

# What causes exertional dyspnoea in patients with atrial fibrillation? Implications for catheter ablation in patients with heart failure

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**This article refers to ‘A prospective Study using invasive haemodynamic measurements following catheter ablation for AF and early HFpEF: STALL AF-HFpEF’ by H. Sugumar et al., published in this issue on pages 785–796.**

Patients with atrial fibrillation (AF) often complain of exertional dyspnoea, and many physicians believe that the atrial tachyarrhythmia is the cause of the impairment in functional capacity. The assumption of a causal relationship has led electrophysiologists to propose that suppression of AF (either pharmacologically or by catheter ablation) can improve exercise tolerance and yield important clinical benefits, both with respect to quality of life and major outcomes.

Yet, how might AF cause exertional dyspnoea? The most commonly-provided explanation is that the rapidity of the ventricular response acts to limit cardiac output or increase pulmonary venous pressures. It is true that, at any given workload, patients with AF have higher exercise heart rates than those in sinus rhythm; yet, in a healthy left ventricle, the shortening of diastolic filling time does not impair the ability of the heart to deliver oxygen to the periphery. Patients with AF with the highest exercise heart rates have the greatest functional capacity.<sup>1</sup> Beta-adrenergic blockade is extraordinarily effective in attenuating exercise heart rates, but uniformly impairs effort tolerance in patients with AF.<sup>2,3</sup>

Furthermore, AF does not impair the ability of the left atrium to accommodate blood without a disproportionate increase in pulmonary venous pressures. In fact, the loss of atrial systole would be expected to not only reduce the transmission of pressure into the left ventricle at end-diastole, but also ameliorate the generation of pressures into the pulmonary veins. Accordingly, restoration of sinus rhythm by cardioversion or catheter ablation often results in immediate increases in pulmonary venous pressures, which may cause worsening symptoms of heart failure.<sup>4,5</sup> It is not clear whether this phenomenon is related to the restoration of atrial systole or to an effect of procedural interventions to cause

atrial stunning with its attendant adverse effects on left atrial compliance. In any case, the injury and scarring produced by catheter ablation might be expected to impair (rather than enhance) the conduit and reservoir functions of the left atrium.<sup>6</sup>

## Heart failure and a preserved ejection fraction is the cause of dyspnoea in patients with atrial fibrillation

These observations indicate that exertional dyspnoea in a patient with AF is not related to the arrhythmia, but instead, AF is a biomarker of an underlying cardiac disorder that is the true cause of exertional dyspnoea. Epidemiological studies have demonstrated a powerful link between AF and heart failure with a preserved ejection fraction (HFpEF).<sup>7</sup> AF often precedes the development of HFpEF in community studies; conversely, most patients with HFpEF are destined to develop AF, if the arrhythmia is not already apparent. The coexistence of AF and HFpEF is greatly underappreciated in clinical practice, presumably because unrecognized AF occurs years before patients are given a diagnosis, and patients experience exertional dyspnoea long before physicians identify the presence of heart failure.

These interrelationships are strongly reinforced by studies that have shown an exceptional high prevalence of HFpEF in patients who present with AF, exertional dyspnoea and a normal ejection fraction. Reddy et al.<sup>8</sup> evaluated 429 such patients who were primarily referred for the evaluation of exertional dyspnoea (with or without AF). When HFpEF was diagnosed by the presence of a pulmonary capillary wedge pressure of  $\geq 25$  mmHg during exercise, 98% of those with persistent or permanent AF and 91% of those with paroxysmal AF fulfilled criteria for HFpEF. These findings are fully supported by the findings of Sugumar et al.<sup>9</sup> published in this issue of the Journal, who evaluated 54 patients who were referred for catheter ablation for AF (with or without exertional dyspnoea).

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When HFpEF was diagnosed by the presence of a pulmonary capillary wedge pressure of  $\geq 25$  mmHg during exercise, two-thirds of the patients met diagnostic criteria for HFpEF, and 92% of those with persistent AF fulfilled diagnostic criteria for HFpEF. Therefore, even though the patients in the studies by Reddy *et al.* and Sugumar *et al.* were identified through two distinctly different clinical pathways, both groups of authors identified underlying HFpEF as an exceptionally common (and typically undiagnosed) disorder in patients with AF who present with exertional dyspnoea.

The observation that exertional dyspnoea in patients with AF is caused by underlying HFpEF can be explained by the fact that both disorders are related to an abnormality of left atrial remodelling. Whereas left atrial distensibility is increased in patients with heart failure and a reduced ejection fraction, left atrial reservoir function is diminished in patients with HFpEF, presumably because the inflammatory and fibrotic processes that afflict the left ventricle in HFpEF also have a deleterious effect on the left atrium.<sup>7</sup> Patients with heart failure and a reduced ejection fraction have larger left atrial volumes but lower peak left atrial pressures, whereas those with HFpEF have greater left atrial stiffness leading to smaller (although still enlarged) left atrial volumes despite higher peak pressures.<sup>10</sup> Despite the lesser degree of left atrial dilatation, patients with HFpEF are more likely to have AF, suggesting that atrial fibrosis (not chamber distension) is the primary determinant of AF in HFpEF. The pulmonary wedge pressure is typically lower than the left ventricular end-diastolic pressure in patients in sinus rhythm, but the reverse pattern is typically seen in patients with left heart disease and AF.<sup>11</sup> Therefore, the exertional dyspnoea that is caused by the increases in left atrial pressures in patients with HFpEF and AF appears to be the result of the underlying atrial myopathy rather than the retrograde transmission of end-diastolic pressures from a non-compliant left ventricle.

## Does catheter ablation treat the underlying atrial myopathy?

If the atrial tachyarrhythmia is not the cause of exertional dyspnoea in patients with AF, then abolition of AF would not be expected to favourably influence effort tolerance in these patients. In fact, catheter ablation typically provokes a local inflammatory and profibrotic response, which can exacerbate left atrial dysfunction. When the ablation is extensive, left atrial reservoir function can be reduced so dramatically that patients can develop profound exertional dyspnoea due to a 'stiff left atrial syndrome'.<sup>12</sup>

Despite these concerns, many electrophysiologists believe that catheter ablation can ameliorate exertional dyspnoea if AF is effectively suppressed. Yet, these subjective benefits have largely been reported in studies that lack an appropriately randomized control group, and measurements of quality of life are often difficult to interpret in unblinded trial where patients are aware of the effect of the procedure on the regularity of their pulse. To complicate matters further, it is often difficult for patients to distinguish the relief of distressing palpitations from a true improvement in effort tolerance. These challenges are well-illustrated by the findings of the study by Sugumar *et al.*<sup>9</sup> Of the 20 patients in their study who

were re-evaluated by right heart catheterization after  $\cong 10$  months, the haemodynamic effects of catheter ablation were unimpressive. Pulmonary wedge pressures during exercise decreased by less than 4 mmHg, and the mean exercise pulmonary wedge pressure remained greater than 25 mmHg, even though it seems likely that patients underwent interval intensification of background medical therapy. Interestingly, quality-of-life measures improved to a similar degree whether patients were arrhythmia free or had recurrent AF; this latter finding would have been easier to interpret if the study had had a control group.

Recently, the effect of catheter ablation in the setting of a randomized controlled trial was evaluated in a subgroup of patients who participated in the CABANA trial.<sup>13</sup> The investigators identified 778 patients who were considered to have heart failure, of whom nearly 75% had an ejection fraction of 50% or greater. The investigators reported that death for any reason occurred in fewer patients assigned to ablation; however, the trial recorded only 60 deaths, leading to imprecise estimates that are prone to yielding non-reproducible results.<sup>14</sup> Interestingly, there were only 30 cardiovascular deaths and only 10 deaths due to heart failure in the trial, even though the median follow-up was 4 years; these low event rates are incompatible with the diagnosis of heart failure. When the number of deaths in a trial is sparse, investigators typically look toward the treatment effect on hospitalizations for heart failure. However, in the CABANA trial, catheter ablation did not reduce the risk of these non-fatal serious adverse heart failure events (hazard ratio 0.89, 95% confidence interval 0.56 to 1.44).

## Conclusions

As Sugumar *et al.* have shown, many patients who are referred for catheter ablation for the treatment of AF have underlying HFpEF, especially if they have exertional dyspnoea or have other comorbidities that are closely linked to HFpEF (e.g. obesity and diabetes).<sup>15</sup> The diagnosis can be readily made when left atrial pressures are measured during the procedure, although confirmation of left atrial hypertension often requires haemodynamic assessments during exercise. HFpEF is the primary cause of exertional dyspnoea in patients with AF who have exertional dyspnoea, and the ability of catheter ablation to ameliorate pulmonary venous hypertension and favourably modify the clinical course of HFpEF in patients with AF has not been established. Physicians should focus on identifying and managing the underlying cause of exertional dyspnoea in these individuals, in addition to treating the presenting arrhythmia.

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