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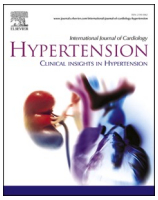

Editorial

Myocardial strain impairment, heterozygous familial hypercholesterolemia and systemic arterial hypertension: Is there a link?

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ABSTRACT

Dyslipidemia is known as a strong risk factor for premature atherosclerotic cardiovascular disease and increased morbidity and mortality and can have an adverse effect on left ventricular function due to direct or indirect macrovascular and/or microvascular damage. Speckle-tracking echocardiography allows the assessment of subclinical cardiac dysfunction in different diseases on the basis of myocardial deformation indices, and decrease in longitudinal and circumferential strain was shown in patients with heterozygous familial hypercholesterolemia (heFH) without comorbidities. In this issue of the journal a new study presents the results in a well-defined population which included asymptomatic treatment-naive heFH individuals without known coronary/peripheral arterial disease, with normal left ventricular ejection fraction and no other risk factors as formal arterial hypertension or diabetes mellitus. A slight impairment of global longitudinal strain was present, despite normal standard echocardiographic parameters. Also, the higher rise in systolic and diastolic blood pressure of heHF patients during exercise treadmill test might reflect early preclinical hypertension. High cholesterol level may have produced endothelial dysfunction, which has been shown to be related to the extent of atherosclerotic process and cardiovascular damage. Relevant findings are reported on left ventricular strain reduction and increase in systolic/diastolic blood pressure in asymptomatic heFH males. The relationship between myocardial strain impairment and developing systemic arterial hypertension in hypercholesterolemic patients could be the subject of further subsequent investigation.

Dyslipidemia is known as a major risk factor for premature atherosclerotic cardiovascular disease and high morbidity and mortality and can have an adverse effect on left ventricular (LV) function due to direct or indirect macrovascular and/or microvascular damage [1]. Atherosclerotic plaques distributed in the proximal and mid portions of the coronary arteries have been reported in adult patients with heterozygous familial hypercholesterolemia. Early structural wall lesions can be detected even in young children. Fibrous plaque is a lesion covered by smooth muscle and collagen due to accumulation of lipid-loaded macrophages (macrophage foam cells), T cells, and monocytes, followed by migration and proliferation of vascular smooth muscle cells and platelet aggregation. Fibrous caps covering the lipid cores vary in cellularity, collagen content and thickness. These atherosclerotic changes (fibrous plaque and cap) are preceded by signs of endothelial dysfunction manifested by activation of leukocyte adhesion molecules, proliferation and transmigration of leukocytes into the arterial wall, enhanced permeation to circulating lipoproteins, and intima damage. Experimental studies demonstrated that hypercholesterolemia can cause cardiac hypertrophy, ventricular remodeling and endothelial dysfunction with various mechanisms [2,3] such as accumulation of 7-ketone cholesterol, increased cardiac oxidative stress, abnormal mitochondrial metabolism with lipid overload, formation of reactive oxygen species, activation of hypertrophic signaling pathways in cardiomyocytes, and increased plasma concentration of endothelin-1 leading to vasomotor alterations and chronic inflammation (Fig. 1). In mice subjected to a hyperlipidic diet LV ejection fraction decreased significantly, and myocardial performance index and isovolumic relaxation time increased significantly, suggesting both systolic and diastolic dysfunction. Lipid-lowering drugs aid in improving LV function and attenuating cardiac hypertrophy and remodeling through inhibition of vascular inflammation and suppression of oxidative stress.

Two-dimensional (2DSTE) and three-dimensional speckle-tracking echocardiography (3DSTE) appeared to be more sensitive to detect subtle myocardial damage compared to conventional LV function parameters. Both methods allow the assessment of subclinical cardiac dysfunction in different diseases on the basis of myocardial deformation indices, and decrease in longitudinal and circumferential strain was shown in children and adolescents with heterozygous familial hypercholesterolemia without comorbidities [4,5]. A significant inverse correlation was found between longitudinal deformation and low-density lipoprotein (LDL) cholesterol level as well as a significant higher correlation between global area strain obtained by 3DSTE and LDL cholesterol.

Three-dimensional speckle-tracking echocardiography provides global and regional longitudinal and circumferential strain values that are comparable to those obtained from 2DSTE, albeit they are not interchangeable with each other for some reasons [4]. Firstly, global longitudinal strain is smaller on 3DSTE than 2DSTE, and the lower strain

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values can be explained by the torsion of the heart and out-of-plane rotation of myocardial segments on 2DE imaging. Secondly, the differences in strain values between the two methods are greater in the basal and apical segments than in the mid-ventricular segments, and these findings can be related to base-diverging ultrasound beams causing worse spatial resolution. Each technique has strengths and limitations. The 3D mode aids in solving the problem of out-of-plane motion present in the 2D mode which tracks the movement of the speckles in all three dimensions, prevents foreshortening of apical views, and has good reproducibility as an automated method with lower intraobserver and interobserver variability. However, this advantage comes at the expense of a lower volume rate, which could alter correlations with measurements obtained by 2DSTE.

In the present issue of the International Journal of Cardiology Hypertension [6], Vartela et al. assessed 46 patients with heterozygous familial hypercholesterolemia (heFH) without known coronary artery disease and 39 normal controls, using exercise treadmill test (ETT) and Bruce protocol. Left ventricular (LV) global longitudinal strain (GLS) was determined additionally to LV ejection fraction (LVEF). Both duration of the ETT and workload in metabolic equivalents was lower in the heFH group compared to controls. HeFH patients had higher rise of systolic (SBP) and diastolic blood pressure (DBP) from baseline to peak, compared to controls. GLS in heHF men was slightly decreased, although LVEF was similar in both groups. They concluded that the higher rise in systolic/diastolic blood pressure of heHF patients during ETT might reflect early preclinical hypertension. Furthermore, slight impairment of LV GLS was present, despite no apparent myocardial dysfunction was revealed by standard echocardiographic parameters.

The paper by Vartela and colleagues adds to the existing literature by assessing both ETT indices and echocardiographic strain parameters as potential markers of clinically silent impaired vascular function with prognostic significance. Previous studies have been published in this

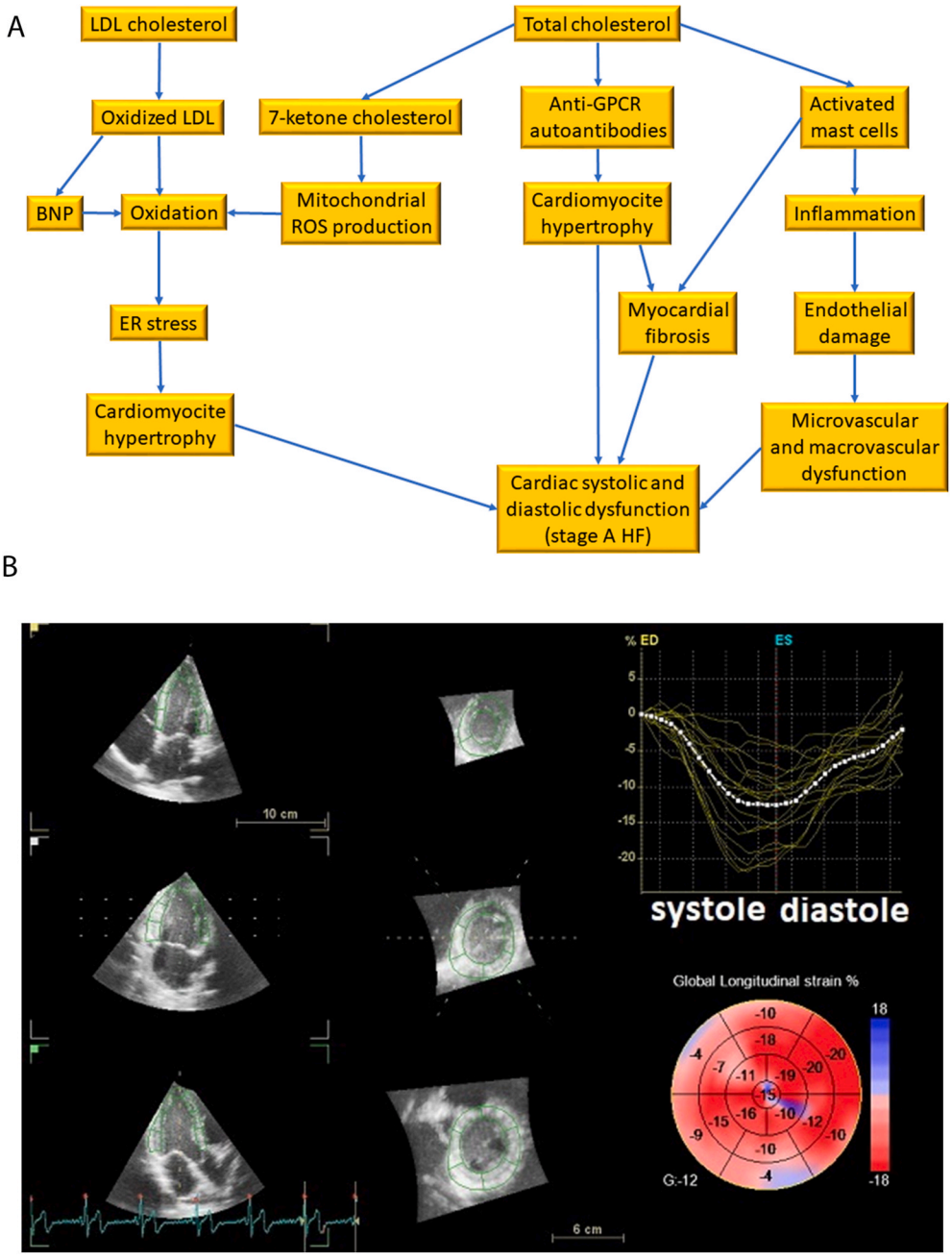

Fig. 1. Cardiac cellular metabolism, myocardial injury and LV strain impairment in heterozygous familiar hypercholesterolemia. A. LV molecular and cellular mechanisms leading to myocardial injury. B. LV global longitudinal strain impairment. BNP = brain natriuretic peptide; ER = endoplasmic reticulum; GPCR = G protein-coupled receptors; HF = heart failure; LDL = low-density lipoprotein; LV = left ventricle; ROS = reactive oxygen species.

area [7,8]. It has been reported that heFH women had an inadequate rise in their systolic and diastolic blood pressure compared with healthy women [7]. In asymptomatic heFH subjects without any evidence of ischemia it has been shown that ETT parameters may predict cardiovascular disease after three decades of observation [8]. The study by Vartela et al. has produced interesting results and is an important step in the quest to understand the connection between myocardial strain and systemic arterial hypertension in hypercholesterolemic patients. It was confined to a well-defined population which included asymptomatic treatment-naive heFH males without known coronary/peripheral arterial disease, with normal LVEF and no other risk factors as formal arterial hypertension or diabetes mellitus. A higher increase of both SBP and DBP during ETT was detected. These findings strongly suggest that heHF patients are at a higher risk of developing systemic arterial hypertension. High cholesterol level may have produced endothelial dysfunction, which has been shown to be related to the extent of atherosclerotic process. Atherosclerosis is associated with increased wall stiffness and reduced distensibility in conduit vessels. There is evidence that endothelial dysfunction in hypercholesterolemic subjects is systemic and spreads beyond the coronary circulation. Moreover, hypercholesterolemia may inhibit the effect of vasodilators like endothelium-derived relaxing factor (nitric oxide) on the vascular smooth muscle of resistance vessels resulting in elevated blood pressure during exercise. Higher aortic pulse wave velocity compared to controls has been demonstrated in ehFH patients, with increased thickness and reduced compliance in the ascending aorta suggesting possible early cholesterol deposition [9]. Decreased aortic strain assessed by tissue Doppler imaging or speckle tracking echocardiography was also shown in hypertensive patients [10]. Low wall strain and high stiffness can concur to arterial systemic hypertension and cardiovascular complications. Decreased aortic strain and heightened blood pressure can be causally related to each other, so blood pressure could become cause and effect: increased arterial stiffness and reduced distensibility raise systolic blood pressure, and the increase in blood pressure contributes to the decrease of arterial elastic properties.

Lower GLS values in heFH patients in the study by Vartela could be attributed to a relative increase in afterload or decreased myocardial contractility. Since no correlation between GLS and exercise blood pressure values was obtained in spite of the known inverse relationship between LV longitudinal strain and afterload, and resting values did not differ significantly between patients and controls, impaired primary myocardial contractility appears to be the most likely explanation, due to diffuse vascular dysfunction which could also be responsible for the inappropriate blood pressure response during exercise.

The conclusions drawn from this study should be evaluated with caution. Authors performed correlation analysis between GLS and resting-exercise blood pressure parameters. A trend towards statistical significance was obtained between GLS and resting diastolic blood pressure, whereas there was no correlation with exercise blood pressure parameters. However, the lack of contemporaneity between the ETT and the echocardiographic examination may have been one of the causes of the absence of correlation. A stress-echo test would have yielded additive information in terms of the etiopathogenetic link between heterozygous familial hypercholesterolemia and development of subtle left ventricular systolic dysfunction in these patients. Stress-echo is a recognized method for the assessment of a broad spectrum of ischemic and non-ischemic clinical conditions. In patients with preserved LVEF, the absence of contractile reserve is frequently associated with limited coronary flow reserve, and it is suggestive of latent LV systolic dysfunction and subclinical cardiomyopathy. Exercise-echocardiography findings can further refine risk assessment in patients with low-intermediate or high short-term versus low or high lifetime cardiovascular risk. Also, the role of aortic function indices in this context could be matter of future investigation since the presence of early aortic changes and arterial stiffening has been demonstrated in young heFH patients as well as in patients with sistemic arterial hypertension. Arterial stiffening has been associated with increased risk for cardiovascular events. Ultrasound-based methods, such as tissue Doppler imaging and speckle-tracking echocardiography, are particularly suitable to assess the biomechanical properties of the aorta in order to determine cardiovascular risk and evaluate disease progression.

There are still some gaps in the comprehension of pathophysiology of myocardial and vascular dysfunction in patients with heFH and their interrelationships. Additional studies dealing with diagnostic imaging and medical treatment in these individuals will sharpen our capacity to prevent cardiovascular complications and improve the quality of life.

Declaration of competing interest

None.

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None.

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