"Rehab for all!" Is it too early in pulmonary arterial hypertension?

To the Editor:

Chronic pulmonary hypertension shares abnormalities found in chronic left heart failure and chronic respiratory failure, in which rehabilitation has been proposed [1, 2]. In a recent statement endorsed by the European Respiratory Society, GRÜNIG *et al.* [3] proposed an exhaustive review of available data on rehabilitation in the setting of chronic pulmonary hypertension. The main messages proposed are "Specialised exercise training in patients with pulmonary hypertension appears to be effective, cost-efficient and safe."

The task force should to be warmly thanked for this important document. However, while we fully share the hope that rehabilitation programmes may improve the lives of patients with pulmonary hypertension, we also believe that more data are needed to transform these experts' opinions into recommendations with a high level of evidence.

The current gold standard to assess the efficacy of any therapeutic intervention remains a randomised controlled trial, designed specifically to avoid related potential bias. As quoted by the authors, most of the current available evidence was provided by a single centre, questioning the scalability thereof to general practice. Moreover, all the current trials suffer from a high risk of bias (mainly performance bias and reporting bias), as illustrated in the last Cochrane review [4]. Although functional exercise capacities may improve with rehabilitation in patients with pulmonary hypertension as reported in chronic heart and respiratory failure, the results remain frail. The major limitation is related to the absence of controlled trials. Lack of long-term data following the rehabilitation programme is another limitation, as the potential effect of rehabilitation depends on the continuation of exercise.

The safety of each intervention is as important as its efficacy. Exercise occupies a paradoxical position in the field of pulmonary hypertension, particularly in patients with pulmonary arterial hypertension (PAH). For instance, the 2015 European guidelines [5] recommend supervised exercise training (IIB), but also advise against physical activity leading to distressing symptoms (recommendation IIIC). Although no concerns were raised from previous studies, the safety results are questioned in multicentre studies.

The common reluctance with rehabilitation is the potential deleterious haemodynamic effect. To date, only one study provides data on the haemodynamic effect of rehabilitation in patients with PAH [6]. Surprisingly, rehabilitation (performed in a single centre) was associated with improved haemodynamics, including cardiac output. These results call for a multicentre validation.

It also seems premature to us to conclude on the cost-effectiveness of rehabilitation, as there are still doubts as to its long-term efficacy and safety. The cost may differ from one country to another, but also from one organisation and one programme to another (inpatient rehabilitation in one or more centres; home-based rehabilitation programmes?)

We then hope that the on-going prospective, randomised trial (FONCE-HTAP trial, NCT02579954) will help to better assess the efficacy and safety of rehabilitation programme in the field of PAH, by addressing some of the questions raised in this correspondence. This trial includes a Zelen method also known as the "two-stage randomised consent design" [7] in order to build comparable groups, with the control group being unaware of the intervention group. This design protects the trial from a disappointment bias, which may lead to a pollution of the control group by the intervention (in this setting, an unsupervised auto-rehabilitation programme of patients randomised to the control group). Our multicentre trial also includes long-term training (52 weeks), with a home-based programme following hospital-supervised

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Rehabilitation appears to be beneficial in PAH patients, but more research is needed before increasing the level of evidence for recommendations. http://bit.ly/33zutuZ

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rehabilitation for the first 12 weeks. Haemodynamic assessment with right heart catheterisation during the study will allow us to confirm the safety of the intervention.

In conclusion, we share with the panellists the opinion that rehabilitation may significantly improve the functional capacity of patients, hopefully without a negative haemodynamic impact; however, we do consider that the evidence currently available is not sufficient to propose a grade I-A level of evidence.

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Multicentre trials on specialised exercise training and rehabilitation are useful in patients with pulmonary hypertension

From the authors:

We would like to thank L. Bertoletti and co-workers for their important comments. We fully agree that more multicentre data, especially on the haemodynamic effects of rehabilitation programmes, are needed and might be helpful for re-evaluating the current level of evidence and indication of exercise training in pulmonary hypertension. A new grading of evidence and recommendation of treatment was not the purpose of the task force statement and hence not alluded to. This has to be done through authorised committees. We also agree with L. Bertoletti and co-workers' excellent description of the methodological difficulties of measuring the efficacy and long-term outcome of exercise training in pulmonary hypertension. Therefore, the new initiative for a prospective, randomised trial using new methods for randomisation is highly welcomed and should be supported. However, while Zelen's design [1], which is implemented in the new study, offers many advantages, it also comes with challenging problems and cannot be generally recommended for rehabilitation trials. The design has to be adapted to comply with the new European Union regulations on data protection (patients have to consent to serve as a control group). Furthermore, the Zelen design has difficulties addressing performance bias, which was pointed out as one of the two main methodological issues in studies on exercise training in pulmonary hypertension by a recent Cochrane review [2]. Specifically, performance bias may not be excluded, as control patients will not receive the amount of care which patients receive in a structured exercise training programme. Reporting bias, the second main shortcoming highlighted by the Cochrane review, should always be avoided, irrespective of the chosen study design.

New multicentre registries and randomised controlled trials of exercise training in pulmonary hypertension patients are clearly needed. In this regard, members of this European Respiratory Society task force built-up a standardised pulmonary hypertension rehabilitation programme in their respective centres across 10 European countries and also started a prospective, randomised controlled trial on the effect of exercise training in pulmonary hypertension (EU-TRAIN-01 trial, NCT03345212).

Hence, we should work together to establish a standardised rehabilitation programme in pulmonary hypertension centres to make this therapy available for the patients within their country and to implement this non-pharmacological intervention into standard care. Therefore, we very much appreciate the comments and initiative of L. Bertoletti and colleagues.

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