

## Invited Editorial / Davetli Editöryal Yorum

### “Thinking globally acting locally” in cryoballoon-based atrial fibrillation ablation

#### Atriyal fibrilasyon kriyoablasyonunda “Küresel düşünüp yerel davranmak”

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans, is associated with higher morbidity and mortality, and has become a major health issue as the population has begun to age in recent decades, in spite of emerging AF management technologies and medications.<sup>[1,2]</sup> Paroxysmal AF usually involves a driver in the muscle sleeve around  $\geq 1$  pulmonary veins (PVs) caused by rapid focal activity or local reentry, leading to electrical remodeling as result of altered expression and/or function of cardiac ion channels and favoring the development of functional reentry substrates, which might be reversed by AF termination (reverse remodeling) and contribute to persistent AF.<sup>[2]</sup> As the disease progresses to irreversible structural changes, AF becomes permanent, with a shift from PV sources to structural reentry substrate.<sup>[1-3]</sup> Reactive interstitial fibrosis is the mainstay of structural remodeling, which separates muscle bundles, thus interfering with electrical continuity, slowing conduction, and creating an ideal environment for reentry.<sup>[3]</sup> Fibroblasts can couple electrically with cardiomyocytes and, when increased in number, could promote reentry or ectopic activity.<sup>[2,3]</sup> Fibrosis causes progression to permanent forms of AF, so fibrosis development might potentially be both a therapeutic target and a predictor of treatment response.<sup>[1-3]</sup> Since AF-begets-AF through the remodeling cascade, timely PV-directed ablation therapies contemporarily became the cornerstone of

catheter ablation-based approach to AF management. However, data regarding evidence about appropriate patient selection and follow-up modalities are still scarce when compared with the ever-growing extent of the disease.<sup>[1]</sup>

In the current issue of the Archives of the Turkish Society of Cardiology, 2 studies aimed to contribute to the current evidence on AF management. In their accomplished work, Güneş et al.<sup>[4]</sup> sought a possible relationship between AF recurrence and one of the known biomarkers considered to be related to fibrotic processes, namely serum osteopontin (OPN). OPN level was measured before ablation procedure and at sixth month follow-up in 60 symptomatic persistent (n=13) or paroxysmal (n=47) patients who underwent pulmonary vein isolation (PVI) by means of cryoballoon catheter ablation (CBA). In the CBA procedure, all PVs were demonstrated to be isolated. At the end of 1 year of follow-up, 22 (36.6%) patients had AF recurrence, and significantly, majority occurred in the persistent AF subgroup (persistent 10 [76.9%] vs paroxysmal 3 [23.1%]; p=0.002). Conventional cardiovascular/AF risk factors, such as hypertension, diabetes mellitus,

#### Abbreviations:

AF	Atrial fibrillation
CBA	Cryoballoon catheter ablation
LA	Left atrium
OPN	Osteopontin
PNI	Phrenic nerve injury
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RF	Radiofrequency
RIPV	Right inferior PV
RSPV	Right superior PV

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dyslipidemia, smoking, or drug use, were similar between the 2 groups; however, those with recurrence had significantly larger left atrial (LA) diameter and higher preprocedural OPN level (13.29 ng/mL vs 19.65 ng/mL;  $p=0.035$ ). Apart from the prominently high, independent predictive value of persistency of AF, which was consistent with the literature, preprocedural OPN level was also determined to be an independent indicator of recurrence (beta: 0.059;  $p=0.048$ ; odds ratio: 1.061; 95% confidence interval 1.001–1.125). Despite increased level of OPN at sixth month, an association with recurrence couldn't be demonstrated.

Rise of biomarkers as a surrogate for the success of AF ablation procedure intra-/peri- and postprocedurally, and association with AF recurrence has been studied before with conflicting results. Increase in acute myocardial injury marker has been found to be more evident in CBA technique than radiofrequency (RF) point-by-point AF ablation procedures in numerous studies, and is generally attributed to the more extensive debulking of the LA in CBA. However, these findings could not be translated into clinical benefit of less AF recurrence.<sup>[5]</sup> On the other hand, biomarkers related to chronic atrial structural remodeling, and especially biomarkers taking part in the fibrosis cascade seem more promising for prediction of AF recurrence.<sup>[6]</sup> The scarce availability and the cost of the aforementioned fibrotic biomarkers are some of the practical limitations preventing the accumulation of more evidence regarding correct implementation in clinical practice. OPN, which is a large-acid phosphoprotein adhesion molecule secreted by both cardiac interstitial fibroblasts and macrophages, is considered to be closely related to the fibrosis process in humans and also takes part as an acute phase protein.<sup>[7]</sup> In the study conducted by Güneş et al., it might be interesting to know about the effect of “acute intraprocedural rise” of OPN (Delta OPN: acute postprocedure OPN level minus preprocedure OPN level) and its association with AF recurrence. The authors nicely demonstrated that groups both with and without AF recurrence had increase in OPN level on follow-up, but it is hard to infer from the data provided whether this finding could be attributed to chronic ongoing AF-remodeling process in the LA and throughout the cardiovascular system, or be a consequence of effective electrical tissue isolation.

In the same issue of the Archives of the Turkish Society of Cardiology there is another study on PVI-based AF treatment by Koçyiğit et al.,<sup>[8]</sup> which deals with a very important practical aspect: PV anatomy and variations in Turkish AF cohort. In this study, they retrospectively analyzed the data of 250 patients with drug-refractory AF who underwent multidetector computed tomography (MDCT) angiography before CBA to evaluate PV and LA anatomy. The authors demonstrated that most patients ( $n=237$ ; 94.8%) had the expected anatomy of 2 atrial ostia for right upper and lower lobe veins. Remaining patients ( $n=13$ ; 5.2%) had variation in the right PV anatomy. On the other hand, there were only 161 (64.4%) patients with 2 ostia for left upper and lower lobe veins and a common trunk was seen in 89 (35.6%) patients. In their data, mean superoinferior dimension for each vein was significantly larger than mean anteroposterior dimension, and right-sided veins were cross-sectionally larger and more circular, and right side was site of the only accessory veins detected in the study data (prevalence of 6%, predominantly draining into right middle lobe).

AF catheter ablation by means of RF energy delivered in point-by-point fashion is still the most prevalent technique worldwide to achieve PVI.<sup>[1,9]</sup> However, due to its high dependency on operator skills and relatively horizontal learning curve, great efforts have been made to simplify AF ablation procedures. The cryoballoon was developed to create a bigger, more homogenous, circular lesion around each PV in a relatively simple manner with single-step mode by means of cryothermal energy.<sup>[11]</sup> In the recent FIRE AND ICE multicenter randomized trial,<sup>[9]</sup> CBA was non-inferior to RF ablation with respect to efficacy for the treatment of patients with drug-refractory paroxysmal AF, and there was no significant difference between the 2 methods with regard to overall safety. Even though CBA technique was superior to RF-PVI in some efficacy end-points, such as LA dwell time and total procedure time, RF-PVI group demonstrated significantly shorter fluoroscopy time and less phrenic nerve injury (PNI). If we look deeper into the data seemingly attenuating the advantages of a relatively easily adopted and clinically effective CBA technique, they mostly derive from variances of PV anatomy that could actually be detected on pre-procedural MDCT imaging and be overcome by the operator's countermeasures. In a recent paper, Ströker et al.<sup>[10]</sup>

presented some important PV anatomy predictors of PNI in the setting of second generation CBA. In this prospective observational study, PNI occurred in 48 patients (8.6%) of 556 CBA index procedures. Eighty percent of PNIs occurred during right superior PV (RSPV) freeze, while the remainder occurred during right inferior PV (RIPV) freeze. More anterosuperior orientation, larger dimensions ( $\geq 275$  mm<sup>2</sup> [88% sensitivity, 85% specificity]), shorter distance to superior vena cava, and wide RSPV–LA angle (between right anterolateral aspect of LA and RSPV) (cut off value  $\geq 141^\circ$  [91% sensitivity, 85% specificity]) were associated with PNI on univariate analysis. All 3 patients with right common trunk developed PNI. RIPV area was an independent predictor for PNI at RIPV. Inconsistent with some previous studies stating the opposite,<sup>[11]</sup> ovality of PV ostia did not predict PNI. In the study conducted by Koçyiğit et al.,<sup>[8]</sup> there was no observance of common trunk on right-sided PVs as a poor PNI predictor; however, there was a small but significant number of accessory veins sharing the same ostium with RSPV and RIPV, and this was found to increase risk of PNI in the above mentioned study by increasing overall ostial area.<sup>[10]</sup> Velagić et al.<sup>[12]</sup> nicely demonstrated the strikingly steep learning curve for CBA techniques, and concluded that after 30 procedures, initial high fluoroscopy time and complication rates of junior operators become comparable to senior operator in a high-volume training center with experienced supervision. Of all the senior hands-on help requests made by junior fellows in training, 55% were for RIPV, 13.7% for left inferior PV, and 7% for left common trunk occlusions. Remaining help requests were for transseptal-puncture assistance. Good preprocedural knowledge of LA anatomy, detection of high-risk PV variant features, and selecting the right cases for the correct type of procedure might improve clinical and procedural end-points in all types of catheter-based AF ablation. For this reason, the data about PV anatomical distribution and variants provided by Koçyiğit et al.<sup>[8]</sup> might be further facilitated by national registries and procedural end-points provided by experienced centers in order to demonstrate national safety and efficacy data sets.

In the latest issue of the journal, 2 separate studies on CBA<sup>[4,8]</sup> were actually sharing the same stage with different roles “from cell to cath lab.” The complex, progressive, and poorly understood mechanisms of AF need a global approach while acting locally about

the problems, either working on the atrial substrate, or in a countrywide fashion, trying to find solutions to implement “excellence centers” and integrated multi-disciplinary AF teams, as recommended by the latest guidelines<sup>[1]</sup> in order to take full advantage of imaging and laboratory modalities.

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