chart review was performed for patients followed in the outpatient CHF clinic at our institution between January 1, 2001 and November 30, 2003. All patients provided informed consent. Patients were enrolled in the program with the goal of improving their quality and length of life while reducing hospitalizations using evidenced-based treatment strategies including ACEIs, ARBs, and β-blockers. Patients were eligible for inclusion in the analysis if they had systolic BP and ICG SVRI measurements recorded in at least two visits.

Data Collection

Measurement of arterial BP was through the oscillometric method (CAS Medical Systems, New York, NY) and expressed in mm Hg. Measurements of SVRI were completed with ICG (BioZ ICG Monitor, CardioDynamics, San Diego, CA) and expressed in dynes · sec · cm^{-5} · m^2. During the ICG test, four dual sensors are placed on the neck and chest. A constant, low amplitude, high frequency alternating electrical current is applied to the thorax and the corresponding voltage changes are measured to calculate changes in thoracic impedance, in accordance with Ohm's law. The baseline and changes in the impedance waveform are digitally processed to identify fiducial points that reflect the maximum blood velocity in the aorta (velocity index), the opening and closing of the aortic valve (left ventricular ejection time), and amount of fluid in the chest (thoracic fluid content). These directly measured variables are applied to an algorithm to calculate stroke volume and cardiac output and their indexed values of stroke index and CI. Other hemodynamic measurements, such as SVRI and left cardiac work index, are calculated based on accepted equations used in invasive patient monitoring systems.[7]

Database and Statistical Analysis

Data from the patient records were entered into a database (MS Excel, Microsoft, Redmond, WA). The absolute values of systolic BP and SVRI, and relative changes in systolic BP and SVRI from the previous visit were compared. Correlation coefficients were determined using Pearson's method and reported as R^2. The contribution of CI and BP to SVRI changes was evaluated, as well as the variability of SVRI in patients with stable BP. Normal SVRI values were considered to be 1337 to 2483 dynes × sec × cm^{-5} × m^2, and normal SVR values were considered to be 742 to 1378 dynes × sec × cm^{-5}.[7] Because SVR does not normalize values to a patient's body size, we used SVRI as the primary comparison variable. The SVRI values were also compared by three systolic BP categories: 1) <100 mm Hg; 2) 100 to 119 mm Hg; and 3) ≥120 mm Hg. Categorical variables are expressed as N (%) and continuous variables were expressed as mean ± standard deviation.

Results

Patients

A total of 71 patients were evaluated, totaling 615 CHF clinic visits. Patient characteristics at the initial visit are shown in Table 1.

BP to SVRI Comparisons

There were 615 absolute and 540 change comparisons between BP and SVRI. The correlation (R^2) of systolic BP to SVRI was 0.21 ($P < .001$) and to SVR was 0.18 ($P < .001$) (Fig. 1). The correlation of diastolic BP versus SVRI was 0.32 ($P < .001$) and versus SVR was 0.23 ($P < .001$). The correlation of changes in systolic BP versus the changes of SVRI and SVR were the same 0.27 ($P < .001$) (Fig. 2). There was no correlation (0.00, P = not significant) between the changes in diastolic BP and the changes in either SVRI or SVR.

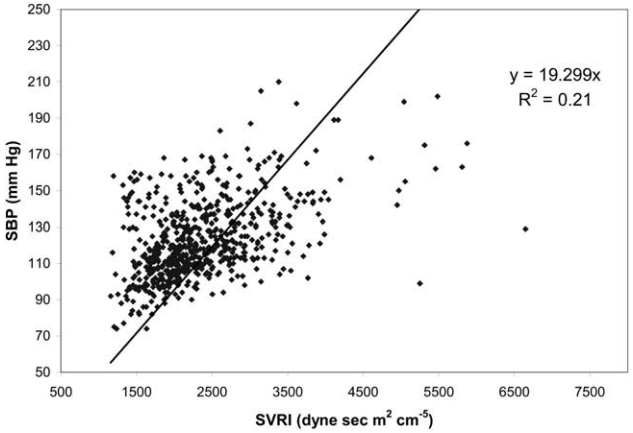

FIG. 1. Scatterplot of SBP vs SVRI (N = 615, $P < .001$). SBP = systolic blood pressure; SVRI = systemic vascular resistance index.

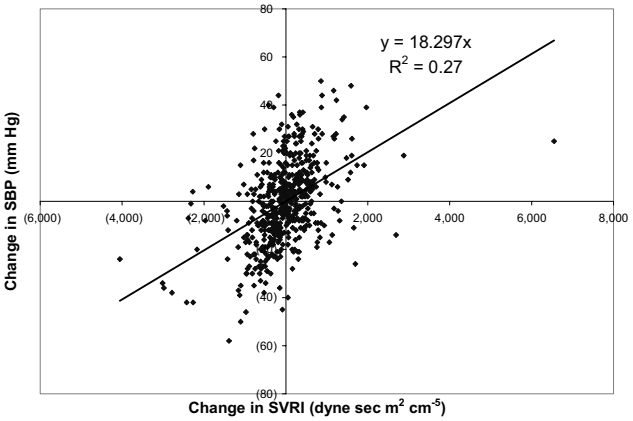

FIG. 2. Scatterplot of change in SBP to change in SVRI ($N = 540$, $P < .001$). Abbreviations as in Fig. 1.

In the 290 visits in which SVRI decreased, CI increased 0.23 ± 0.40 L/min/m^2 and the SBP decreased 6.5 ± 16.4 mm Hg. When SVRI decreased, CI increased in 189 (65.2%) and SBP decreased in 186 (64.1%). In the 250 visits in which SVRI increased, CI decreased 0.24 ± 0.41 L/min/m^2 and SBP increased 6.7 ± 15.4 mm Hg. In visits in which SVRI increased, CI decreased in 176 (70.4%) and systolic BP increased in 168 (67.2%). When SVRI increased, systolic BP actually decreased in 82 (32.8%), and when SVRI decreased, systolic BP actually increased in 104 (35.9%).

In the 540 visit comparisons, systolic BP did not change more than 5 mm Hg from the prior visit in 138 visits (25.6%). In these 138 visits, SVRI increased or decreased by 20% or more in 41 (29.7%). In the 13 visits with a 20% or greater decrease in SVRI, the mean SVRI change was −781 ± 523 dynes · sec · cm^{-5} · m^2. In the 28 visits with a 20% increase in SVRI change, the mean SVRI change was 670 ± 267 dynes · sec · cm^{-5} · m^2.

Table 2 shows the frequency of low SVRI by systolic BP grouping. Vasodilation evidenced by low SVRI was present in only 12 (2.0%) of all comparisons. With systolic BP below 100 mm Hg, only 6 (9.0%) had low SVRI and 57 (85.1%) had normal SVRI. With systolic BP 100 to 119 mm Hg, 185 (75.5%) had high SVRI. In addition, 19 patients with systolic BP ≤90 mm Hg had an average systolic BP of 83.9 ± 5.5 mm Hg, diastolic BP 49.2 ± 5.9 mm Hg, SVRI 1571 ± 254 dynes · sec · cm^{-5} · m^2, and SVR 830 ± 152 dynes × sec × cm^{-5}. Of the 19, 3 (15.7%) had SVRI in the low range and 7 (36.8%) had SVR in the low range.

Discussion

The accuracy of ICG hemodynamics has been validated in patients with CHF.[5,6] Therefore, ICG provides a simple and reliable basis in which to compare systolic BP to a CHF patient's vasoactive status. Increased vascular resistance is a known cause of left ventricular remodeling[8] and treatment with ACEI has been shown stop the progressive ventricular dilatation through a variety of neurohormonal and hemodynamic mechanisms including a reduction in vascular resistance.[9] Although current recommendations for ACEI initiation and up-titration are based on patient tolerance and not systolic BP, most clinicians rely at least in part on systolic BP to make treatment decisions. Tailored therapy with ACEIs has been shown to decrease symptoms in association with improvement in hemodynamic parameters, including reduced wedge pressure and vascular resistance and increased stroke volume. Hemodynamic monitoring with ICG has been used to characterize hemodynamic changes in CHF patients due to ACEI[10] and β-blocker therapy.[11]

The patients with CHF in this study were well managed, with 87% on ACEI or ARB and 79% on β-blockers at baseline. In this population, systolic BP and SVRI were statistically correlated, but the correlation of SVRI and systolic BP categories indicates that measurement of BP in isolation is not a reliable indication of a patient's vasoactive status. In addition, changes in systolic BP to changes in SVRI from serial measurements correlated only marginally better than the absolute comparisons. This indicates that changes in BP are also not a reliable indication of the changes in vasoconstriction or vasodilation that occur due to disease progression or therapeutic interventions.

In visits where systolic BP did not change appreciably (<5 mm Hg), SVRI changed 20% or more in 30% of the cases. A brief glance at the scatter plot of changes in systolic BP versus changes in SVRI reveals surprising increases in SVRI when BP decreased and decreases in SVRI when BP increased. This indicates that changes in systolic BP may be at times misleading and that SVRI may

Table 2. SVRI values by systolic BP category

Systemic Vascular Resistance Index Characteristic (dyne · sec · m^2 · cm^{-5})	Systolic Blood Pressure (mm Hg)			
	All Comparisons $N = 615$ (100%)	<100 $N = 67$ (10.9%)	100–119 $N = 245$ (39.8%)	≥120 $N = 303$ (49.3%)
Low (<1337)	12 (2.0%)	6 (9.0%)	2 (0.8%)	4 (1.3%)
Normal (1337–2483)	381 (62.0%)	57 (85.1%)	185 (75.5%)	139 (45.9%)
High (>2483)	222 (36.1%)	4 (6.0%)	58 (23.7%)	160 (52.8%)

provide additional insight to clinicians seeking more objective rationale for therapeutic decisions and to monitor the hemodynamic effectiveness of treatment. Many clinicians are concerned about initiating or up-titrating vasodilating medications in patients with low systolic BP. However, the vast majority (85.1%) of patients in this study with systolic BP <100 mm Hg had SVRI levels in the normal range, suggesting hemodynamic tolerance for additional afterload reduction. In the patients considered to have extremely low systolic BP of <90 mm Hg, only 15.7% had an SVRI in the low range. In addition, in spite of high use of ACEI or ARB therapy, a significant number (23.7%) of patients with systolic BP between 100 and 119 mm Hg were vasoconstricted based on their high SVRI value.

The use of ACEIs is the mainstay of therapy for patients with CHF, and ACEIs have both neurohormonal and hemodynamic effects. Although the benefits of ACEIs are well known and advancements in prescribing patterns have been made, they are still widely underprescribed.[12] Elderly patients may receive ACEIs at similar rates as other patient categories, but often do so at significantly lower doses.[13] The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial revealed that patients on high dose ACEIs had a 24% reduction in heart failure hospitalizations and a 12% reduction in all-cause mortality and hospital admissions versus those patients on low dose ACEIs.[14] Although these differences appear to be less significant in patients also on β-blockers,[15] it possible that the patients with persistently high SVRI independent of BP level may be most likely to benefit from high dose ACEI therapy.

The use and effectiveness of ACEIs in African-American patients with CHF is less than that in whites.[16] Of interest are the recent results from the African American Heart Failure Trial (A-HeFT) trial, which showed a significant reduction in mortality and hospitalization in African Americans with CHF through the combination therapy of isosorbide dinitrate and hydralizine versus placebo.[17] The nitric oxide protection that these two agents provide is a likely factor in their benefit, but it is also quite possible that these agents lowered vascular resistance, decreasing myocardial oxygen demand, and stimulating ventricular remodeling. Previous studies have shown that hydralazine significantly reduces SVR and increases CO in patients with CHF.[18,19] A recent study using ICG demonstrated that at similar BP levels, African Americans had increased ventricular wall thickness that was mediated by hemodynamic differences including an increased SVR.[20] This may provide some rationale for the hemodynamic benefit of decreasing SVR in African-American patients. It is also possible that any patient with a higher SVR, in spite of active treatment with ACEIs or ARBs, would benefit from more aggressive vasodilator therapy, and we encourage specific investigation of this possibility.

The ARBs are commonly used in HF patients who are intolerant to ACEIs or who are symptomatic in spite of maximal dosing.[21] However, asymptomatic patients with elevated SVRI despite maximally tolerated ACEI dosing may also benefit from the addition of an ARB or other vasodilators through a further reduction in vascular resistance. Although the side effects of ACEI therapy are relative low,[22] clinicians who are more aggressive with ACEI dosing may be concerned about hypotension. Although not investigated in the current study, the presence of normal or elevated SVRI might provide clinicians reason to expect tolerance of higher ACEI dose. Alternately, it is also possible that monitoring for low SVRI may provide additional information that would prevent up-titration or addition of another vasodilating agent in the face of substantial peripheral vasodilation.

The results of this study are limited by its retrospective design and that it involved data collection at a single center. The study did not evaluate changes in medications and their subsequent effect on BP, SVRI, and outcomes. The inclusion of ICG hemodynamics in major multicenter CHF trials of novel agents would allow examination of these and other remaining questions.

In conclusion, this study demonstrates that systolic BP does not reliably reflect absolute and relative changes in vasoactive status in patients with CHF. On the basis of these findings, systolic BP alone is not likely to provide adequate guidance for therapeutic decisions often aimed directly at reducing vascular resistance. The use of ICG-derived SVRI yields additional information about such patients that may provide guidance for clinicians about patient status and tolerance for vasodilating medications.

Large trials provide excellent direction for populations as a whole, but in the individual patient it is common for a degree of uncertainty to exist. The individualization and optimization of therapy through objective markers of patient response has been proposed to improve heart failure therapy in the future.[23] We believe that ICG-based, goal-directed therapy in CHF may provide additional insight that could aid in the effective individualization of therapies in CHF that will improve both short- and long-term outcomes.

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AJH 2005; 18:87S–91S

Case Study

Use of Noninvasive Hemodynamics in Hypertension Management

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Hypertension is a chronic disease that is controlled in the United States in only 34% of those taking antihypertensive medications. Because hypertension is a hemodynamic disorder, the patient's hemodynamic profile before and after medical intervention may assist in the decision and evaluation of ongoing antihypertensive therapy. There are several medication classes used in the management of hypertension and it is challenging at best for the clinician to determine the optimal therapeutic combination of medications for each patient. Physician perceptions and patient symptoms are examples of barriers affecting the management and control of hypertension. Impedance cardiography is a noninvasive monitoring technique that provides reliable and reproducible hemodynamic measurements. Three case studies are presented that illustrate how hemodynamic parameters were used to achieve hypertension control in the outpatient setting. Am J Hypertens 2005;18:87S–91S

Key Words: Noninvasive hemodynamics, antihypertensive therapy, hypertension.

Blood pressure (BP) levels are determined by the interaction of the vascular, renal, hormonal, and sympathetic nervous system mechanisms[1] and hypertension (HTN) occurs when there is abnormal regulation of one or more of these systems. Hypertension affects more than 50 million individuals in the US and it is estimated that only 70% of those affected are aware of their condition.[2] In addition, only 59% of patients with HTN are treated with medications and only 34% achieve target BP $<$140/90 mm Hg.[2] Adequate HTN management requires combination therapy with two or more medications in the majority of patients.[2]

Hypertension is a major risk factor in the development of ischemic heart disease (IHD), heart failure, kidney disease, and cerebrovascular disease leading to stroke.[2] Antihypertensive agents control BP and reduce the morbidity and mortality associated with HTN. Studies have indicated that even small reductions in systolic or diastolic BP result in 30% and 40% reductions in the risk of IHD and fatal stroke, respectively.[3]

The classes of antihypertensive medication include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, calcium channel blockers, and direct vasodilators. Because BP, and specifically mean arterial pressure (MAP), is the product of cardiac output (CO) and systemic vascular resistance (SVR), antihypertensive medications exert their effects by lowering CO, SVR, or both. From a hemodynamic standpoint, the ideal treatment regimen for HTN should lower BP while normalizing CO and SVR. Studies have shown that when medications appropriately target the underlying hemodynamic abnormalities in patients with HTN, BP control will be more effective.[4] The Seventh Report of the Joint National Committee (JNC-7) recommends the use of thiazide-type diuretics in the treatment regimen for the majority of patients. Diuretics are known to reduce CO by reducing the extracellular fluid volume, but also reduce SVR by reducing intracellular sodium and causing vascular smooth muscle cell relaxation.[5]

Other agents that primarily affect CO are β-blockers and the non-dihydropyridine calcium channel blockers, diltiazem and verapamil. Drugs that have their primary action to reduce SVR include ACE inhibitors, angiotensin receptor blockers, α-adrenergic blockers, dihydropyridine calcium channel blockers, centrally acting α_2-agonists, and direct vaosdilators.[5] Dihydropyridine calcium channel blockers dilate the arterial resistance vessels without direct effects on cardiac systolic function or heart rate (HR). These agents act to relax blood vessels and improve myocardial blood flow while reducing workload.[6]

Reasons that HTN is poorly controlled include a suboptimal medical regimen, medication intolerance, physi-

Received October 26, 2004. Accepted November 4, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.11.025

cian perceptions about drug effectiveness, medication samples available in the office, and patient noncompliance.[7,8] Historically, the choices of antihypertensive medications have been empirically based. Yakovlevitch and Black[9] found that the choice of drug regimen was the most important reason for suboptimal BP control in patients with resistant HTN. Berlowitz et al[10] concluded in their study that those patients who received more aggressive therapy had better BP control. Regardless of the reasons, poor control of HTN increases drug costs and frequency of physician visits. Aggressive treatment based on objective data has the potential to reduce these costs and thus resource utilization.[10,11]

Hypertension is a heterogeneous hemodynamic disorder and knowledge of the hemodynamic effects of medications in a particular patient can facilitate appropriate antihypertensive drug initiation and titration. Impedance cardiography (ICG) is a noninvasive technique that uses bioimpedance to determine hemodynamic measurements. The ICG provides the clinician with information that could only previously be obtained in the critical care unit of a hospital using a pulmonary artery catheter (PAC). In contrast, ICG allows the clinician access to reliable hemodynamic information in the outpatient as well as the hospital setting. The ICG aids in identifying the hemodynamic components of HTN, allowing initiation and titration of medications that act more effectively and result in fewer side effects. In studies using ICG, HTN specialists and generalists in the office setting have demonstrated improved BP control rates approaching 60% when ICG information is included in treatment decisions.[12,13] Three case studies are presented that demonstrate how ICG parameters may be used to guide the prescription of antihypertensive agents.

Case Studies

Case One: Two-Medication Regime

A 73-year-old white woman with a known history of HTN for 3.5 years presented to the physician's office for BP management. The primary diagnosis was HTN with secondary diagnoses of gastroesophageal reflux disease (GERD), osteoporosis, tremor, unspecified inflammatory polyarthropathy, and hyperlipidemia. Of significance is a previous history of a transient ischemic attack (TIA) 2 years earlier. Her symptoms at that time included sudden, temporary visual loss in one eye. Recent laboratory tests demonstrated a normal creatinine level of 0.8 mg/dL and total cholesterol was 174 mg.

Upon physical examination, her BP was 167/88 mm Hg, HR 62 beats/min, height 4 ft 11 inches, and weight was 139 lbs. She was taking perindopril 4 mg daily for HTN with her other medications of methotrexate, six tablets a week, celecoxib, omeprazole, folic acid, and calcium with vitamin D daily. She presented with symptoms of dizziness and stated she did not want to increase the dose of perindopril and preferred a change to a different antihypertensive medication. The ICG was performed with baseline and postinterventional parameters listed in Table 1. Cardiac index (CI) was 2.0 L/min/m^2, stroke index (SI) 32 mL/beat/m^2, SVR index was 4364 dynes · sec · cm^{-5} · m^2. and thoracic fluid content (TFC) was 23 $kOhm^{-1}$. Consistent with the patient's wishes, perindopril was discontinued and she was prescribed a single pill consisting of two antihypertensive compounds (amlodipine 5 mg/benazepril 10 mg) daily.

Table 1. HTN Management on two medications—amlodipine and benazepril

Parameter	Baseline	Post Intervention	
Heart rate	62	64	69
BP (mm Hg)	167/88	143/72	120/59
MAP (mm Hg)	115	95	77
CI (L/min/m^2)	2.0	1.7	2.3
CO (L/min)	3.1	2.7	3.5
SI (ml/beat/m^2)	32	27	33
SVRI (dyne · s · cm^{-5} · m^2)	4364	4094	2458
SVR (dyne · s · cm^{-5})	2779	2624	1617
ACI (/100/s^2)	46	45	64
VI (/1000/s)	39	29	46
TFC ($kOhm^{-1}$)	23.0	25.4	22.7

ACI = acceleration index; BP = blood pressure; CI = cardiac index; CO = cardiac output; MAP = mean arterial pressure; SI = stroke index; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; TFC = thoracic fluid content; VI = velocity index.

Approximately 1 month later, she was seen in the office with the symptoms of dizziness fully resolved and had no new symptoms. Her BP was143/73 mm Hg, much improved from pretreatment, and HR was 64 beats/min. Weight was 141 lbs, a 2-lb increase from previous visit and CI was 1.7 L/min/m^2, a slight reduction from previous visit, and SVRI was 4094 dynes · sec · cm^{-5} · m^2, still quite elevated. The TFC value increased to 25.4 $kOhm^{-1}$. The clinician doubled the dose of medication of amlodipine to 10 mg and benazepril to 20 mg daily.

The patient returned 6 weeks later without symptoms and BP was 120/59 mm Hg, HR 69 beats/min. She lost 3 lbs from the previous visit, weighing 138 lbs, and TFC had decreased to 22.7 $kOhm^{-1}$. The CI had now increased to above pretreatment level at 2.3 L/min/ m^2 and the SVRI was significantly reduced to 2458 dynes · sec · cm^{-5} · m^2. The patient was instructed to remain on this current medication regime and scheduled to return in 6 months.

Discussion

As noted, BP is the product of SVR and CO. This elderly patient presented with symptoms of dizziness and was found to have a markedly elevated SVRI and low CI. Elderly hypertensive patients tend to have high afterload as reflected by elevated SVRI. The hemodynamic findings

of elevated SVRI and reduced CI often reflect increased vascular and ventricular stiffness, altered ventricular contractility.[14] The renin-angiotensin-aldosterone system (RAAS) plays an important role in BP control. The goal of therapy is to decrease SVRI without compromising CO. The ACE inhibitors reduce BP through reduction in the formation of angiotensin II—a powerful vasoconstrictor that leads to salt retention and ventricular remodeling with hypertrophy. The ACE inhibitors decrease SVRI and promote natriuresis without a direct effect on CI or HR.[15] The TFC value for the patient trended upward from 23.0 to 25.4 $kOhm^{-1}$, but once dosages became therapeutic, hemodynamic balance was achieved through a reduction in SVR and increase in CI and subsequent reduction in TFC. The addition of a dihydropyridine calcium channel blocker to the ACE inhibitor further enhanced the desired vasodilatory effects.

In this case, ICG helped guide appropriate changes in medications. Physicians perceive that diuretics are less effective than other agents and β-blockers, calcium antagonists, and ACE inhibitors are less well tolerated due to side effects.[16] The patient's symptoms of dizziness were not due to excessive vasodilation and the hemodynamic information resulted in use of a different ACE inhibitor in combination with a second agent that lowers SVRI. At the subsequent visit, the hemodynamic data suggested that it was appropriate to double the calcium channel blocker in view of the persistently high afterload.[17] Findings of high SVRI in elderly patients with low or normal TFC and low CI may suggest the use of combination therapy with a calcium channel blocker and ACE inhibitor. Diuretics may not be advantageous in the elderly due to the susceptibility for dehydration as compared to younger age groups.[18] The ACE inhibitors and calcium channel blockers act as vasodilators, improve coronary and renal blood flow, and are useful in the reduction of hypertensive complications.

Results from the ALLHAT study focused on three different medication classes and their effects on the reduction of HTN complications. Both calcium channel blocking agents and ACE inhibitors reduced cardiovascular events including stroke.[19] In this patient's case, ICG identified a hemodynamic profile where the initiation and titration of the combination calcium channel blocker and ACE inhibitor might be expected to improve the hemodynamic status. The ICG-guided therapy resulted in BP control to goal without side effects and in three physician visits. The patient's perception that perindopril was causing side effects was addressed and yet the hemodynamic information provided the confidence to initiate a different agent within the same class. In so doing, this approach not only targeted the antihypertensive therapy to the hemodynamic abnormalities, but it helped reduce the risk of nonadherence to prescribed medications.[20] Achieving target BP levels with well-tolerated medications allowed for less frequent future visits and surveillance.

Table 2. HTN Management on three medications—HCTZ, atenolol, and lisinopril

Parameter	Baseline	Postintervention
Heart rate	59	56
BP (mm Hg)	166/94	132/70
MAP (mm Hg)	120	91
CI ($L/min/m^2$)	2.6	2.7
CO (L/min)	4.9	5.1
SI	44	48
SVRI (dyne · s · cm^{-5} · m^2)	3503	2506
SVR (dyne · s · cm^{-5})	1853	1325
ACI ($/100/s^2$)	47	70
VI (/1000/s)	36	50
TFC ($kOhm^{-1}$)	27.2	26.3

Abbreviations as in Table 1.

Case Two: Three-Medication Regime

A 68-year-old white man presented to the office with a 2-year history of HTN and chronic obstructive pulmonary disease (COPD). His only symptom at the time of the office visit was his usual dyspnea. The patient had been taking hydrochlorothiazide HCTZ 25 mg and atenolol 100 mg daily. His only additional medication was an inhaler that included the combination drugs ipratropium bromide and albuterol, taking two puffs four times a day. At physical examination, his height was 5 ft 9 inches, weight 163 lbs. His BP was 166/94 mm Hg with a HR of 59 beats/min. His creatinine level was normal at 1.1 mg/dL. The electrocardiogram revealed left atrial enlargement but was otherwise unremarkable. The ICG measurements at baseline and postintervention are listed in Table 2. At his first visit, CI was 2.6 $L/min/m^2$ with a high SVRI of 3503 dynes · sec · cm^{-5} · m^2. The TFC was 27.2 $kOhm^{-1}$. The clinician added lisinopril 20 mg once a day in addition to his regularly prescribed regimen.

The patient returned for an evaluation approximately 4 weeks later and denied any new symptoms. The BP was now 132/70 mm Hg, HR was 56 beats/min, CI was 2.7 $L/min/m^2$ and SVRI demonstrated a reduction to 2506 dynes · sec · cm^{-5} · m^2. His weight was 162 lbs and TFC 26.3 $kOhm^{-1}$. On the basis of the stability of CI and TFC with significant improvement in BP and SVRI, this new medication regime was continued and he was scheduled to return for an evaluation in 1 month for consideration of reducing his β-blocker therapy.

Discussion

This case illustrates a common situation in patients with both COPD and HTN who may be on moderate doses of a β-blocker and taking albuterol, a β_2-adrenergic agonist. Atenolol is a cardioselective β_1 antagonist; however, at higher doses it may have β_2 receptor-blocking effects. The β_1 receptors are responsible for effects on HR and con-

tractility, whereas β_2 receptors act peripherally to relax smooth muscle in arteries and bronchioles.[21] This patient's HR was below 60 beats/min, suggesting significant β blockade. The ICG measurements were important in determining drug choice. The decision to initiate an ACE inhibitor, lisinopril, was the result of the elevated SVRI and the need to reduce SVRI without compromising CO. Because ACE inhibitors have both vasodilating and natriuretic actions, the patient did not experience fluid retention as evidenced by the stable TFC value. The CI increased slightly with increases in acceleration index (ACI) and velocity index (VI), measures that reflect improved cardiac performance that can accompany arterial vasodilation. The ACE inhibitors are valuable antihypertensive agents due to their impact on cardiovascular protection. Once BP control has been achieved, hemodynamic measurements will be helpful to monitor the effects of future reductions in the patient's β-blocker.

Case Three: Five-Medication Regime

The third case study is a 67-year-old white woman with a history of HTN for many years, reaching measurements up to 210/110 mm Hg. In addition to her HTN, she had osteoporosis and hyperlipidemia. She presented without symptoms, experiencing recent stress and anxiety related to elevated BP levels at home. Physical findings included a height of 5 ft, 2 inches, and weight of 133 lbs. Her BP was 206/103 mm Hg and HR was 62 beats/min. The examination was pertinent for an increase in A2 and presence of an S4 gallop without other findings. Her antihypertensiove medications included a combination of triamterene/HCTZ (37.5/25 mg) daily, atenolol 100 mg, doxazosin 8 mg, lisinopril 20 mg each daily, and clonidine 0.1 mg as need when systolic BP at home was more than 170 mm Hg. Her other medications included alendronate 70 mg a week and atorvastatin 10 mg at bedtime. Previous evaluation included a noninvasive renal artery study that was unremarkable, electrolytes, creatinine, blood urea nitrogen (BUN) levels, and a 24-h urine collection for catecholamines, vanillylmandelic acid (VMA), and metanephrines. All studies were normal except for the serum potassium of 2.7 mEq/L. The ICG was performed and baseline and postinterventional measurements are presented in Table 3. At her initial visit, the CI was 2.0 L/min and SVRI was 5478 dynes · sec · cm^{-5} · m^2. The TFC was 26.9 $kOhm^{-1}$. In view of the significant elevation of SVRI and low CI, atenolol was decreased to 50 mg daily, lisinopril increased to 20 mg twice a day, clonidine started on regular dosing at 0.1 mg twice a day, and amlodipine was initiated at 10 mg daily. Doxazosin was decreased to 4 mg daily and due to the low potassium level, potassium replacement was started at 20 mEq three times a day for 5 days then twice a day. Two weeks after her initial visit, she called the office with symptoms of sedation and dry mouth and was seen by the office nurse with continued BP elevation. Her clonidine was stopped due to her side effects and amlodipine was increased to 10 mg twice a day. She returned to the office 1 month later and her BP was 143/68 mm Hg. She felt well and multiple home BP readings show that the BP ranged between 120 and 140/65 mm Hg, with rare episodes above 140/80 mm Hg. Hemodynamic parameters showed improvement in CI to 4.1 L/min with a reduction in SVRI to 1816 dynes · sec · cm^{-5} · m^2. Because she was much improved on the multiple medication regimen, the decision was made to continue her current medications and re-evaluate the patient in 6 weeks. If BP remains controlled, consideration to the discontinuation of doxazosin will be given.

Table 3. HTN management on five medications—triameterene/HCTZ, atenolol, doxazosin, lisinopril, and amlodipine

Parameter	Baseline	Postintervention
Heart rate	62	74
BP (mm Hg)	206/103	143/68
MAP (mm Hg)	144	98
CI (L/min/m^2)	2.0	4.1
CO (L/min)	3.2	6.4
SI	32	55
SVRI (dyne · s · cm^{-5} · m^2)	5178	1816
SVR (dyne · s · cm^{-5})	3424	1149
ACI (/100/s^2)	73	121
VI (/1000/s)	40	93
TFC ($kOhm^{-1}$)	26.9	26

Abbreviations as in Table 1.

Discussion

This woman presented with uncontrolled BP on five antihypertensive medications. She was on atenolol, a drug with β-adrenergic receptor antagonist that reduces CI and may increase SVR. Clonidine affects the α-adenergic receptors near the vasomotor center of the nervous system. This medication will reduce BP through modest reductions in CI and HR and in long-term therapy reduces SVRI. Doxazosin is an α-blocker that reduces BP through a reduction in SVRI without affecting CI.[22] The patient's hemodynamic profile at initial visit revealed an extremely elevated SVRI and decreased CI. The ACE inhibitor and calcium channel blocker medication classes lower SVRI without causing a reduction in CI. The information obtained using ICG was important in the decision to increase the ACE inhibitor and add a calcium channel blocking agent while reducing atenolol and doxazosin. Concern over potential side effects may, in certain instances, act as a barrier to the up-titration of antihypertensive medications. In this case, ICG-derived hemodynamic data assisted the clinician by suggesting that the patient might tolerate higher doses of lisinopril as well as the addition of amlodipine. With ICG-guided therapy, CI increased and SVRI was reduced to achieve better cardiac performance and normotension. The vasodilation and improved CO that

resulted may have contributed to the stable fluid status without increase in diuretic dose.

Conclusions

The ICG helps clinicians identify the specific mechanisms of high BP in a given patient and tailor a pharmacologic regimen to address the underlying hemodynamic status. This individualized approach to therapy may lead to fewer side effects from medications and reduce the number of office visits required to achieve BP control. The cases presented demonstrate that ICG provides useful objective data that aid decision-making in patients with HTN.

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