EDITORIAL COMMENT

Diastolic Heart Failure, Diastolic Left Ventricular Dysfunction and Exercise Intolerance*

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The phenomenon of “diastolic heart failure” is rightly receiving greater attention (1–4); community-based studies such as those in Framingham (5) and Olmsted County (6) show that up to 50% of older persons with heart failure do not have impaired left ventricular (LV) systolic function to account for this, and that the condition is usually associated with LV hypertrophy and is preceded by elevation of systolic blood pressure. Modern medicine has been slow to accept diastolic dysfunction as a cause of heart failure, largely because there are no accepted noninvasive measures of diastolic dysfunction, there is a wide overlap in diastolic function between persons with apparent diastolic heart failure and the normal aged community, and the profession has focused on impaired LV systolic function and coronary arteriosclerosis as the cause of myocardial scarring and impaired LV contractility. Up until the year 2000 there had been no randomized therapeutic studies of patients with diastolic LV dysfunction. With a blank slide, Dr. W. Little of Wake Forest University illustrated this to packed sessions of the 49th and 50th American College of Cardiology (ACC) meetings.

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In this issue of the Journal, Hundley et al. (7) draw attention to the relationship between evidence of isolated diastolic LV dysfunction and aortic stiffening, showing that in older persons with diastolic heart failure, impaired exercise tolerance correlates with aortic stiffening, and that there is a highly significant difference between these patients and a normal age-matched group. They also confirm that there is a significant difference in exercise tolerance and aortic stiffness between normal young persons <30 years of age and those over age 60. They argue that reduced aortic distensibility (increased stiffness) is the likely cause of diastolic dysfunction, reduced exercise tolerance and cardiac failure.

This attention to aortic stiffness and cardiac dysfunction may seem new, but it was the dominant focus in studies of cardiovascular aging and arterial disease a century ago. The English physiologist C.S. Roy in 1880 stated of humans that “only in the case of young children do we find that the elasticity of arteries is so perfectly adapted to the requirements of the organism as in the case of the lower animals” (8). The Nobel Laureate A. V. Hill along with J. C. Bramwell stated that “the amount of energy expended by the heart...has been shown to be proportional to the pressure developed...hence the amount of energy that the heart has to expend per beat, other things being equal, varies with the elasticity of the arterial system” (9). The same investigators confirmed increase in arterial stiffness with age from noninvasive measurement of pulse-wave velocity (10). Queen Victoria’s physician, W. H. Broadbent, in 1875 described characteristic features of increased arterial tension (from the radial pulse), of clinical LV hypertrophy (heaving apex beat and fourth heart sound), exercise intolerance and development of cardiac failure (11). The Senile Heart (12) by G. W. Balfour in 1894 related symptoms of heart failure to LV hypertrophy and stiffened arteries. The founder of English cardiology, James Mackenzie, discussed developing arteriosclerosis as causing impaired exercise capacity in the fourth decade of life, and the progress of this to LV hypertrophy and cardiac failure (13). Osler (14) described arteriosclerosis as “nodular” (atherosclerosis), “diffuse” (hypertensive) and “senile,” noting that the degenerations could be mixed, but were progressive, and commonly culminated in cardiac failure.

If this subject of arterial stiffening and cardiac failure is so old, why has it been overlooked? Perhaps Peter Libby has the answer when noting that practitioners of an era become slaves to the technology of the era (15). By the late 20th century, we had become preoccupied by the technologies that define coronary artery narrowing and LV contractility. The clinical era of sphygmonography and pulse-wave analysis in the early 20th century closed with the introduction of the cuff sphygmomanometer. The cuff carried a mixed blessing. Although it did provide noninvasive measures of systolic and diastolic pressure, it also created preoccupation with diastolic pressure as a measure of peripheral resistance, and the view that diastolic pressure need be elevated for a diagnosis of hypertension to be made and treatment initiated. It is just one decade back that this concept was overturned by the Systolic Hypertension in the Elderly Program (SHEP) and other studies (16,17).

Sphygmomanometric studies of systolic pressure and pulse pressure first drew modern attention to arterial stiffness and its ill effects on the heart. The Framingham Study showed marked increase in pulse pressure over age 50 (18), whereas Framingham (19) and other studies (20,21) consistently showed a positive relationship between pulse pressure and cardiovascular events in persons over age 50 and associated this with an increase in arterial stiffness. A neutral (22) or inverse (23) relationship between pulse pressure and cardiac events in persons under 50 years can be attributed to

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

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amplification of the arterial pulse (24,25), which is greatest in this younger age group and makes brachial pulse pressure an uncertain index of aortic pulse pressure.

In the accompanying article by Hundley et al. (7) aortic distensibility was measured from aortic pulsatile expansion (using magnetic resonance imaging [MRI]) and brachial pulse pressure (with a cuff sphygmomanometer). No account was taken of pressure-wave amplification between the aorta and brachial artery. For distensibility or like indices to be measured accurately, pressure and diameter change should be measured at the same site. This is a fault in the study, though not a fatal flaw, as pulsatile expansion was significantly diminished in the diastolic heart failure group compared to age-matched controls. Individuals wishing to extend this work are advised to consider this issue carefully especially when, as in the heart failure patients described here, factors such as high heart rate and brisk LV ejection might amplify the brachial pressure pulse with respect to the aortic pulse pressure (25). Measurement of pulse-wave velocity by MRI or simpler noninvasive methods would have been a helpful complement. Another methodologic anomaly was that arterial systolic and pulse pressures in the older normal cohort, 124 and 52 mm Hg, respectively, were considerably less than in the Framingham and the National Health And Nutrition Examination Survey population at a similar age, and no different from the younger group.

Several questions follow from the work of Hundley et al. (7). These include:

1. How does aortic stiffness cause diastolic heart failure?
2. How can aortic stiffening be identified?
3. How can diastolic heart failure be separated from systolic heart failure?
4. What is the most appropriate treatment of diastolic LV dysfunction and of diastolic failure?

The first question is readily answered. Aortic stiffening increases aortic pulse-wave velocity so that wave reflection returns earlier, augmenting the aortic pressure in systole and causing relative reduction of aortic pressure throughout diastole (13,24,25). Effects are of increased aortic and LV systolic pressure with increased myocardial oxygen demands and LV hypertrophy, and decreased aortic pressure throughout diastole with compromised coronary perfusion. Coronary perfusion is further impaired in LV hypertrophy when ejection duration also increases and the diastolic period is compromised (26). All these factors—increased systolic LV pressure, LV hypertrophy and myocardial ischemia—delay myocardial relaxation and lead to diastolic heart failure.

Aortic stiffening can readily be identified from the arterial pulse (11,13,14,25). Early return of wave reflection causes exaggeration of the second systolic peak—a feature of the “senile” pulse, which was recognized by Marey (27) in 1860, and Mahomed in 1872 (28) and was used in the 19th century to decline applicants for life insurance (29) as well as in routine clinical practice (11,13). Measurement of aortic pulse-wave velocity can be accomplished readily (9,10,24,25) and is particularly useful when systolic heart failure or change in heart rate alters LV ejection period, and so complicates interpretation of the arterial pulse (25).

Diastolic dysfunction typically is characterized by delayed LV relaxation, but there is prolongation of mechanical systole as well, such that ejection duration is usually increased (25,30). This may provide a practical measure to identify predominantly diastolic heart failure and separate this from systolic heart failure because in the latter, ejection duration typically is decreased (25,31).

If diastolic LV dysfunction is caused by early return of wave reflection, either directly by raising late systolic pressure or indirectly by causing LV hypertrophy and ischemia, then it should be relieved by reducing or delaying wave reflection. This is achieved with angiotensin-converting enzyme inhibitors, calcium channel antagonists, A2 antagonists and nitrates (24,25). These drugs are effective in the management of diastolic heart failure, especially when combined with measures or drugs (beta-blockers), which reduce heart rate and so preserve diastolic relaxation period. In a recent study (32) verapamil was shown to be particularly effective in reducing indices of arterial stiffness (carotid augmentation and aortic pulse-wave velocity), for improving ventricular/vascular interaction and for increasing capacity for exercise in older persons with diastolic LV dysfunction. It is quite likely that agents with similar properties (33) will be shown to have similar beneficial effects.

The study by Hundley et al. (7) in this issue of the Journal and other recent articles turn the clock back to the beginning of the 20th century, to Osler’s (14) and Mackenzie’s (13) interest in arteriosclerosis and its subtle effects on cardiac function as well as a cause of heart failure. Mackenzie (13) related arteriosclerosis to declining physical performance even at the age of 30, when “running after trains is not to be done in comfort, and the ascent of hills is undertaken with more deliberation. All this proceeds pari passu with diminished resiliency of the arterial wall” (13). Diastolic heart failure appears to result from the culmination of stresses on the arteries and heart, and to be the end result of a process of gradual aortic stiffening, gradual decline in exercise performance, progressive detuning of vascular/ventricular interaction, progressive increase in LV myocyte size, with “pathological” hypertrophy and a situation that evolutionary forces never had to face when the human life span was just 20 to 30 years. The subject of diastolic heart failure is fascinating, and for many reasons; it takes one back in one dimension to medicine of a past age, and in another to the links among competitive athletic prowess, aging and development of frank disease.

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