



Invited commentary

Primary prevention of diastolic dysfunction in the normal heart: The “Eyes Wide Shut” on a statin pleiotropic effect?

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As defined by Braunwald's textbook of Cardiology, diastole includes the period of time during which the myocardium loses its capacity to shorten and returns to an unstressed length [1], accordingly, diastolic dysfunction occurs when this process is prolonged, slowed, or incomplete [2]. Diastolic dysfunction of the left ventricle (DDLV) is thus a pathological condition that may progress to congestive heart failure (HF). Generally, two forms of HF have been identified; i.e., Heart Failure with Normal Ejection Fraction (HFNEF) and Heart Failure with Reduced Ejection Fraction (HFREF). The former, also recognised as Heart Failure with Preserved Ejection Fraction (HFPEF) – a definition which probably better delineates the fact that systolic function is not completely normal in such patients but only apparently preserved [3] is currently observed in about 50% of HF patients [4,5]. It usually involves the older and the female population, in particular those with a history of hypertension [5–8], and its incidence and prevalence has increased with worsening morbidity and mortality [5,9]. Conversely, patients with HFREF are more likely to be younger, male and to have an ischaemic aetiology compared with HFNEF patients [5]. The European Society of Cardiology (ESC) recently underlined the clinical importance and complexity of HFNEF, and issued new definition criteria, based on clinical signs and/or symptoms of HF, echocardiographic and biological parameters [10].

In this context, diastolic dysfunction refers to mechanical and functional abnormalities present during relaxation and filling of the left ventricle (LV), such as a prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness [11]; whereas HFNEF refers to the clinical syndrome in which patients with HF have little or no ventricular dilatation, preserved EF, and significant, often dominant, diastolic dysfunction. Diastolic dysfunction can thus, be quantified with indices of LV pressure decline and filling. Abnormal pressure decline is characterized by decreased peak

-dP/dt, prolonged isovolumic time constant (τ), and increased isovolumic relaxation time. Abnormal filling is characterized by slow and incomplete filling, increased atrial contribution to filling, and increased chamber stiffness, which can be caused by abnormalities in both cardiomyocytes and extracellular matrix (ECM) [11–14]. Changes in the amount, composition, and geometry of such ECM proteins, such as collagen and elastin, can alter LV stiffness and causes decreased or delayed relaxation, slow or incomplete filling, and increased diastolic stiffness, leading to the development of HFNEF [12]. Indeed, stiffness of the ECM is largely determined by tissue collagen amount, which in turn depends on the regulatory mechanisms of its synthesis and degradation, relative quantity of collagen type I, and degree of collagen cross-linking [11]. Moreover, cardiac inflammation can also contribute to diastolic dysfunction by triggering the accumulation of ECM through the induction of collagen gene expression and inhibition of cardiac degradation system [15].

Modern evidence-based therapy for HF has shown an improvement in prognosis of patients affected by HF with reduced left ventricular ejection fraction (HFREF). Our group reported the beneficial pharmacological effect of the combination of an aldosterone inhibitor with an angiotensin-converting enzyme inhibitor limiting the synthesis of collagen and reducing the post-infarct remodeling [16]. On the contrary, the prognosis of patients with HFNEF has remained unchanged despite the use of same class pharmacological agents [5,17–21].

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) are well-known potent lipid lowering agents. Additionally to their primary effects, statins have been shown to have several pleiotropic effects on the cardiovascular system [22], including antiinflammatory, antioxidative, and endothelial protective effects. Controversial results have been reported with statin administration in HFNEF. Some experimental and clinical studies have suggested a beneficial effect after statin therapy in HFNEF [23–27]. Fukuta and co-authors were the first to report that in patients with HFPEF statins was associated to improved

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survival [23]. Conversely, another study in animal model showed no effect on the progression of HF neither on survival, despite the attenuation of myocardial fibrosis and improved diastolic stiffness observed in the group treated with statins [28]. Moreover, a recent prospective trial by Gissi-HF-Investigators did not show differences in survival between daily statin therapy in comparison to placebo in patients with chronic HF, including patients with preserved systolic function [29].

In this issue of the Journal, Lerman and associates performed a study in which three groups of pigs ($n = 6$ each) were sacrificed after 12 weeks of normal diet, hypercholesterolemic (HC) diet, and HC diet with simvastatin (80 mg/day) treatment, respectively. Cardiac function was assessed by electron beam computed tomography and myocardial vascular fraction by micro-computed tomography. Histologic evaluations included collagen content quantification by Sirius Red staining and a hydroxyproline-based assay. The authors observed that LDL serum concentration was significantly higher in HC diet group, and in HC diet treated with simvastatin compared to normal diet group. Cardiac early diastolic filling was reduced in HC diet group compared with normal diet group and “preserved” in HC diet with simvastatin treatment group. In addition, myocardial vascular fraction and myocardial collagen content was higher in HC group but not in normal diet group and in HC diet with simvastatin group. Immunoblotting showed an increase in myocardial expression of b-FGF, VEGF and TGF- β 1 in HC diet group compared with normal group while the expression was attenuated in the HC diet with simvastatin treatment group.

How can we move from bench to bedside after reading the study done by Lerman and co-authors? First, this study provides additional evidences that experimental hypercholesterolemia leads to diastolic dysfunction due to increase myocardial collagen content, especially in the perivascular compartment, along with upregulation of pro-fibrotic and proangiogenic pathways. Second, as also stated by the authors, the present study shows for the first time in a large size animal model, that administration of a statin prevents these myocardial morphological changes independently of any lipid-lowering effect. These results represent an evidence to support the model of hypercholesterolemia-induced diastolic dysfunction as a reactive process amenable to the non-lipid-lowering properties of statins. Third, the non-lipid-lowering properties of statins already reported in both animal and clinical studies of LV hypertrophy are thought to result from mild statin-induced reduction of blood pressure, alterations in myocardial growth regulatory signal transduction pathways, changes in inflammatory or immune-mediated systems, or increased arterial compliance [30,31]. Statins may alter arterial compliance by changing the composition of the vascular wall or by changing endothelial response to local and circulating vasoactive compounds and neurohormones [32]. The present study suggests another lipid-independent property, administration of statins could prevent the increase in myocardial collagen content at the bottom of diastolic dysfunction.

Albeit this study opens a new horizon in the field of diastolic dysfunction prevention showing on one side the “indirect” role of hypercholesterolemia in promoting diastolic dysfunction and, on the other side, the ability of simvastatin for preserving normal diastolic function through a mechanism of action independent of cholesterol reduction, it is hard to believe that lipid lowering therapy will be clinically relevant in normalizing LV structural changes or LV function in patients with HFNEF [32]. Finally, we should keep in mind that these results are based on animal models, and at this moment should be applied with caution to human. Given the important public health impact of diastolic dysfunction, large prospective clinical trials should be performed to evaluate the therapeutic potential of statins in this important field of prevention. –

only in this way we could look deeply into this topic with “eyes wide opened”.

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