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.

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 and has been reviewed extensively by leaders in the field.

The hemodynamic components of BP, CO, and SVR, and other related parameters such as arterial compliance provide insight into mechanisms of hypertension 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-
Hypertension substantially increases the incidence of cardiovascular events, especially the risk of stroke. Wilking et al., 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
prospective studies and 1 million patients, Lewington et al 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.

The financial implications of hypertension and hypertension management are substantial. 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
expensive—costing businesses an average of $392 per eligible employee per year. 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 3. Trends in awareness, treatment, and control of high blood pressure in adults with hypertension 18 to 74 years of age

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td>51</td>
<td>73</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Treatment</td>
<td>31</td>
<td>55</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>29</td>
<td>27</td>
<td>34</td>
</tr>
</tbody>
</table>

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

### Table 4. Direct and indirect costs attributable to hypertension

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

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.
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 al24 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 al30 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
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; 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. 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

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**Table 5.** Impedance cardiography variables

<table>
<thead>
<tr>
<th>Impedance Cardiography Variable</th>
<th>Units</th>
<th>Measurement/Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>mL</td>
<td>VI × LVET × VEPT (Z MARC algorithm)</td>
</tr>
<tr>
<td>Stroke index</td>
<td>mL/m²</td>
<td>SV/BSA</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>L/min</td>
<td>SV × HR</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>L/min/m²</td>
<td>CO/BSA</td>
</tr>
<tr>
<td>Resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>dyne · sec · cm⁻⁵</td>
<td>[(MAP - CVP)/CO] × 80</td>
</tr>
<tr>
<td>Systemic vascular resistance index</td>
<td>dyne · sec · cm⁻⁵ · m²</td>
<td>[(MAP - CVP)/CI] × 80</td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity index</td>
<td>/1000/sec</td>
<td>1000 × first-time derivative of ΔZmax/baseline impedance</td>
</tr>
<tr>
<td>Acceleration index</td>
<td>/100/sec²</td>
<td>100 × second-time derivative of ΔZmax/baseline impedance</td>
</tr>
<tr>
<td>Pre ejection period</td>
<td>msec</td>
<td>ECG Q wave to aortic valve opening</td>
</tr>
<tr>
<td>Left ventricular ejection time</td>
<td>msec</td>
<td>Aortic valve opening to closing</td>
</tr>
<tr>
<td>Systolic time ratio</td>
<td></td>
<td>PEP/LVET</td>
</tr>
<tr>
<td>Cardiac work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cardiac work index</td>
<td>kg · m/m²</td>
<td>(MAP - PCWP) × CI × 0.0144</td>
</tr>
<tr>
<td>Fluid status</td>
<td>/kOhm</td>
<td>1000 × 1/baseline impedance</td>
</tr>
<tr>
<td>Thoracic fluid content</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 capillary 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.

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**Table 6.** Validation studies of impedance cardiography (ICG)

<table>
<thead>
<tr>
<th>Population</th>
<th>AuthorRef</th>
<th>Parameter</th>
<th>Comparison</th>
<th>r Value</th>
<th>Bias</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF in ICU</td>
<td>Albert et al²⁵</td>
<td>CO</td>
<td>ICG-TD</td>
<td>0.89</td>
<td>0.08</td>
<td>1.38</td>
</tr>
<tr>
<td>HF in catheterization</td>
<td>Drazner et al²⁶</td>
<td>CO</td>
<td>ICG-Fick</td>
<td>0.73</td>
<td>0.74</td>
<td>1.1</td>
</tr>
<tr>
<td>laboratory</td>
<td></td>
<td></td>
<td>TD-Fick</td>
<td>0.81</td>
<td>0.75</td>
<td>0.95</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Ziegler et al²⁷</td>
<td>CO</td>
<td>ICG-TD</td>
<td>0.76</td>
<td>0.03</td>
<td>1.1</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>Sageman et al²⁸</td>
<td>CI</td>
<td>ICG-TD</td>
<td>0.89</td>
<td>-0.45</td>
<td>1.2</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>Van De Water et al²⁴</td>
<td>CO</td>
<td>ICG-TD</td>
<td>0.81</td>
<td>-0.17</td>
<td>1.09</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Yung et al²⁹</td>
<td>CO</td>
<td>ICG-Fick</td>
<td>0.84</td>
<td>-0.24</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TD-Fick</td>
<td>0.89</td>
<td>0.19</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICG-TD</td>
<td>0.80</td>
<td>-0.43</td>
<td>1.01</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass surgery; CO = cardiac output; HF = heart failure; ICU = intensive care unit. TD = thermodilution;
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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,\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{43}

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Correlation (r value)</th>
<th>SD (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD 2 v TD 1</td>
<td>0.83</td>
<td>1.02</td>
</tr>
<tr>
<td>TD 3 v TD 2</td>
<td>0.84</td>
<td>1.01</td>
</tr>
<tr>
<td>TD 3 v TD 1</td>
<td>0.83</td>
<td>1.07</td>
</tr>
<tr>
<td>ICG 2 v ICG 1</td>
<td>0.97</td>
<td>0.44</td>
</tr>
<tr>
<td>ICG 3 v ICG 2</td>
<td>0.98</td>
<td>0.39</td>
</tr>
<tr>
<td>ICG 3 v ICG 1</td>
<td>0.97</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Adapted from Van De Water et al.\textsuperscript{24}
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. 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. Others have shown that the earliest hemodynamic abnormalities may be changes in arterial compliance. 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. 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. 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. 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. 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. Yu et al. studied hemodynamic parameters in patients with different mood states. Findings of correlation of CO and SVR—but not SBP, DBP, or

**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. 

**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.
Hypertension as a Hemodynamic Disease

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

<table>
<thead>
<tr>
<th>Hazard rate, CV event</th>
<th>Hazard rate, mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP</td>
<td>1.46 (0.91–2.35)†</td>
</tr>
<tr>
<td>PP to SVIR</td>
<td>1.79 (1.15–2.80)‡</td>
</tr>
</tbody>
</table>

CV = cardiovascular.

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

*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* 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. 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. 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 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/m²) 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 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., 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 arterial compliance (ie, hypertrophy and remodeling) than did BP levels alone.
Gender has long been known to affect prognosis in patients with hypertension. In 1913, Janeway 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 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. 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, 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. For example, Vakili et al 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, 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 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.

Additional structural changes occurring 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. 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 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. Mathew et al 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, 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 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 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.
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. 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. 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. 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 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 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), 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 hypertension was controlled, 63% were on two or more medications, indicating that BP control required combination therapy in the majority of cases. Yakovlevitch and Black 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, 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. 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. 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. 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 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 evaluated other hemodynamic parameters in untreated patients with hypertension. They found impairment of cardiac performance with decreased indices of contractility and evidence for increased water content of the lungs or thoracic wall tissues.

Thoracic fluid content, the reciprocal of total thoracic

<table>
<thead>
<tr>
<th>Effect</th>
<th>SVR</th>
<th>CO</th>
<th>Stroke volume</th>
<th>Heart rate</th>
<th>Intravascular volume</th>
<th>LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>↓ or NC</td>
<td>➩ or NC</td>
<td>➩ or NC</td>
<td>↑ or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
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<tr>
<td>β-blockers</td>
<td>➩ or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
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<td>β- and β-blockers</td>
<td>➩ or NC</td>
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<td>NC or NC</td>
<td>NC or NC</td>
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<tr>
<td>Calcium channel blockers</td>
<td>➩ or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
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<tr>
<td>ACE inhibitors</td>
<td>➩ or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
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<tr>
<td>Central α-agonists</td>
<td>➩ or NC</td>
<td>NC or NC</td>
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<tr>
<td>Direct vasodilators</td>
<td>➩ or NC</td>
<td>NC or NC</td>
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<tr>
<td>with ISA</td>
<td>➩ or NC</td>
<td>NC or NC</td>
<td>NC or NC</td>
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</tr>
</tbody>
</table>

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

Adapted from Houston.
impedance, is strongly correlated with amount of fluid in the chest cavity, whether intravascular or extravascular. In patients undergoing thoracentesis, Petersen et al. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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. studied a cohort of patients in the primary care office setting with drug-resistant hypertension, defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg during treatment with two antihypertensive
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/H110060.7 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 al105 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 achievement.
systolic time ratio, may be the initial signs of the development of LV dysfunction.\textsuperscript{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.\textsuperscript{108} Endothelial dysfunction, as measured by reduced flow-mediated arterial dilation, is associated with abnormal hemodynamic measures, including elevated SVR.\textsuperscript{109} In the HOPE study,\textsuperscript{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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