Don't Call the Electrician When the Problem is the Plumbing: Resolution of Paroxysmal Atrial Fibrillation after Aggressive Treatment of Pulmonary Hypertension

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ABSTRACT

Atrial fibrillation (AF) is the most common type of cardiac rhythm disturbance, affecting 1.2 million people in the United States each year.[1] Development of AF involves an interplay between a triggering factor, an arrhythmogenic substrate, and modulating factors.[2] It has a variety of potential causes including hypertension, hyperthyroidism, ischemic heart disease, valvular abnormalities and lung problems.[3] While therapy aimed directly at the prevention or recurrence of AF with pharmacotherapy or catheter ablation is often necessary,[4] it is also important to identify and modify the underlying cause if at all possible. One such potential underlying cause is pulmonary arterial hypertension (PAH). While direct causation has not been demonstrated, PAH has demonstrated a strong association with the development of AF.[5-8] PAH may cause AF through increased atrial stretch secondary to right ventricular failure, hypoxia, and autonomic dysregulation.[9-12]

We report herein a case of a 72-year-old man with PAH and paroxysmal AF. The patient's underlying pulmonary problems and poor right ventricular (RV) function made direct treatment of the AF with ablation or pharmacotherapy risky. On the day of his office visit, a right heart catheterization was performed, showing a pulmonary capillary wedge pressure of 7 mmHg (normal values [NV]: 8-10 mmHg) and a pulmonary artery pressure of 110/44 mmHg (NV: 15-25/8-15 mmHg) with a mean of 70 mmHg (NV: 10-20 mmHg). He was admitted to the ICU, and his sildenafil was increased gradually to 80 mg 3 times daily. Interestingly, treatment aimed at improving his pulmonary hemodynamics led to an improvement of his symptoms and resolution of his AF. This case illustrates that treatment of the underlying hemodynamic problems creating the milieu for AF can provide an excellent alternative or adjuvant to direct therapy in the case of PAH. Furthermore, consideration should be given to the causative factors of AF when considering treatment plans.

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INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac rhythm disturbance, affecting 1.2 mil-

lion people in the United States each year.[1] The estimated incidence is 78 in men and 60 in women per 100,000 person years.[13] It has a variety of potential causes including hypertension, hyperthyroidism, ischemic heart disease, valvular abnormalities, and lung problems.[3] One potential cause is pulmonary arterial hypertension (PAH).[5-8] PAH is a relatively rare disease, with an estimated prevalence of 15-25 cases/million[14,15] that has demonstrated a strong association with the development of AF.[5-8] In a five year prospective study of 235 patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (n=82), Olsson et al.[5] found a cumulative incidence of atrial flutter and fibrillation of 25.1%. In this same cohort, development of these arrhythmias was associated with clinical exacerbation in 80% of patients and was an independent risk factor for death in a simple Cox regression analysis. In a 6 year prospective study of 280 patients with PAH, Wen et al.[16] found a cumulative incidence of supraventricular arrhythmias (SVA) of 14.3% and a cumulative incidence of AF of 5.7%. Clinical deterioration and worsening right-sided heart failure was noted in 97.5% of the patients in this cohort with SVA. When retrospectively examining the prognostic role of AF in 2755 patients with severe PAH, Mojadidi et al. [17] found 1 year mortality rates of 33.4% in the AF group compared to 24.8% in the group without AF. In a 6 year retrospective study of 231 PAH patients, Tongers et al[8] found the average time from diagnosis of PAH until documentation of an arrhythmia to be 3.5 years. This suggests that PAH is present for some time before the subsequent development of the arrhythmia.[6]

While direct causation of AF by PAH has not been well established, there is reasonable evidence to suggest its role as a significant contributing factor. The development of an arrhythmia involves the interplay between a triggering factor, an arrythmogenic substrate, and modulating factors.[2] Ectopic firing originating predominantly from the pulmonary vein region,[18] the ligament of Marshall,[19] and the superior and inferior vena cava[20,21] can provide a triggering factor for the initiation of atrial fibrillation in the susceptible individual. Multiple factors contribute to this susceptibility such as age, fibrosis, and conduction heterogeneity.[2] Many aspects of PAH create a favorable milieu for both the initiation and perpetuation of AF. Impairment of pulmonary function has previously been demonstrated as an independent risk factor for development of AF.[22] PAH is known to cause increased RV afterload, RV failure, tricuspid regurgitation, and RA dilation.[16, 23-26] The increased atrial stretch can lead to both initiation and perpetuation of AF through altered calcium handling and stretch activated channel activity[27,28] that leads to "stretch induced depolarization, shortened refractoriness, slowed refractoriness, and heterogeneity of refractoriness and conduction."[2] Furthermore, increased atrial stretch has also been shown to contribute to structural remodeling and increased fibrosis of the myocardium.[2] In the Wen et al. cohort,[16] right atrial (RA) length, RA diameter, and mean RA pressure were all risk factors for development of a SVA. PAH is also associated with hypoxia and reduced cardiac output.[22,25,29] These factors have been shown to increase atrial fibrosis[29] and autonomic imbalance,[30] two well-known pro-arrhythmogenic modulating factors.[2,3] Taken together, this evidence suggests PAH plays a significant role in the development and maintenance of AF. We present herein a case in which a patient's AF resolved after aggressive treatment of his PAH. We suggest that the improvement of his pulmonary hemodynamics led to decreased atrial stretch, decreased hypoxia, decreased autonomic imbalance, and the subsequent resolution of AF.

CASE PRESENTATION

A 72-year-old man was seen in the office for progressive and increasingly frequent bouts of palpitations associated with increasing dyspnea. He has longstanding shortness of breath due to progressive interstitial lung disease and associated PAH. His medical history was also notable for coronary artery disease for which he had undergone bypass surgery and catheter-based intervention, hyperlipidemia, Raynaud's phenomenon, gastroesophageal reflux, depression, and postoperative atrial fibrillation. There were initially concerns about worsening of his baseline hypoxia with pulmonary vasodilators, but he had been started on a phosphodiesterase type 5 inhibitor (sildenafil citrate) two years prior without complications. Bosentan (dual endothelin receptor antagonist) 62.5 mg had been added 9 months afterwards, and he was also initiated on iloprost 10 mcg/mL nebulizer solution 6-10 times per day at 5mcg dose 6 months prior to presentation. In addition to these agents, his outpatient medications also included ipratropium/albuterol inhalers 18-103 mcg/actuation 2 puffs, alprazolam 0.25 mg, pantoprozole 40mg, atorvastatin 40 mg, aspirin, calcium plus vitamin D, and paroxetine 10mg. At his last office visit one month prior, he had presented with recurrent palpitations and increased fatigue. A Holter monitor revealed paroxysmal atrial fibrillation (PAF) multiple times a day, correlating with the patient's palpitations. A beta-1 receptor blocker (metoprolol 12.5mg) was initiated, but advancing this medication was limited by bronchospasm. Additionally, his low blood pressure limited the use of calcium channel blockers. He had been evaluated two weeks previously for potential catheter ablation of his arrhythmia, but the risk of anesthesia for this procedure was judged to be prohibitive due to his PAH and decreased RV function.

On the day after his office visit, a right heart catheterization was performed and showed a pulmonary capillary wedge pressure of 7 mmHg (normal values [NV]: 8-10 mmHg) and a pulmonary artery pressure of 110/44 mmHg (NV: 15-25/8-15 mmHg) with a mean pressure of 70 mmHg (NV: 10-20 mmHg). This was increased from catheterization 2 years prior when his wedge pressure was 7 mmHg, pulmonary artery pressure was 80/30 mmHg and mean pressure was 53 mmHg. A Swan-Ganz catheter was left in place and he was admitted to the ICU, where his sildenafil was gradually increased over the next 3 days from 40 mg 3 times daily to 60 mg 3 times daily to 80 mg 3 times daily. The patient tolerated the change well and was discharged 2 days later with no chest pain, dizziness, or nausea. Interestingly, there was also complete resolution of his AF, which did not recur after discharge. This was supported by normal sinus rhythm on a Holter moniter, multiple follow-up electrocardiograms over the next 4 years, and a cessation of his palpitations.

DISCUSSION

AF is the most common heart rhythm disorder in America, resulting in considerable morbidity and mortality.[1] It is associated with 15% of all strokes each year in the United States.[31] In addition, AF may result in significant hemodynamic compromise in some individuals, particularly those with underlying cardiovascular or pulmonary disease.[1,3,31] Often the emphasis is on the direct treatment of AF by utilizing such modalities as cardioversion, antiarrhythmic medications and catheter ablation.[4] While these therapies can be successful at preventing recurrence of AF, they also carry with them a significant number of risks and side effects. Many of these risks are magnified in patients with additional underlying medical problems. For example,

catheter ablations of AF are commonly done under general anesthesia (GA). Patients with PH are at significant risk for perioperative and postoperative morbidity and mortality when undergoing GA.[32-34] Furthermore, these therapies do not often address the underlying cause of AF. In some cases, such as hyperthyroidism, correction of the underlying cause can lead to the cessation of AF.[35] In the case of pulmonary hypertension, the increased pulmonary vasculature pressure causes increased dilation and pressure in the right atrium and ventricle, hypoxia, and autonomic imbalance.[16,23-36] This leads to cardiac structural remodeling, electrical dissociation between muscle bundles, and conduction heterogeneity; it also creates a favorable milieu for the initiation and perpetuation of AF.[2,3,5] The above case suggests the aggressive pharmacologic therapy of PAH helped alleviate the RA strain, hypoxia, autonomic imbalance, subsequently terminating the paroxysmal AF.

Addressing the underlying mechanisms of AF cannot only prevent recurrence but is also an important adjuvant to direct therapy. Moreover, this approach may itself be sufficient to treat AF, especially in new onset AF before extensive cardiac remodeling has occurred. Additionally, as illustrated by our case, treating the underlying condition is an option for controlling AF when other methods are contraindicated, ineffective, or poorly tolerated.

LEARNING POINTS

1. Treatment of the underlying hemodynamic problems creating the milieu for atrial fibrillation can provide an excellent alternative or adjuvant to direct therapy in the case of pulmonary arterial hypertension.

2. Consideration should be given to the causative factors of atrial fibrillation when considering treatment plans.

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