Conventional Wisdom in HF Treatment Challenged Again:

Does Heart Rate Lowering Worsen Exercise Intolerance in Heart Failure with Preserved Ejection Fraction?

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Modern therapy for HF with reduced EF (HFrEF) is a success story, with multiple classes of pharmacological agents that are safe and effective for improving survival and other key outcomes. It is easily assumed that this success resulted from a straightforward progression of studies from bench to animal model to human hemodynamic testing to large clinical trials.

Instead, it was a wild ride. Frequently, the prevailing conventional wisdom was wrong, at least initially, and often repeatedly. Oral inotropes, thought to be the magic bullet, increased mortality. Beta-blockers, thought to be contraindicated, produced the largest improvement in survival.

These mostly forgotten lessons can help temper the current frustration in the search for effective therapy for HF with preserved ejection fraction (HFpEF). HFPEF is now the most common form of HF, its prevalence and incidence are increasing, and its prognosis is worsening.\(^1\) To date, all of the large, multicenter clinical endpoint trials, including ones that used agents proven effective for HFrEF, have been neutral on their primary outcomes.

Exercise intolerance, the primary manifestation of chronic HFpEF, is a major determinant of these patients’ severely reduced quality-of-life, can be measured objectively and reproducibly as peak exercise oxygen consumption (peak\(\text{VO}_2\)), and is responsive to therapies.\(^2-4\) The reduction in peak \(\text{VO}_2\) in HFpEF is similar in severity to age-matched HFrEF patients with \(\text{EF} \leq 35\%\).\(^2\) However, this clinically meaningful outcome has received much less attention than clinical endpoints in the quest for HFpEF treatments.

It has been widely thought that one potential mechanism for reduced peak \(\text{VO}_2\) in HFpEF is that short LV filling times associated with high heart rate (HR) during exercise impair LV filling, limiting stroke volume and increasing LV filling pressure. Current HF treatment guidelines empirically suggest control of tachycardia to improve symptoms in HFpEF. However, beta-adrenergic blockers can impair LV diastolic relaxation and systolic contraction in
addition to slowing exercise HR, generally suppress peak VO₂, and have had mixed, mostly negative, results in HFpEF.

In this issue of Circulation, Ashrafian et al⁵ examined the hypothesis that selective HR reduction with ivabridine, which doesn’t impair LV systolic or diastolic function and decreases mortality in HFrEF, would improve peak VO₂ in HFpEF. Twenty-two well-characterized HFpEF patients with severely reduced peak VO₂ received 2 weeks of 7.5 mg ivabridine daily vs. placebo in a cross-over design. There was a parallel trial of 22 patients with hypertension (HTN) but not HF.

At baseline HFpEF patients had significantly reduced peak HR, 30 bpm lower than the HTN patients. Ivabridine produced a large additional decrease in peak HR, averaging 20 bpm in both HFpEF and HTN patients. In contrast to the hypothesis, the decreased HR was associated with a substantial, statistically significant reduction in peak VO₂ in HFpEF patients and a trend to reduced peak VO₂ in HTN patients. The detrimental effect on peak VO₂ with ivabridine was starkly consistent and uniform across HFpEF patients (see figure 2). Ivabridine also significantly reduced submaximal exercise performance, which is more relevant to activities of daily living than peak VO₂, and also worsened the O₂ uptake efficiency slope which has been associated with poor clinical outcomes, including survival. These adverse outcomes occurred despite mild increases (improvements) in transmitral E/A ratio and early annulus tissue Doppler velocity (e’); there was no effect on E/e’ ratio a measure of LV filling pressure.

How could lowering peak HR impair rather than improve exercise intolerance in HFpEF? By the Fick equation for oxygen consumption, peak VO₂ is determined as: HR X stroke volume X arteriovenous oxygen difference (A VO₂Diff). In healthy human subjects, the increase in VO₂ during maximal exercise is achieved by a 150% increase in HR, a 40% increase in stroke
volume, and a 150% increase in A VO2Diff. Thus, HR is the dominant determinant of peak VO2 along with A VO2diff, which is determined by peripheral vascular and skeletal muscle function. Stroke volume, on the other hand, is a relatively minor contributor to peak VO2. The contribution of increasing stroke volume to VO2 occurs primarily during early stages of exercise. At high levels of exercise, nearly all of the increase in VO2 results from increasing HR.

As reviewed in detail elsewhere, in healthy persons, the rise in HR with exercise occurs from coordinated reductions in parasympathetic tone and enhanced sympathetic drive. It is well known that in HFrEF patients, the HR response to exercise is blunted, and >30% meet formal criteria for chronotropic incompetence (CI). We first reported and several others have confirmed that HFpEF patients also have blunted exercise HR, up to 63% meet formal criteria for CI, and CI is associated with more severely reduced peak VO2. We subsequently reported that the reduced peak HR in HFpEF accounts for about 50% of the reduction in peak VO2. We also found that increased peak HR accounts for all of the cardiac contribution to the improvement in peak VO2 with exercise training, the only intervention shown to date to improve exercise intolerance in HFpEF.

Thus the detrimental effect of HR lowering on peak VO2 observed by Ashrafian et al, while contrary to the study hypothesis and to conventional wisdom, would be predicted based on basic exercise physiology and HFpEF pathophysiology. Indeed, some have proposed, based on multiple lines of evidence, increasing HR during exercise via atrial pacing as a means to increase peak VO2 and relieve symptoms of exercise intolerance in HFpEF. For example, in HFrEF patients with CI, rate-adaptive pacing significantly improves peak VO2.

In addition to overlooking the above facts, the HR lowering hypothesis also overlooks
others. First, the interplay between HR and LV filling isn’t a zero-sum game. In healthy persons, the same rapid, sustained increase in beta-adrenergic stimulation that drives the increase in HR also significantly enhances the rate and extent of LV relaxation, allowing adequate LV filling even at very high heart rates.\textsuperscript{15} Admittedly this mechanism could be diminished in many HFP EF patients but it is unlikely to be absent. Second, HFP EF patients commonly have symptoms of exercise intolerance even at relatively low levels of exercise intensity and HR. Further, Doppler flow studies show that at HR <100bpm, where most daily activities occur, filling is complete and diastasis (spare filling time) remains. Third, a significant proportion of HF patients, both HFrEF and HFP EF, terminate exercise not due primarily to dyspnea but instead due to severe leg fatigue, indicating insufficient skeletal muscle oxygen delivery and/or utilization.\textsuperscript{16}

It should be noted that a previous study reported by Kosmala et al\textsuperscript{17} had findings that contrast sharply with those of Ashrafian et al. Kosmala et al studied HFP EF patients who had similar selection criteria as Ashrafian except that they also had to have a post-exercise E/e’ ratio > 13, suggesting increased LV filling pressure. Patients were randomized to 7 days of 5 mg ivabridine twice daily (n=30) vs. placebo (n=31). The investigators observed a significant increase in peak VO\textsubscript{2} with ibavridine treatment that appeared associated with lower increases in E/e’ measured immediately post-exercise.

Interstudy comparisons are difficult, but in addition to a lower dose of ivabridine and the post-exercise E/e’ selection criteria, the Kosmala patients appeared to have less CI at baseline and less HR reduction with ibavridne than the Ashrafian patients. Of note, while ivabridine did reduce the magnitude of rise in E/e’ in the Kosmala study, there was no intergroup treatment difference in post exercise E/e’, raising some doubt regarding lowering of peak LV filling
pressure as the mechanism of increased peak VO₂.

What then can we conclude regarding ivabradine for HFrEF, and for the future of the HR lowering hypothesis in HFrEF? The most obvious is that considerably more work is needed. Both trials had relatively small sample sizes and were very short in duration. Short exposure trial results have modest relevance to patient management where the goal is sustained improvement. Further, hemodynamic / exercise trials in HFrEF established that short term results can be favorable while at 6 month follow-up results have become completely neutral. In addition to longer follow-up, future trials should consider using the 5 mg twice daily dose, though caution is in order when data suggest a narrow therapeutic window.

Future trials that choose to test this hypothesis further should maximally utilize the power of exercise hemodynamic testing to the select patients most likely to benefit. Patients who already have CI at baseline at baseline should probably be excluded. Inclusion should probably be limited to patients with abnormally increased filling pressure with exercise. Results should be assessed during submaximal as well as peak exercise.

Future HFrEF studies in general should include a greater focus on exercise intolerance, an outcome that is clinically meaningful, a key determinant of quality-of-life, a strong, independent predictor of survival, and that can be definitively tested with moderate sample sizes and as little as 6 months of follow-up. Also, recent consensus statements suggest that cardiopulmonary exercise testing (CPX) is under-utilized, even though it provides a wide range of robust, meaningful data in both clinical practice and clinical trials. \(^{18}\) CPX testing helps: 1) help confirm the diagnosis of chronic HFrEF by assuring that a central feature, exercise intolerance, is present; 2) discern hemodynamic subsets that may have distinct pathophysiologic mechanisms for their exercise intolerance (such as CI and pulmonary hypertension); 3) monitor
response to therapy; 4) gauge prognosis. CPX also gives insight into the peripheral, extra-cardiac factors which have recently been proved to be major contributors to exercise intolerance in HFpEF and its improvement with exercise training.\textsuperscript{12,16}

It is often viewed that CPX testing is technically difficult to perform, resource intensive, and variable. However, modern instruments for expired gas analysis are highly automated, durable, reliable, easy to operate, and relatively inexpensive. CPX can be successfully incorporated into large, multicenter HF trials,\textsuperscript{19} and with good reproducibility.\textsuperscript{20} CPX is feasible and safe even in elderly frail HFpEF patients.\textsuperscript{3,19} CPX is also widely available clinically and relatively inexpensive. In chronic HFpEF, symptoms occur primarily during exertion. Assessing a HFpEF patient without exercise testing and based only on evaluation of resting hemodynamics is like declining a test drive and purchasing an automobile after merely observing it idling on the car lot.

In HFrEF, there has sometimes been divergence between the outcomes of exercise intolerance and mortality. So these outcomes should be seen as complementary and should be tested individually. Of note, elderly patients who dominate the HFpEF population often value symptom relief and quality-of-life and physical function improvement at least as highly as improved survival.

Time will tell whether ivabradine will join the growing ranks of agents found unsuccessful in HFpEF even though they were successful in HFrEF, and whether the HR hypothesis in HFpEF is proven or conventional wisdom is once again refuted. Along the way, it’s possible that exercise / hemodynamic testing may help enhance progress in the frustrating search for effective therapies for HFpEF.
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