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EDITORIAL COMMENT

Natriuretic Peptides for Predicting Left Atrial Reverse Remodeling After Atrial Fibrillation Ablation

Too Much of a Stretch?*

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As techniques for successful ablation and maintenance of sinus rhythm in patients with atrial fibrillation (AF) evolve, identifying the group of patients who will respond successfully is becoming an important clinical goal. The efficacy of a single ablation is approximately 60% to 80% (1,2), and many patients require repeat procedures (3). Recently, biomarkers such as atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and its N-terminal prohormone (NT-proBNP), C-reactive protein, and matrix metalloproteinase-2 have been evaluated as predictors of post-ablation AF relapse (4-7). Left atrial (LA) size may also have prognostic utility that could be related to or independent of the influence of these biomarkers. Left atrial enlargement likely reflects structural remodeling and fibrosis, which further perpetuate arrhythmia (8). Thus, reduction in LA size (or reverse remodeling), associated with improved atrial function, is considered a surrogate for treatment success (9,10).

In this issue of *JACC: Clinical Electrophysiology*, Nakanishi et al. (11) present a single-center study of 104 consecutive patients who underwent AF ablation. The authors assessed whether ANP, BNP, or high-sensitivity C-reactive protein were associated with LA reverse remodeling. Among their findings, they observed that pre-procedural ANP levels were significantly higher in the 49 responders (those who exhibited ≥15% decrease in LA volume index) than in the nonresponders ($p < 0.01$). On multivariable analysis, higher pre-procedural ANP level and maintenance of sinus rhythm during the 6-month follow-up period were independent predictors of LA reverse remodeling ($p < 0.01$), although ANP levels themselves did not predict maintenance of sinus rhythm at 6 months.

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Although LA reverse remodeling is generally believed to portend a better prognosis in patients with AF undergoing ablation, LA reverse remodeling by itself does not necessarily equate with successful ablation outcome. Muller et al. (12) studied 91 patients who underwent catheter ablation for AF and demonstrated that biatrial reverse remodeling often occurs despite AF recurrence. In fact, patients with AF recurrence showed atrial volume reduction that was similar to that in patients who had no evidence of recurrence (12). In the present study, Nakanishi et al. (11) found that, compared with nonresponders, significantly fewer responders (who by definition exhibited greater decreased LA volume) experienced AF recurrence in the 6-month post-ablation period (36% vs. 18%, respectively; $p = 0.04$). However, they found no significant differences between pre-procedural ANP levels among responders with and without AF recurrence. The same was true for ANP levels of nonresponders with and without AF recurrence. These data underscore an important point in interpreting the study results: higher pre-procedural ANP levels were associated with LA reverse remodeling

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responder status, and responder status was associated with a good outcome, but ANP levels themselves did not independently predict less AF recurrence after ablation.

At first, the association between higher NP levels and better LA reverse remodeling outcomes may seem counterintuitive. After all, a number of heart failure studies have shown the opposite, that is, more effective treatment interventions in those with lower NP levels. In both the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study and the Heart Protection Study, for example, statin therapy was most effective in subjects with lower BNP levels (13–15). Similarly, in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) and I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study), 2 studies of patients with heart failure and preserved ejection fraction, spironolactone and irbesartan, respectively, were effective only among patients with lower NP levels (16,17). The prevailing hypothesis is that a marked elevation in BNP (or NT-proBNP) may signify a more advanced disease state that is beyond the "tipping point," i.e., the point of no return' and less amenable to improvements with medical treatment.

Nakanishi et al. (11), however, have made the opposite observation in the present study, that is, patients with higher ANP levels were more likely to show substantial reverse LA remodeling after AF ablation. A possible explanation relates to the extent to which fibrosis affects ANP compared with that of BNP secretion. Both ANP and BNP are secreted in response to myocyte stretch. Studies have shown that in the setting of fibrosis, ANP levels are lower (18). ANP levels may reflect LA myocyte viability; with advanced fibrosis comes decreased ability to secrete ANP. Viable myocytes that can secrete ANP are theoretically able to reverse the LA remodeling that is often seen with AF. On the other hand, mild to moderate degrees of fibrosis may be associated with elevated not decreased BNP levels. This association has been demonstrated in several disease states (19–21), and it may not be until fibrosis becomes quite extensive, at least one-third of the myocardium in one study, that lower BNP levels are seen (22).

Another provocative finding in the present study is that pre-procedural ANP levels did not predict maintenance of sinus rhythm after ablation (even though ANP levels predicted LA reverse remodeling "responder" status, and being a "responder" predicted sinus rhythm maintenance). The lack of ANP's ability to predict AF recurrence may be because a low ANP level can reflect 2 distinct phenotypes that lie on opposite ends of the spectrum: a healthy, unstretched LA without much stimulus for ANP secretion, versus a fibrotic, burnt-out LA, unable to muster an ANP response.

The use of BNP (and/or the ANP/BNP ratio) could help explore this hypothesis and facilitate differentiating the 2 extremes. One study of AF found that the ANP/BNP ratio was inversely correlated with LA fibrosis even though the individual markers were not (23). Along these lines, one can conceive of 3 subpopulations of patients with AF, as follows. 1) Patients with low ANP (due to minimal atrial pathology/stretch) and low BNP levels (and thus a low ANP/BNP ratio) would in theory have a high likelihood of maintaining sinus rhythm; however, by definition, if their LA were small at baseline, they might also be less likely to show a large reduction in LA size; rather, they would more likely be "nonresponders." 2) Patients with high ANP (due to more LA stretch) and elevated BNP levels (and thus intermediate ANP/BNP ratio) would more likely be "responders." 3) Patients with low ANP due to LA fibrosis would be expected to have a high BNP (and thus a low ANP/BNP ratio) and might be less likely to respond with either reverse remodeling or with successful maintenance of sinus rhythm. The current study opens the possibility of future studies to investigate the ANP/BNP ratio as predictive of response and AF recurrence after ablation.

If fibrosis is indeed the critical issue governing the association between ANP and reverse remodeling after AF ablation, assessing biomarkers of myocardial fibrosis may also prove enlightening. Studies have shown that galectin-3 levels are associated with LA fibrosis in AF (24), but whether galectin-3 (or other fibrosis markers) can help predict AF ablation success is unknown. Additionally, future work could be targeted at elucidating whether biomarkers such as ANP, BNP, and others are associated with the outcomes that matter most to patients and clinicians, specifically, maintenance of sinus rhythm and freedom from stroke, heart failure, hospitalizations, and mortality.

Appropriate patient selection is critical to maximizing the likelihood of ablation success in AF. Biomarkers hold promise in assisting with identification of patients most likely to benefit from this procedure, but much work remains before they can be properly implemented.

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