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Viewpoint

Blood Pressure Lowering in Patients with Left Ventricular Hypertrophy – Navigating between Scylla and Charybdis

Ever since the randomized controlled Systolic Blood Pressure Intervention Trial (SPRINT), we have known that targeting a systolic blood pressure of less than 120 mm Hg compared with less than 140 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause (Wright et al., 2015). However, given the extensive exclusion criteria, SPRINT's participants represented a relatively healthy study population. Less is known about the optimal blood pressure (BP) targets in more diseased populations such as frail older patients or, specifically, patients with left ventricular hypertrophy (LVH). Data in aggregate have documented that hypertensive patients with LVH, regardless of whether defined by electrocardiogram (ECG), echocardiography, or magnetic resonance imaging (MRI), exhibit a distinctly higher risk of morbidity and mortality than those without LVH. This holds true not only for cardiovascular outcome, as expected, but for cerebrovascular disease as well. Obviously, LVH patients have been exposed to a higher BP load over time than non LVH patients, which has affected the whole vascular tree and all target organs. This brings up the question as to the optimal systolic and diastolic BP in hypertensive patients with LVH. The best possible evidence is coming from cohort studies and retrospective data analyses, which have reported conflicting evidence. Recent data from the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial reported increased mortality when systolic BP was lowered below 130 mm Hg in LVH patients (Okin et al., 2012; Lembo et al., 2024). Of note, in this retrospective data analysis LVH was defined by ECG criteria, and ECG-detected LVH occurs in only a small proportion of patients (e.g., 10% or fewer of those with hypertension of average severity), whereas in a similar population echocardiography-detected LVH is about five times more prevalent. ECG-detected LVH is a measure for the electrically active myocardial tissue, whereas echocardiography-detected LVH simply measures myocardial wall thickness regardless of its function or specific constituents. Not surprisingly, on average hypertensive heart disease is clinically much more severe when defined by ECG than by echocardiography.

In the present issue of the *Journal of Pharmacology and Experimental Therapeutics*, Lembo et al. (2024) now present results from an open electronic registry containing more than 15,000 hypertensive patients (Messerli et al., 2006). They made a statistical analysis from the registry at a certain point in time, selecting patients aged 18 years or older, with an available follow up of 6 months or more, with no heart or cerebrovascular disease, and with available baseline echocardiography. The so-selected 9511 registry participants were classified into six groups according to the presence or absence of LVH and according to their achieved BP levels. For systolic and diastolic BP, they chose three classes each (≤130 mm Hg, >130–139 mm Hg, and ≥140 mm Hg for systolic BP and ≤80 mm Hg, >80–89 mm Hg, and ≥90 mm Hg for diastolic BP, respectively). Their primary outcome was a composite endpoint of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, sudden cardiac death, heart failure requiring hospitalization, myocardial revascularization, de novo angina, or carotid stenting. The authors showed that this outcome was significantly less prevalent in patients with systolic BP ≤130 mm Hg than in patients with higher systolic BP regardless of the presence of LVH. We should notice, however, that the composite outcome in the present study was different from the one in SPRINT; it included items like de novo angina, myocardial revascularization, and carotid stenting. And startingly, even in SPRINT, despite an impressive reduction in the primary (composite) endpoint, there was no significant reduction in the two most powerful cardiovascular events associated with

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ABBREVIATIONS: BP, blood pressure; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; SPRINT, Systolic Blood Pressure Intervention Trial; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation.

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high blood pressure, namely stroke and myocardial infarction. Thus, any information of the individual components of the primary endpoint would have been helpful in the study of Lembo et al. (2024), as their clinical relevance is by no means created equal.

In contrast, for diastolic BP the authors reported higher rates of adverse outcomes the lower the diastolic BP was. They suggest that these findings highlight that too low diastolic BP values during antihypertensive treatment in hypertensive patients, even when systolic BP values are at target, can become a predictor of cardiovascular complications. In the International Verapamil SR/Trandolapril Study (INVEST) trial, in which all 22,000 patients had coronary artery disease and hypertension, the nadir for diastolic BP was between 84 mm Hg (unadjusted) and 76 mm Hg (fully adjusted). Most importantly, the risk of primary outcome doubled when diastolic BP was below 70 mm Hg and quadrupled when it fell below 60 mm Hg (Messerli et al., 2020). Unfortunately, since the present analysis merged a large number of possible cardiovascular complications, the exact mechanism(s) underlying the negative effect of too low a diastolic BP value cannot be determined. The authors do not present a multivariate regression analysis for diastolic BP, and the nonsignificant association of diastolic BP with the primary endpoint in the regression model for systolic BP suggests that diastolic BP was not an independent factor for adverse outcomes. Thus, when systolic BP was taken into account, diastolic BP did not seem to have a notable impact on adverse outcomes by itself.

What then is the take-home message from the provocative data of Lembo et al. (2024)? First, the good news: even in the presence of LVH, systolic pressure can be treated fairly aggressively as long as LVH has been defined by echocardiographic criteria. To the clinician that means that a systolic BP target can be achieved that has been shown to reduce the risk of stroke despite the fact that the patient does have some degree of hypertensive heart disease. Once hypertensive heart disease becomes more pronounced (which is the case when LVH has been defined by ECG criteria), obviously caution has to be exerted in lowering BP as documented by the VALUE trial. The not-so-good news is that diastolic BP lowering remains ill-defined with regard to benefit or harm. However, this becomes somewhat of an academic argument since neither systolic nor diastolic BP can be lowered in isolation. By definition, all antihypertensive drugs lower BP and, apart from negative chronotropic drugs, there are very few differences among them with regard to their effect on systolic and diastolic BP. A slowing of the heart rate will increase pulse pressure, thus lowering systolic BP less and diastolic BP more than an antihypertensive that maintains (or even increases) heart rate.

This brings us to the topic of target organ heterogeneity. Aggressively lowering systolic BP to levels below 120 mm Hg may confer optimal stroke protection. However, the accompanying fall in diastolic BP may hamper coronary perfusion and actually increase the risk of cardiac events. In other words, the optimal BP for the brain is the one that the heart cannot afford. In the VALUE substudy, ECG-detected LVH in patients with a systolic BP $>$130 mm Hg was associated with higher cardiac mortality (and all-cause mortality but not with cerebrovascular endpoints). For clinicians, there is no easy way to navigate this Scylla and Charybdis situation. We should remember that diastolic BP values lower than 60 to 70 mm Hg may increase fatality rates, particularly in older patients, most of whom have isolated systolic hypertension. By aggressively lowering systolic BP in these patients, diastolic BP may fall to values that increase the mortality risk. Lamentably, designer antihypertensive drugs that lower systolic pressure while maintaining or even increasing diastolic pressure have yet to be invented.

Large population studies like the one by Lembo et al. (2024) in concert with SPRINT, INVEST, VALUE, and many others merely provide us with BP targets that allow to estimate statistical risk-benefit ratios. These may be exceedingly helpful to writers of policies and guidelines. However, as clinicians we have to titrate blood pressure to levels that best fit the individual needs of the patient sitting in front of us.

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