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COMMENTARY

Do we understand the relationship between left ventricular structural remodeling and stroke in arterial hypertension?

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LEFT VENTRICULAR HYPERTROPHY AND STROKE

Left ventricular hypertrophy (LVH) is a well-known cardiovascular risk factor. Two decades ago, the results from the Framingham study revealed the relationship between LV mass and risk of stroke in the elderly. Verdecchia *et al.*,[1] in a population of 2363 initially untreated hypertensive patients, demonstrated that LVH significantly increased the risk of stroke and transient ischemic attack independent of blood pressure and other risk factors. The authors showed that LVH based on echocardiography increased the risk of cerebrovascular events by 64% in hypertensive patients (relative risk 1.64; 95% confidence interval (CI): 1.07–2.68). Similar findings have been published more recently using a smaller group of hypertensive patients.[2]

Di Tullio *et al.*[3] conducted a case–control study that included 394 patients with his or her first ischemic stroke and 413 age-, sex- and race-ethnicity-matched controls, finding that LVH was associated with an increased stroke risk (adjusted odds ratio (OR) 2.5; 95% CI: 1.7–3.5). This increase was observed in all age, sex and race-ethnic groups. Interestingly, the authors did not find a significant interaction between LVH and arterial hypertension and other risk factors on stroke risk.[3]

A recently published meta-analysis that included 12 809 hypertensive patients from 14 different studies with a follow-up from 0.5 to 5 years demonstrated that the LV mass reduction induced by antihypertensive treatment significantly reduced the risk of stroke (OR 0.76, 95% CI: 0.64–0.89, $P<0.001$) but did not change the risk of myocardial infarction or heart failure.[4] Verdecchia *et al.*[1] previously published similar results in a population of 880 initially untreated hypertensive subjects.

In the last several years, a number of large studies have confirmed the relationship between LVH and cerebrovascular events in a general population.[5,6] The MESA study, which included 5098 participants initially free of cardiovascular disease, showed that LV mass adjusted for body size was positively associated with the incidence of stroke (hazard ratio (HR) 1.2 per 10% increment, $P=0.01$).[5] Bouzas-Mosquera *et al.*[6] included 40 138 adult patients from the general population (mean age 61.1 ± 16.4) and followed them for 5.6 ± 3.9 years. The investigators found that LV mass had a graded, independent association with all-cause mortality, myocardial infarction and stroke (HR 1.26, 95% CI: 1.13–1.40, $P<0.001$ in women and HR 1.19, 95% CI: 1.09–1.30, $P<0.001$ in men).[6] When the authors analyzed specific types of stroke separately, LV mass was significantly related to ischemic stroke in both genders and to hemorrhagic stroke in men, with a nonsignificant trend in women.[6] Similar findings were shown in a small observational study in Sri Lanka in patients hospitalized for ischemic stroke.

In this issue of *Hypertension Research*, Wang *et al.*[7] reports a significant relationship between LVH and stroke in a hypertensive Chinese population, and the results of this study largely confirm previous knowledge on this topic. The authors found that LVH was associated with an increased stroke risk (adjusted OR 1.52; 95% CI: 1.25–1.85; multivariate-adjusted OR, 1.43; 95% CI: 1.16–1.75). This trend was observed in both genders equally, but not in different age groups. In particular, Wang *et al.*[7] showed that LVH was not a risk factor for stroke between 40 and 55 years of age but was associated with an increased stroke risk in hypertensive patients between 55 and 74 years of age. This result is not in accordance with Di Tullio *et al.*,[3] who found this association in all age groups.

The investigators also revealed that the relative LV wall thickness is associated with an increased risk of stroke independent of LV mass index and other risk factors of stroke (adjusted OR 3.97; 95% CI: 1.10–14.34). The authors used two different formulas to calculate the LV mass index and LV relative wall thickness, and succeeded in demonstrating a relationship between all four of these LV structural parameters and risk of stroke in a hypertensive population.[7] This finding has important clinical implications because the authors utilized the two most frequently used formulas of LV mass index, adjusted by body surface area or body height, and the two most commonly used equations for LV relative wall thickness. The obtained results show that in everyday clinical practice, which formula a clinician uses is not important because the conclusion will remain the same.

LEFT VENTRICULAR GEOMETRY AND STROKE

The influence of LV geometry on stroke occurrence is less investigated. Di Tullio *et al.*[3] reported that concentric LVH carries

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the greatest stroke risk, followed by eccentric hypertrophy. The authors claimed that LV concentric remodeling was associated with a modest risk increase of stroke. The risk of stroke was increased independent of arterial hypertension and other risk factors.[3] The researchers also found a relationship between LV geometry and type of stroke. Concentric LVH was more associated with lacunar (32.7%) and cryptogenic (23.1%) strokes than other LV geometries. Eccentric LVH was associated with cardioembolic stroke (26.5%), whereas concentric remodeling was associated with lacunar stroke (26.2%).[3] Concentric LVH was revealed to be the most frequent type of LV geometry among patients with ischemic stroke.

The LIFE study showed that concentric remodeling (HR 2.99; 95% CI: 1.16–7.71, $P<0.05$), eccentric hypertrophy (HR 1.79; 95% CI: 1.17–2.73, $P<0.05$) and concentric hypertrophy (HR 2.71; 95% CI: 1.13–6.45, $P<0.05$) are independent predictors of primary composite end points (cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction).[8] Indeed, the composite end points in this study were cardiovascular death, myocardial infarction and stroke; thus, the results could not be the same as the studies that only investigated the relationship between LV geometry and stroke.[3] However, this study also confirms the fact that LV geometry has an important influence on stroke occurrence.

The recently published AFFIRM trial showed that LV geometry does not affect stroke occurrence in hypertensive patients with atrial fibrillation, although concentric LVH, unlike eccentric hypertrophy and concentric remodeling, increased mortality in these patients.[9]

In this issue, Wang *et al.*[7] report that LV concentric hypertrophy carries the highest risk of stroke (unadjusted OR 1.93, 95% CI: 1.48–2.53; adjusted OR 1.62, 95% CI: 1.21–2.17), followed by eccentric hypertrophy (unadjusted OR 1.61, 95% CI: 1.08–2.54; adjusted OR 1.51, 95% CI: 1.12–2.03), and concentric remodeling ranked third (unadjusted OR 1.47, 95% CI: 1.12–1.93; adjusted OR 1.34, 95% CI, 1.01–1.80). Concentric hypertrophy increased stroke risk in both genders in unadjusted and adjusted models. Eccentric hypertrophy was related to an increased stroke risk in both genders in unadjusted models, but was only associated with stroke risk in women in the adjusted model; in contrast, concentric remodeling was associated with stroke risk in women in all models.[7]

POSSIBLE MECHANISMS LINKING LV REMODELING AND STROKE OCCURRENCE

The particular mechanism explaining the relationship between LVH and increased risk of stroke is unclear, but there are several possibilities. First, LVH increases myocardial oxygen consumption, which can induce an imbalance between oxygen demand and supply in the myocardium, consequently leading to myocardial ischemia[10] and inducing small areas of hypokinetic myocardium. These areas might serve as an origin for small thrombi to provoke an ischemic stroke. Second, LVH positively correlates with carotid intima-media thickness, which represents a significant predictor of stroke. In addition, hypertension is also an important predictor of carotid atherosclerosis, which significantly contributes to stroke occurrence. Third, LVH is associated with a higher prevalence of atrial fibrillation, which is a significant risk factor for stroke. Fourth, LVH is usually associated with other risk factors, such as obesity, insulin resistance, diabetes and metabolic syndrome, which significantly increase the risk of stroke. Fifth, a molecular mechanism could also explain the relationship between LVH and stroke; for example, a polymorphism of the platelet glycoprotein IIIa gene, present in high-risk hypertensive patients, increases the risk of ischemic stroke in these patients.[11]

The association between LV geometry and stroke is even less clear and more controversial. Studies have shown that asymptomatic lacunar lesions are more frequent in patients with an abnormal LV geometry.[12] Arterial structure and function are abnormal in patients with concentric LVH and may partly explain the increased risk of stroke. Neurohormonal changes, such as aldosterone and atrial natriuretic peptide elevations, are related to an abnormal LV geometry (concentric and eccentric LV hypertrophy)[13] and could partly be responsible for stroke occurrence. Di Tullio *et al.*[3] showed that increased LV relative wall thickness was more frequently associated with lacunar infarcts, indicating an important role for LV relative wall thickness in the development of small-vessel disease, which could induce strokes. In the aforementioned study, cryptogenic stroke was less present in the patients with concentric LVH;[3] however, eccentric LVH seems to be associated with cardioembolism, suggesting that LV dilation has an important role as a possible embolic source.

Further investigation is required to clarify the complex association between LV remodeling (LV mass and geometry) and stroke occurrence and possible approaches to reduce stroke risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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