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The Role of Pravastatin in Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

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In this issue of *Clinical Science* Lee *et al* report a placebo-controlled study of 53 patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) on echocardiography, in which six-months of pravastatin treatment was associated with a significant increase in exercise time (660 to 1006s, $p < 0.0001$) and improvement in Borg dyspnoea score. COPD is clearly a significant health concern as the fourth leading cause of morbidity and mortality in the US, costing up to £1 billion per year in the UK. The exact prevalence of PH in COPD is uncertain. However, it is estimated that mean pulmonary artery pressure will rise on average by 0.28 to 0.6 mmHg per year per patient, so occurring in up to 95% of patients awaiting lung volume reduction surgery or transplantation. However, PH in this context is usually mild to modest in severity, except for a small number with COPD 'out-of-proportion' to their underlying airflow limitation. Certainly, the presence of PH is a risk factor for mortality in patients with COPD. We review the role of PH in COPD and its pathophysiology, with reference to endothelin-1, cigarette smoke, as well as exercise and nocturnal hypoxia. We also explore potential mechanisms for the observed improvement in exercise tolerance seen in six months' pravastatin treatment, including possible effects upon endothelin-1, Rho-kinase, or antioxidant effects, which may be particularly relevant in this group of mainly current smokers.

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In this issue of *Clinical Science* Lee *et al* report a placebo-controlled study of 53 patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) on echocardiography, in which six-months of pravastatin treatment was associated with a significant increase in exercise time (660 to 1006s, $p < 0.0001$) and improvement in Borg dyspnoea score¹.

COPD is clearly a significant health concern as the fourth leading cause of morbidity and mortality in the US, costing up to £1 billion per year in the UK. But how important is the association of PH with this condition? The exact prevalence of PH in COPD is uncertain. However, it is estimated that mean pulmonary artery (PA) pressure will rise on average by 0.28 to 0.6 mmHg per year per patient^{2, 3}. The outcome of this is that it is likely that a significant proportion of patients will develop PH over their lifetime, with reports extending up to 95% in patients awaiting lung volume reduction surgery or transplantation⁴⁻⁶. However, PH in this context is usually mild to modest in severity. The exception to this is the group of 'outliers' with more significant PH 'out-of-proportion' to the underlying airflow limitation⁶. Importantly, the presence of PH does confer a worse prognosis, being an independent factor for both mortality and frequency of COPD exacerbations^{7, 8}.

PH in the context of COPD, is classified as PH related to hypoxia and/or chronic respiratory disease^{9, 10}. However, is it reasonable to consider PH in COPD as primarily hypoxia-related? Traditionally, PH in COPD was thought to be related to destruction of the vascular bed which occurs in emphysema, and as a response to chronic hypoxia. However, PH is not associated with the degree of emphysema⁴, occurs independent of hypoxia and is not completely ameliorated by oxygen replacement⁷. Other mechanisms, must, therefore, be considered in the pathophysiology of PH, particularly when 'out-of-proportion' to the underlying airflow limitation. The role of transient hypoxia and PH seen on exercise, at night, and during COPD exacerbations, is yet to be determined in the pathophysiology of resting PH^{2, 11, 12}. It is also possible that cigarette smoke, itself, may play a role in endothelial dysfunction, and subsequent vascular damage^{13, 14}. Currently, apart from oxygen therapy, there is no treatment for PH associated with COPD.

Endothelin-1 (ET-1) is a vasoactive mediator that causes vasoconstriction and vascular cell proliferation. In idiopathic pulmonary arterial hypertension (PAH) levels of ET-1 in plasma correlate to pulmonary vascular resistance and inversely to prognosis^{16, 17}. Blockade of the ET-1 A and B receptors with a mixed receptor blocker, bosentan, improves functional status and overall mortality. There is gathering evidence that blockade of the ET-1 system may also benefit patients with PAH in association with Eisenmenger syndrome, connective tissue disease, HIV and thromboembolic disease. ET-1 also has potent bronchoconstrictive properties and has been implicated in the pathogenesis of airways disease. The role of ET-1 in the pathophysiology of COPD remains uncertain, and may be related to its effect upon bronchoconstriction, or its pro-inflammatory properties. Plasma ET-1 levels are elevated in COPD patients compared to control subjects¹⁸. Plasma ET-1 increases during acute exacerbations, and falls following one hour of oxygen replacement. Patients with COPD with nocturnal desaturation have

higher day and night ET-1 plasma levels¹⁹. It is possible that ET-1 may contribute to the development of PH in COPD. However, reports of ET-1 levels in PH in COPD have been conflicting; with one study showing no difference in levels amongst patients with or without PH²⁰, and another study demonstrating increased exhaled and arterial ET-1 levels in patients with PH (with ET-1 levels correlating with echocardiographic systolic pulmonary arterial pressures)²¹. There has been one randomised study investigating the effect of bosentan (versus placebo) on cardiopulmonary hemodynamics during exercise in patients with severe COPD, but importantly, with no resting PH. There was no improvement in six-minute walk test, the primary outcome measure. In addition, there was deterioration in oxygenation and quality of life with no change in pulmonary artery pressure¹⁵.

Statins, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, including pravastatin, block the rate-limiting step in cholesterol synthesis. However, their benefit clearly extends beyond the effect upon lowering cholesterol. Statins have 'pleiotropic' effects including the improvement of endothelial dysfunction, inhibition of vascular smooth muscle proliferation, and induction of vascular smooth muscle cell apoptosis. The mechanisms by which these effects is uncertain, but appears to be related to the inhibition of synthesis of small GTP binding proteins required for the RhoA activation. This, in turn, leads to the reduction in endothelial nitric oxide synthase (eNOS) and decreased nitric oxide production and subsequent vasoconstriction. Moreover, RhoA/Rho-kinase signalling plays an important role in the sustained phase of vasoconstriction mediated by ET-1. While statins prevent and ameliorate PH in animal studies, there is no data for their use in the treatment of PH from any cause.

In this context, the study by Lee *et al* reported in this Journal, sets out to test the hypothesis that statins may improve hemodynamics in patients with COPD and PH, by affecting ET-1 synthesis. This was based on a previous observation that statins inhibit prepro ET-1 transcription *in vitro*. 53 patients with stable COPD (FEV1 56% predicted) and PH (defined as systolic PA pressure greater than 35 mmHg by echocardiography) were randomised to receive either pravastatin or placebo in a double-blind manner over a period of 6 months. Exercise capacity, tested using a Naughton stress-test treadmill protocol, was significantly improved in the pravastatin treated group and remained static in the placebo group. Systolic PA pressure significantly fell from 47 mmHg to 40 mmHg and Borg dyspnoeic index also improved. There was no change in plasma ET-1 measured in peripheral vein but a slight decrease in urinary excretion of ET-1. There was a significant correlation between changes in exercise time and levels of ET-1 excreted in the urine. The main conclusion of the authors was that "pravastatin significantly improved exercise tolerance, decreased PH, and dyspnoea during exercise, probably by inhibiting endothelin-1 synthesis in COPD patients with PH".

So where does this leave us with the story of COPD, PH and ET-1? The most impressive finding of the study by Lee *et al* was the improvement in exercise capacity in patients receiving pravastatin. Was this due to an improvement in PH? Of course, this study was not designed to answer this question. We note the parallel study published by the same authors, in which a similar benefit was demonstrated across COPD patients independent

of the presence of PH²². Also, given the modest elevation in systolic PA pressure in patients at the beginning of the study, it is unlikely that PH was the limiting factor and therefore that the improvement in PH on treatment was the reason for improved exercise capacity. The caveat to this statement is that we do not know if pravastatin (acutely and with time) ameliorates the transient elevation in PA pressure seen on exercise, which is a known risk factor for the development of resting PH in COPD⁷. Also, as the authors note, it is difficult to assess the therapeutic benefit with regard to PH, in the absence of the resting, exercise and nocturnal oxygen levels.

What about the role of ET-1? In the reported study, there was no change in venous plasma ET-1 with treatment. As most ET-1 is produced in the lung, perhaps a better measure would have been trans-pulmonary ET-1 production (i.e. comparisons of central venous and arterial samples). However, a reduction in renal excretion of ET-1 was observed, although, as the authors stated, the magnitude was not enough to explain the change in exercise capacity ($R^2 = 0.22$). It is difficult to propose how a reduction in renal excretion of ET-1 would account for the improved exercise capacity. The authors note that urinary ET-1 excretion correlates with global ET-1 levels, and may be more sensitive to changes in overall endogenous ET-1 production than serum ET-1 levels.

However, the beneficial effect of pravastatin is more likely to be independent of ET-1. The authors mention two possible alternative mechanisms in which pravastatin may affect vascular function: oxidative stress and the RHO-kinase system. Oxidative stress is increased in COPD, and is obviously important in cigarette induced vascular injury. Statins may reduce free radical generation. In this cohort of mainly (81%) current smokers, any antioxidant mechanisms may have been particularly effective. It would be interesting to determine if a similar benefit is seen in ex or never smokers. Statins are also known to effect apoptosis of vascular cells, which may have a longer-term effect on vascular remodelling.

In summary, the most exciting finding from the study of Lee *et al* is the beneficial effect of pravastatin on exercise capacity in patients with COPD and PH. The exact mechanism of this benefit is uncertain, as is the contribution of PH. The role of ET-1 in PH in association with COPD is also unclear and some doubt has already been cast on the usefulness of ET-1 receptor antagonists in this condition. Clearly, more work needs to be done on the contribution of exercise-induced increases in PH in COPD and the effect of this upon exercise capacity. In addition, we need to study the importance of ET-1 and blocking its action in patients with COPD and moderate to severe PH, although this appear to be a minority group.

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