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Review

Diabetes mellitus and atrial fibrillation: Pathophysiological mechanisms and potential upstream therapies

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ABSTRACT

Diabetes mellitus (DM) represents one of the most important risk factors for atrial fibrillation (AF) while AF is a strong and independent marker of overall mortality and cardiovascular morbidity in diabetic patients. Autonomic, electrical, electromechanical, and structural remodeling, including oxidative stress, connexin remodeling and glycemic fluctuations seem to be implicated in AF pathophysiology in the setting of DM. The present review highlights the association between DM and AF, provides a comprehensive overview of the responsible pathophysiological mechanisms and briefly discusses potential upstream therapies for DM-related atrial remodeling.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice associated with increased cardiovascular morbidity and mortality [1,2]. Apart from intrinsic cardiac causes such as valve disease and congestive heart failure, classic cardiovascular risk factors such as hypertension and diabetes mellitus (DM) promote AF [3]. In fact, individuals with DM have approximately 40% greater risk of incident AF compared with unaffected individuals [4]. On the other hand, AF in diabetic patients is associated with a 61% greater risk of all-cause mortality and comparable higher risks of cardiovascular death, stroke, and heart failure [5]. Even though the precise pathophysiological mechanisms implicating DM in AF development have not been completely elucidated, autonomic, electrical, electromechanical and structural remodeling, as well as oxidative stress, connexin remodeling, and glycemic fluctuations seem to play important roles. This article highlights the association between DM and AF providing a concise overview of the underlying pathophysiological mechanisms and discusses potential upstream therapies for AF prevention in this setting.

2. Diabetes mellitus as a risk factor for atrial fibrillation

Numerous studies have shown that DM, and poor glycemic control reflected by glycated hemoglobin A1c (HbA1c) levels are independently associated with new onset AF. In the pivotal Framingham Heart Study, DM was significantly associated with risk for AF in both sexes [3]. In the same line, the VHAH study reported that DM is a strong and independent risk factor for AF occurrence [6] while the PROACTIVE trial reported that the cumulative incidence of AF in patients with type 2 DM and macrovascular disease was 2.5% during a mean follow-up of 34.5 months [7]. Interestingly, The VALUE trial showed that hypertensive patients who developed new onset DM had a significantly higher rate of new onset AF and a higher risk of developing persistent AF [8]. Of note, Ostgren et al. demonstrated that the presence of DM in the setting of hypertension further increases the odds ratio of AF but this increase was not significant after adjusting for insulin resistance suggesting that insulin resistance may be an underlying mechanism of AF [9]. In a recent study, it was concluded that DM, HbA1c levels/poor glycemic control are independently associated with increased risk of AF [10]. Moreover, a linear trend between incident AF and HbA1c level (for every 1% point increase in HbA1c) in individuals without DM was also evident [10]. In keeping with this findings, Igushi et al. reported that the level of HbA1c, especially in patients with HbA1c > 6.5%, was associated with AF occurrence [11]. Another study showed that the prevalence of AF was significantly greater among patients with DM than in

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non-diabetic patients but after full adjustment for other risk factors, DM was associated with a 26% increased risk of AF only among women [12]. Women with AF are more likely to suffer from DM [13,14]. In a large prospective cohort of initially healthy middle-aged women, baseline DM was a modest but statistically significant risk factor of incident AF after multivariable adjustment [15]. In specific, the risk of incident AF among women with DM was increased approximately 2-fold after adjustment for age, and this risk was attenuated to about 1.4 after more extensive multivariable adjustment for baseline risk factors, suggesting that the increased risk associated with diabetes is mainly mediated by changes of other AF risk factors such as hypertension and obesity [15]. It was also recently demonstrated that ultrasound-diagnosed non-alcoholic fatty liver disease is strongly associated with increased prevalence of persistent or permanent AF in patients with type 2 DM, independently of several clinical risk factors for AF [16]. Even though the relationship between non-alcoholic fatty liver disease and AF in type 2 DM is currently unknown, the putative role of non-alcoholic fatty liver disease in AF development may have significant implications in terms of screening the increasing population of patients with liver abnormality [16]. Apart from the aforementioned risk factors, several additional parameters (aging [17], ethnicity [18–22], hyperuricemia [23], pulse pressure [24], heart rate recovery [25], and heart failure [26]) seem to be associated with increased AF risk in the setting of DM. The clinical and demographic parameters that influence the relationship between DM and AF are presented in Table 1.

In a population-based case–control study, patients receiving pharmacologic treatment for DM had 40% higher risk of developing AF than people without DM, and risk was higher with longer duration of treated DM and worse glycemic control [27]. Furthermore, it was recently indicated that in women without AF or cardiovascular disease at baseline, increasing age, adiposity, and higher HbA1c levels were preferentially associated with the early development of nonparoxysmal AF [28]. Finally, a recent meta-analysis indicated that DM is associated with about 40% increased risk of AF compared with non-DM patients and after adjusting for multiple risk factors the relative risk of AF in patients with DM is 1.24 [4].

3. Pathophysiological mechanisms implicating diabetes mellitus in atrial fibrillation

Diabetic cardiomyopathy implies diabetes-associated changes in the structure and function of the myocardium that are not directly attributable to other confounding factors, such as coronary artery disease or hypertension [26]. Diabetic cardiomyopathy can lead to left ventricular hypertrophy, increased susceptibility to ischemic injury, and congestive heart failure. The potential pathophysiological mechanisms of diabetic cardiomyopathy include myocardial hypertrophy, myocardial lipotoxicity, oxidative stress, cellular apoptosis, interstitial fibrosis, contraction–relaxation dysfunction, impaired myocardial contractile reserve, mitochondrial dysfunction, and other associated myocardial metabolic disorders [26]. On the other hand, pathophysiological mechanisms implicating DM in AF occurrence include autonomic, electrical, electromechanical and structural remodeling, oxidative stress, connexin remodeling, and glycemic fluctuations (Fig. 1). Undoubtedly, there seems to be some overlap between the mechanisms of diabetic cardiomyopathy and those of diabetic-induced atrial remodeling. Regardless of the presence or not of diabetic cardiomyopathy specific alterations seem to be involved in atrial remodeling and will be discussed in detail.

Table 1
Clinical and demographic risk factors associated with atrial fibrillation in the setting of diabetes mellitus.

Aging
Sex (female)
Race (white)
Obesity
Hypertension
Hyperuricemia
Non-alcoholic fatty liver
Pulse pressure
Heart rate recovery
Heart failure

4. Autonomic remodeling

Hyperglycemia plays an important role in the pathogenesis of cardiac autonomic neuropathy by impairing nerve blood perfusion and activating cellular metabolism and redox-associated biologic pathways [29]. Autonomic dysfunction in DM patients can be caused by hyperglycemia-related pathophysiologic pathways such as formation of advanced glycation end products (AGEs), elevated oxidative/nitrosative stress with increased production of free radicals and activation of the polyol and protein kinase C pathway, as well as poly-ADP ribosylation and neuronal damage-associated genes [29]. Diabetic patients have increased sympathetic and decreased parasympathetic cardiac activity regardless of the presence of autonomic neuropathy. Remarkably, glycemic control and treatment with ACE inhibitors may favorably influence heart rate variability in diabetic patients without autonomic neuropathy [30].

In a rat model of streptozotocin-induced DM it was indicated that sympathetic stimulation increases the incidence of AF in diabetic rats but not in controls [31]. Specifically, sympathetic stimulation significantly shortened the effective refractory period (ERP) of atrial cells in both groups, but the heterogeneity of atrial ERP was increased only in diabetic rats. Immunohistochemical staining of the right atrium aimed at determining the distribution of sympathetic nerves revealed that tyrosine hydroxylase positive nerves were significantly more heterogeneous in DM rats than in control rats whereas the heterogeneity of acetylcholine esterase positive nerves did not differ between the two groups [31]. Given that heterogenous increase in sympathetic innervation contributes to the development of AF, the creation of homogenous sympathetic milieu may confer antiarrhythmic protection. In this context, Yano et al. reported that bilateral stellectomy is effective in AF prevention in a dog rapid atrial pacing model suggesting that β-adrenoreceptor blockade might prevent AF in the diabetic heart [32]. In the clinical setting, it has been demonstrated that in patients with type 2 DM with preserved left ventricular ejection fraction reduced heart rate recovery (a marker of impaired vagal activation after sympathetic withdrawal when exercise is stopped) is associated with AF [25]. Therefore, autonomic neuropathy seems to be involved in the pathophysiologic pathways linking DM and AF.

5. Electrical remodeling

The main features of atrial electrical remodeling include shortening of the atrial effective refractory period (AERP), increased AERP dispersion, and loss of its frequency adaptation [33]. In the experimental setting it has been shown that diabetic atrium is characterized by increased conduction slowing, heterogeneity of conduction slowing, prolongation of action potential duration (APD), increase in spatial dispersion, absence of frequency-dependent shortening of APD, and increased incidence of APD alternans [34]. Interestingly, in a diabetic rabbit model Liu et al. indicated decreased I_{Na} currents, increased I_{CaL} currents, increased AERP dispersion and interatrial conduction time, and increased inducibility of AF [35]. In addition, increased intra-atrial activation time in diabetic rats has also been reported [36]. In the clinical setting, Chao et al. reported that during catheter ablation of paroxysmal AF the activation time of both atria was significantly longer, while bipolar voltage was significantly decreased in the abnormal glucose metabolism group [37]. Moreover, AF recurrence rate after ablation was greater in patients with abnormal glucose metabolism [37].