Letters to the Editor must not exceed 400 words in length and must be limited to three authors and five references. They should not have tables or figures and should relate solely to an article published in Circulation within the preceding 12 weeks. Authors of letters selected for publication will receive prepublication proofs, and authors of the article cited in the letter will be invited to reply. Replies must be signed by all authors listed in the original publication. Please submit three typewritten, double-spaced copies of the letter to Herbert L. Fred, MD, % the Circulation Editorial Office. Letters will not be returned.

Ramipril and Cardiovascular Risk Reduction

To the Editor:

Mathew et al\(^1\) reported that in the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril causes regression of electrocardiographic (ECG) left ventricular hypertrophy (LVH) independent of blood pressure reduction, with changes associated with reduced risk of death, myocardial infarction, stroke, and congestive heart failure. This conclusion is based on the false assumptions that blood pressure is the same in the brachial artery and central aorta and that neither changes with vasodilator medication. This same mistake was made in the original HOPE study and other clinical trials that investigated the cardiovascular effects of ramipril.\(^2\) Apparently our earlier letter to the editor in The New England Journal of Medicine\(^3\) in response to the HOPE study was totally disregarded by Mathew et al.\(^1\)

We do not question the beneficial effects of ramipril, but we do question the mechanism of LVH regression. It cannot be concluded from measurements of sphygmonanometric cuff brachial artery blood pressure that LVH regression is independent of aortic or left ventricular systolic blood pressure reduction. ACE inhibitors have been shown to reduce arterial wave reflection, and so to reduce central aortic pressure and left ventricular afterload to a far greater degree than would be apparent from measurements of pressure in a peripheral artery.\(^4\) Similar effects have been demonstrated at cardiac catheterization with drugs that reduce wave reflection, such as nitroglycerin and nitrprusside, and noninvasively, using applanation tonometry, with nitrates, ACE inhibitors, calcium antagonists, and a vasodilating β blocker.\(^5\)

The cuff sphygmonanometer is an important instrument, but cannot be relied on exclusively for interpretation of hemodynamic benefit in trials such as HOPE. We contend that regression of ECG-LVH is explicable on the basis of reductions in wave reflection amplitude and central aortic systolic pressure, and we urge that this possibility be explored in addition to the other mechanisms proposed by the HOPE investigators.

Wilmer W. Nichols, PhD
Brian Schuler, MD
Department of Medicine/Cardiology
Box 100277
University of Florida
Gainesville, FL 32610

Michael F. O’Rourke, MD
University of New South Wales
Sydney, Australia


Response

According to Nichols and colleagues, the conclusion in our study\(^1\) that ramipril causes regression of electrocardiographic markers of left ventricular hypertrophy (LVH) independent of blood pressure reduction is based on the false assumptions that blood pressure is the same in the brachial artery and in the central aorta and that neither changes with vasodilator medication. We did not make these assumptions, nor did we make such statements. It is common knowledge that central and peripheral blood pressures are different in amplitude and waveform and that they differ as a function of distance from the heart.\(^2\) It is also common knowledge that both central and peripheral blood pressures change with vasodilator treatment. However, what is relevant is that hypertension in humans is diagnosed by cuff pressure in the arm, and major epidemiological studies and randomized trials in hypertension use this method to measure blood pressure.

Nichols and colleagues also ask if changes in blood pressure and waveform by ramipril in the central aorta could have contributed to LVH regression. The answer is yes; several hemodynamic mechanisms, including the favorable effect of ramipril on vessel wall compliance and wave reflection, might have contributed to afterload reduction and LVH regression. It is also probable that ACE inhibitors cause LVH regression through neurohormonal mechanisms independent of their hemodynamic properties. Angiotensin II promotes the growth of myocytes independent of loading conditions,\(^3\) and ACE inhibitors block the hypertrophic effect of angiotensin II without affecting blood pressure.\(^4\) In the Heart Outcomes Prevention Evaluation (HOPE) study, the beneficial effect of ramipril on LVH was seen in patients with or without hypertension by history and across various blood pressure levels; the change in blood pressure by ramipril during the study was small (3.3 mm Hg systolic and 1.4 mm Hg diastolic), and LVH regression was independent of blood pressure change. Additionally, vasodilators in general reduce blood pressure, improve arterial compliance, and diminish wave reflection.\(^5\) Yet, direct-acting vasodilators may not be effective in causing LVH regression\(^6\) or in reducing clinical events in patients with normal blood pressure, which thus reinforces the view that ACE inhibitors might cause LVH regression and reduction in clinical events by mechanisms beyond blood pressure reduction.

James Mathew, MD
University of Iowa College of Medicine
Iowa City, Iowa
manthi@galesburg.net

Peter Sleight, MD
John Radcliffe Hospital
Oxford, United Kingdom


