JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 7, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2015.12.026

EDITORIAL COMMENT

The End Is Near...Do We Know Everything About Cardiopulmonary Exercise Testing in HF Patients?*

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Cardiopulmonary exercise testing (CPX) using a treadmill or cycle ergometer has been employed to assess patients with heart failure and reduced ejection fraction (HFrEF) since the late 1970s (1). Exercise testing as a way to assess symptoms and functional capacity in patients with heart failure grew in popularity during the 1980s (2). CPX is used to noninvasively identify impaired aerobic capacity and anaerobic threshold in patients with HFrEF, which in turn provides important information regarding the functional capacity of the patients and the severity of the underlying heart failure. It has been featured in numerous clinical trials as a means of measuring drug or device efficacy, and is widely employed clinically as a measure to help guide decisions regarding the suitability of patients for heart transplantation. There is no question regarding its utility, as it is now engrained in current heart failure guidelines and utilized in the day-to-day evaluation of patients with HFrEF (3,4). One might then ask, what does the current paper in this issue of the *Journal* by the HF-ACTION (Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing) (5) investigators bring to our attention that is new and of value?

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We believe the answer is straightforward: these investigations provide the strongest data collected to date on the prognostic value of CPX in a large cohort of patients with HFrEF. Two thousand one hundred patients enrolled in the HF-ACTION trial underwent CPX using a treadmill (modified Naughton protocol) at baseline. Death occurred in 357 of these 2,100 patients over a median follow up of 32 months. Ten CPX variables measured at baseline were examined in detail using thorough statistical analysis. These are more variables and more data than we have previously seen from a single study. As such, the investigators were able to study and compare the prognostic ability of these variables simultaneously in the same study. The results indicate that all variables except the respiratory exchange ratio (RER) to some extent predict all-cause mortality in patients with HFrEF. Peak oxygen uptake (Vo_2), exercise duration, and percent-predicted peak Vo_2 (%ppVo_2) have the strongest ability to predict and discriminate the likelihood of dying in patients with HFrEF. The best predictor of mortality in men is peak Vo_2, whereas in women, it is exercise duration. This is of some importance, because both men and women with heart failure who demonstrate a peak Vo_2 <14 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} have generally been assigned a similar prognosis.

Importantly, this study provides new clarity on the relationship between gender and prognostic ability of peak Vo_2 in patients with HFrEF. The power of peak Vo_2 to predict all-cause mortality varies by sex. In men, a peak Vo_2 of 10.9 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} corresponds to a 1-year mortality rate of 10%, whereas in women, peak Vo_2 corresponding to a 10% 1-year mortality is significantly lower at 5.3 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}. These results are similar to the observations from a previously published single-center study (6). The exact mechanism for lower relative peak Vo_2 (adjusted to body weight) in women with HFrEF is unknown, but it has been proposed that this is perhaps due to higher body fat in women. Adipose tissue is not aerobically active, and

*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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thus, when peak V_{O_2} is adjusted for total body weight, women tend to have a lower peak V_{O_2} (7). Consistent with this concept, peak V_{O_2} adjusted to lean body mass has been shown to be a better predictor of mortality in women and in obese patients with HFrEF (8). Currently, a peak V_{O_2} of <14 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} (12 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} in those who are on beta-blockers) is generally used as the cutoff value to determine the need for advanced heart failure therapies in patients with HFrEF irrespective of sex (3). However, the results of this study challenge this standard clinical practice and raise a critical question: should we use a lower peak V_{O_2} cutoff value in women with HFrEF to evaluate the need and the optimal timing for cardiac transplantation?

A peak RER $\geq$1.1 is recommended by the current guidelines to be indicative of maximal exercise effort (9). Traditionally, it has been thought that in the presence of inadequate exercise effort (RER $<$1.1), peak V_{O_2} and other CPX variables lose their prognostic ability to predict mortality. However, in the present analysis, RER did not affect the predictive ability of peak V_{O_2} on mortality. Peak V_{O_2} <12 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} was a strong predictor of mortality irrespective of whether RER was above or below 1.05. These findings confirm a prior observation by Chase et al. (10), who also demonstrated that peak V_{O_2} and the VE/VC_{O_2} slope maintain their prognostic value in patients with low RER.

There are some minor issues, which the authors have addressed. The modified Naughton treadmill protocol is not widely popular outside of the United States, so one must be aware that these results may not be generalizable to exercise testing performed using different protocols. Moreover, as the authors point out, peak V_{O_2} may be somewhat higher using a treadmill as opposed to a cycle ergometer. The patient population in the HF-ACTION trial is somewhat younger (median age 59 years), relative to many patients with heart failure we see in our daily practice. In addition, the patients enrolled in the HF-ACTION trial are stable ambulatory heart failure patients with New York Heart Association functional class II to IV symptoms. Thus, these results may not be generalizable to patients with more advanced symptoms. For example, many advanced heart failure centers tend to evaluate a large proportion of patients with very severe heart failure (Interagency Registry for Mechanical Assist Devices [INTERMACS] Levels 4 and 5) who perhaps might not have been enrolled in the HF-ACTION clinical trial. The current study only examined the utility of CPX variables in predicting mortality in the study population. It did not include clinical variables found useful for prediction as reported in a prior publication of the HF-ACTION study, such as the Kansas City Cardiomyopathy Questionnaire symptom stability score, higher serum urea nitrogen, and lower body mass index (11). Which set of variables prevails—simple clinical metrics, sophisticated CPX variables, or some combination thereof—in a prediction model of CHF patients remains open to further study.

Despite these minor concerns that are clearly addressed by the authors, the message rings loud and clear: CPX testing in patients with HFrEF still offers a powerful evaluation tool. The study is conclusive and provides definitive data regarding a test that many of us have used for years. In addition to exercise time, % ppV_{O_2} and peak V_{O_2}, the VE/VC_{O_2} slope (ventilatory efficiency), oxygen pulse, data on exercise oscillatory ventilation, and end tidal CO_2 should be carefully considered following CPX in each individual patient. The HF-ACTION investigators are to be congratulated on what may be the most definitive such study to date. Could it mark the end of CPX investigation in patients with HFrEF? Probably not. But it makes a powerful statement.

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KEY WORDS peak Vo_2, respiratory exchange ratio, sex, survival