Invited Editorial / *Davetli Editöryal Yorum*

Fragmented QRS and serum propeptide of type I procollagen in hypertensive patients: Putting another brick in the wall

Hipertansif hastalarda fragmente QRS ve serum tip I prokollajen propeptidi: Duvara bir tuğla daha koymak

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Left ventricular (LV) hypertrophy is the physiological compensatory mechanism that aims to restore normal wall stress of LV in presence of pressure overload. With time, however, this "physiological" compensatory reaction is gradually replaced with a "pathological" condition that is characterized by alterations in cellular mechanisms, myocardial ischemia, and wall fibrosis.[1] Histologically, up to 30% of LV wall could be replaced with fibrotic tissue.[1,2] This replacement is caused by an increase in collagen synthesis (mainly types I and III), reduction in degradation of collagen, or both.[3] As a consequence of hypertrophy and fibrosis, LV repolarization is prolonged and foci with heterogenous repolarization period form within the myocardium.[4] These alterations within LV myocardium lead to prolonged and dispersed QT interval on surface electrocardiogram (ECG), which is considered as the electrophysiological basis for increased frequency of torsades des pointes and sudden cardiac death observed in subjects with LV hypertrophy.[4–6]

In this issue of the journal, Bekar and colleagues report on investigation of levels of carboxy-terminal propeptide of type I procollagen (PICP) in patients with LV hypertrophy (secondary to hypertension) and fragmented QRS (fQRS) complexes on ECG.[7] They included 90 consecutive patients with hypertension in the study, and 47 of 90 hypertensive patients had fQRS on ECG. They demonstrated an increased PICP concentration in patients with fQRS and found that increased serum PICP concentration is an independent predictor for fQRS on surface ECG.[7] Fragmented QRS complexes represent an alteration in normal depolarization vector of myocardium and is a risk factor for ventricular arrhythmias and mortality for various cardiac disorders, including dilated and hypertrophic cardiomyopathies.[8,9] Similar to prolongation of QT interval and dispersion of QT, fQRS forms a pathophysiological link between pathological hypertrophy/fibrosis and ventricular arrhythmias in patients with hypertension. It is thought that QRS fragmentation occurs as a result of myocardial fibrosis,[10] and presence of fQRS on ECG in patients with systemic hypertension is related to degree of LV hypertrophy.[11] Therefore, present study establishes another link between myocardial fibrosis and arrhythmogenic electrophysiological substrate of LV hypertrophy (Figure 1).

Abbreviations:

ECG	*Electrocardiogram*
fQRS	*Fragmented QRS*
LV	*Left ventricular*
MMPs	*Matrix metalloproteinases*
PICP	*Procollagen type I C-terminal propeptide*

Beyond structural and electrophysiological al-

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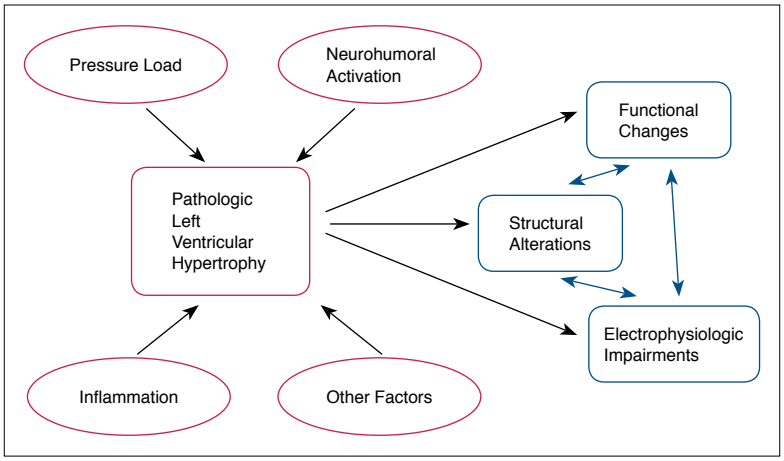

Figure 1. Scheme illustrating main pathophysiological pathways that convert a physiological mechanism to a pathological state characterized by structural, functional, and electrophysiological alterations within left ventricular myocardium. Pathological changes within myocardium seem to be interrelated, as suggested by various studies that have found a relationship between myocardial fibrosis or serum biomarkers of fibrosis, diastolic dysfunction, and alterations on surface electrocardiogram.

terations, LV hypertrophy is also characterized by impaired relaxation, reduced diastolic filling, and steeper pressure-volume curve during diastole. With echocardiography, degree of increased intraventricular pressure can be estimated by grading severity of diastolic dysfunction. In patients with LV hypertrophy, both the degree of fibrosis and presence of electrophysiological abnormalities seem to correlate with impairment of diastolic filling.[12–14] Specifically, both presence of fQRS and alterations in serum PICP are related to diastolic dysfunction in patients with hypertension.[14,15] Considered together with findings of the present study, the data suggest that these structural, functional, and electrophysiological alterations could ultimately be interlinked (Figure 1). There is no doubt that further studies are required to elucidate the relationship between these pathophysiological processes.

While these findings are nonetheless interesting, cross-sectional nature of the present study, as well as limited sample size do not allow for definite assumptions. Results should be replicated in a larger and preferably more comprehensive trial. The researchers did not show presence of myocardial fibrosis with imaging modalities and assumed that high PICP levels are adequate to confirm myocardial fibrosis. However, some (but not all) investigators have failed to show a link between serum PICP and degree of fibrosis in patients with LV hypertrophy.[15,16] The relationship of other biomarkers of fibrosis and collagen degradation, particularly N-terminal propeptide of procollagen III, matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs, with QRS fragmentation and arrhythmogenesis should be investigated further. Moreover, key evidence that would ultimately link primary pathogenetic mechanisms such as pressure overload, activation of neuroendocrine pathways or inflammation with QRS fragmentation or PICP is missing. While the present study demonstrated a link between PICP and fQRS, it is not clear whether higher PICP levels are related to arrhythmias or sudden death rather than intermediaries like fQRS. This latter is particularly important for the practicing clinician.

Therefore, the study of Bekar et al. provides more questions than answers, and should be viewed as hypothesis-generating rather than definitive. Relationship between circulating biomarkers of fibrosis and electrophysiological alterations in LV hypertrophy is an important topic for both the researcher and the clinician, and more work is definitely needed to understand and explain various structural, functional, and electrophysiological abnormalities that characterize LV hypertrophy. Finally, the usefulness of biochemical markers of LV hypertrophy in the clinic is unknown, and there is a need for answers on this topic.

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