



# Exercise pulmonary haemodynamics: a test in search of purpose

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**Borderline PH at rest predicts abnormal exercise pulmonary haemodynamics and exercise intolerance** <http://ow.ly/YVQTC>

Ever since the entity of “exercise induced pulmonary hypertension” was banned from the pulmonary hypertension (PH) dictionary in 2008, during the World Symposium on Pulmonary Hypertension at Dana Point (CA, USA) [1], there has been a concern that by just measuring pulmonary haemodynamics at rest, many patients with subclinical pulmonary vascular disease go unrecognised. This could be harmful, if subjects with an abnormal pulmonary haemodynamic response to exercise are at particular risk of developing PH and that early recognition of PH in these patients would improve their outcome. It may even be that the presence of an abnormal pulmonary haemodynamic response to exercise represents a treatable condition. To date, there is no proof to validate any of these assumptions.

The plea in favour of invasive exercise testing so far has failed to overcome several important obstacles. First, there has been a lack of standardisation of invasive cardiopulmonary exercise testing, while the mode of testing and intensity of exercise may certainly affect outcomes. For example, particularly elderly patients may fulfil criteria of an abnormal haemodynamic response at submaximal exercise levels, but no longer at maximal exercise [2]. Second, there remains uncertainty about the physiological limits of a normal response to exercise of pulmonary artery pressure, cardiac output and pulmonary vascular resistance. Third, there is no evidence that treatment of subjects with an abnormal pulmonary haemodynamic response but without PH would improve their outcome. An additional question, to the usefulness of invasive exercise testing, is whether the population of subjects with an abnormal pulmonary haemodynamic response to exercise overlaps with another population that physicians are struggling with, *i.e.* those with resting mean pulmonary artery pressures ( $P_{pa}$ ) below the definition of PH, but clearly higher than the normal physiological limits. Just like patients with abnormal exercise pulmonary haemodynamics, these subjects suffer from increased mortality and hospitalisation [3].

In this issue of the *European Respiratory Journal* LAU *et al.* [4] report on exercise pulmonary haemodynamics in 290 consecutive patients at risk for PH with a resting mean  $P_{pa}$  of  $\leq 25$  mmHg. They found that an “abnormal” response was common in those with borderline elevation of resting pressures (86%) and further that the likelihood of an “abnormal” response increased progressively as resting mean pressure increased from 13 mmHg upwards. There was no systematic follow-up, thus we have no direct insight into the prognostic significance of these observations. However, patients with exercise PH were more symptomatic and had reduced exercise tolerance. We must, therefore, consider whether the proposed definition of an “abnormal” exercise response is valid, whether the population investigated includes biases that would increase the

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This article has been revised according to the erratum published in the July 2016 issue of the *European Respiratory Journal*.

Received: Feb 23 2016 | Accepted: Feb 23 2016

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likelihood of a false positive association, and whether evaluation of exercise haemodynamics can assist in identifying patients in the process of developing PH or identify a treatable cohort of patients.

The normal value for mean  $P_{pa}$  has been established at  $14\pm 3$  mmHg by KOVACS *et al.* [5], based on a review of 1187 invasively studied healthy volunteers from the literature. In the same review exercise haemodynamics among 404 patients were reported showing that even with “slight” exercise mean  $P_{pa}$  exceeded 30 mmHg in 47% of the 91 volunteers aged  $>50$  years. Furthermore, among 193 volunteers where more than one level of exercise was reported, mean  $P_{pa}$  exceeded 30 mmHg in 21% of those aged  $<50$  years at maximal exercise. From this it has been concluded that we do not have an established upper limit of normal for pulmonary pressures during exercise.

Recently data has begun to emerge to suggest that increases in m  $P_{pa}$  that are driven purely by cardiac output are probably normal, while escalation of pressures beyond that expected for a given change in cardiac output is abnormal.

The best data on the normal relationship between cardiac output and m  $P_{pa}$  during exercise comes from a previous publication by the authors of the current study [6]. The “control” group consisted of 69 patients undergoing evaluation for dyspnoea that had no obvious disease on history, noninvasive testing and in whom the pulmonary capillary wedge pressure ( $P_{pcw}$ ) did not exceed 20 mmHg on exercise. Of note the “control” population were significantly younger than either disease populations, and age is an important contributor to exercise elevation of mean  $P_{pa}$  [5]. The findings were supported by a review of published data on 78 healthy volunteers undergoing supine bicycle ergometry from the literature. Thus we have reasonably robust data to suggest that with standardised supine maximal exercise testing, normal individuals only rarely exhibit a mean  $P_{pa} \geq 30$  mmHg with a transpulmonary gradient (TPR)  $\geq 3$  WU. However further studies particularly in elderly (between the control and volunteer populations we have data on only 42 individuals aged  $>50$  years, of which 14 were aged  $>70$  years) and obese volunteer populations are required to underpin claims of specificity.

The remaining issue is the clinical significance of a positive test. Relying on TPR we cannot differentiate precapillary from post-capillary abnormalities. We have limited previous data to suggest that exercise elevation of pulmonary pressure in disease populations is associated with progression to PH [7, 8] or worse outcomes [9–11]. The “disease” population consisted of those with standard risk factors for pulmonary arterial hypertension (PAH), those with chronic thromboembolic disease, those with Sickle cell disease and those with risk factors for left heart disease. Over 40% simply had risk factors for left heart disease – thus a body mass index (BMI)  $>30$  or aged  $>65$  years was sufficient to have a patient classified as at risk of PH. One may question whether a 65 year-old patient being investigated for breathlessness can be regarded as a member of the “disease” population while a 64-year-old with the same background is a valid member of the control population.

The value of an abnormal haemodynamic response to exercise relies on the ability to predict the development of overt PH or to identify a cohort that would benefit from therapy. From VALERIO *et al.* [12], we know that among scleroderma patients the likelihood of developing PH over 3 years is  $\sim 18.5\%$  among those with an mean  $P_{pa}$  of 21–24 mmHg, and only 5% among those with normal resting pressure. Given that 86% of the 21–24 mmHg population and 47% of those with normal resting pressures in this study had abnormal exercise responses, it is unlikely that the exercise response will help to significantly enrich the population requiring follow-up for the development of PH. Previous studies have, however, identified reduced exercise tolerance [13, 14] among those with abnormal exercise response and this finding is again confirmed in this cohort. If  $P_{pcw} < 20$  on exercise reliably discriminates between those with precapillary and post-capillary PH, it is possible that a treatment study could be constructed to determine if improved symptoms and effort tolerance is achievable in those with abnormal exercise haemodynamics.

To conclude the present work adds to our understanding of the characteristics and prevalence of abnormal exercise haemodynamics and may potentially point the way to identifying new populations that could benefit from treatment. However, remains significant work before exercise evaluation of pulmonary haemodynamics becomes a clinically useful test.

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