Pattinson KTS, Herigstad M, Faul OK, Hayen A, Evans E, Hardinge FM, Wiech K. Rehabilitation in Brain Activity Over a Course of Pulmonary Rehabilitation.

Abstract: Breathlessness in chronic obstructive pulmonary disease (COPD) is often discordant with airway pathophysiology (“over-perception”). Pulmonary rehabilitation profoundly affects breathlessness, without influencing lung function. Learned associations influence brain mechanisms of sensory perception. We hypothesised that improvements in breathlessness with pulmonary rehabilitation may be explained by changing neural representations of learned associations.

In 31 patients with COPD, we tested how pulmonary rehabilitation altered the relationship between brain activity during a breathlessness-related word-cue task (using functional magnetic resonance imaging), and clinical and psychological measures of breathlessness.

Changes in ratings of breathlessness word cues positively correlated with changes in activity in the insula and anterior cingulate cortex. Changes in ratings of breathlessness-anxiety negatively correlated with activations in attention regulation and motor networks. Baseline activity in the insula, anterior cingulate cortex and prefrontal cortex correlated with improvements in breathlessness and breathlessness-anxiety.

Pulmonary rehabilitation is associated with altered neural responses related to learned breathlessness associations, which can ultimately influence breathlessness perception. These findings highlight the importance of targeting learned associations within treatments for COPD, demonstrating how neuroimaging may contribute to patient stratification and more successful personalised therapy.

Editor’s Comment: Breathlessness is by far the most limiting symptom associated with COPD. The majority of interventions applied are aimed at improving this in particular and pulmonary rehabilitation (PR) is reliably associated with benefit. Surprisingly little is known about the neurocognitive determinants of dyspnea and, until fairly recently, even the areas of the brain involved were poorly defined. It is also being recognized that the reason dyspnea correlates poorly with pulmonary function abnormalities is because there are learned associations that amplify the unpleasant components. Improvements in dyspnea following pulmonary rehabilitation, especially since they occur in the absence of pulmonary function improvement, may include neural changes in these learned associations.

This study evaluated 31 patients with mild-moderate COPD with brain functional magnetic resonance imaging (fMRI) before and after standard PR, looking for changes in activity patterns, in relation to word cues to trigger symptoms. Brain responses were evaluated in the presence of this provoked breathlessness and anxiety. After PR there was a significant improvement in anxiety responses, and this showed a negative correlation with activity in the posterior cingulate cortex, angular gyrus, primary motor cortex, and supramarginal gyrus. Improvements in breathless rating were positively correlated with activity in the left anterior insula, left posterior insula, left supramarginal gyrus, and anterior cingulate cortex, but, overall, there was no significant improvement in word cue provoked breathlessness after PR.

A change in responses over pulmonary rehabilitation was positively correlated with baseline activity in the ventromedial prefrontal cortex and anterior cingulate cortex (anxiety ratings), and in the anterior insula (bilateral), orbitofrontal cortex, and motor cortex (breathlessness ratings). These areas comprise much of the stimulus valuation network, and these findings suggest that people with greater brain activity during word-cue presentation are more likely to benefit from pulmonary rehabilitation, particularly with regard to anxiety.

This study explores an infrequently used technique, fMRI, and an area of word cue triggered symptom responses that are not currently evaluated in any routine clinical setting. By mapping these areas of anxiety and breathlessness associated brain activity, it offers new insights into the neural localization of symptoms and their possible value in predicting PR benefit, and underlines the complex learned patterns and associations that produce unpleasant symptoms in patients with COPD. It is too early to attest to the validity of such assessments, but they do add an objectively quantitative tool to an area that is notoriously subjective in its measurement at present.

Effectiveness of Pulmonary Rehabilitation in Patients With Interstitial Lung Disease of Different Etiology: A Multicenter Prospective Study

Tonelli T, Cocconcelli E, Lanini B, Romagnoli I, Fiorini F, Castaniere I, Andrisani D, Cerri S, Luppi F, Fantini R, Marchioni A, Baghè B, Gigliotti F, Cini EM

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Background: Recent evidences show that Pulmonary Rehabilitation (PR) is effective in patients with Interstitial Lung Disease (ILD). It is still unclear whether disease severity and/or etiology might impact on the reported benefits.
We designed this prospective study 1) to confirm the efficacy of rehabilitation in a population of patients with ILDs and 2) to investigate whether baseline exercise capacity, disease severity or ILD etiology might affect outcomes.

Methods: Forty-one patients (IPF 63%, age 66.9 ± 11 ys) were enrolled in a standard PR course in two centers. Lung function, incremental and endurance cyclo-ergometry, Six Minutes Walking Distance (6MWD), chronic dyspnea (Medical Research Council scale-MRC) and quality of life (St. George Respiratory Questionnaire-SGRQ) were recorded before and at the end of PR to measure any pre-to-post change. Correlation coefficients between the baseline level of Diffuse Lung Capacity for Carbon monoxide (DLCO), Forced Vital Capacity (FVC), 6MWD, power developed during incremental endurance test, GAP index (in IPF patients only) and etiology (IPF or non-IPF) with the functional improvement at the 6MWD T (meters), at the incremental and endurance cyclo-ergometry (endurance time) and the HRQoL were assessed.

Results: Out of the 41 patients, 97% (n = 40) completed the PR course. Exercise performance (both at peak load and submaximal effort), symptoms (iso-time dyspnea and leg fatigue), SGRQ and MRC significantly improved after PR (p < .001). Patients with lower baseline 6MWD showed greater improvement in 6MWD (Spearman r score = −.359, p = .034) and symptoms relief at SGRQ (r = −.313, p = .025) regardless of underlying disease.

Conclusion: Present study confirms that comprehensive rehabilitation is feasible and effective in patients with ILD of different severity and etiology. The baseline submaximal exercise capacity inversely correlates with both functional and symptom gains in this heterogeneous population.

Editor's Comment: The use of pulmonary rehabilitation (PR) in a broad variety of interstitial lung diseases (ILDs) is now accumulating a respectable corpus of data that, so far, suggests at least short term (<6 mo) benefit. This study, a prospective one, sets out to (1) confirm the efficacy of PR in a population of patients with ILDs and (2) investigate whether baseline exercise capacity, disease severity, or ILD etiology might affect outcomes. It enrolled 41 patients, 26 with idiopathic pulmonary fibrosis (IPF) and the rest with a mixture of other conditions (connective tissue disease-associated interstitial lung disease, hypersensitivity pneumonitis, sarcoidosis, asbestosis) with 40 completing both the PR as well as the pre- and post-PR assessments. As expected, the usual improvements were seen. Exercise performance, both cycle ergometry and 6-min walk distance (6MWD), dyspnea, and health-related quality of life all improved, with the greatest improvement in 6MWD seen in those most limited at baseline.

The study does confirm its first objective, establishing efficacy, but this is neither new nor unexpected. It also reestablishes, in a limited way, that those with greater impairment benefit most; however, the spectrum of severity in this study tilts towards mild to moderate, and the question remains whether this applies to those who are severely impaired. Also, the number of patients included, and especially the small numbers with non-IPF diagnoses, makes any meaningful assessment of etiology-linked response impossible. Lastly, given the unspecified but short follow-up (a few weeks at the most), this study falls short of convincingly establishing truly useful efficacy.

In the present, PR in ILDs remains a treatment option, but much uncertainty remains about appropriate diagnoses and disease stage for optimal referral. Overall, any early improvements seen tend to decay rapidly, and the confounding effects of disease activity, treatment side effects, comorbidities, etc. make patient selection and program design fairly hit or miss.

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Percutaneous Coronary Intervention in Stable Angina (ORBITA): A Double-Blind, Randomised Controlled Trial

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Background: Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.

Methods: ORBITA is a blinded, multicentre randomised trial of PCI versus a placebo procedure for angina relief that was done at five study sites in the UK. We enrolled patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received 6 weeks of medication optimisation. Patients then had pre-randomisation assessments with cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. Patients were randomised 1:1 to undergo PCI or a placebo procedure by use of an automated online randomisation tool. After 6 weeks of follow-up, the assessments done before randomisation were repeated at the final assessment. The primary endpoint was difference in exercise time increment between groups. All analyses were based on the intention-to-treat principle and the study population contained all participants who underwent randomisation.

Findings: ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase and between Jan 6, 2014, and Aug 11, 2017, 200 patients underwent randomisation, with 105 patients assigned PCI and 95 assigned the placebo procedure. Lesions had mean area stenosis of 84.4% (SD 10.2), fractional flow reserve of 0.69 (0.16), and instantaneous wave-free ratio of 0.76 (0.22). There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16.6 s, 95% CI −8.9 to 42.0, p = 0.200). There were no deaths. Serious adverse events included four pressure-wire related complications in the placebo group, which required PCI, and five major bleeding events, including two in the PCI group and three in the placebo group.

Interpretation: In patients with medically treated angina and severe coronary stenosis, PCI did not increase exercise time by more than the effect of a placebo procedure. The efficacy of invasive procedures can be assessed with a placebo control, as is standard for pharmacotherapy.

Editor's Comment: Coronary angioplasty was developed 40 years ago as a less invasive alternative to bypass surgery for patients with stable ischemic disease. Over the past generation, percutaneous coronary interventions (PCI) for acute coronary syndromes has grown to become the pre-dominant option for coronary revascularization. The ORBITA study results have no direct bearing on this indication, but they do raise questions about the true effects of many of the half million or so PCI procedures performed each year on stable patients. In the early years of PCI, it was widely believed that opening a severely blocked artery with PCI would have long term cardiovascular benefits, even in stable patients. It’s been widely believed that even stable coronary artery disease patients are at higher risk for cardiovascular
events and death and that PCI or bypass surgery lowered that risk by restoring flow through the blocked vessel and preventing a future myocardial infarction (MI). However, it has become increasingly clear that MIs are more likely to occur at other, less obvious blockages. Coronary artery disease has begun to be seen more as a systemic condition and less as a localized obstruction. The positive role of medical therapy, including statins and aspirin and other lifestyle changes (diet, exercise, smoking cessation, etc) have become increasingly recognized. In fact, the COURAGE trial (conducted 10 years ago) has led to agreement that PCI in stable lesions do not produce long-term improvements in outcomes when compared to optimal medical therapy. Despite this important finding, PCI for stable angina has maintained a strong clinical presence as a new consensus emerged indicating that PCI was superior to optimal medical therapy in the relief of symptoms.

In the Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) study, 200 patients were randomized to receive either PCI or a placebo “sham” procedure at 5 sites within the United Kingdom. All patients were clinically eligible for PCI based on symptoms and at least 1 angiographically significant lesion ≥70% in a single vessel that was clinically appropriate for PCI. Patients with multi-vessel disease were excluded. The primary endpoint was change in exercise time on a treadmill. The trial was designed to detect an effect size difference of 30 seconds between the 2 study arms at 6 weeks.

After enrollment, patients entered a 6-wk medical optimization phase, which included the introduction and intensive up-titration of anti-anginal medications. This was followed by a pre-randomization assessment that included symptom burden with Canadian Cardiovascular Society Class and the Seattle Angina questionnaire, functional capacity using cardiopulmonary exercise testing, myocardial ischemic burden using dobutamine stress echocardiography, and quality of life assessment using an EQ-5D-5L questionnaire. Patients then underwent the blinded invasive angiography procedures.

For the primary endpoint results, there was no significant difference in mean exercise times at 6 wk between the 2 groups. Furthermore, there were no significant differences between study arms in other secondary endpoints of health-related quality of life measures including anginal symptom scores or quality of life, although improvements were noted in both arms at 6 wk.

While this is a relatively small clinical trial and will likely be challenged by many in the interventional cardiology community, it may have enormous potential impact on practice. This study raises major questions about 1 of the core beliefs of clinical cardiology as it suggests that PCI for stable coronary disease has no more effect than a sham procedure. Although there are a number of necessary caveats and cautions, the trial will likely force a debate on the possibility that many of the benefits of PCI, at least in the population with stable disease, have been the result of a placebo effect both in patients and in their cardiologists.

Purpose: Although athletes demonstrate lower cardiovascular risk and superior vascular function compared with sedentary peers, they are not exempted from cardiac events (i.e., myocardial infarction [MI]). The presence of an MI is associated with increased cardiovascular risk and impaired vascular function. We tested the hypothesis that lifelong exercise training in post-MI athletes, similar as in healthy controls, is associated with a superior peripheral vascular function and structure compared with a sedentary lifestyle in post-MI individuals.

Methods: We included 18 veteran athletes (ATH) (>20 yr) and 18 sedentary controls (SED). To understand the effect of lifelong exercise training after MI, we included 20 veteran post-MI athletes (ATH + MI) and 19 sedentary post-MI controls (SED + MI). Participants underwent comprehensive assessment using vascular ultrasound (vascular stiffness, intima-media thickness, and endothelium (in)dependent mediated dilatation). Lifetime risk score was calculated for a 30-yr risk prediction of cardiovascular disease mortality of the participants.

Results: ATH demonstrated a lower vascular stiffness and smaller femoral intima-media thickness compared with SED. Vascular function and structure did not differ between ATH + MI and SED + MI. ATH (4.0% ± 5.1%) and ATH + MI (6.1% ± 3.7%) had a significantly better lifetime risk score compared with their sedentary peers (SED: 6.9% ± 3.7% and SED + MI: 9.3% ± 4.8%). ATH + MI had no secondary events versus two recurrent MI and six elective percutaneous coronary interventions within SED + MI (P < 0.05).

Conclusion: Although veteran post-MI athletes did not have a superior peripheral vascular function and structure compared with their sedentary post-MI peers, benefits of lifelong exercise training in veteran post-MI athletes relate to a better cardiovascular risk profile and lower occurrence of secondary events.

Editor’s Comment: The health benefits of regular physical activity on the cardiovascular system are irrefutable. The cardioprotective effects of exercise training are only partly explained as a function of improvements in cardiovascular disease risk factors, such as decreases in blood pressure and body mass index. Even though athletes have a lower status on cardiovascular risk factors compared to sedentary peers, they are not exempted from development of ischemic coronary artery disease. Athletes who suffer from myocardial infarctions (MI) may question whether their physically active lifestyles were of value in terms of their long-term health. This study addressed this question by examining vascular structure and function in veteran athletes, with and without a history of MI, in comparison to their sedentary peers. Eighteen asymptomatic veteran athletes, 18 sedentary controls, 20 post-MI veteran athletes, and 19 post-MI sedentary controls underwent a comprehensive vascular ultrasound assessment. Veteran athletes were those who reported regular participation in moderate-vigorous exercise during the past 20 years. Measures of peripheral vascular function (vascular stiffness and flow-mediated dilation) and vascular structure (intima-media thickness) were obtained. Participants also performed an incremental exercise test, had lipid profiles assessed through fasting blood samples, and had cardiovascular disease risk status determined by calculating a lifetime risk score.

First, this study found that some markers of vascular function (arterial stiffness) and structure (femoral intima-media thickness) were significantly better in veteran athletes compared to their sedentary peers. As expected, the veteran athletes also had better cardiorespiratory fitness and lower scores on the cardiovascular risk profile.

Vascular Function and Structure in Veteran Athletes After Myocardial Infarction

Maessen MF, Eijssvogels TM, Hijnmans-Kersten BT, Grotens A, Schreuder TH, Hopman MT, Thijssen DH
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compared to their sedentary peers. Unexpectedly, there were no differences in vascular function and structure between post-MI veteran athletes and post-MI sedentary controls. These observations may be a consequence of prescriptive medication regimens affecting cardiovascular risk factors, which did not differ between post-MI groups. Nonetheless, post-MI veteran athletes had better cardiopulmonary fitness and cardiovascular risk profiles than their sedentary MI counterparts. It is important to note that the post-MI veteran athletes reported no secondary cardiovascular events, which contrasts the occurrence of eight events in the post-MI sedentary control group.

Although not consistent for all vascular measures, some measures show better vascular function and structure in post-MI veteran athletes. Moreover, benefits of lifelong exercise training in post-MI veteran athletes, demonstrated by the fewer secondary events in post-MI veteran athletes, may also relate to a better cardiovascular fitness and lower cardiovascular risk status. Even though exercise cannot fully protect physically active humans against myocardial events, lifelong exercise before and after MI is associated with a lower risk and fewer cardiovascular events compared to their nonactive peers. Importantly, these benefits are unlikely to be fully explained through changes in traditional cardiovascular risk factors only. –PHB