Hyperglycemia and atrial fibrillation: new clinical information on electrophysiological changes

Hiperglisemi ve atriyal fibrilasyon: Elektrofizyolojik değişiklikler ile ilgili yeni klinik bilgi

Atrial fibrillation (AF) is one of the most clinically diagnosed cardiac arrhythmia. Heart failure, age, valvular heart disease, hypertension, obesity, alcohol consumption and smoking are risk factors for the AF (1). AF is associated with an increased incidence of complications such as heart failure, thromboembolism, renal failure, morbidity and mortality (2). Recent findings showed that AF induces atrial electrical remodeling, increases dispersion of atrial effective refractory period and decreases atrial conduction velocity. Any decrease of intra-atrial conduction time is considered to be one of the most important factor for the formation of reentry, which is necessary for the induction of AF (3, 4).

Over the recent decades, people with diabetes mellitus (DM) has more than doubled and it has become one of the most important public health problem entire the world (5). For this reason, one of the recent interest in the field of AF is that hyperglycemia may be independent risk factor for AF and a recent meta-analysis indicated that individuals with DM had an approximate 40% greater risk of AF compared with unaffected individuals. We know that DM has pathophysiological links with AF, but the exact molecular mechanism of electrical and structural remodeling is not clear (6, 7).

In the article published in the current issue of the Anatolian Journal of Cardiology, Liu et al. (8) carried out a study to investigate the effects of hyperglycemia on atrial interstitial fibrosis, ionic remodeling and vulnerability to atrial fibrillation (AF) in alloxan-induced diabetic rabbits. Ten rabbits in each group were respectively used to electrophysiological, histological, patch-clamp study and Western blotting analysis.

The results of this study showed that in DM group inter-atrial conduction time (IACT), atrial effective refractory period (AERP) and inducibility of AF were increased and LA interstitial fibrosis was evident and may constitute a substrate for the development of AF. Also action potential duration (APD90) and APD50 of atrial myocytes were prolonged in diabetic rabbits. The densities of reduced INa and increased ICaL in the atria were associated with DM ionic remodeling. DM increased fibrosis-related transforming growth factor β1 proteins in rabbit atrium. These findings can provide pathophysiological insights for the mechanisms of atrial electrical and structural remodeling in the setting of DM.

Unfortunately, there are several limitations of the study, firstly; the sample size is very small, secondly; they have only analyzed the left atrial cells and the response of the right atrium to hyperglycemia is still unknown and thirdly; they have not assessed the possible paradoxical response of AERP to increased heart rate which is another characteristic of electrical remodeling.

Many epidemiological studies have examined risk of AF in relation to DM with conflicting results. Often, prior studies examined many possible predictive factors and were not designed to evaluate the role of DM specifically (1, 7, 9). However, few data exist regarding electrophysiological changes that induce AF in DM patients. People with DM have higher levels of C-reactive protein, which may also promote myocardial fibrosis and diastolic dysfunction. DM is associated with left atrial enlargement which causes the development and propagation of reentrant electrical circuits. DM also causes neural remodeling in the atrium, including parasympathetic denervation and heterogeneous sympathetic denervation (7).

Hyperglycemia and AF have been studied by others in more detailed experiments in mice, but not in rabbits. Kato et al. (10) showed that inter-atrial conduction disturbance and increased fibrotic deposition in atrium play a major role in producing atrial arrhythmogenicity in DM. Otake et al. (11) hypothesized that neural remodeling enhances AF vulnerability in diabetic hearts. Eight weeks after creating streptozotocin-induced diabetic rats inducibility of AF was measured. They have repeated sympathetic nerve stimulation (SNS) or parasympathetic nerve stimulation (PNS). SNS significantly increased the incidence of AF in DM rats, although AERP was significantly decreased by SNS in both rats, increased heterogeneity of AERP by SNS was seen only in DM rats. PNS significantly decreased AERP and increased the incidence of AF in both rats suggesting that neural remodeling may play a crucial role for increased AF vulnerability in DM (11). Diabetic cardiomyopathy consists of the extracellular matrix (ECM) remodeling leading to the increased fibrosis of

Address for Correspondence/Yazışma Adresi: Dr. Hasan Güngör, Aydın Medline Hastanesi, Kardiyoloji Kliniği, Aydın-*Türkiye*
Phone: +90 256 212 00 12 Fax: +90 256 225 25 40 E-mail: drgungorhasan@yahoo.com
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myocardium. TGFβ1 cascade is most important key factor in this process, which includes disproportionate increase in collagen and excessive ECM deposition due to enhanced expression of TGFβ1 (12). Authors showed the elevation of TGFβ1 in LA tissue of DM rabbits had positive correlation with atrial fibrosis.

In conclusion, the quality of glycemic control is directly related with the risk for AF; the risk is higher with longer duration of treated diabetes and poorer glycemic control. This study Liu et al. (8) provide us new clinical information on electrophysiological changes in DM patients. Counterbalancing the hyperglycemia actions may represent a novel pathway to prevent atrial remodeling, and perhaps an important medical approach to the prevention of AF.

Hasan Güngör, Fatih Çam, Ufuk Eryılmaz[1]
Clinic of Cardiology, Aydın Medline Hospital, Aydın-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Adnan Menderes University, Aydın-*Turkey*

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References

11. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 2011; 108: 56-62. [CrossRef]
2. Güngör H, Ayık MF, Kırılmaz B, Ertugay S, Gül I, Yıldız BS, et al. Serum resistin level: as a predictor of atrial fibrillation after coronary artery bypass graft surgery. Coron Artery Dis 2011; 22: 484-90.
3. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-68. [CrossRef]
4. Nattel S, Shiroshita-Takeshita A, Cardin S, Pelletier P. Mechanisms of atrial remodelling and clinical relevance. Curr Opin Cardiol 2005; 20: 21-5.
5. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nat Rev Endocrinol 2011; 8: 228-36. [CrossRef]
6. Lip GYH, Varughese GI. Diabetes mellitus and atrial fibrillation: Perspectives on epidemiological and pathophysiological links. Int J Cardiol 2005; 105: 319-21. [CrossRef]
7. Dublin S, Glazer NL, Smith NL, Psaty BM, Lumley T, Wiggins KL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med 2010; 25: 853-8. [CrossRef]
8. Liu C, Fu H, Li J, Liu T, Yang W, Cheng L, Li G. Hyperglycemia aggravates atrial interstitial fibrosis, ionic remodeling and vulnerability to atrial fibrillation in diabetic rabbits. Anadolu Kardiyol Derg 2012; 12: 543-50.
9. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care 2009; 32: 1851-6. [CrossRef]
10. Kato T, Yamashita T, Sekiguchi A, Sagara K, Takamura M, Takata S, et al. What are arrhythmogenic substrates in diabetic rat atria? J Cardiovasc Electrophysiol 2006; 17: 890-4. [CrossRef]
11. Otake H, Suzuki H, Honda T, Maruyama Y. Influences of autonomic nervous system on atrial arrhythmogenic substrates and the incidence of atrial fibrillation in diabetic heart. Int Heart J 2009; 50: 627-41. [CrossRef]
12. Kaminski KA, Szepietowska B, Bonda T, Kozuch M, Mencel J, Malkowski A, et al. CCN2 protein is an announcing marker for cardiac remodeling following STZ- induced moderate hyperglycemia in mice. Pharmacol Rep 2009; 61: 496-503.