Near everything that modern practicing clinicians know about hypertension and its treatment is based on simple noninvasive measurement of brachial artery blood pressure. As the study by Williams and colleagues illustrates, however, additional knowledge of pulse-wave characteristics may be important in the future to fully assess optimal cardiovascular drug therapy.

The study of pulse-wave characteristics is far older than the study of absolute pressure values, dating back thousands of years to the Chinese masters who used their fingertips and their powers of observation to associate “hardening of the pulse” with adverse outcomes in people who ingested too much salt. These qualitative observations were less well developed in Western medicine, but as early as the 1870s, the sphygmocardiogram was developed as a reproduction of a peripheral pulse wave on a rotating drum via a tonometer attached to a levered stylus. Morrell and other early investigators were clearly able to differentiate the effects of nitrovasodilators from digitalis using this early equipment, but interpretations remained largely qualitative. Within a few decades, the development of sphygmomanometry by Korotkova and Rivac-Rocci allowed quantitation of brachial cuff blood pressures, and the more descriptive methods largely disappeared.

Indeed, brachial cuff blood pressure has become an enduring clinical variable. Actuarial data from the life insurance industry and subsequent prospective observational data have clearly shown that hypertension, or elevated cuff blood pressure, is closely related to many forms of cardiovascular disease. Most recently, a very large meta-analysis by the Prospective Studies Collaborators that involved almost 1 million persons enrolled in 61 prospective observational studies demonstrated a log-linear relationship between cuff systolic or diastolic blood pressure and mortality due to ischemic heart disease or stroke in middle-aged and elderly adults who did not have overt vascular disease at the beginning of the observation period.

Abundant clinical trial data indicate that lowering cuff blood pressure with antihypertensive drugs effectively reduces the risk of a variety of cardiovascular outcomes, including cardiovascular death, as well as total mortality. Regarding the benefits of individual drug classes, a meta-analysis of data by the Blood Pressure Lowering Treatment Trialists’ Collaboration from randomized, controlled trials did not show significant differences in total major cardiovascular events among regimens based on angiotensin-converting enzyme inhibitors, calcium antagonists, diuretics, or β-blockers, as long as similar cuff blood pressure reductions were achieved, although there were some differences in cause-specific outcomes. When specifically tested in randomized trials, however, β-blockers have fallen short of other therapies in preventing hypertensive complications. The Losartan Intervention For Endpoint reduction (LIFE) and the Anglo-Scandinavian Cardiovascular Outcomes (ASCOT) trials compared active treatments based on an angiotensin receptor blocker (losartan with or without a diuretic) or a calcium antagonist (amlodipine with or without perindopril) with treatment based on a β-blocker (atenolol). Brachial cuff blood pressure differences between the treatment arms in LIFE and ASCOT were very small and were judged by the investigators to be insufficient to explain the large treatment-related differences in outcomes, which favored the other drugs over the β-blocker. However, the editorial accompanying the ASCOT main results publication attributes the benefits of amlodipine-based treatment to superior cuff blood pressure reduction, whereas others, including the main investigators of the ASCOT trial, have adduced effects beyond blood pressure lowering to explain the results.

In this issue, Williams et al describe results of the Conduit Artery Function Evaluation (CAFE) study, a substudy of the ASCOT trial, which compared the effects of the ASCOT blood pressure-lowering regimens on central aortic pressure and hemodynamics in more than 2000 patients in 5 ASCOT centers. The CAFE study, using radial applanation tonometry and pulse-wave analysis to calculate derived central blood pressures using the Sphygmacor system, describes a subtle but important difference in arterial puls in hypertensive patients treated with β-blockers compared with those taking calcium antagonists. The central finding of the CAFE study is that β-blockers do not lower central systolic pressure as much as calcium antagonists, an observation that is predictable based on the relative inability of β-blockers to reduce the magnitude of the reflection (augmentation) wave. This observation is similar to that of Morgan and colleagues, who used a 5-way crossover study to determine that only β-blockers (compared with thiazides, angiotensin-converting enzyme inhibitors, and calcium antagonists) increased the placebo-subtracted magnitude of the reflected wave. Compared with β-blockers, calcium antagonists and other vasodilators are thus more effective in reducing central systolic pressure, cardiac afterload, and left ventricular mass. The results from the CAFE study parallel those of the LIFE trial, in which angiotensin receptor blocker–based therapy was more effective than β-blocker–based therapy in reducing left ventricular hypertrophy and its consequences.

The present application of “pulsology” to clinical trials would no doubt please the Chinese masters and the sphygmacardiologists. With β-blocker–based therapy, as with aging or hypertension in
general, the arterial pulse taken at the wrist is more “sustained,” because of a larger reflected wave in late systole. The absence of “pulsology” in Western medical curricula probably contributes to the skepticism of many physicians, along with the ongoing debate over the validity of the techniques currently used.

Although technical questions remain problematic in interpretation of the CAFE results, the overall conclusions drawn by the investigators are reasonably conservative. Radial tonometry, without question, produces a high-fidelity pulse contour that is identical to high-frequency catheter-based data. It easily can be shown that the radial or brachial systolic pulse contour in aging is essentially a “sustained” systolic pulse composed of an increased first peak followed by a secondary shoulder peak (due to wave reflection) that is generally lower. In contrast, the central systolic contour in aging or hypertension is composed of a lower first peak followed by a higher second systolic peak (augmentation pressure). It has been proposed that a generalized transfer function can be applied to a radial tonogram to yield a derived central pulse waveform; this technique has been well validated to estimate peak central systolic blood pressure. Although there is ongoing debate over whether the transfer function can be applied to interindividual comparisons, in the CAFE study, each individual was compared with his/her own baseline, so the data are probably valid. Other alternative explanations for the differences between treatment arms in CAFE also exist, including differences in 24-hour blood pressure control or other “tissue” mechanisms yet to be described.

What is the overall value of the CAFE study? At the very least, it opens our eyes to alternative explanations beyond the reach of conventional sphygmomanometry. In the context of clinical trials, radial tonometry adds to our knowledge of the pharmacodynamic effects of vasoactive drugs. Present findings have importance in describing why some classes of antihypertensive agents yield better profiles of target-organ protection than others. For example, the observation that β-blockers do not reduce central systolic pressure as much as other antihypertensive drug classes may account for the finding from meta-analyses of antihypertensive trials that β-blocker–based treatment is no better than placebo for prevention of cardiovascular disease. This has led many authorities to recommend that β-blockers not be prescribed as first-line treatment for hypertensive treatment patients in the absence of compelling indications (heart failure, post myocardial infarction, high coronary heart disease risk, angina) for their use. Whether radial tonometry should be performed routinely in individual patients as a diagnostic or therapeutic indicator, however, remains a matter of considerable debate. At present, the technique is probably not quite ready for “prime time” in routine clinical practice.

Disclosures

Dr Oparil has served on a speaker’s bureau for, served as a consultant to/on the advisory board of, and received honoraria from Pfizer, Inc. Dr Izzo has received research grants from Pfizer, Inc, Alteon, GlaxoSmithKline, Sankyo/Forest, and Omron; has received other research support from Omron; has served on a speaker's bureau for Pfizer, Inc, Boehringer-Ingelheim, Merck, Novartis, and Sankyo/Forest; and has served as a consultant to/on the advisory board of Pfizer, Inc, Atocon Medical, Omron, Boehringer-Ingelheim, Merck, AstraZeneca, Novartis, GlaxoSmithKline, Intercor, Sankyo/Forest, and Cardiovascular Therapeutics.

References


20. Key Words: Editorials ■ blood pressure ■ hypertension
Pulsology Rediscovered: Commentary on the Conduit Artery Function Evaluation (CAFE) Study
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_Circulation_. 2006;113:1162-1163
doi: 10.1161/CIRCULATIONAHA.105.609313
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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