The left atrium (LA) plays a key role in the filling of the left ventricle (LV). In systole, pulmonary venous flow fills the LA when the mitral valve is closed. In addition, normally, during LV ejection, the mitral annulus is pulled toward the apex, increasing pulmonary venous flow into the LA. Then, LV ejection compresses elastic elements storing some of the energy produced by cycling of the cross-bridges (1). With LV relaxation, this energy is released as elastic recoil. This produces an early diastolic intraventricular pressure gradient that progressively extends from the LA toward the apex of the LV (2). This process of LV suction accelerates blood flow out of the LA toward the LV apex. Thus, the LV is able to fill even from 0 LA pressure (3). Early in diastole, the mitral annulus rapidly moves away from the apex into the LA. This shifts blood that was above the mitral valve at end-systole into the LV (4). Thus, early in diastole, LA volume decreases and LV volume increases. This early diastolic decrease in LA volume, which Farzaneh-Far et al. (5) term “passive LA emptying,” provides a measure of the early diastolic LV filling.

The pericardial sac limits the total cardiac volume, which stays nearly constant during the cardiac cycle (6). Thus, the decrease in right ventricular and LV volumes during ejection is balanced by an increase in right atrial and LA volumes, whereas the increase in RV and LV volume in diastole is accompanied by a decrease in right atrial and LA volumes. In this way, the LA can be considered to mirror the function of the LV (7).

In the presence of LV diastolic dysfunction, slowed relaxation, and reduced elastic recoil results in higher early diastolic LV pressures and the loss of the progressive early diastolic pressure gradient from the LA to the LV apex. In addition, any LV dilation increases the dissipation of the pressure gradient due to convective deceleration (2,8). This diminished or absent LV suction means that early diastolic filling is more dependent on LA pressure. If LA pressure is not elevated, early diastolic filling is reduced, and the importance of late diastolic filling driven by LA contraction is enhanced. This is the “impaired relaxation” pattern of mitral flow with a reduced E-wave and large A-wave and will be accompanied by less early diastolic LA emptying (9,10). Early diastolic filling can be restored to normal or even above normal despite impaired diastolic suction when LA pressure is elevated. This is the situation with pseudo-normalized and restricted filling patterns (9–11). In these situations, LA passive emptying fraction may be normal. The restricted LV filling pattern is differentiated from normal by a shorter E-wave deceleration time (reflecting decreased LV compliance) and a reduced and delayed early diastolic mitral annular velocity (e’) (9–12).

In response to stress, adrenergic stimulation normally increases LV ejection and the rate of LV relaxation, producing lower LV early diastolic pressures and more rapid filling (8,13,14). This would be expected to augment the early diastolic reduction in LA volume. In contrast, the failing myocardium has a diminished response to adrenergic stimulation. Thus, there would be less augmentation of early diastolic flow. Similarly, if adrenergic stimu-
lation produces myocardial ischemia, LV ejection and suction may not increase, or may even be reduced. Thus, one would expect that early diastolic filling (and reduced LA emptying) would not increase as much with adrenergic stimulation in the presence of myocardial dysfunction and/or the induction of ischemia (8,15). It is important to recognize that the expected responses may be altered if LA pressure increases.

In this issue of iJACC, Farzaneh-Far et al. (5) report using cardiac magnetic resonance to measure LA volumes during adrenergic stimulation produced by infusing dobutamine in 108 patients being evaluated for the presence of myocardial ischemia. They defined LA “passive emptying” as the decrease in LA volume from mitral valve opening to before the onset of LA systole normalized to the maximum LA volume. This change in volume is a reflection of the early diastolic LV filling. Compared with 23 healthy subjects, the patients’ LA passive emptying fraction (LAPEF) was reduced and LA volume was increased. Although LV diastolic filling dynamics were not assessed, this suggests that the patients predominantly had an impaired relaxation pattern at rest.

The median change in LAPEF (ΔLAPEF) was about 11%. Patients with ΔLAPEF below the median had lower baseline LV ejection fractions and larger LV volumes. A total of 29 diverse, adverse events occurred over a mean follow-up period of about 2 years, including death, myocardial infarction, unstable angina, and heart failure hospitalizations. By both univariant and multivariant analyses, ΔLAPEF was strongly associated with adverse events. ΔLAPEF remained associated with subsequent events even after adjustment for inducible wall motion abnormalities and myocardial delayed enhancement. Out of the 80 patients without evidence of ischemia, 16 subsequently experienced adverse events. A reduced ΔLAPEF was strongly associated with events in these patients. Farzaneh-Far et al. (5) speculate that this may be due to a greater sensitivity in detecting ischemia.

Although provocative, the results of this study (5) must be interpreted in light of some limitations. First, the outcome end point combines ischemic and heart failure events. Second, the reduction of the augmentation of ΔLAPEF might be due to the induction of ischemia or to an abnormal myocardial response to dobutamine. Third, because the LAPEF was abnormal in the patients at rest, it is not known if their findings would be similar in patients with normal resting LAPEF or those with greater abnormalities at rest. Finally, the response of ΔLAPEF may be confounded by changes in LA pressure.

Conventional functional stress testing relies on the development of regional or global systolic dysfunction to recognize ischemia. However, diastolic dysfunction precedes systolic dysfunction in the ischemic cascade. There is increasing evidence that stress-induced diastolic dysfunction may be more sensitive than systolic dysfunction in detecting ischemia (15–17). Because ΔLAPEF with dobutamine infusion presumably reflects LV diastolic function, more sensitive measures of LV diastolic function might be better. Such measures include mitral Doppler inflow velocities, color M-mode measurement of the speed and extent of early diastolic flow propagation, and tissue Doppler measurement of the velocity and timing of early diastolic mitral annular velocity (11). In addition, the spatial-temporal map of early diastolic LV inflow velocities obtained by the color M-mode provides the information necessary to integrate the Euler equation and calculate intraventricular pressure gradients (18,19). LV diastolic function, measured as mitral annular velocity, and the peak intraventricular pressure gradient are augmented in response to dobutamine (8,15). This augmentation of LV diastolic function is impaired in the presence of myocardial ischemia or heart failure (8,15,20). However, conventional measurement of diastolic function may have technical limitations during stress testing. For example, the early and late diastolic components of mitral inflow and mitral annular movement may merge, and the color M-mode image may be compromised by motion artifacts during rapid heart rates. Although ΔLAPEF is an indirect measure, it could provide a more stable, integrative marker of LV diastolic function.

The importance of the study by Farzaneh-Far et al. (5) is that it contributes to the growing information indicating that the response of LV diastolic function to stress is valuable and suggests that measuring LA emptying function may provide an additional method to assess this response. Future studies of a larger, more diverse group of patients that include measures of LA emptying and LV diastolic function are needed.

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Key Words: atrium ■ cardiac magnetic resonance ■ diastole ■ ischemia ■ prognosis ■ suction.