

EDITORIAL COMMENT

Left Ventricular Geometry, Blood Pressure, Arterial Hemodynamics, and Mortality After Ischemic Stroke*



Thierry C. Gillebert, MD, PhD,^a Julio A. Chirinos, MD, PhD^b

The importance of left ventricular (LV) remodeling as a determinant of cardiovascular risk is widely recognized. With age, stroke volume, and LV volumes decrease (1,2). LV mass decreases as well, albeit to a lesser extent. As a consequence, the LV mass/volume ratio and the relative wall thickness (RWT) increase. Hemodynamic load and other forms of cardiovascular stress trigger processes that lead to increased LV mass, remodeling, and hypertrophy. Grossmann et al. (3) linked the type of hemodynamic stress to the type of remodeling of the ventricle. They described concentric hypertrophy (thick-walled ventricle) in response to pressure overload and increased systolic wall stress as well as eccentric hypertrophy (dilated ventricle) in response to volume overload and increased diastolic wall stress. Ross (4) applied this concept to hemodynamic load in aortic and mitral heart diseases. Recent research refined this paradigm in view of ventricular-arterial interactions and revealed the importance of the timing of systolic load, with early-systolic load triggering adaptive and late-systolic load maladaptive hypertrophy (5). The timing of systolic load underlies the importance of arterial stiffening and prominent/premature arterial wave

reflection for predicting LV hypertrophy, incident heart failure, and mortality (6,7).

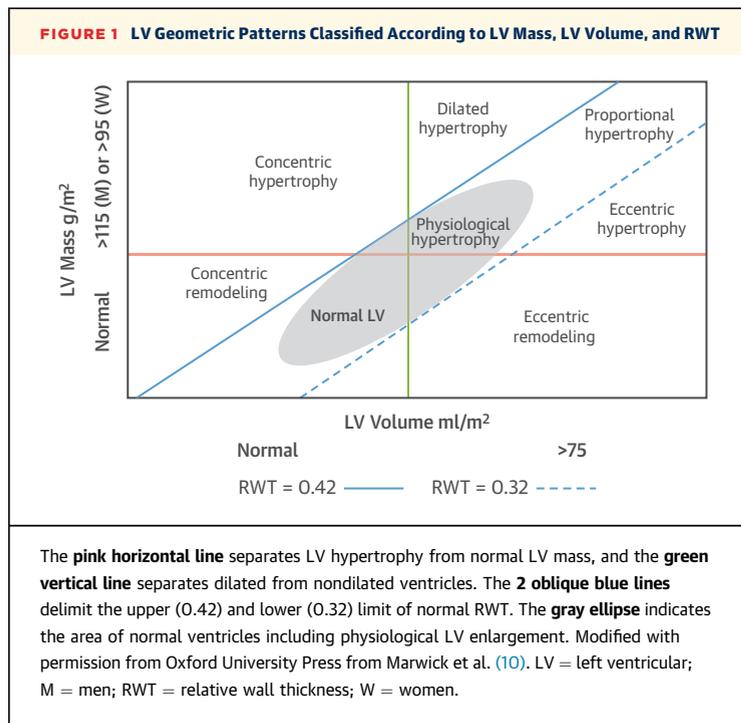
In large community-based cohort studies, such as the Framingham Heart Study, LV remodeling and hypertrophy have been associated with poor long-term outcome (8). It has been recommended (9,10) to describe LV geometry as a function of LV mass and RWT. This leads to 4 categories: normal geometry, concentric remodeling (increased RWT), concentric hypertrophy (increased LV mass and RWT), and eccentric hypertrophy (increased LV mass and normal RWT). Further studies (11) have linked cardiovascular risk mainly to increased LV mass and concentricity (or RWT). The geometry of the ventricle is an established prognostic factor, not only in the general population but also in the setting of hypertension, valvular heart diseases, heart failure with preserved ejection fraction, and after myocardial infarction. However, no data are available regarding the prognostic role of LV mass in patients with acute ischemic stroke. Long-term mortality after ischemic stroke remains high, which indicates the need for more aggressive therapeutic interventions that should be tailored to the risk of individual patients. Echocardiography is widely used in patients with acute ischemic stroke to assess for the presence of cardiac sources of emboli. Therefore, the identification of echocardiographic parameters that can aid in the risk stratification of this patient population could be readily applied in clinical practice, without additional cost.

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From the ^aDepartment of Cardiology, Ghent University, Ghent, Belgium; and the ^bDivision of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine and Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Dr. Chirinos has received honoraria from Bristol-Myers Squibb, OPKO Healthcare, Fukuda Denshi, Microsoft, Vital Labs, and Merck; received research grants from the National Institutes of Health, the American College of Radiology Network, the American Heart Association, Fukuda Denshi, Bristol-Myers Squibb, Microsoft, and CVRx, Inc.; and device loans from AtCor Medical. Dr. Gillebert has reported that he has no relationships relevant to the content of this paper to disclose.

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In this issue of *iJACC*, Park et al. (12) report on the prognostic value of LV geometry and its interaction with blood pressure (BP) as a predictor of mortality in a large cohort of patients with acute ischemic stroke. In this study, 2,069 patients hospitalized for acute ischemic stroke were followed up for a median of 37.6 months, during which 367 deaths occurred



(of which 166 were of a cardiovascular cause). This is an important cohort study with careful follow-up and with mortality data collected from the governmental statistics office in South Korea. The main finding of the study is that concentric remodeling and hypertrophy, but not eccentric hypertrophy, were independently associated with a higher risk of mortality than normal LV geometry. Accordingly, RWT was a significant independent predictor of all-cause mortality, whereas LV mass was not. These results pinpoint concentricity as a maladaptive phenotype that is associated with a poor outcome. A second important finding is that there was a significant interaction between LV geometry and systolic BP during hospital admission as predictors of mortality, such that mortality decreased as systolic BP was lower in patients with normal LV geometry, whereas in patients with abnormal LV geometry, mortality risk increased at both extremes of the BP range but more prominently among patients with lower (<~150 mm Hg) systolic BP on admission. These findings suggest that in patients with abnormal LV geometry, cerebral autoregulation is more disturbed (shifted to higher pressures), presumably as a consequence of chronic hypertension and arterial stiffening. In this situation, lower BP can cause cerebral hypoperfusion and further ischemic insult, whereas similar BP values are within the range of cerebral autoregulation in patients with normal LV geometry.

Arterial hemodynamics could also be at play. With every heartbeat, the pulse wave generated by LV contraction becomes partially reflected at sites of impedance mismatch along the arterial tree (13). Whereas a local wave reflection at the aortic-carotid interface has been proposed to prevent penetration of pressure and flow pulsatility into the brain (14), the bulk of wave reflections, which arise at the lower body, travel back to the heart and penetrate the carotid artery as a forward wave, which increases pulsatile pressure and flow in the cerebrovascular bed (15). Chronically increased pressure and flow pulsatility in the cerebrovascular territory is thought to be linked to chronic microvascular disease in the brain (14), which could lead to impaired cerebral autorregulation. These wave reflections increase the mid to late systolic wall stress of the LV (5), which leads to maladaptive concentric remodeling and hypertrophy (7). Therefore, abnormal LV geometry could be a marker of prominent wave reflections, increasing late-systolic LV wall stress on the one hand and leading to microvascular dysfunction with impaired cerebrovascular regulation on the other. The microvascular function of other vascular beds (e.g., kidneys) could be similarly impaired. Impaired tissue perfusion of critical organs might contribute to the total and cardiovascular mortality observed after stroke by Park et al. (12).

The lesser risk of patients with eccentric hypertrophy deserves further attention. When the presented data are examined, there is a trend toward increased mortality in eccentric hypertrophy that might statistically not differ from the effect of concentric remodeling or hypertrophy. The authors (12) argue that the peripheral circulation might be better preserved in patients with eccentric hypertrophy. But admittedly, eccentric hypertrophy, as classically defined by LV mass and RWT, is a melting pot of dissimilar ventricles. For this and other reasons, Zile et al. (16) proposed a classification of the geometry of the ventricle as a function of LV volume, combined with LV mass and RWT. They tested this classification in the Cardiovascular Health Study. The proposed classification is based on the presence or absence of LV enlargement and LV hypertrophy, and RWT is valuable primarily for subclassifying people with normal LV size and mass. Compared with the American Society of Echocardiography criteria, the proposed scheme requires the presence of a normal LV volume for concentric remodeling or concentric hypertrophy, whereas an enlarged LV volume is required for classification as eccentric hypertrophy (17). An American Society of Echocardiography/European Association of Echocardiography writing

group (10) recently expanded this classification (Figure 1) and defined categories on the basis of LV volume, LV mass, and RWT. The advantages of this expanded classification are that it includes physiological hypertrophy, categorizes dilated ventricles, and can be used in various patient populations, including valvular heart diseases. Of note, dilated hypertrophy was previously categorized as concentric hypertrophy, and proportional hypertrophy was previously categorized as eccentric hypertrophy.

The findings of Park et al. (12) should prompt more tailored studies to examine the mechanisms of the

interaction between LV remodeling, BP, and arterial hemodynamics as prognostic factors after acute ischemic stroke. Similarly, whether antihypertensive therapy should be tailored according to the prevalent LV geometry in patients with ischemic stroke remains to be addressed in properly designed prospective clinical trials.

ADDRESS FOR CORRESPONDENCE: Prof. Thierry C. Gillebert, Department of Cardiology, Ghent University Hospital, 8K12IE, De Pintelaan, 185 9000, Ghent, Belgium. E-mail: thierry.gillebert@ugent.be.

REFERENCES

1. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009;2:191-8.
2. Poppe KK, Doughty RN, Gardin JM, et al., for the Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL Study. *J Am Coll Cardiol Img* 2015;8:656-65.
3. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975;56:56-64.
4. Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. *J Am Coll Cardiol* 1985;5:811-26.
5. Chirinos JA, Segers P, Rietzschel ER, et al., for the Asklepios Investigators. Early and late systolic wall stress differentially relate to myocardial contraction and relaxation in middle-aged adults: the Asklepios study. *Hypertension* 2013;61:296-303.
6. Chirinos JA, Kips JG, Jacobs DR Jr., et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012;60:2170-7.
7. Zamani P, Bluemke DA, Jacobs DR Jr., et al. Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2015;65:85-92.
8. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. *J Am Coll Cardiol* 1995;25:879-84.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [published correction appears in *Eur Heart J Cardiovasc Imaging* 2016;17:412]. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70.
10. Marwick TH, Gillebert TC, Aurigemma G, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *Eur Heart J Cardiovasc Imaging* 2015;16:577-605.
11. Tsao CW, Gona PN, Salton CJ, et al. Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study cardiac magnetic resonance study. *J Am Heart Assoc* 2015;4:e002188.
12. Park CS, Park J-B, Kim Y, et al. Left ventricular geometry determines prognosis and reverse J-shaped relation between blood pressure and mortality in ischemic stroke patients. *J Am Coll Cardiol Img* 2018;11:373-82.
13. Nichols W, O'Rourke M, Vlachopoulos C. McDonald's Blood Flow in Arteries, Sixth Edition: Theoretical, Experimental and Clinical Principles. Boca Raton, FL: CRC Press, 2011.
14. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility-Reykjavik study. *Brain* 2011;134:3398-407.
15. Chirinos JA. Large artery stiffness, microvascular function, and cardiovascular risk. *Circ Cardiovasc Imaging* 2016;9:e005903.
16. Zile MR, Gaasch WH, Patel K, Aban IB, Ahmed A. Adverse left ventricular remodeling in community-dwelling older adults predicts incident heart failure and mortality [published correction appears in *J Am Coll Cardiol HF* 2014;2:678]. *J Am Coll Cardiol HF* 2014;2:512-22.
17. Shah AM, Pfeffer MA. Left ventricular size, mass, and shape: is the sum greater than the parts? *J Am Coll Cardiol HF* 2014;2:523-5.

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