The average blood pressure (BP) level has certainly decreased in Japan since 1960, but the prevalence of hypertension (HT) may be on the rise in the next 2–3 decades. When considering national healthcare costs, the treatment of HT and prevention of related diseases is crucial. The target of treatment is to lower BP in patients with HT, primarily in order to avoid cardiovascular events. Left ventricular hypertrophy (LVH) is a compensatory reaction to HT that causes myocardial ischemia and diastolic dysfunction, consequent heart failure. There is a report of the predictive power of LVH assessed by ECG for cardiac events in the general Japanese population, and echocardiographically assessed LVH strongly predicts cardiovascular events in hypertensive patients. Furthermore, reduction of LVH is related to favorable outcomes, so LVH may become an important therapeutic target in hypertensive patients.

**Figure.** Signaling pathways involved in the development of left ventricular hypertrophy. ANII, angiotensin II; DAG, diacylglycerol; ERK, extracellular regulated kinase; ET1, endothelin 1; FAK, tyrosine-kinase and focal adhesion kinase; IP3, inositol triphosphate; IRS, insulin-receptor substrate; MAPK, mitogenic-activating protein kinase; mTOR, mammalian target of rapamycin; NE, norepinephrine; NFAT, nuclear factor of activated T cell; P13K, phosphatidylinositol 3 kinase; PLC, phospholipase C; Shc, SRC homology and collagen protein; Src, steroid receptor coactivator; TLCC, type L calcium channel.

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Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan
Mailing address: Tohru Masuyama, MD, PhD, FACC, Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya 663-8501, Japan. E-mail: masuyama@hyo-med.ac.jp
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patients with HT. There are many factors related to ventricular hypertrophy. Although mechanical stimulus is a cause, neurohumoral factors such as catecholamines and angiotensin II (angII) induce LVH either individually or in combination (Figure). Hypertrophy indicates increased size of cardiomyocytes, and is usually associated with alteration of the collagen matrix components. This molecular process includes membrane receptors, second messengers, and transcriptions, resulting in gene expressions that induce increases in protein synthesis and changes in sarcomeric structure. Therefore, the 2 main systems involved in hypertrophy are mechanical stress and release of neurohumoral factors. The mechanical signaling has not been completely elucidated, but it activates multiple messengers and intracellular cascades, and also induces the local release of cytokines. For the many neurohumoral factors related to hypertrophy (ie, catecholamines, angII, aldosterone, insulin, oxidative stress, cytokines and growth factors induced by the inflammatory process), the main stimulus comes from hepthahelical G protein coupled receptor, including β1-adrenergic receptors for epinephrine and norepinephrine, the AT1 receptor for angII and the ET receptor for endothelin-1. The process of pathological myocardial hypertrophy is highly complex, but elucidation of the pathways enables application to medical treatment.

Most antihypertensive medication is associated with reduction of LVH, but the degree of the reduction is not uniform. The PRESERVE5 and ELVELA6 trials showed similar reduction of LVH between long-term calcium channel blockade and angiotensin-converting enzyme inhibitor (ACEI) therapy. However, a meta-analysis of treatment for the regression of LVH reported that ACEI and angiotensin receptor blocker (ARB) showed greater reduction of left ventricular (LV) mass.7 Now, there is no doubt that the angiotensin system is the greatest target for regression of LVH. Furthermore, the LIFE study showed the effectiveness of ARBs on reducing LVH when compared with β-blocker.8 In clinical cases, most hypertensive patients need to take multi-class antihypertensive medication to obtain their target level of BP. The combination therapy of an ARB and hydrochlorothiazide (HCTZ) is more effective for reducing BP than monotherapy of either.9 In the sub-study of the LIFE trial, the efficacy of adding diuretics for treating LVH has been reported.10 These several trials have demonstrated that ARBs are more effective in reducing LVH when used with HCTZ than without HCTZ.

In this issue of the Journal, Sawa et al11 report the different therapeutic effects between adding diuretics and increasing the dosage of the ARB. The regression of the ECG signs of LVH was better with the combined therapy of diuretic and ARB than by increasing the dosage of ARB, and the difference was independent of the degree of BP reduction. Diuretics are rarely used in Japanese hypertensive patients as a first-line medication, because doctors are apprehensive about adverse effects. However, Sawa et al also report that no significant adverse effects were seen when low-dose diuresis was combined with ARB therapy.

For the assessment of LVH, ECG is the initial method used to recruit patients in many clinical studies. However, some ECG studies do not support the result that lowering BP induces a reduction in LVH during treatment of HT.12,13 Echocardiography is the standard method of measuring LV mass, and the results of Sawa et al’s study are consistent with the results of previous studies in which LV mass was assessed with echocardiography.14,15 Cardiac hypertrophy is induced by not only HT but also valvular disease, diabetes, ischemic heart disease, and so on, and it is an important predictor by itself irrespective of the cause. HT is the most frequent cardiac disease in clinical practice, and LVH is an important target in the treatment of HT. The most important thing is to lower BP strictly for the prevention of cardiovascular events and the reduction of LVH. However, the different effects of the medications on reducing LVH should be taken into consideration when treating hypertensive patients with LVH.

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