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Diastolic stress testing: a new trick to evaluate the ageing heart

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Exertional shortness of breath in the absence of an obvious cardiac abnormality is a perplexing and relatively common clinical scenario especially in older patients. These patients often undergo multiple evaluations by different specialists and end up without a definitive diagnosis and, more importantly, without any specific therapeutic target to improve their symptoms. In some of these patients, exercise intolerance is attributed to respiratory disease, in others to deconditioning or obesity and in many diastolic abnormalities are claimed as the underlying problem without substantiating data. In their article in this edition of *Heart*, Tan *et al* describe a study of diastolic function on exercise in a group of patients with treated hypertension without significant diastolic dysfunction at rest whose functional capacity is significantly reduced (***see page 948***).[1] Their findings that these patients exhibit significant abnormalities of diastolic function on limited exercise and that these induced diastolic abnormalities relate to the degree of functional limitation are an important contribution to our understanding of the pathophysiology of functional impairment in older hypertensive patients. This paper also highlights the potential utility of diastolic stress testing as a diagnostic modality in this patient population.

It is not surprising that exercise stress will provoke diastolic abnormalities that are not apparent at rest. Indeed, diastolic abnormalities, as a rule, accompany systolic abnormalities during stress, and demand ischaemia leads first to diastolic, and then to systolic abnormalities. One can roughly divide diastolic function parameters into 'traditional' or 'hard', and 'contemporary' or 'soft' indices. Traditional diastolic function indices are usually considered as measures of relaxation, diastolic stiffness and filling pressure (which results from the interaction of relaxation, stiffness and preload). Relaxation occurs first with mitral valve closure, followed by left ventricular (LV) filling along the pressure—volume curve that is defined by LV stiffness, and finally, results in LV end-diastolic pressure. By default, measuring traditional indices means measuring LV filling pressures invasively, which is impractical in routine clinical diagnostic assessment and is particularly difficult on exercise.

In clinical practice, we most often use 'contemporary' indices, almost exclusively obtained by echocardiography. These indices can be considered 'soft' as they often reflect factors other than 'traditional' indices.[2] However, 'contemporary' indices give us a slightly different description. Here, the diastolic process starts with LV untwisting. This represents the early relaxation of epicardial fibres, which in turn releases the elastic elements within the ventricle and leads to clockwise motion of the apex. This process starts in the second part of the systole, and reaches its maximum at the time of aortic valve opening, preceding the beginning of isovolumic relaxation as defined by 'traditional' indices. Next, the mitral valve opens owing to development of LV suction. Suction can be quantified by early diastolic intraventricular pressure gradient, or by its surrogate, colour-M mode flow propagation velocity. This is followed by downward motion of the mitral annulus and outward motion of the LV wall, which results in the early filling flow through the mitral valve. Of note, all of the previous phenomena occur in this definite order both in sickness and disease, and show some correlation with 'traditional' parameters of relaxation. In contrast, the shape of the second half of the early mitral filling wave depends on LV stiffness: the greater the stiffness, the shorter the LV filling.

The biggest drawback of 'contemporary' indices is that their values are a result of mixed influences of relaxation, stiffness and filling pressures or even some other parameters, such as LV geometry. A potential strength is that in contrast to 'traditional' pressure-based parameters, echocardiography can provide regional estimates of both relaxation and stiffness indices obtained by measurement of regional deformation (strain and strain rate) and velocity. However, the comprehensive non-invasive assessment of diastolic dysfunction is complex and time consuming at rest and becomes more difficult with the effect of increased heart rate with exercise. Fusion of the early diastolic flow velocity and the atrial contraction velocity occurs at higher heart rates and makes their differentiation impossible. Furthermore, obtaining a technically adequate assessment is difficult in a patient who is fighting for breath while exercising.

Despite these difficulties, Tan and colleagues have shown that diastolic stress testing by Doppler echocardiography is both feasible and useful.[1] They compared patients with heart failure and normal ejection fraction (HFNEF) due to hypertension with healthy volunteers. Patients had a much lower exercise tolerance than healthy volunteers, despite being of similar age, gender, blood pressure and ejection fraction. Both groups underwent a challenging exercise protocol of supine symptom limited exercise testing, with the target heart rate of 100 bpm during which two-dimensional, pulsed and colour-M mode Doppler data were collected. The

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data were used to obtain multiple indices of LV diastolic function.

Several previous studies assessed diastolic function during submaximal stress testing, mostly focusing on the ratio between early diastolic velocities of mitral inflow and mitral annulus (E/E′ ratio).[2 3] In a series of patients undergoing left heart catheterisation, Burgess *et al* showed that the E/E′ ratio increases during exercise in patients who also show an increase in LV mean diastolic pressure, suggesting that E/E′ can serve as a surrogate of filling pressure during exercise.[4] Increase of E/E′ during exercise is non-specific, and may be due to the presence of coronary artery disease,[5] or to other pathological processes that affect cardiac function.[6] Even more important is the relationship between E/E′ and exercise capacity, as a resting abnormal E/E′ predicts poor exercise capacity in patients with HFNEF.[4 7]

We have shown that in normal subjects untwisting velocity increases with exercise, and that this is followed by an increase in LV suction.[8] In contrast, these phenomena are lost (or blunted) in hypertrophic cardiomyopathy. Our group has also shown that decreased augmentation of LV suction appears to correlate with reduced exercise capacity.[9] Tan and colleagues have recently described in another paper the impact of exercise in patients with HFNEF.[10] In that study, patients with HFNEF had a reduced and delayed untwisting rate during exercise, reduced left ventricular suction at rest and on exercise, and a higher E/E′ ratio at rest and during exercise. Furthermore, they had mildly depressed mid-wall systolic function at rest that became markedly pronounced during exercise, indicating that HFNEF is not an isolated disorder of diastole.

The current study should be viewed in continuity with their previous one, as it was almost identical in design. The patient population was less sick in the current study as patients with uncontrolled blood pressure, LV hypertrophy, pulmonary hypertension or atrial fibrillation were excluded. Nevertheless, the results of the two studies were essentially similar. Longitudinal strain, early untwisting, flow propagation velocity and E′, while similar at rest in both patients and controls, showed less augmentation upon stress in the patients. In the previous study of sicker patients, small differences could also be detected even at rest in these parameters. More important, was the behaviour of E/E′. In the current study, E/E′ was not significantly increased at rest or on exercise, whereas in the previous study of unselected patients with HFNEF it was increased both at rest and during exercise, but did not increase further with exercise. One might expect that preload increases more in patients with HFNEF than in healthy controls, especially on exercise. The absence of this increase may reflect either a failure of pulmonary capillary wedge pressure to increase, or more likely that E/E′ is not always a sensitive marker of preload.[11]

So what are the causes of the current findings of exercise-induced changes in diastolic filling parameters? Diabetes present in some may have played a part. Although severe coronary disease was not apparent in any, only a minority had coronary angiography. Conceivably, submaximal stress echocardiography was falsely negative and the diastolic abnormalities were the early manifestation of unrecognised ischaemia. Another more tantalising possibility is that the patients' intrinsic ability to shorten relaxation during exercise was significantly impaired even in the setting of well-regulated hypertension without LV hypertrophy.

What diastolic parameters should be measured on exercise, and can these findings point us to therapeutic targets in this hitherto difficult to treat patient population? Given that the measurements need to be rapidly acquired and based on previous reports,[7] either E′ or E/E′ would seems a logical choice, especially as E′ can even be obtained post hoc, using retrospective analysis of colour Doppler or speckle tracking data. It is more difficult as yet to define appropriate therapeutic targets. Interestingly, mitral deceleration time, which is linked to LV operative stiffness, did not differ between controls and patients. All the diastolic abnormalities induced were associated with impairment of relaxation. Thus, therapeutic measures to improve LV stiffness might not be expected to lead to clinical improvement. The current study suggests that the relaxation process is simply too slow in this group of patients and implies that rate control may show some benefit. However, a problem with currently available treatment is that β blockers, at least acutely, slow the relaxation process even further even as they slow heart rate. The current study has improved our ability to diagnose cardiac abnormalities in functionally limited patients but given the conflicting data currently available on treatment of diastolic dysfunction,[12 13] further studies are needed to hone in on specific therapeutic targets in this patient population.

Competing interests None.

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