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## Noninvasive Hemodynamic Measurements An Important Advance in Individualizing Drug Therapies for Hypertensive Patients

John M. Flack

It has been well established that effective blood pressure (BP) lowering, using various antihypertensive agents with different mechanisms of action, lowers the risk for cardiovascular morbidity and mortality.<sup>1-4</sup> However, when hypertensive populations are partitioned into subgroups by race, sex, geography, and age, differences in BP responses to single antihypertensive drugs emerge, albeit at the group level, that have been used to guide therapy for individuals within these contrasted groups.<sup>1,5,6</sup> With respect to race, perhaps the most widely used group characteristic used to guide individual therapy, we<sup>5</sup> and Sehgal<sup>6</sup> have argued that the observed racial differences in BP response overlap to such a large degree that, by far, the greatest source of variation in BP response is within rather than between groups. This observation renders the use of group characteristics as grossly suboptimal criterion on which to base therapy for all individuals of a group. The inaccuracy of blanket extrapolation of group characteristics to predict BP responses for individuals is also likely to be true for traits such as geographic residence, age, and sex.

Thus, the findings reported by Smith et al<sup>7</sup> in this issue of *Hypertension* were very encouraging. These investigators showed that consideration of hemodynamic parameters, as determined noninvasively by impedance cardiography (IC) (BioZ, Cardiodynamics), in the selection of antihypertensive therapy in primary care practice settings improved rates of BP control and normalization of selected hemodynamic parameters in drug-treated hypertensives with BP >140/90 mm Hg. They used sequential measurement of hemodynamic parameters to guide the selection of antihypertensive drug therapy for individuals irrespective of immutable group identity.

Although other physiological parameters that vary at the level of the individual are potentially available, the use of hemodynamic parameters is intuitively appealing, because BP, per se, represents the confluence of multiple hemodynamic parameters, such as systemic vascular resistance, cardiac output, and intravascular volume. Indeed, they were able to show higher rates of BP control and simultaneous

normalization of BP along with systemic vascular volume index (SVRI) and cardiac index (CI) in participants randomized to the therapeutic decision making guided by the results of IC relative to standard care. Accordingly, in the IC group, vasodilators (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and calcium antagonists) were used more often when SVRI was elevated than in the standard care group. Likewise,  $\beta$  blockade was less often used when CI was low or normal in the IC compared with the standard care group.

The results of this study extend the observations by Taler et al,<sup>8</sup> showing that IC-aided antihypertensive therapeutic decisions improved BP control in resistant hypertensives in a hypertension specialty practice. Interestingly, in the current study, there were similar proportions of thiazide diuretic users in the IC and standard care groups, and, although higher doses were used in the latter group, it resulted in less impressive BP lowering. However, in the *Hypertension* specialty clinic report by Taler et al,<sup>8</sup> higher doses of diuretics (not a greater prevalence of use) were prescribed for the IC-hemodynamic management group leading to greater BP lowering than in the hypertension specialist standard care group.

The current study reported no difference between the 2 randomized treatment arms in terms of diuretic use. This occurred, at least in part, because practitioners did not follow the suggested treatment algorithm to add or increase diuretics when thoracic fluid content did not decrease in response to diuretic initiation or dose escalation. It is, therefore, likely that the magnitude of BP lowering in the IC group is an underestimate of the maximum attainable BP lowering that could have been obtained if the treatment algorithm had been more closely followed. The data presented do not invalidate the importance of the prevention or, at least, limitation of intravascular expansion by the use of diuretics (and dietary sodium restriction) in refractory hypertensive patients on complex (>2) drug regimens.

There are considerable clinical implications of this study. By using individualized hemodynamic measures on patients at multiple visits, it was possible to improve BP control, as well as to more often normalize SVRI and CI. These favorable outcomes occurred even though the practitioners did not comply equally with all of the suggested therapeutic decisions in the study treatment algorithm. The difference in BP (6/7 mm Hg lower in the cardiography impedance group), if sustained over the long term, would also lead to significantly lower rates of cardiovascular morbidity and mortality. These data have considerable relevance to actual primary care clinical practice sites, because the data were derived from

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such practice locations. The concern about the portability of these findings into routine clinical practice is, therefore, minimal.

Without question, there is some linkage between abnormal hemodynamic parameters and elevated BP. For example, higher levels of SVRI can track higher levels of BP. In turn, when BP falls, SVRI also tends to fall if elevated at baseline. However, what therapeutic decision should be made when BP normalizes but SVRI, CI, and/or other hemodynamic parameters have, perhaps, improved but remain outside the normal range? An important question arises as to whether abnormal hemodynamic parameters, independent of BP, should also be targeted for normalization. This cannot be answered until future studies link improvements in pressure-related clinical outcomes or, at the very least, in clinically relevant measures of target-organ damage, such as left ventricular mass and function and/or microalbuminuria, to normalization of hemodynamic parameters independent of BP normalization.

This study offers the practitioner a tool that provides validated, noninvasive measures that can vary even within an individual over time to assist in the selection of optimal therapeutic choices for lowering BP. It is likely that IC, along with emerging molecular genetic markers and other complementary noninvasive hemodynamic measurements,<sup>9</sup> will be used in combination to optimize pharmacological BP lowering and target-organ protection while minimizing side effects and adverse events.

Although this study provides important information to the medical and scientific communities, a number of questions remain to be answered. Does use of IC to pharmacologically target major hemodynamic derangements lead to more rapid control of BP? Additionally, once goal BP has been attained, does BP persist at goal or lower levels more often with IC-aided therapeutic decisions? How will therapeutic decision making be undertaken in hypertensive patients with multiple hemodynamic abnormalities? Also, will these hemodynamic markers ultimately be shown to merit pharmacological targeting even after BP has been normalized? Finally, how quickly will practicing physicians (and third party payors, treatment guideline writers) accept this new, noninvasive technology in the battle against hypertension, our resilient and tough old nemesis?

It is very encouraging to see a new, valid technology available in the practitioner's office that can be used to improve the likelihood of successful BP control by improving therapeutic decision making. This, I believe, will be one of several advances in the coming years that will truly usher in the era of individualized hypertension management.

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