Letters

TO THE EDITOR

The Role of Pro-Fibrotic Biomarkers in Atrial Fibrillation

How Good Are We in the Translational Interpretation?

We read with interest the paper by Takemoto et al. (1), where the translational aspect of profibrotic biomarkers in atrial fibrillation (AF) is discussed. The authors showed higher intracardiac levels of galectin-3 in patients with persistent AF compared with paroxysmal AF as well as a significant association between galectin-3 levels and arrhythmia recurrences after catheter ablation. Furthermore, in an animal model, the authors analyzed the role of GM-CT-01 inhibitor and showed a significant reduction of galectin-3 and transforming growth factor (TGF)-β1 levels, indicating protective effects on profibrotic processes in fibrillating atria.

The authors should be congratulated for their interesting translational research and the promising aspects of a potential upstream therapy in AF. Nevertheless, we have some comments, mainly on the basis of our and other studies.

Several clinical and experimental studies have highlighted the role of interstitial fibrosis in the initiation and maintenance of AF (2). Atrial fibrosis might disturb anisotropic conduction and change the duration and dispersion of the effective refractory period. This explains the intra-atrial re-entry circuits leading to the electrophysiological and structural remodeling in atrial tissue that facilitates AF initiation and perpetuation. Besides the proinflammatory state, the profibrotic pathway is the most plausible cause for arrhythmia recurrences following catheter ablation so far (3). There are several profibrotic markers of great interest that may be associated with rhythm outcome. Different studies have suggested that TGF-β1 is involved in the mechanisms of atrial fibrosis and AF pathogenesis, and plasma TGF-β1 levels might be considered as a surrogate marker for atrial fibrosis (2). Because of its involvement in profibrotic remodeling and inflammation, galectin-3 is one of the emerging biomarkers in different cardiac diseases and gains recent attention as a novel biomarker in AF.

What is the clinical reality when we try to translate hypotheses from experimental studies? Several clinical studies have aimed to analyze the role of galectin-3 in AF, but the results are not consistent (4). In contrast to the current study (1), we found significantly higher levels of proinflammatory and profibrotic biomarkers in *peripheral* blood than in *cardiac* circulation (J. Kornej et al., unpublished data, April 2016)—probably indicating the washout phenomenon. Also, we could not find any significant differences in galectin-3 levels in a subgroup of patients with blood taken from different cardiac sites (4). Furthermore, higher galectin-3 levels found in AF patients might be mediated by cardiometabolic disturbances rather than by heart rhythm itself, which is in accordance with other studies (4). Finally, galectin-3 was not useful to predict arrhythmia recurrences (4,5).

Similar inconsistency regarding prediction of arrhythmia recurrences had also been shown in clinical studies with TGF-β1. For example, despite its known role in the pathophysiology of cardiac fibrosis, TGF-β1 failed to improve the value of widely used clinical scores for the prediction of arrhythmia recurrences (3).

In conclusion, it remains challenging to translate the findings from experimental settings to "real-world" (multi)morbid patients.

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REPLY: The Role of Pro-Fibrotic Biomarkers in Atrial Fibrillation

How Good Are We in the Translational Interpretation?

We appreciate the interest of Drs. Kornej and Bollmann in our work, and their kind words about our recent paper (1). For the most part, their letter focuses on the challenge of translating our experimental findings "to 'real-world' (multi)morbid patients."

In criticizing our paper, Drs. Kornej and Bollmann base their arguments on both unpublished data and a published study (2) in which they were unable to find any differences in galectin (Gal)-3 levels in blood from the left atrium, the coronary sinus, and a peripheral vein. They concluded that higher Gal-3 levels in patients with atrial fibrillation (AF) are likely to be mediated by cardiometabolic disturbances rather than by AF itself.

One cannot argue with unpublished data, which remain anecdotal. However, we can look at their published data that do show higher Gal-3 levels in blood from their AF cohort relative to their AF-free cohort (2), which is a result that certainly agrees with ours. However, unlike our data, Kornej et al. (2) found no relationship between Gal-3 levels and AF recurrence. Here, we argue, the difference was in experimental design. The elevated $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74 years, sex category [female]) scores of their AF patients suggested that they had significant comorbidities, which may have confused the results. Notably, our translational approach, which was on the basis of a large animal model of lone AF with no heart failure or other comorbidities, required specific exclusion criteria in our patients. This enabled us to focus on biomarkers related to AF-related changes in the absence of comorbidities. Consequently, our data speak for themselves: experimentally they demonstrate for the first time that Gal-3 mediates sustained AF-induced atrial structural and electrical remodeling and contributes to AF perpetuation (1). In selected patients, intracardiac serum Gal-3 levels were greater in persistent than paroxysmal AF, and the Gal-3 level was an independent predictor of AF recurrences after a single ablation procedure (1).

Now, coming back to the issue of "'real-world' (multi)morbid patients," we are not disputing the importance of considering Gal-3 as a marker of cardiometabolic disease. In fact, Gal-3 has been shown to be involved in many diseases; recent studies have focused on the effects of Gal-3 on adipocytes, and it is difficult to exclude the importance of obesity in the pathogenesis of AF (3). However, it is again essential to recall that our tachypacing model leads to Gal-3 elevation and persistent AF unaffected by comorbidities, which strongly supports the involvement of Gal-3 in the mechanism of AF progression and AF recurrence after ablation. In this regard, Drs. Kornej and Bollmann seem to have missed the paper by Wu et al. (4), which also reported that patients who experienced recurrences after AF ablation had significantly higher Gal-3 levels in peripheral vein blood (p = 0.007) than those who did not experience such recurrences. One important difference among the 3 studies was the length of the follow-up period. In the study by Kornej et al. (2), the follow-up period was reported to be 6 months; Wu et al. (4) followed their patients for about 17 months; and we (1) used a 12-month follow-up period. Although in the report by Kornej et al. (2) Gal-3 levels did not correlate with AF recurrences, in the latter 2 studies it did, and very strongly. Therefore, it seems likely that longer follow-up periods might be necessary to see a relation between Gal-3 and AF recurrence outcome after catheter ablation.

Finally, we certainly agree that translating laboratory observations to clinical utility is challenging and requires caution. Effective translational research is hampered by a poor understanding of the biology of disease. Notably, despite more than 100 years of progress in basic research in AF biology, today we do not adequately understand the pathogenesis of human AF. To our knowledge, our study is the first of its kind to address it systematically, aiming to understand how human AF perpetuation, apparent at the whole-organism scale, emerges from molecular, cellular, tissue, organ, and organ-system interactions. Therefore, we submit that our study is a clear example of successful translational research, which is a function of not only the quality of the science, but also appropriate design and effective collaboration between the scientist and the clinician.

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