EDITORIAL COMMENT

Presto Untwisting and Legato Filling*

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It has been suggested that, “As a stand-alone term, diastolic dysfunction is ambiguous (1). A clear distinction between abnormalities of active and passive diastolic properties (2,3) needs to be established. The cellular and molecular mechanisms governing these 2 aspects of diastole are distinct and not directly linked.” We agree and welcome new insights into the fundamental physiologic principles of diastolic function and its noninvasive assessment offered in an article by Burns et al. (4) in this issue of iJACC.

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Until the 1980s, assessment of the active and passive aspects of diastole was almost exclusively the province of the invasive hemodynamic laboratory. With the development of pulsed Doppler echocardiography, patterns of left ventricular (LV) filling could be discerned, and their relationship to the physics and physiology of diastole was established (5). Acceleration of the E-wave (and for the most part its maximal velocity) is proportional to left atrial pressure divided by \( \tau \), the exponential time constant of isovolumic LV pressure decay and a key active component of diastole. Conversely, E-wave deceleration time was shown to be inversely related to passive ventricular stiffness (6,7). Unfortunately, all flow-based indexes, whether transmitral or pulmonary venous, suffer from dependency on loading conditions, a situation partly overcome with direct recording of early diastolic myocardial (\( E_m \)) and annular (\( E_a \) or \( e' \)) velocities by Doppler tissue imaging (8) and blood flow propagation velocity through the mitral valve to the apex by color M-mode (\( V_p \)) (9), both shown to be related to LV relaxation. Filling pressure estimation by the ratios E/Ea or E/Vp has been shown to be useful in many clinical situations, although recent work has shown conditions where these relations are less reliable (10). All this emphasizes the complexity of ventricular filling and our own naivete in trying to shoehorn a multidimensional entity into a simple linear scale of Stage I to IV. Indeed, “diastolic function” involves a complex interplay of molecular, mechanical, and architectural phenomena all playing out on different time scales to affect efficient, low-pressure filling of the ventricle.

Figure 1 attempts to show the relationship of some of these indexes to the timing of LV filling and mechanical events in normal diastole. Not shown are upstream molecular events, such as the phospholamban-modulated reuptake of calcium into the sarcoplasmic reticulum by SERCA2, which initiates myocardial relaxation. Within 300 ms of the onset of relaxation, the early events of diastole are normally complete, events that we conceptualize into 3 phases. The first phase is mechanical recoil resulting from the release of elastic energy stored both in individual sarcomeres by the giant molecular spring titin and within the myocardial interstitium by the shear strain and torsion induced by the helical architecture of the ventricular muscle fibers. This recoil phase begins at the end of contraction and includes isovolumic pressure decay, setting up an intraventricular pressure gradient (diastolic suction), which assists the low-pressure filling of the ventricle. Phase 3 comes after the ventricle is almost completely relaxed and marks the passive filling period of diastasis followed by atrial contraction. Note that as each interval of \( \tau \) passes, the “excess” ventricular stiffness over the fully relaxed pressure-volume curve is reduced by another factor of \( 1/e \) (36.8%). After a period of \( 4\tau \) from closure of the aortic valve, the ventricle is more than 98% of the

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

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way from the systolic to the diastolic curve. Phase 2 is the intermediate phase, where LV volume is increasing but ongoing relaxation leads to a continued fall in LV pressure. Thus, the first mechanical manifestation of diastole is LV untwisting, which begins while the ventricle is still ejecting, ushering in a sequence of temporally linked events in the normal heart: isovolumic pressure decay, intraventricular pressure gradient, basilar recoil, and finally mitral valve opening and early diastolic filling (11–13).

The remaining ventricular systolic elastance decays exponentially to the fully relaxed pressure-volume curve of the ventricle, and passive aspects of LV filling ensue. In pathological situations of slow relaxation (i.e., longer $\tau$), $E_a$ is decreased and delayed, which means that the transition from active to passive diastole (phase 2) is extended and the passive phase 3 is shortened and might not even occur during tachycardia when relaxation is incomplete at the end of diastole (14). Kasner et al. (15) reported that $E_a$ was related not only to $\tau$ but also to LV stiffness indexes, further blurring the distinction between active and passive diastole. These findings suggest that, although $E_a$ is useful to evaluate diastolic function, it is not a purely active diastolic property and includes components of passive diastolic function. The study by Burns et al. (4) extends our search for a relatively pure marker for active relaxation.

Although limited by small numbers and a narrow range of ventricular function, Burns et al. (4) found significant, albeit weak, correlations between LV untwisting and the early diastolic parameter of $E_a$ and minimal LV pressure measured invasively in the catheterization laboratory. In contrast, they found no relationship between untwisting and passive LV compliance. Several factors might have contributed to the relatively weak correlations found. First, these are all challenging parameters to measure, and a certain amount of “noise” is expected in the data. Second, they specifically selected patients with relatively normal LV function, so there was only a narrow range of stiffness and $\tau$. Finally, although they used nitroglycerine and volume infusion to modulate preload, they did not alter afterload or inotropic state (with exercise or catechol infusion), which would have led to more dramatic changes in early diastole, increasing the variance to which untwisting indexes could correlate. Despite these limitations, this investigation...
helps to illuminate “ambiguous diastolic dysfunction.” Better assessment of diastolic dysfunction is badly needed, because diastolic dysfunction significantly increases mortality, independent of the presence of a major comorbidity. The degree of diastolic dysfunction remains stable in approximately 50% of patients, whereas those whose diastolic function improves over time have a more favorable prognosis (16).

We suggest, as a perspective, that diastolic LV mechanics and filling dynamics be explored with Figure 1 in mind, recognizing that, although some parameters are relatively pure active and passive components, most of them are blends of both. We remain limited to indirect measures of diastolic function, because we cannot measure absolute pressure, force, or tension in the ventricle or the myocardium, even with advanced echocardiography.

In short, diastolic function is the ability of the ventricle to fill at low atrial pressure. To perform this critical function, presto untwisting and smooth legato filling in dulcet tones are both indispensable. Active untwisting leads to isovolumic pressure decay and generates intraventricular pressure gradients, which leads to LV suction and efficient filling. Untwisting seems to be independent of LV passive compliance (4) and can be easily measured in the clinical setting. Returning to Maurer’s suggestion of the initial citation, we might now establish a distinction between abnormalities of active and passive diastole to more precisely define diastolic function and to develop more specific treatments for patients with diastolic dysfunction.

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Key Words: diastole • echocardiography • speckle tracking imaging • torsion • untwisting.