Conduction Intervals and Atrial Fibrillation in Chronic Kidney Disease

Cevher Ozcan

Department of Medicine, Section of Cardiology, Herat and Vascular Center, University of Chicago, Chicago, IL, USA

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice with increasing incidence and prevalence in the USA and around the world [1]. AF is associated with a higher risk of all-cause mortality and morbidity including hospitalizations, stroke, systemic thromboembolism, myocardial infarction, heart failure, dementia, and chronic kidney disease (CKD). An association between AF and CKD has been reported in multiple studies by the way of bidirectional relations [2, 3]. AF is very common in CKD patients and has significant impact on overall clinical outcomes. Yet the predictors of hospitalization with AF in patients with CKD are not well-characterized.

In this issue of American Journal of Nephrology, Scovner et al. [4] investigated whether the cardiac conduction intervals (QTc, QRS, and PR intervals) can predict hospitalization with AF in patients with nondialysis dependent CKD. Electrocardiograms were analyzed in 2,759 participants of the Chronic Renal Insufficiency Cohort Study, a large prospective multicenter study of patients who did not have AF at the time of enrolment. During a mean follow-up of 6.6 years, 50 hospitalizations with AF occurred among 224 participants. Shorter (<407 ms) or longer (>431 ms) baseline QTc interval was associated with higher adjusted risk of AF hospitalization. Each 10 ms increase in QTc from 420 ms was associated with a

14% increased risk of hospitalization with AF. Longer QRS duration was an indicator for AF hospitalization in patients with a history of heart failure, while there was no significant association in those without HF. However, authors found no relation between PR interval and AF hospitalization in CKD.

This interesting study has many strengths as well as few weaknesses, as acknowledged by its authors. It provides significant data from a large and ethnically diverse population. Women are well represented in this secondary analysis of the Chronic Renal Insufficiency Cohort Study. AF hospitalization and conduction intervals are likely influenced by multiple confounding systemic processes, comorbidities, electrolytes, and variable use of medications in this population along with CKD. Event rate is relatively low and therefore the utility of QRS duration and QTc interval to serve as a risk marker for future AF hospitalization in CKD needs to be tested in a larger cohort with more effective rhythm and conduction interval surveillance. Prolonged QRS and QTc intervals characterize delay in ventricular depolarization and repolarization processes. Both have been associated with increased risk of AF in different populations. However, the impact of QRS and QTc interval on atrial electrical properties is not clearly explained. Scovner et al. [4] found that PR interval is not a predictor for AF hospitalization even

though several studies showed prolonged PR interval is associated with AF in the general population and various disease conditions including CKD [5]. Differences between these 2 findings would benefit from further analysis. AF and CKD are associated with mutual risk factors that may have determined the clinical outcome including hospitalization and cardiac conduction intervals.

Pathogenesis of AF is a complex process with multiple contributing molecular and clinical factors including CKD. The underlying mechanisms of the initiation and progression of AF in CKD are not yet known. Clinical and experimental studies demonstrated that arrhythmogenic atrial electro-anatomical remodeling is a critical substrate for the development of AF in patients and animal models of the disease [1, 6]. Atrial remodeling is associated with enlarged atria, patchy fibrosis, loss of atrial muscle mass, inflammation, extracellular matrix remodeling, heterogeneous conduction velocity, and altered membrane potential and atrial refractory periods [6]. These pathogenic changes were reflected in the electrocardiogram as altered p-wave morphology and PR interval. The epidemiologic association between prolonged atrial conduction intervals and AF has been documented [5]. Prolonged conduction intervals are surrogates for pathologic structural and electrical remodeling with fibrosis and dysfunctional atrial or ventricular myocardium. Delayed conduction intervals (QRS, QTc, or PR) promote reentry and susceptibility to ectopic triggers. Conduction velocities become abnormal in fibrotic tissue with both loss of side-to-side and the longitudinal end-to-end cardiomyocyte connections [7]. This leads to micro-reentry and arrhythmias. CKD may facilitate atrial enlargement and scar resulting in conduction delay through increased atrial pressure and

strain. In addition, CKD may promote myocardial fibrosis through inflammation or stress that contributes to structural remodeling of atria forming a substrate for AF. The global metabolic dysfunction in CKD may lead to electrical and mechanical instability in the atria through oxidative and metabolic stress, impaired ionic homeostasis, disrupted membrane potentials, reduced conduction velocity, and cardiomyocyte injury. This can be associated with hemodynamic change in LA with an increased pressure and volume as well as atrial refractoriness that facilitates AF. Thus, the mechanisms of the association between atrial and ventricular conduction properties need to be investigated further in CKD.

In conclusion, both AF and CKD are serious public health and economic burdens. Understanding the complex interrelations between AF and CKD is the first step to reduce this burden. Scovner et al. [4] provide evidence that monitoring cardiac conduction intervals, particularly QTc and QRS duration, are important in management of patients with CKD in an effort to reduce AF hospitalization. Clinicians and investigators need to address many important questions in future studies including how to prevent the coexistence of AF and CKD. In addition to risk prediction via machine learning by using conduction intervals, further mechanistic and therapeutic studies are required to identify potential targets for the intervention and effective biomarkers for their association.

Conflict of Interest Statement

The author has no conflicts of interest, financial or otherwise, relevant to this manuscript.

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