Culprit Mechanism(s)
for Exercise Intolerance
in Heart Failure With
Normal Ejection Fraction*

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Heart failure with normal ejection fraction (HFNEF) currently accounts for >50% of all heart failure patients, and its prevalence relative to heart failure with reduced ejection fraction (HFrEF) is rising at a rate of 1% per year. Despite this worrisome epidemiological trend, pathophysiological mechanisms underlying HFNEF and diagnostic or treatment strategies for HFNEF remain the subject of controversy (1,2). That also holds for the cause of exercise intolerance in HFNEF, as evident from this issue of the Journal, which features 2 papers on this subject (3,4) and from a series of recent studies addressing left ventricular (LV) filling mechanics in stressed HFNEF patients (5–7). In these studies, various mechanisms were proposed, which either alone or in concert could account for low exercise tolerance of HFNEF patients. The mechanisms are multiple and include deficient early diastolic LV recoil, blunted LV lusitropic response, low LV pre-load reserve, high pulmonary capillary wedge pressure (PCWP) at low workload, blunted LV inotropic response, chronotropic incompetence, vasodilator incompetence, and deranged ventriculo-vascular coupling. Confronted with this plethora of mechanisms, it seems appropriate to scrutinize their supporting evidence, their independent mode of action, and their HFNEF specificity.

Diastolic LV dysfunction. Recently proposed mechanisms for exercise intolerance in HFNEF that relate to diastolic LV dysfunction comprise deficient early diastolic LV recoil (6), blunted LV lusitropic response (5,7), low LV pre-load reserve (4), and elevated PCWP at low workload (3).

Initial studies using speckle-tracking echocardiography showed LV myocardial twisting and untwisting rates of control subjects to be comparable to those of HFNEF patients (8). A recent study performing the same speckle-tracking analysis, however, came up with a different result showing an impairment of twist and untwisting rate (p = 0.06) in HFNEF, which worsened during exercise (6). This study, therefore, attributed lower exercise tolerance in HFNEF to blunted early diastolic LV recoil, which displaced LV filling to middle and late diastole with a concomitant rise in left ventricular end-diastolic pressure (LVEDP) because of a steep diastolic LV pressure-volume relation. As blunted early diastolic LV recoil requires a steep diastolic LV pressure-volume relation to exert its limiting effect on exercise tolerance, it qualifies to be an important accomplice but not the prime suspect for exercise intolerance in HFNEF.

When exposed to dobutamine stress, HFNEF patients had a fall in Ea (early diastolic mitral annular velocity), which predicted their 6-min walk distance (7). This lack of LV diastolic reserve raised LVEDP and was presumed to cause exercise intolerance in HFNEF. Absent LV diastolic reserve in HFNEF was also evident from a lower LV peak filling rate and a paradoxical lengthening of the time to peak filling rate on exercise radionuclide LV angiograms (5). These deficient lusitropic responses to adrenergic stimulation seem to be unique to HFNEF because in HFrEF, beta-adrenergic receptor downregulation blunts chronotropic and inotropic but not lusitropic responses to adrenergic stimulation (9). These differential effects in HFNEF and HFrEF are also consistent with the recently reported divergent expression in both heart failure phenotypes of proteins involved in beta-adrenergic signaling (10). Finally, as lack of diastolic LV reserve again exerts its effect through displacement of LV filling to middle and late diastole, thereby raising LVEDP because of a steep diastolic LV pressure-volume relation, it also qualifies to be an accomplice but not the prime suspect for low exercise tolerance in HFNEF.

In 1 of the studies (4), HFNEF patients tended (p = 0.2) to have less increase during exercise in left ventricular end-diastolic volume index (LVEDVI) despite high LVEDP. In this study, LVEDVI at rest was similar in HFNEF patients, hypertensive patients, and control subjects. In the other study (3), LVEDVI at rest was, however, significantly smaller in HFNEF subjects than in control subjects. Similar “shrinkage” of LVEDVI had previously already been observed in an epidemiological survey of HFNEF patients among Olmsted County residents (11). Assessment of LV pre-load reserve in HFNEF patients with a characteristically shrunken left ventricle would probably have revealed a more drastic impairment. Impaired LV pre-load reserve is highly relevant to the main finding of 1 of

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the current studies, which consisted of a low PCWP/work rate ratio in exercising HFNEF patients (3). The latter corresponded with a prompt elevation of PCWP elicited by a small rise in venous return when exercising at low workload. Impaired LV pre-load reserve and low PCWP/ work rate ratio both imply that HFNEF patients operate on a steep diastolic LV pressure-volume relation, and both findings reveal the true identity of the prime suspect for exercise intolerance in HFNEF, namely, a steep diastolic LV pressure-volume relation.

**Chronotropic and vasomotor incompetence.** Chronotropic incompetence or an inadequate heart rate response to exercise is defined either by peak heart rate at peak workload or by heart rate increment at matched workload increment. Using the first definition, 2 recent studies observed smaller changes in peak heart rate at peak workload in HFNEF patients (4,12). These changes in peak heart rate were observed, however at vastly different peak workloads, and the lower peak heart rate in HFNEF could therefore merely have resulted from premature cessation of exercise. This is indeed suggested by the other study (3), which observed similar heart rate increments at similar workload increments in both HFNEF subjects and control subjects, especially in the initial stages of exercise. Therefore, this study concluded that, in contrast to an earlier study (13), there was no evidence for chronotropic incompetence. Furthermore, as previously demonstrated in the cardiac allograft, a blunted heart rate response in the initial stages of exercise reduces exercise tolerance because of an early rise in PCWP, which is caused by the absent LV pre-load reserve of the cardiac allograft (14). Hence, even if chronotropic incompetence would be present in HFNEF (4,13), it would still qualify for an ancillary role reducing exercise tolerance only because LV pre-load reserve is restricted.

An inconsistent outcome of both studies unfortunately also applies to exercise-induced vasomotor responses. One group of investigators (4) observed smaller reductions in systemic vascular resistance (SVR) in HFNEF both at a low workload and at peak exercise. However, the other group of investigators (3) observed similar reductions in SVR in HFNEF and in controls at matched workloads.

**Blunted LV contractile response.** Depressed LV contractility in HFNEF remains debated. Earlier invasive studies showed no LV contractile depression (15), but a recent noninvasive epidemiological survey observed lower LV contractility indices (16). This recent evidence does not necessarily prove that LV contractile depression actually contributes to LV failure in HFNEF. A significant contribution of LV contractile depression to LV failure requires left ventricular end-systolic volume index (LVESVI) to be enlarged so that the left ventricle is forced to operate on a steeper portion of its diastolic pressure-volume relation. Most studies, however, including the 2 current ones (3,4), observed either normal or smaller LVESVI in HFNEF. Furthermore, there is no mechanistic evidence that supports depressed myocardial contractile performance in HFNEF. In HFNEF, the myocardial force-frequency relation is preserved consistent with normal calcium handling (17), and cardiomyocytes isolated from HFNEF myocardium have increased myofilamentary calcium sensitivity (18).

In HFNEF, assessment of LV contractile response to exercise has become a perfect mirror image of assessment of baseline LV contractility. The invasive study (3) observed similar increases in cardiac index in HFNEF patients and controls for the same increase in work load. Conversely, the noninvasive study (4) observed, at matched low-level exercise workload, smaller increases in cardiac index and in LV contractility indices in HFNEF patients than in controls. The latter study thereby confirmed the lower LV long-axis shortening reserve previously reported in exercising HFNEF patients (6). Again, however, mechanistic evidence of a blunted myocardial inotropic response to adrenergic stimulation is absent because administration of dobutamine to HFNEF patients resulted in a normal increase in LV long-axis shortening velocity (7).

**Conclusions**

The search for the culprit mechanism for exercise intolerance in HFNEF evolved from a single indictment of diastolic LV dysfunction to identification of a “gang” action. The “gang” consists of diastolic LV dysfunction and blunted lusitropic, chronotropic, vasomotor, and inotropic responses to exercise. The relative importance of the blunted responses remains uncertain, however, because of conflicting evidence between invasive and noninvasive studies, and because their effects frequently depend on a steep diastolic LV pressure-volume relation, which therefore remains the uncontested leader of the “gang.”

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