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COMMENTARY

Baroreceptor reflex after pulmonary vein isolation assessed by tilt table test: adding another piece to the puzzle

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The intrinsic cardiac autonomic nervous system (ANS) is a vast neural network comprised from numerous ganglionated plexuses, nerve axons, and interconnecting neurons. The dysregulation of the intrinsic cardiac ANS is crucial in initiating and sustaining atrial fibrillation (AF) and may serve as both the substrate and trigger for AF [1, 2]. Due to the growing evidence supporting the involvement of the cardiac ANS in AF, attention has shifted towards neuroablative and neuromodulatory methods targeting the ANS including ganglionated plexi ablation, vagus nerve stimulation, renal denervation, and spinal cord stimulation [2]. Catheter ablation has been known to inadvertently injure the ganglionated plexi and alter the ANS function [1]. Common noninvasive methods to assess ANS function include heart rate variability, based on 12-lead ECG, in both the time domain and frequency domain, imaging using radiolabeled sympathomimetic amines that can be taken up by sympathetic terminals, and baroreflex sensitivity (BR) [3]. The latter reflects parasympathetic activity and can be calculated from the measurement of the heart rate response to drugs that affect the blood pressure (e.g., phenylephrine), or by assessing the slope between spontaneous changes in heart rate and changes in blood pressure [3]. A recent study suggested that catheter ablation for AF depressed the BR sensitivity, irrespective of the type of AF [4]. However, there is a need for further exploration of the effects of catheter ablation on BR function, which reflects parasympathetic activity, and its impact on clinical outcomes in patients undergoing AF ablation.

In this issue of *the Journal of Interventional Cardiac Electrophysiology*, Zuk et al. [5] contributed to our understanding of this important clinical issue. The authors should be congratulated for undertaking such a time-intensive study. In this observational, prospective, single-center study, the authors assessed changes in BR function in 78 patients with AF undergoing point-by-point radiofrequency (RF) ablation versus cryoballoon (CB). Noninvasive assessment of BR function was conducted using tilt testing, involving three parameters: baroreceptor event count (BREC), depicting overall BR activity; slope mean, representing BR sensitivity; and BR effectiveness index (BEI). They found that before CA, tilting resulted in a substantial decrease in BR function parameters for the entire study group, indicating the expected physiological response. These changes were consistent across both RF and CB groups. In post-CA, there was a significant reduction in BR function for the entire cohort. Notably, BREC, BR sensitivity, and BEI were more decreased in the CB group compared to RF, suggesting a significant difference in the impact of the two techniques on BR function.

The strengths of this study include the assessment of BR function both at rest and during tilt. While the significance of the BR during tilt remains unclear, it provides another piece of information about the effects of catheter ablation on ANS function. Furthermore, the differential effect of CB and RF on the ANS function is interesting and merits further investigation. Modification of the cardiac ANS by CB has been previously demonstrated, as evidenced by significantly reduced vagal responses to high-frequency stimulation of the four major atrial ganglionated plexi [6]. It is possible that the choice of ablation technique influenced BR function through injury of the ganglionated plexi, as evidenced by the release of S100B, a widely recognized biomarker for neural damage. Scherschel et al. showed that S100B release in patients undergoing pulmonary vein isolation using CB was 3.9 times higher compared to patients undergoing pulmonary vein isolation using RF [7]. Moreover, cryogenic lesions were histologically characterized as being more homogeneous and better demarcated when compared to RF lesions [8]. However, caution is advised when interpreting

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these results. First, the population of autonomic neurons included in the ganglionated plexi is not homogenous and therefore it is too simplistic to assume that the ganglionated plexi behave as one unit [9]. In addition, the specific population of neurons that is related to the ablation outcome has yet to be defined. Second, modification of the ANS does always translate into improved clinical outcomes. The results of the CIRCA-DOSE trial, in which patients with AF who underwent RF ablation experienced a lower incidence of progression to persistent AF compared to those treated with CB ablation [10], highlight this notion.

How could these findings impact clinical practice, and what are their implications for future research? The observed changes in BR function following CA, especially with CB, emphasize the necessity for a comprehensive understanding of autonomic changes post-ablation. Clinicians should be attentive to these variations, as they may have implications for patient outcomes and the overall success of the ablation procedure. While this study provides valuable insights, there is a need for additional research to thoroughly investigate the mechanisms that contribute to the observed variations between RF and CB.

The interpretation of the study's findings should be conducted considering the potential limitations associated with the data. One significant limitation of the study is the absence of specific data correlating baroreflex function with ablation outcomes. The lack of correlation data restricts our ability to establish a direct relationship between BR function and long-term ablation success or other clinical outcomes. Another limitation is associated with the timing of assessments. Baroreflex function was evaluated shortly after ablation and not at later time points. This design choice limits the capacity to observe potential longitudinal changes in baroreflex function over an extended post-ablation period. Therefore, a more prolonged follow-up period would have offered a deeper understanding of the effects on autonomic function and their relation with clinical outcomes.

Limitations notwithstanding, this study highlights the significant impact of CA on BR function in patients undergoing AF ablation. These findings indicate areas for future research and underscore the need to study autonomic influences on outcomes of AF ablation. Investigating the long-term implications of altered BR function post-CA will contribute to our better understanding of ANS dynamics in AF patients. It is only with studies like this, adding one piece at a time, that the puzzle of the complex and dynamic nature of the relationship of ANS function with AF outcomes be solved.

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Declarations

Competing interests The authors declare no competing interests.

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