Prognosis in patients with chronic heart failure: it’s the way they breathe that matters

Roland Wensel, Darrel P Francis

Cardiopulmonary exercise testing (CPX) is a gold-standard element of evaluation of patients with chronic heart failure (CHF), a disease of exercise. The initial rationale for cardiologists was that peak oxygen uptake (peakVO2) served as a surrogate of cardiac output. The breakthrough of CPX, however, came when Mancini’s group showed that the prognostic importance of a peakVO2 threshold of 14 mL/kg/min eclipsed that of all other major clinical or functional variables (including left ventricular EF) in their cohort. In the ensuing years its dominance has been gnawed away, first by the increasingly disappointing rate of replication in other studies, and second by the emergence of alternative markers from the same test that focus on efficiency of pulmonary gas exchange.

In the current issue of this journal Ingle et al report on the predictive power of CPX data on all-cause mortality in patients with mild to moderate chronic heart failure.

For individual variables they found optimal cut points located where the statistical analyses would suggest. They went on to develop a composite risk score for individual risk stratification. While there are already many risk scores for patients with CHF, Ingle et al include novel CPX variables like the nadir of the ventilation/carbon dioxide production ratio on exercise (VE/VCO2-nadir), the presence of exercise oscillatory ventilation (EOV) and circulatory power. The authors used a hybrid analysis of bootstrapping and Cox proportional hazards analysis to generate the final multivariable Cox model, on which the selection of the risk score variables was based.

Their model identified four variables, EOV, VE/C02-slope, oxygen uptake efficiency slope (OUES) and VE/VCO2-nadir, most prevalent in the boosted multi-variate analyses (98–34%) and therefore consistently contain independent prognostic information.

The authors courageously break the mould by reporting variables not found to consistently show independent prognostic information. Probably the most prominent ‘loser’ in this regard is peakVO2, traditionally considered the main prognostic variable from CPX and a key part of many existing risk models. However, on closer inspection of the data, peakVO2 was only mildly if at all reduced in the current study population (21 (17–23) mL/kg/min), which might explain its relatively smaller prognostic power here. A similar finding has been reported by Ponikowski et al who only specifically focused on patients with a peakVO2 of >18 mL/kg/min. This is not to say that the present patients did not have significant CHF, since their mortality was still 28% in 8.6 years, but underlines that a universal prognostic dominance of peakVO2 need not be assumed. Heart failure can still be dangerous even if peakVO2 is preserved or mildly impaired.

The current risk score contains variables related to gas exchange efficiency or control of ventilation. Why do so many indices of exercise pulmonary gas exchange contain independent prognostic information?

VE/VCO2 has probably the largest bulk of prognostic evidence. While described as linear, it has many reasons to be more complex. It reflects regulation of arterial pCO2 and physiological dead space ventilation, in turn related to the haemodynamic (pulmonary ventilation/perfusion mismatch) and ventilatory (low tidal volumes) changes, and control of arterial pCO2 to peripheral and central (skeletal muscle deconditioning, metabolite trapping, increased ergoreflex sensitivity) changes.

However, the hyperventilatory (lowered arterial pCO2) contribution to the increased VE/VCO2 relationship appears significant only in late exercise beyond the respiratory compensation point. Before that, physiological dead space ventilation appears the major determinant. Hence the VE/VCO2 slope, which includes all data from rest to peak exercise, contains different information from VE/VCO2-nadir, which occurs before the respiratory compensation point and is therefore dominated by abnormal physiological dead space ventilation.

OUES, like the VE/VCO2 slope, describes kinetics of gas exchange efficiency over the entire duration of exercise. There are two main differences: it addresses O2 exchange and it measures O2 uptake in relation to a 10-fold scaling up in ventilation and not in relation to an absolute increment in ventilation. The mathematical impact of this transformation is to give relatively greater weighting to the earlier parts of exercise.

While pulmonary gas exchange for O2 and CO2 share common physiological determinants (like ventilation/perfusion matching), significant differences exist as well. In the absence of arterial hypoxaemia arterial pO2 is not tightly regulated but passively follows O2 consumption and ventilation, the latter being regulated by pCO2 and other mechanisms. This means that production of CO2 arising outside of oxidative metabolism will increase ventilation (and tend to keep arterial pCO2 stable) in excess to that required to keep arterial pO2 stable and therefore result in increased arterial and alveolar pO2, thereby reducing the efficiency for O2 uptake. Accordingly, increased CO2 production from buffering of lactate arising from anaerobic metabolism will drive the O2 uptake efficiency down before hyperventilation ensues and is linked to early occurrence of anaerobic metabolism in CHF. Furthermore, O2 diffusion is more susceptible to reduced conductance of the alveolarcapillary membrane.

In the current study the prevalence of EOV was high (34%) and consistently showed prognostic value. EOV reflects instability of the regulation of ventilation caused by a combination of prognostically adverse processes (like increased chemoreflex-sensitivity and prolonged circulatory delay) that all are related to poor prognosis in CHF. The observed strong prognostic effect therefore is very plausible.

The current study extends existing CPX derived risk scores by including novel parameters like VE/VCO2-nadir and EOV and also by focusing on patients with mild-to-moderate CHF. In previous studies by Myers and Guazzi the average peakVO2 of the patient population has been lower (17.5 ±6.6 mL/kg/min and 15.3±5 mL/kg/min, respectively). This may explain the most
prominent difference between the current and these previous studies, which is the lack of independent prognostic information of peakVO2.

Each variable in the current risk model carries specific information on abnormalities of pulmonary gas exchange and control of ventilation, underlining CHF as not a purely circulatory disorder but a multisystem disease. These abnormalities can therefore occur even with only mildly impaired exercise tolerance.

In other words, it does not matter how much a patient can breathe (in the sense of O2 uptake) but exactly in what pattern his physiology causes him to breathe. These eye-opening results should encourage others similar explorations.

Our field does need to move beyond testing a single variable with a threshold, an approach offering seductive simplicity and thrilling curves, but disappointingly little beneath the surface.2

Ultimately, sharing the content of large CPX databases may be the next big step towards further improving risk stratification in CHF.

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