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COMMENT

Risk factors for atherosclerosis as direct causes of left atrial dysfunction independent of left atrial–left ventricular–arterial coupling

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Reducing the incidence of heart failure, especially heart failure with preserved ejection fraction (HFpEF), should receive high priority in the setting of an aging population [1]. In addition to age, various risk factors including hypertension, diabetes, and dyslipidemia are believed to play complex roles in the pathogenesis of HFpEF. These factors are thought to cause endothelial inflammation, endothelial dysfunction of pulmonary and renal arteries, and the formation of lesions extending from the intima to the media of the endocardial side of the myocardium and the aorta [2]. Given this background, it is important to detect and treat cardiac dysfunction in the preclinical stages (A and B) [3]. Early intervention with diet, statins, angiotensin II inhibitors, and incretin-related drugs may ultimately help prevent progression to HFpEF stages C and D [1, 3]. In stage B, the stiffening of elastic arteries such as the aorta is accelerated, resulting in left atrial (LA) diastolic stiffness and impaired longitudinal left ventricular (LV) relaxation. As a result, LV myocardial lesions spread from the longitudinal subendocardial fibers to the circumferential fibers in the mid-wall with LV hypertrophy, eventually leading to a decrease in LV ejection fraction. Thus, LA–LV–arterial coupling has been proposed as a new concept for evaluating cardiac dysfunction [4]. LA function includes a reservoir function that stores blood during LV systole by relaxing and stretching the left atrium, and a booster pump function, during which the atrium contracts and expels blood into the LV in the late diastole phase. LA function has been evaluated by computed tomography and magnetic resonance imaging, but echocardiography is the most commonly used, as it is simple, inexpensive, and free of radiation exposure. Echocardiographic evaluations of LA function include endocardial tracing, pulsed Doppler technique, and tissue Doppler imaging. Unfortunately, these methods are limited by hemodynamics, preload, image quality, and the effect of whole-heart translation. Recently, however, the reproducibility of LA strain evaluated by two-dimensional speckle tracking echocardiography (2DS) has become excellent, providing reliable evaluation of LA function [5]. The most commonly used indices are the ventricular systolic strain (LA-Ss), which reflects the reservoir function, and the late diastolic strain (LA-Sa), which reflects the booster pump function. The 2DS method can detect potential LA dysfunction in patients with paroxysmal atrial fibrillation, hypertension, and diabetes mellitus, even when the size and function of the left atrium are normal as assessed by conventional echocardiographic methods [6]. In the above-mentioned report, LA-Sa, which reflects LA reservoir function, is often decreased while LA-Sa, which reflects pump function, is preserved. In addition, LA strain has been shown to be useful in predicting recurrence after catheter ablation therapy in patients with AF. On the other hand, it should be noted that LA strain was not selected as an independent predictor of cardiac events in studies that included global longitudinal strain (GLS) as a factor [7, 8] because of the effect on LA reservoir function of LV longitudinal contractility. In the future, when LA strain, especially LA-Sa, is used to predict cardiac events, GLS should also be taken into account in the analysis. Impaired LA and LV relaxation in the longitudinal direction are early signs of abnormal LA–LV coupling related to arterial stiffness in preclinical patients with cardiovascular risk factors. Miyoshi et al. showed that arterial stiffness is associated with changes in LA reservoir function (passive filling rather than active relaxation) as well as impairment of diastolic LV function (i.e., of active relaxation) in preclinical patients with cardiovascular risk factors [4]. These results demonstrated that 2DSTE enables the quantitative assessment

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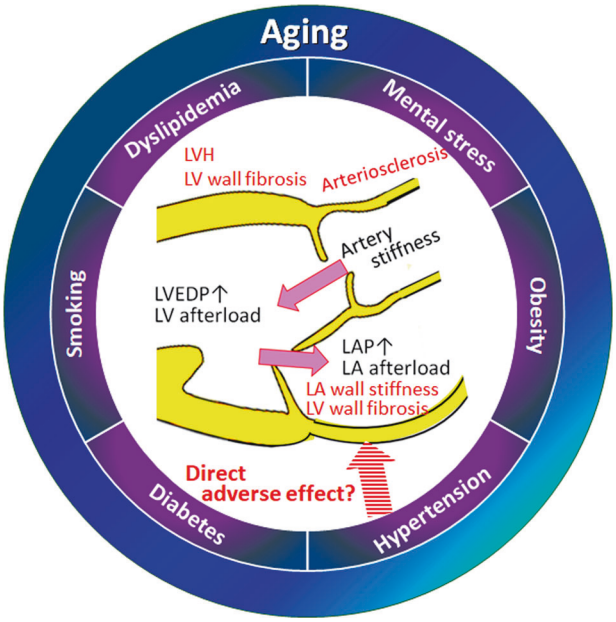

Fig. 1 Possible active mechanisms of risk factors for LA dysfunction in addition to LA-LV–arterial coupling: LA left atrial, LV left ventricle, LVEDP left ventricular end-diastolic pressure, LAP left atrial pressure, LVH left ventricular hypertrophy

of the LA and LV function and can be considered a sensitive tool for detecting abnormal LA–LV–arterial coupling. Information regarding these preclinical developments cannot be obtained using conventional two-dimensional, blood flow and tissue Doppler velocity echocardiography.

We have read with interest the recently published work by Fu et al. in *Hypertension Research*, "Associations of Brachial-Ankle Pulse Wave Velocity with LA Stiffness and LA Phasic Function in Inpatients with Hypertension" [9]. The purpose of their study was to investigate the association of brachial-ankle pulse wave velocity (baPWV) with LA stiffness and LA phasic function in hypertension. Fu's group reported that baPWV was independently associated with LA stiffness in hypertensive inpatients. The baPWV also exhibited a certain predictive value for LA stiffness in this group. It is interesting that the regulation of LA–arterial coupling involves other mechanisms beyond LV function. Increased baPWV is the result of arterial stiffness induced by risk factors such as hypertension. Fu and colleagues' study implies that arteriosclerosis causes LA dysfunction by a different mechanism than by LA–LV–arterial coupling. Their findings may be related to the inflammatory effects of hypertension related to myocardial fibrosis independent of blood pressure, for instance involvement of the renin–angiotensin–aldosterone system. Studies of the direct relationship between other risk factors such as diabetes, obesity, and lipid abnormalities and LA function are warranted. The associations that might be found between individual risk factors and LA dysfunction will go far in helping to elucidate the pathogenesis of HFpEF. Too often in our daily clinical practice, we treat diseases as syndromes; in other words, we recognize and understand disease targets from a univariate rather than a multivariate perspective. It seems more important to consider what complex and intertwined risk factors are the direct causes of the overall disease pathophysiology (Fig. 1) and to implement treatments that address those causes.

Compliance with ethical standards

Conflict of interest KH has no conflicts of interest to disclose. KK reports scholarships from Daiichi Sankyo, Sumitomo Dainippon Pharma, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals, as well as Honoraria from Daiichi Sankyo and Novartis Pharma outside the scope of the submitted work.

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