Rate-Limiting Step
Can Different Effects of Antihypertensives on Central Blood Pressure Be Translated Into Outcomes?

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See related article, pp 1122–1128

Whether individual classes of antihypertensives have specific benefits for prevention of cardiovascular disease, over and above blood pressure reduction, has been the subject of long and often heated debate. Meta-analyses of many studies, involving thousands of patients, suggest minimal or no additional benefit from specific antihypertensive regimens.\(^1\)\(^2\) However, this view has been challenged recently following evidence that β-blockers may be less efficacious than other agents.\(^3\) Importantly, this evidence is based on comparisons of blood pressure measured at the brachial artery, which may not accurately reflect pressure in the aorta. Indeed, pressure varies throughout the arterial system because of changes in vessel compliance and wave reflections. Brachial blood pressure is considerably higher than aortic pressure in young individuals, a phenomenon known as pulse pressure amplification, which declines with age. The degree of pressure amplification also varies considerably between individuals and depends on a number of factors, such as heart rate, height, and sex. However, the heart, brain, and kidneys are exposed to aortic (or central) pressure rather than brachial pressure. Central blood pressure, either assessed in the carotid artery or estimated from radial artery waveforms using applanation tonometry and a transfer function, is more closely correlated with the change in central rather than peripheral blood pressure.\(^4\)\(^5\) Accumulating data also suggest that antihypertensives may have differential effects on central pressure, providing an explanation for the "benefits beyond blood pressure reduction" paradox.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated superiority in cardiovascular outcomes from primary treatment of hypertension with calcium-channel blockers (amlodipine) compared with β-blockers (atenolol).\(^6\) The results of the Conduit Artery Function Evaluation substudy of ASCOT provided one potential mechanism for these outcome differences, because central aortic pressure was substantially lower in the calcium channel blocker compared with the β-blocker treatment arm, despite only small differences in brachial blood pressure.\(^7\) A number of other studies, before and after Conduit Artery Function Evaluation, have reported similar findings with β-blockade when compared against a range of other agents.\(^8\)\(^9\) In this respect, β-blockers appear to stand out from other standard antihypertensive agents in reducing aortic pressure less for a given fall in brachial pressure. However, β-blockers vary considerably in their chemical and pharmacodynamics properties and also appear to differ in their relative effects on central and peripheral pressure. Atenolol, used in the majority of outcome studies, is relatively selective for β-1 adrenoceptors and has little direct effect of peripheral vascular tone. Although nebivolol is more β-1 selective, it also has substantial vasodilating properties, because of endothelial nitric oxide production,\(^10\) and previous data indicate that it reduces central systolic pressure more than atenolol despite similar reductions in peripheral blood pressure.\(^11\) This “preferential” effect on central pressure is also seen with other nitrovasodilators, and small doses of nitrate may reduce central systolic pressure without lowering peripheral blood pressure measurably.\(^12\) The likely mechanism is reduced wave reflection because of dilatation of the small preresistance arteries, which improves impedance mismatch and moves the reflectance site distally.

In this issue of Hypertension, a carefully conducted study by Kampus et al\(^13\) brings new evidence to this debate. In this randomized, double-blind study of 80 treatment-naive hypertensive patients followed for a year, the authors compare the effects of nebivolol and the β-1 selective agent metoprolol on several hemodynamic parameters. Both drugs reduced heart rate and brachial blood pressure to the same extent, but there was a fall in brachial pulse pressure and central blood pressure only in the nebivolol group. For the first time, this study suggests that the fall in central blood pressure may translate to a reduction in target organ damage, with a reduction in echocardiographic markers of left ventricular wall thickness observed only in the nebivolol arm. In addition, the changes in left ventricular parameters were more closely correlated with the change in central rather than peripheral blood pressure.

The limitations of this study need some consideration. Metoprolol has a shorter duration of action than nebivolol, so once-daily dosing may have led to inferior blood pressure control over 24 hours. There were also nonsignificant trends to older age, higher blood pressure, and greater left ventricular dimensions at baseline in the nebivolol-treated group. Finally, a higher percentage of people in the nebivolol group received a second agent (hydrochlorothiazide) to meet study blood pressure targets. These factors taken together may have contributed to the results, but nonetheless this study under-
lines the importance of understanding the effects of antihypertensive treatments on central hemodynamics.

Taking the results of this study forward will not be easy, but we believe that sufficient evidence now exists to support a large outcome study of nebivolol in hypertension. In such a trial it will be vital, although challenging, to ensure that there is a comparator agent that provides a matched reduction in brachial blood pressure, because interpretation will otherwise be impossible. Similar trials are also warranted with other nitrovasodilators such as isosorbide mononitrate, which lowers central and peripheral blood pressure but has never been subject to outcome trials. The data from such studies will be invaluable in establishing whether central pressure estimation is useful in routine clinical practice. However, the real paradigm shift will only come if and when studies demonstrate that selective reduction in central pressure reduces cardiovascular events.

Disclosures
None.

References
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Hypertension. 2011;57:1047-1048; originally published online May 2, 2011; doi: 10.1161/HYPERTENSIONAHA.111.172908

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/57/6/1047

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