EDITORIAL COMMENT

HFpEF, Diastolic Suction, and Exercise*

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Heart failure with preserved ejection fraction (HFpEF) is a disease of the myocardium, the vascular tree, the pulmonary circulation, and the kidneys. It may to some extent be attributed to unsuccessful aging. Why is a patient with HFpEF short of breath when exercising? In order to differentiate between a cardiac and a pulmonary etiology, Borlaug et al. (1) subjected patients (with exertional dyspnea, ejection fraction >0.50, and normal filling pressures at rest) to leg lifting and recumbent biking. For differentiating between cardiac and noncardiac origin of dyspnea, they defined a pulmonary capillary wedge pressure cutoff of 25 mm Hg. The subgroup of patients exceeding this value during exercise was deemed to have HFpEF. These patients developed a mean left ventricular (LV) end-diastolic pressure of 34 mm Hg as opposed to 14 mm Hg for noncardiac dyspnea. This study identifies elevated filling pressures as the causal mechanism of cardiac dyspnea in patients with HFpEF. This elevation occurred at leg lifting and low exercise workloads.

The culprit mechanism for exertional elevation of filling pressures is a stiffer ventricle, characterized by a steep diastolic pressure-volume relation (2). This is the definition of diastolic dysfunction. The stiff ventricle may still have enough reserve to keep filling pressures low at rest, but this reserve is rapidly exhausted during exercise. A sound approach to exertional dyspnea is to consider that you are facing both a failing heart and a deficient vascular tree, and that multiple domains of

cardiovascular function contribute in an integrated fashion to produce exercise limitation (3). Reduced left atrial function contributes to exercise intolerance and breathlessness (4). A recent study provides evidence for an additional role of peripheral factors in patients with HFpEF and implicates skeletal muscle metabolism and function in the observed exercise intolerance (5,6).

Proposed mechanisms of diastolic dysfunction include deficient early elastic LV recoil, blunted LV lusitropic response, and low LV pre-load reserve (2). Systolic dysfunction is inevitably present as well. Myocardial contraction and relaxation are based on the same cross-bridge interaction and respond similarly to load alterations (7). Elastic restoring forces are built up during systole and contribute to early diastolic suction. In a study on HFpEF patients, Tan et al. (8) showed that systolic longitudinal and radial strain, systolic mitral annular velocities, and apical rotation were lower in HFpEF and failed to rise normally during exercise. In diastole, HFpEF patients had reduced and delayed untwisting, and reduced LV suction at rest and during exercise. In that study, the peak velocity of early-diastolic mitral flow propagation velocity (Vp) was used as an approximation for ventricular suction.

Vp represents an early-diastolic flow wave propagating toward the apex of the ventricle. The signal displays velocities on a line extending from the mitral annulus to the apex and optimally located in the middle of the flow signal, at a distance of the peripheral vortex formation. For each pixel of the displayed color M-mode map, time, depth, and numerical velocity can be precisely determined, processed offline, and used for directly calculating an intraventricular pressure difference (IVPD), rather than assuming that Vp reflects these gradients.

Three-dimensional flow across a cardiac chamber is governed by the Navier-Stokes equation, based

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on the conservation of energy principle. The best known and most simplified of these equations is the Bernoulli formula, which is only applicable in the presence of a severe narrowing. The Euler equation is a simplified form of the Navier-Stokes equation for a single spatial direction of flow.

$$\frac{\delta p}{\delta s} = -\rho \cdot \left(\frac{\delta v}{\delta t} + v \cdot \frac{dv}{\delta s} \right)$$

Where p is pressure, s is position, and v the velocity along the streamline, t is time, and ρ is blood density. Fluid acceleration holds a first inertial component that designates the change in velocity through time at a given position. This component promotes filling. The second convective component represents the change in velocity through space at a given instant. This component opposes filling. The resulting IVPD is the mathematical sum of the 2 components. The Euler equation allows computation of IVPD, defining suction as the physiological IVPD generated between apex and base promoting early diastolic filling. Limitations are that the flow is not truly symmetrical and unidirectional, and that the interrogation line may deviate from the core of the flow volume. This approach could prove to be hazardous in the presence of regionally altered LV function or in the presence of dyssynchronous wall movements.

Rovner et al. (9) showed that the increase in IVPD during exercise is blunted in heart failure with reduced ejection fraction (HFrEF) and that the change in IVPD during exercise was a powerful predictor of VO$_2$max. In 2005, Yotti et al. (10) published a milestone article on HFrEF patients showing that the IVPD was reduced at rest and failed to increase under dobutamine. In terms of flow dynamics, reduced suction resulted from lower inertial flow acceleration and proportionally higher deleterious convective deceleration. The latter finding is consonant with fluid dynamics and increased vortex formation in dilated ventricles (11).

In this issue of *iJACC*, the paper by Ohara et al. (12) extends our knowledge on 166 consecutive patients undergoing dobutamine echocardiography, with no inducible ischemia and with preserved ejection fraction. The patients were classified according to diastolic function as normal, grade 1, 2, or 3, defined as per the prevailing recommendations (13). The patients with normal diastolic function were not healthy subjects and were suffering from hypertension, renal disease, and dyslipidemia. The overall finding is that in patients with HFpEF, the

IVPD is normal at rest but fails to increase under dobutamine. In order to differentiate between the effect of atrial filling pressure and ventricular suction, IVPD was subdivided into basal (from annulus to mid-LV) and apical (from mid-LV to apex) IVPD. Both normal subjects and patients with diastolic dysfunction showed similar increases of basal IVPD in response to dobutamine. In patients with HFpEF, there was a selective failure in augmentation of apical IVPD, attributed to deficient suction. The authors conclude by suggesting that a failure of augmentation of longitudinal contraction and subsequent lengthening in response to adrenergic stimulation could contribute to the reduced response of the IVPD in patients with diastolic dysfunction.

Adrenergic stimulation and exercise are quite distinct challenges for the diseased heart. The predominant challenges during exercise are related to increased stroke volume and increased cardiac load, in addition to increased heart rate and contractility. It therefore cannot be inferred from the present experimental data that deficient suction is an important mechanism of exertional dyspnea.

When looking at the graphs in the paper, a consistent finding is that deficient adrenergic augmentation of IVPD is most pronounced in grade 1 diastolic function and that the difference of augmentation between the normal subjects and grade 2 to 3 diastolic dysfunction are less important and even no more significant. How to explain this pseudonormalization of the adrenergic response of IVPD, with grade 1 being the least responsive? Are we sure that the adrenergic augmentation of apical IVPD is not dependent on filling pressures? Appendix D provides some additional information. When the patients are analyzed by tertiles of averaged e′ instead of grade of diastolic dysfunction, we see that only the lower tertile (e′ <6.5 cm/s) shows a blunted increase of apical IVPD with preservation of the increase of basal IVPD. Baseline e′ clearly predicts response of IVPD to dobutamine. This is not surprising as e′ is similarly determined by relaxation and restoring forces in addition to lengthening load (14).

In HFrEF, deficient adrenergic augmentation of IVPD was attributed to both an impaired inertial and an enhanced convective component (10). The failure of the convective component was attributed to the spherical remodeling and the dilation of the ventricle. In the present study of HFpEF, only the adrenergic augmentation of the inertial component of IVPD is deficient. The convective component is similar in all patient groups and does not change

under dobutamine. Of note, the absolute values of this convective component are much lower than in the study by Yotti et al. (10), even in normal subjects, suggesting methodological differences and the need for standardization.

To summarize, Ohara et al. (12) elegantly showed that apical IVPD response to adrenergic stimulation is blunted in some but not all patients with HFpEF, mainly in the patient with deficient myocardial relaxation (evaluated by averaged e′) at baseline. Future research will have to focus on a better characterization of HFpEF patients with loss of adrenergic augmentation of diastolic IVPD. The relevance of this finding for exertional dyspnea in HFpEF still has to be further investigated.

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