Cardiopulmonary Exercise Testing and Outcomes in Women With Heart Failure—Examining the “Female Advantage”

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See article by Corrà et al., pages xxx-xxx of this issue.

Cardiopulmonary exercise testing (CPET) has long been shown to provide important prognostic information in patients with heart failure. Since the 1991 publication by Mancini et al., CPET, and specifically peak oxygen consumption (pVO₂), has been used in prognostication for patients with heart failure being assessed for cardiac transplantation. pVO₂ is essentially an assessment of cardiac reserve (the ability of the heart to increase cardiac output), and patients unable to achieve a pVO₂ of ≥14 mL/kg/min were shown to have improved survival with transplantation as opposed to without transplantation.

However, multiple subsequent studies have shown that women with heart failure have better overall survival than do their male counterparts, despite women having a comparatively low pVO₂.²⁻⁵ Placing into question the role of CPET in prognostication for women with heart failure, pVO₂ is, of course, far from the only parameter assessed with CPET, despite being arguably the most used by heart failure clinicians. Also commonly used is ventilatory response; the response of minute ventilation to CO₂ production (VE/VCO₂ slope), which is an indicator of the presence of heart failure—related physiological consequences such as V:Q mismatch and aberrancies of autonomic function. VE/VCO₂ has been shown to be of prognostic value in heart failure, with higher values corresponding to worse prognosis, and specifically may be more predictive of adverse heart failure outcomes in women.⁴⁻⁶

There are many potential reasons for the sex-related discrepancy in the predictive value of CPET parameters. Women were not well represented in the initial studies done to derive the equations for prediction of maximum VO₂, resulting in a sex bias on this basis alone. There is also a significant male predominance in studies assessing CPET for prognosis. The reasons for this are likely related to the demographics of women with heart failure: they tend to be older at the onset of heart failure, have more heart failure with preserved ejection fraction, and have more comorbidities. Women are also less likely to be able to exercise to the levels believed to be necessary for CPET analysis. Exercise effort in CPET is assessed by the peak respiratory exchange ratio (pRER)—the ratio of expired CO₂ to O₂ consumed—which is an indicator of cardiometabolic stress. A pRER of >1.0 is considered indicative of adequate exercise effort and has been believed to be necessary for prognostic reliability of pVO₂, with most studies excluding patients who fail to achieve this level. The combination of demographics of women with heart failure and the reduced likelihood of these women exercising to achieve a pRER of >1.0 would exclude many women from most CPET trials. Thus, the women who end up being enrolled in CPET trials are by definition only the “best exercising” women with heart failure. This is supported by the fact that the women in CPET trials are younger, have lower body mass index (BMI), and have less atrial fibrillation, which is much different from the demographics of the women we see in other heart failure trials. Differences in female versus male physiology may also contribute to the apparent difference in predictive value of CPET in women compared with men, and perhaps the traditionally accepted absolute values for predictive cutoffs are not as applicable to women as they are for men. Perhaps we are using the wrong CPET parameters for women.

In a recently published article, a comprehensive evaluation of multiple CPET parameters with regard to mortality in patients with heart failure was undertaken.⁷ Looking specifically at their results in women, that study also showed that among women, pVO₂ was not associated with survival at 1 year. The authors suggest that percentage of predicted maximum VO₂, which quantifies the patient’s absolute pVO₂ according to age and sex, may be the preferred prognostic indicator. The study did not exclude patients with a pRER <1.0, and in fact found that the CPET parameters of VE/VCO₂ slope, percentage of predicted maximum VO₂, among others, were equally as predictive in these “poorly exercising” patients as with patients who attained a pRER >1.0. This finding may be particularly relevant to women, who traditionally may have been excluded from CPET studies based on an inability to achieve “adequate” exercise levels.
Despite the best intentions of investigators to identify and control for factors that would account for differences in outcomes between men and women in observational studies, it is often difficult to identify and control for patient characteristics that may be associated with both the participation in the trial (ie, women with heart failure less likely to get into the trial, resulting in selection bias) as well as the study outcomes. These patient characteristics may be measured (eg, ability to exercise), or unmeasured (eg, patient values and preferences).

In the current issue of the Canadian Journal of Cardiology, Corrà et al.8 evaluate the role of sex selection bias in CPET risk assessment of patients with heart failure, using propensity score matching (PSM),8 which is performed to match groups (in this case men and women) so that measured confounders can be equally distributed between these groups, statistically accounting for confounding bias between groups, and thus improving the precision of estimates of outcomes.9 PSM has been applied widely in the social sciences and is increasingly used in cardiovascular research to reduce bias in observational studies.10,11

In this study, the authors evaluated the apparent female prognostic advantage based on values of pVO2 and VE/VCO2 slope and sought to determine whether sex itself or sex-specific characteristics were responsible for the improved survival in women compared with men, despite less favourable CPET results in women. They performed a retrospective analysis using the database from the multicentre Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes (MECKI) trial. Almost 3000 patients were included in this study, 17% of whom were women. Of note, as is seen in other CPET studies, the investigators excluded patients who failed to achieve a pRER of > 1.0, those whose exercise limitation was other than fatigue or shortness of breath, and those with a left ventricular ejection fraction (LVEF) > 40%, potentially excluding more women than men. Again, the women represented in this study are younger, with lower BMI and a lower incidence of atrial fibrillation compared with women in most non-CPET heart failure studies. During the 3-year follow-up, female sex was linked to better survival on univariate analysis. On multivariate analysis, a female protective trait was independent of pVO2 and VE/VCO2 slope.

Using PSM, 498 men from the study group were selected and compared with the entire cohort of 498 women. The PSM model included the variables of age, BMI, New York Heart Association class, ischemic cause, presence of atrial fibrillation, LVEF, medications used, presence of an implantable cardioverter defibrillator, indices of renal function, electrolyte levels, hemoglobin values, and CPET parameters (pVO2, VE/VCO2 slope, pRER). At outcome analysis for the propensity-matched patients, outcomes were not significantly different between men and women. Female sex benefit was not significant on univariate analysis in this cohort, although VE/VCO2 remained predictive. Interestingly, percentage predicted maximum VO2 was only minimally predictive in the propensity-matched cohort. The authors point out that their findings suggest that sex-related characteristics, rather than female sex itself, may be confounding the relationship between survival and pVO2 in women. They conclude that for a prognostic heart failure model to perform optimally, adjustments should be made for sex-related characteristics and not just sex alone.

As the authors identify, there are limitations to their study related to study design and inclusion criteria. Although the percentage of women in this study was low, the absolute number of women studied is quite large, and they were treated similarly to the male patients according to modern evidence-based heart failure guidelines. This study has provided further insights into the perceived sex differences with CPET-based outcomes and has identified an approach for additional study into the optimal use of CPET parameters in the prognostication of outcomes in women with heart failure.

CPET provides useful information regarding functional capacity, exercise physiology, and prognosis in our patients with heart failure. As illustrated by this study, we are still learning how to best take advantage of all of the information that can be afforded by this valuable tool.

Disclosures
The author has no conflicts of interest to disclose.

References