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## An Unusual Pulmonary Complication of Statin Medication

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## **An unusual case of shortness of breath with statins**

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## Abstract

Statins or hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have proven efficacy at decreasing cardiovascular morbidity and mortality. Although statins have been prescribed safely, there should be more awareness of the possible adverse effects. Recently, we encountered a patient who had unexplained dyspnea, weakness, and immobility. The patient's symptoms were alleviated after discontinuing the statin medication. Although we have no concrete evidence that her symptoms were due to the medication, the temporal relationship of symptom improvement upon discontinuation of the statin led us to the conclusion that it could potentially have been the cause. Unexplained dyspnea is not listed as an adverse effect in the prescribing information, but interstitial lung disease is listed as a possible complication of statins and there are a few other case reports of statin related unexplained dyspnea in the literature. Physicians should be aware of statins as a possible cause of unexplained dyspnea and consider a drug holiday as a therapeutic trial.

## Introduction

Statins, also known as HMG-CoA reductase inhibitors, are some of the best-selling prescription drugs in the world.<sup>1</sup> They lower the incidence of cardiovascular disease and stroke morbidity and mortality.<sup>1</sup> The US Preventive Services Task Force (USPSTF) recommends moderate-dose statin for treating lipid disorders in adults aged 40 to 75 years who have a 10-year cardiovascular risk of more than 10% and recommends using it selectively in patients who have a 10-year cardiovascular risk of 7.5% to 10%.<sup>2</sup> There is insufficient evidence regarding statin use for the primary prevention of cardiovascular events and mortality in adults aged 76 years and older.<sup>2</sup> Still, with this guideline, large numbers of people will be eligible to take statin medication.

Statins act by competitively inhibiting HMG-CoA reductase in the mevalonate pathway, which is the key rate limiting enzyme for the biosynthesis of cholesterol.<sup>1,3</sup> In addition to cholesterol, this pathway generates a range of other products, such as coenzyme Q-10, heme A, and isoprenylated proteins, which play a role in the benefits as well as potential adverse effects.<sup>1,3</sup> Muscle related side effects are the most commonly reported adverse effects of statins, however, other possible adverse effects include diabetes mellitus, hemorrhagic stroke, decreased cognition, tendon rupture, and interstitial lung disease.<sup>1,3</sup>

There are very few other reports of unexplained dyspnea and generalized weakness related to statin use. We report a case of a patient with a history of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypertension, and hyperlipidemia who experienced an unusual presentation of dyspnea, weakness, and immobility that significantly improved after discontinuing statin medication.

## Case Description

An 82-year-old female with a history of CAD, COPD, hypertension, hyperlipidemia and 4-vessel coronary artery bypass graft surgery eight years prior to presentation complained of progressively worsening dyspnea and generalized weakness. The patient stated that she had recurrent episodes of subjective intermittent shortness of breath without cough, fever, chills,

chest pain, or sputum production. She indicated that the episodes of increasing dyspnea were associated with tremor in her upper and lower extremities and a feeling of generalized weakness.

Prior to these episodes, the patient demonstrated an active lifestyle with regular ballroom dancing. As her symptoms became severe, the patient had multiple visits to the ER, cardiologist, pulmonologist, and her primary care physician, where she underwent thorough evaluation with pulmonary function tests (read as normal), arterial blood gas (respiratory alkalosis), chest x-ray (some hyperinflation), chest CT scan (negative for pulmonary embolus), stress test (normal), echocardiogram (slightly elevated right sided pressures) and right heart catheterization (negative for pulmonary hypertension). Labs revealed normal to only slightly elevated CPK (30-220 U/L, normal 22-198 U/L) and normal 25-OH vitamin D (32.8 ng/mL, normal 30-50 ng/ml). Her statin medication at the time of presentation was simvastatin 40mg once daily. She was on this medication for six years prior to developing dyspnea. She was not on calcium channel blockers or other medications now known to interfere with dosing of simvastatin.

Several months after the initial presentation, the patient had a left heart catheterization with stent placement to the proximal LAD after which she initially improved, but symptoms quickly returned two months later and a repeat left heart catheterization showed a patent stent. All of her physical examinations were similar with her general appearance of moderate respiratory distress and generalized weakness and disability, requiring the use of a wheelchair for mobility. One year after initial presentation, the patient visited a neurologist at a tertiary care institution; however, just prior to this visit, she discontinued statins on the advice of a friend. She had EMG/NCS at this institution that were negative for neuropathy. The patient was told at this tertiary care facility that potential etiologies of her dyspnea and weakness included anxiety and cataplexy. Anxiety was considered by her primary care physician who started a therapeutic trial of buspirone without improvement in her symptoms. It was suggested that the patient undergo formal psychiatric evaluation; she refused.

A month after discontinuing statins, the patient presented for follow up and reported a drastic improvement in her dyspnea and generalized weakness that began almost immediately after stopping the statin drug. She regained mobility and was once again able to walk without assistance. Eight months after discontinuation, she is still having some mild dyspnea and, although she is 90% better, she is not back to her baseline.

## Discussion

Statins or HMG-CoA reductase inhibitors have proven efficacy in reducing cardiovascular events, but are associated with several adverse effects.<sup>1,3</sup> New cholesterol guidelines have the potential for an even higher number of patients who may be given these medications.<sup>2</sup> As more people are exposed to these medications, knowledge of new side effects may arise. We present an unusual case of dyspnea and weakness that improved after discontinuing statin medication.

Literature review found ten cases where discontinuing statins demonstrated improvement in shortness of breath, either clinically or radiographically.<sup>4-9</sup> Three of the ten patients with dyspnea did not have abnormal radiographic findings and had similar comorbidities to our patient such as CAD, COPD, and hypertension. Two of these three patients were taking lovastatin and one was

on simvastatin. The time between starting statins and symptom development in these cases was two to four years with our patient developing symptoms six years after starting simvastatin. In another case report, Chatham et al. showed decreased respiratory muscle performance with statins as a cause of the dyspnea with subsequent improvement in muscle performance after statin cessation.<sup>8</sup> They suggested respiratory therapy as a potential intervention for statin related dyspnea. Another possible intervention, prednisone therapy (10mg-60mg), was given in the cases of statin induced interstitial lung disease that improved symptoms and led to radiographic clearing of the infiltrates.<sup>4,8</sup>

It is clear that patients who receive statin medications have muscle side effects. Statin-Associated Muscle Symptoms (SAMS), at a frequency of 10-25%, are the most common side effects.<sup>1,3</sup> SAMS include myalgia and rhabdomyolysis. Patients with myalgia with or after exercise often have normal creatine phosphokinase (CPK) levels.<sup>1,3</sup> Rhabdomyolysis occurs when muscle damage becomes severe, sometimes accompanied by renal failure.<sup>1,3</sup> As opposed to myalgia, rhabdomyolysis is accompanied by marked elevation of CPK.<sup>1,3</sup> The etiology for muscle adverse effects due to statin therapy remains unknown.<sup>1,3</sup> The FDA reports that women who are older, like our patient, are more likely to be at risk of myopathy with the use of simvastatin 80mg compared to patients on lower doses.<sup>10</sup> One hypothesis for our patient's dyspnea is that the statin affected the function of her diaphragm muscle similar to the case described by Chatham et al, although we do not have objective evidence for this dysfunction. Statins are known to predispose to mitochondrial dysfunction due to the reduction of coenzyme Q10 and heme A in the mevalonate pathway.<sup>1</sup> Mitochondrial myopathy, a cause of respiratory muscle weakness, has been described as an etiologic factor for unexplained dyspnea.<sup>11</sup>

A limitation of our report is that we have no laboratory evidence such as elevation in CPK that links her symptoms to the statin medication. However, many patients who report muscle aches on statins similarly do not have elevation in CPK.<sup>1,3</sup> Our association is based on the fact that her symptoms abated significantly and almost immediately upon discontinuation of simvastatin. Due to the severity of the patient's symptoms, we would not consider a repeat medication challenge to see if the symptoms recurred.

Unexplained dyspnea is not listed as a potential side effect in the prescribing information for statin drugs. However, we report a case of unexplained dyspnea and weakness that resolved after stopping statin medication and there are other similar cases reported. This side effect may occur after years of statin use, making a drug side effect not obviously the cause of new symptoms. Since advancing age is a risk factor for the statin associated muscle symptoms, we must be vigilant for other possible adverse effects from these drugs as our patients on statins get older. Sometimes healthcare providers are too quick to assign a psychiatric cause to unexplained symptoms and they may miss an important and reversible condition. Physicians should be aware that unexplained dyspnea and weakness could be associated with the use of statins and should consider a therapeutic drug holiday for these patients.

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