Brief Report

The Power of Cardiac Output

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In the current issue of the journal, Myers and colleagues[1] report on the combined use of impedance cardiography with cardiopulmonary stress testing (CPX) as an improved technique to risk-stratify patients with heart failure (HF). The patients referred for HF evaluation who underwent this testing at a single institution numbered 1236. The composite endpoint included cardiac-related death, hospitalization for HF, cardiac transplantation or left ventricular assist device implantation. The addition of impedance cardiography variables to standard CPX variables enhanced the predictive power of CPX testing.

Since the early 1990s, measurement of peak oxygen consumption (VO_2) has been used as a predictor of outcome in patients with HF and reduced ejection fraction (HFrEF).[1,2] Derived from the Fick equation, peak VO_2 was believed to represent a noninvasive surrogate for patients' ability to increase their cardiac output. There are central and peripheral factors that contribute to peak exercise performance in a normal subject, but the key determinant of peak performance is individuals' abilities to increase cardiac output. The same can be said for patients with HF, though with increasing severity of HF, peripheral factors become increasingly contributory.

Previous studies have measured cardiac output during exercise with invasive techniques and have demonstrated the predictive value of cardiac power, left ventricular stroke work index and peak cardiac output for survival[3–5] in patients with HF with reduced ejection fraction (HFrEF). There are no comparable data in patients with HF and preserved ejection fraction (HFpEF). The use of a hemodynamic cardiopulmonary exercise test (Level 3 CPX) has been limited mostly to a few specialized centers due to the complexity of this testing. Newer techniques using CO_2 rebreathing methods or inert gases to measure cardiac output noninvasively have also been shown to have predictive power greater than CPX-derived variables.[4,6,7]

In the current study, Myers et al[1] used a simple technique to estimate cardiac output noninvasively, that is, change in thoracic misspelled-impedance. The cardiac output response to exercise can be reliably estimated by impedance cardiography (PhysioFlow, Manatec Biomedical, Macheren , France). The net reclassification improvement index and integrated dissemination improvement were the statistical approaches used for addition of noninvasive impedance cardiography data (peak cardiac index, ejection fraction, stroke volume, cardiac time interval, left cardiac work index, and end diastolic filling ratio) to standard CPX variables. These statistical approaches are not familiar to the majority of general cardiologists, though these techniques have been applied to improve prognostication in other subspecialties. Applying these techniques, Myers demonstrated, improved risk stratification.

There are several issues that need to be raised in regard to the analysis. First, although the mean EF is 56%, the patient population is extremely varied, including 50% of patients with HFpEF, 36% with HFrEF, 20% with hypertrophic cardiomyopathy, and 3.5% with congenital heart disease. These patients were drawn from the Veterans Administration system, in which the members are known to be predominantly male and have multiple comorbidities, including chronic obstructive pulmonary disease, diabetes, obesity, obstructive sleep apnea, anemia, and psychiatric disorders, which have significant impacts on outcomes.[8] Importantly, more than half of patients with HFpEF die due to deterioration of their comorbidities and not due to HF.[8] However, the primary outcome of the present study was a composite endpoint of cardiac-related death, hospitalization due to HF, orthotopic heart transplant and left ventricular assist devices that fits a study population of patients with HFrEF but not HFpEF. Accordingly, the implied relationship between the cardiac output response to exercise and death is somewhat tenuous in the present study population. The majority of events reported were HF hospitalizations. It is unclear how these hospitalizations were adjudicated. The number of Status 2 transplants and elective left ventricular

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assist device surgeries were not reported, and whether these events were censored was not addressed. The impact of the impedance variables on the prediction of cardiac mortality alone was not reported.

The data were derived over an 8-year period when there was evolving medical therapy. The authors state that all were already on optimal medical therapy. However, medications included beta-adrenergic blockade and diuretics in 43% and 24% of patients, respectively. This does not reflect current guideline-directed medical therapy for either HFrEF or HFpEF.

The exercise protocols used included both treadmill and ramp bicycle exercise. The authors state that in their published experience, there are no differences in the predictive power of CPX variables regardless of protocol used. Although this may be true when all patients are exercised consistently with only bicycle or treadmill exercise, there are clear differences in peak VO_2 and VO_2 at the ventilatory threshold, depending on the type of exercise, and it is speculative whether grouping these tests together is valid.

Myers et al do not reconcile their current finding of adding peak CO to peak VO_2 for reclassification of the risk in HF; this group's prior report demonstrated that the VE/VCO_2 slope has a better predictive value than peak VO_2.[9] It is unclear why a parameter that does not account for the CO response to exercise may have a superior predictive value.

Does the addition of hemodynamic variables complement CPX variables? Prior evidence from single-center studies and from this report suggests that it would. Does the current study by make a definitive case for routine application of this technology for risk stratification? The present report underlines the essential role of cardiac output in the progression of HF, whereas left ventricular filling pressure is most often considered to have superior prognostic significance.[10] Impedance cardiography allows noninvasive determination of an impaired CO response to exercise in HF. Whether noninvasive determination of the CO response adds to the predictive value of peak VO_2 in patients with advanced HF awaits further studies.

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