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EDITORIAL COMMENT

AV Junction Ablation in Heart Failure Patients With Atrial Fibrillation Treated With Cardiac Resynchronization Therapy

The Picture Is Now Clear!*

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Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function and reduces morbidity and mortality (1). Randomized controlled trials enroll virtually only sinus rhythm (SR) patients, establishing CRT as a class IA indication for patients in New York Heart Association (NYHA) functional class II through IV despite optimal medical therapy, with ejection fraction (EF) ≤35%, wide QRS, and SR (2). However, approximately 25% of patients eligible for CRT experience concomitant atrial fibrillation (AF). After several observational studies and 2 meta-analyses, the most recent guidelines qualify patients with AF as class IIA (1). Therefore, while there is now general agreement on the indication for CRT in AF patients, their optimal management may remain a matter of discussion.

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In this context, the meta-analysis by Ganesan et al. (3) in this issue of the *Journal* provides an important contribution confirming unequivocal favorable results of AV junction (AVJ) ablation in AF patients treated with CRT.

The problem of optimal "CRT dose" in AF. AF poses a number of challenges for adequate CRT delivery. An intrinsic irregular spontaneous AF rhythm may significantly reduce the percentage of effective biventricular pacing (BVP%). Even during low-rate AF, phases of completely effective biventricular capture alternate with phases of competing AF rhythm, thereby creating spontaneous, fusion, or pseudo-fusion beats. Consequently, in patients with AF, the global effective "CRT dose" may be markedly reduced compared with SR patients, usually paced in atrial synchronous modality, with short and optimized AV intervals. In AF patients, lowering heart rate allows better diastolic filling and increases stroke volume according to the Frank-Starling mechanism. The regularization of heart rate further reinforces favorable effects on diastolic function.

Which tools maximize BVP% in AF patients? The spectrum of negative chronotropic drugs considered effective in heart failure (HF) patients with AF is limited and includes beta-blockers, digoxin, and amiodarone, although the latter 2 may increase morbidity and mortality (4). Some device-derived features (e.g., conducted AF response, biventricular trigger, and ventricular rate regulation) are specifically designed to improve rate control in atrial arrhythmias, and they should always be initiated. However, if partially effective at rest (despite higher average rates, which are clearly deleterious on diastolic function), their efficacy during exercise seems to be marginal. AVJ ablation is the only tool that allows complete rhythm regularization and heart rate control, thus favoring a "pure," constant delivery of CRT.

Positive effects of AVJ ablation in CRT. SOFT ENDPOINTS. Soft endpoint improvements have been extensively documented after CRT, both short-term and long-term in AF patients. It is important to stress that these benefits seem more relevant in AF patients treated with AVJ ablation or spontaneous low-rate AF. The largest experience on this topic was presented by our group (2) in 2006: this prospective study specifically assessed the effects of AVJ ablation in AF patients treated with CRT. Using a predefined protocol, we showed that significant improvements in NYHA functional class, left ventricular ejection fraction (LVEF), LV end-systolic volume, and exercise capacity were confined to those patients treated with AVJ ablation.

In the meta-analysis by Ganesan et al. (3), NYHA functional class improvement was more evident in AVJ ablation patients, whereas no definitive conclusions were drawn on the 6-min walk test, probably due to insufficient data. In this meta-analysis, only 3 studies reported LVEF modification after AVJ ablation: the increase of EF in the AVJ ablation group was not statistically superior compared with the group without AVJ ablation, even if the degree of EF improvement in ablated patients seems to be remarkable (10.3% vs. 4.2%).

A hypothetical explanation for the lack of significance may be correlated to the limited follow-up. In 2 of the 3 studies evaluating EF (6 and 9 months for Molhoek et al. [5] and Dong et al. [6], respectively, 25 months in our experience [7]), this is even more important if we consider that, in the majority of cases, AVJ ablation is performed 2 to 3 months after CRT. It is reasonable to expect that longer follow-up might have permitted the detection of a progressive EF increase after CRT, particularly evident after AVJ ablation.

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HARD ENDPOINTS. The most important finding by the meta-analysis of Ganesan et al. (3) focuses on the dramatic reduction of total and cardiovascular mortality conferred by AVJ ablation. It is surprising to note that in many different studies, the mortality rate in nonablated AF patients was always approximately 14% per year, whereas in AVJ-ablated patients, a 3-fold reduction of mortality was observed (8). In this context, the work by Ganesan et al. (3) would seem to provide a definitive conclusion on the survival benefit conferred by AV node ablation, showing a significant reduction of both total (risk ratio: 0.42) and cardiovascular (risk ratio: 0.44) mortality.

A questionable point of this paper, however, regards the lack of correlation between mortality and EF. Because there was no significant difference observed in CRT defibrillator or pacing device utilization between patients with or without AVJ ablation, cardiac mortality reduction seems to be driven mainly by a significant reduction of HF death, which in turn usually correlates strictly to EF increase and reverse remodeling.

In the discussion, Ganesan et al. (3) seem to be surprised by the lack of significant LVEF improvement in the AVJ ablation group with respect to the nonablation group, despite the dramatic mortality reduction. A possible explanation, in our opinion, may be that a hazard ratio of 0.42 for total mortality implies a much better survival in ablated patients: this determines that the echocardiographic data at follow-up of nonablated patients are related only to the 40% "survivors" of this group, clearly with a much better LV function and prognosis. The very short follow-up after AVJ ablation in the Molhoek and Dong experiences and the "natural selection bias" associated with the limited number of "nonablated survivors" might well explain the nonsignificant superior increase of EF in ablated patients.

ADJUNCTIVE POTENTIAL FAVORABLE EFFECTS OF AVJ ABLATION IN AF AND CRT. AVJ ablation is the most powerful predictor of SR resumption in permanent AF patients treated with CRT (9). The conversion from AF to SR even after many years seems to be related to the higher BVP observed in ablated patients and consequent reverse remodeling. Last, but not least, we should always remember the possibility of inappropriate shocks during fast AF and their negative impact on quality of life; this problem is completely abolished by AVJ ablation.

POTENTIAL NEGATIVE ASPECTS OF AVJ ABLATION IN CRT. AVJ ablation is usually an easy and safe procedure; nonetheless, it is often perceived as a potentially harmful therapy that should be avoided as much as possible because it causes pacemaker dependency. However, as correctly reported by Ganesan et al. (3), no studies on conventional ablate and pace therapy have reported significant complications during the follow-up. Furthermore, the aforementioned benefits of AVJ ablation in this HF population seem to well outweigh possible risks associated with pacemaker dependency.

The presence of 2 ventricular leads should theoretically protect from problems related to increased lead threshold or dislocation; in any case, it could be appropriate to perform AVJ ablation after lead stabilization (at least 2 months).

The long "Gold Rush" to reach 100% BVP. The need to optimize medical treatment is well established, using the maximized dosage of beta-blockers and angiotensin-converting enzyme inhibitors in patients with HF. The same holds true for optimizing CRT: maximal BVP% should always be pursued and reached. Currently, there is a growing body of evidence on the necessity of reaching the highest possible BVP%. Starting from our arbitrary cutoff of "theoretically effective" BVP pacing >85%, presented in 2006 (7), during the last 5 years, a substantial amount of consistent and homogeneous data continuously raised this "gold rush" standard to 92% and recently to 97.8% (using home monitoring data on 40,000 patients) (10). This cutoff seems to highlight the dramatic survival difference in any patient undergoing CRT, but it seems mandatory in the subgroup of AF patients. As a matter of fact, the meta-analysis by Ganesan et al. (3) confirms that the highest BVP%s and a complete effect of CRT may be achieved in AF patients only via AVJ ablation.

We may therefore conclude that, currently, AVJ ablation should always be considered a fundamental step of a "combined strategy" to obtain the best results of CRT in this complex HF population.

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REFERENCES

1. Dickstein K, Vardas PE, Auricchio A. 2010 focused update of ESC guidelines on device therapy in heart failure: an update of the 2008 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Europace 2010;12:1526–36.
2. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation 2008;117:e350–408.
3. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization therapy in patients with coexistent atrial fibrillation and heart failure: a systematic review. J Am Coll Cardiol 2012;59:719–26.
4. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. N Engl J Med 2005;352:225–37.
5. Molhoek SG, Bax JJ, Bleeker JB. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. Am J Cardiol 2004;94:1506–9.
6. Dong K, Shen WK, Powell BD, et al. Atrioventricular nodal ablation predicts survival benefits in patients with atrial fibrillation receiving cardiac resynchronization therapy. Heart Rhythm 2010;7:1240–5.

7. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 2006;48:734–43.
8. Gasparini M, Cappelleri A. Atrial arrhythmias after cardiac resynchronization therapy: an inverse correlation with achieving 100% biventricular pacing and cardiac resynchronization therapy effectiveness. Europace 2010;12:9–10.
9. Gasparini M, Steinberg JS, Arshad A, et al. Resumption of sinus rhythm in patients with heart failure and permanent atrial fibrillation undergoing cardiac resynchronization therapy: a longitudinal observational study. Eur Heart J 2010;31:976–83.
10. Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm 2011;8:1469–75.

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