Atrial fibrillation and its pernicious role in heart failure with preserved ejection fraction: a new frontier in interventional electrophysiology

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Heart failure with preserved ejection fraction (HFpEF) has emerged as a particularly challenging clinical and public health disorder [1]. An extraordinary research commitment over the past four decades has been rewarded by the development of effective drug, surgical, antiarrhythmic, and device therapy for patients suffering from heart failure with reduced ejection fraction (HFrEF). The most recent development has been the pivotal randomized clinical trial (RCT) showing the mortality and morbidity benefits of catheter ablation in HFrEF [2].

In contrast, the search of good therapeutic options for HFpEF has been difficult. There is no “triple” drug regimen as in HFrEF. Diuretics can relieve congestion, and some angiotensin receptor antagonists may reduce hospitalization for heart failure but neither has been shown to prolong survival [3]. Nitrates remain controversial, with trials challenging even symptom relief [4]. Spironolactone may have benefits in subpopulations [5, 6]. Atrial fibrillation (AF) in HFpEF can be the clinical trigger for cardiovascular collapse, as many clinicians can testify from their own individual experiences, and is substantiated by culled data from population studies such as the Framingham study and AF clinical trials [7, 8]. The prevalence of AF in HFpEF is high, with both being diseases of the elderly and hypertension is a frequent comorbidity that promotes both conditions. Obesity may also have a role in promoting HFpEF and AF. The mechanical basis for HFpEF has been a subject of debate and few definitive atrial or ventricular function parameters have been identified as being pathognomonic with HFpEF. Most recently, attention has focused on global longitudinal strain, left atrial volume, right

ventricular volumes and mitral valvular regurgitation in this entity [9, 10]. Left atrial dysfunction is intimately linked to left ventricular systolic and diastolic dysfunction. In fact, variation in therapeutic effect may exist with different strata of left ventricular ejection fraction in HFpEF [10].

Antiarrhythmic interventions for AF associated with HFpEF are scarce. Antiarrhythmic drugs have been used in this setting but clinical trial data are sparse. Some recent reanalyses of the AFFIRM trial have shown that the rhythm control strategy delayed the development of progressive heart failure compared to a rate control approach [11, 12]. More recent analyses suggest that even a modest amount of documented sinus rhythm was associated with this benefit [13]. Dronedarone employed in the ATHENA trial was used in a subpopulation with impaired and preserved left ventricular function and a history of prior heart failure [14]. In a post hoc analysis, 693 patients were identified who had a NYHA class I/II/III heart failure of whom 184 had HFrEF. The remainder had HFpEF and but their outcomes were not reported separately from those without HF. Catheter ablation has been applied in HFrEF in observational studies and now in an RCT [2]. However, no significant published data is currently available in AF with HFpEF.

Interestingly, pacing studies have emerged for this condition. Multisite atrial pacing has been shown to have beneficial hemodynamic and rhythm control effects in this condition. In an early report in brady-tachy population without clear identification of HFpEF, dual site atrial pacing combined with antiarrhythmic drugs and/or limited ablation showed favorable left atrial and ventricular hemodynamic effects as well as rhythm control efficacy [15, 16]. Early acute studies with biatrial dual site pacing have shown acute hemodynamic benefits for left atrial and cardiac performance [17, 18]. However, the electrophysiologic community focused largely on the beneficial effects of electrical atrial resynchronization and had limited attention span for its hemodynamic benefits. While the role of atrial performance in HFpEF has long been considered, few have examined the value of multisite atrial pacing interventions. There has been no extrapolation of the obvious

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potential clinical benefit to the AF–HFpEF population. In one clinical series, Eicher et al. described an atrial “dyssynchrony” syndrome in patients with interatrial conduction delay, atrial fibrillation and symptomatic HFpEF [19]. They noted the dramatic decongestive effects of biatrial pacing in patients with NYHA class III and IV heart failure symptoms, harkening back to similar reports in HFrEF and ventricular dyssynchrony. Nagarakanti and coworkers reported significant atrial reverse remodeling and preservation of left ventricular systolic function with long-term dual site right atrial pacing [20]. Of importance is the suggestion that both restoration of rhythm control and beneficial effects on left atrial–left ventricular transport could be synergistic in this scenario. The latter mechanism may be a unique benefit of atrial resynchronization approaches in AF with HFpEF. Our group has recently described survival and rhythm control with long-term dual site right atrial pacing in a hybrid therapy prescription in AF with HFpEF [21]. While this observational data is consistent with significant improvements in outcomes, including severity of heart failure and all-cause mortality, these findings would require prospective trials for validation.

It is increasingly apparent that electrophysiologic interventions could have potential benefit in the clinically challenging and unsolved dilemma of managing patients with AF associated with HFpEF. The role of rhythm control and its electrophysiologic benefits and resynchronization therapy with attendant hemodynamic benefits needs to be explored. The added value of pacing techniques in resynchronization therapy for hemodynamic advantage is similarly ripe for exploration in HFpEF, akin to ventricular-paced resynchronization in HFrEF. These pilot studies could engender real value clinical trials in this unsolved enormous and, as yet, unsolved public health challenge.

References

- Owen TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355(3):251–9.
- Marrouche N, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. Feb 1, 2018;378:417–27.
- Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure–Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol*. 2006;47(10):1997–2004.
- Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015;373(24):2314–24.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383–92.
- Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.
- Oluleye OW, Rector TS, Win S, McMurray J, Zile MR, Komajda M, et al. History of atrial fibrillation as a risk factor in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2014;7:960–6.
- Kotecha D, Lam CSP, van Veldhuisen DJ, et al. Heart failure with preserved ejection fraction: vicious twins. *J Am College of Cardiology*. 2016;88:2217–28.
- Santos AB, Roca GQ, Claggett B, Sweitzer NK, Shah SJ, Anand IS, et al. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2016;9(4):e002763.
- Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37(5):455–62.
- Saksena S, Slee AE, Saad M. Rate and rhythm control strategies in atrial fibrillation patients with heart failure and preserved or reduced left ventricular ejection fraction: an AFFIRM substudy. *Heart Rhythm*. 2017;14:S124.
- Slee A, Saksena S. Can heart failure development in atrial fibrillation patients be impacted by initial choice of treatment strategy? *J Intervent Card Electrophysiol*. 2018. (in press)
- Slee A, Saksena S. Is there a relationship between rhythm control and the development of heart failure. (submitted for publication)
- Hohnloser SH, Crijns HJGM, van Eickel M, et al. Dronedronone in patients with congestive heart failure: insights from ATHENA. *Eur Ht J*. 2010;31(14):1717–21.
- Prakash A, Saksena S, Ziegler PD, Lokhandwala T, Hettrick DA, Delfaut P, et al. Dual site right atrial pacing can improve the impact of standard dual chamber pacing on atrial and ventricular mechanical function in patients with symptomatic atrial fibrillation: further observations from the dual site atrial pacing for prevention of atrial fibrillation trial. *J Intervent Card Electrophysiol*. 2005;12(3):177–87.
- Rao HB, Saksena S. Impact of “hybrid therapy” on long-term rhythm control and arrhythmia related hospitalizations in patients with drug-refractory persistent and permanent atrial fibrillation. *J Intervent Card Electrophysiol J Interv Card Electrophysiol*. 2007;18(2):127–36.
- Burri H, Bennani I, Domenichini G, Ganiere V, Sunthorn H, Stettler C, et al. Biatrial pacing improves atrial haemodynamics and atrio-ventricular timing compared with pacing from the right atrial appendage. *Europace*. 2011;13(9):1262–7.
- Matsumoto K, Ishikawa T, Sumita S, Matsushita K, Inoue N, Kobayashi T, et al. Assessment of atrial regional wall motion using strain Doppler imaging during biatrial pacing in the bradycardia-tachycardia syndrome. *Pacing Clin Electrophysiol*. 2006;29(3):220–5.
- Eicher J-C, Laurent G, Mathe A, et al. Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of “diastolic” heart failure. *Eur J cardiac Failure*. 2012;14:248–58.
- Nagarakanti R, Slee A, Saksena S. Left atrial reverse remodeling and prevention of progression of atrial fibrillation with atrial resynchronization device therapy utilizing dual-site right atrial pacing in patients with atrial fibrillation refractory to antiarrhythmic drugs or catheter ablation. *J Interv Card Electrophysiol*. 2014;40(3):245–54.
- Saksena S, Saad M, Slee AE, Laharawani H, Nagarakanti R. Long term rhythm control and survival improves after dual site right atrial pacing combined with “background” antiarrhythmic therapy in patients with atrial fibrillation and heart failure with and without systolic left ventricular dysfunction. *Heart Rhythm*. 2015;12:S86.