Archives of Cardiovascular Disease (2015) 108, 269—276

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

REVIEW

Type 2 diabetes mellitus and atrial fibrillation: From mechanisms to clinical practice

Diabète de type II et fibrillation atriale : des mécanismes à la pratique clinique

Marijana Tadic[a,b,*], **Cesare Cuspidi**[c]

[a] *University Clinical Hospital Centre ''Dr. Dragisa Misovic - Dedinje'', Belgrade, Serbia*
[b] *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[c] *Clinical Research Unit, University of Milan-Bicocca and Istituto Auxologico Italiano, Meda, Italy*

Received 11 November 2014; received in revised form 26 January 2015; accepted 26 January 2015
Available online 6 April 2015

KEYWORDS
Type 2 diabetes mellitus;
Atrial fibrillation;
Mechanisms;
Treatment;
Clinical studies

Summary Type 2 diabetes mellitus is one of the most common chronic conditions and its prevalence has increased continuously over the past decades, primarily due to the obesity epidemic. Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in clinical practice and is associated with increased cardiovascular and cerebrovascular morbidity and mortality. Recent studies have shown that patients with diabetes have an increased risk of AF. However, the results about the relationship between diabetes and AF are still conflicting. Mechanisms that are responsible for an association between diabetes and AF, as well as the adequate treatment of AF in patients with diabetes, are still insufficiently studied. The aim of this review is to summarize the current knowledge of mechanisms that connect AF and diabetes, the clinical studies that include patients with both conditions, and the treatment options in modern pharmacology.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CI, confidence interval; HOMA, homeostatic model assessment; RAAS, renin-angiotensin-aldosterone system.

* Corresponding author at: University Clinical Hospital Center ''Dr. Dragisa Misovic - Dedinje'', Heroja Milana Tepica 1, 11000 Belgrade, Serbia.
E-mail address: marijana_tadic@hotmail.com (M. Tadic).

http://dx.doi.org/10.1016/j.acvd.2015.01.009
1875-2136/

MOTS CLÉS
Fibrillation atriale ;
Mécanismes ;
Traitement ;
Études cliniques

Résumé Le diabète de type II est une des affections chroniques les plus fréquentes et sa prévalence a augmenté de façon régulière au cours des dernières décennies, essentiellement du fait de l'épidémie d'obésité. La fibrillation atriale est l'arythmie cardiaque la plus fréquente en pratique clinique et est associée avec une augmentation de la morbi-mortalité cardiovasculaire et cérébrovasculaire. Des études récentes ont montré que les patients diabétiques avaient un risque accru de fibrillation atriale. Cependant, ces résultats établissant la relation entre diabète et fibrillation atriale sont controversés. Les mécanismes responsables d'une telle association, ainsi que le traitement de la fibrillation atriale chez les diabétiques sont insuffisamment étudiés à ce jour. L'objectif de cette revue générale est de résumer les données actuelles des mécanismes liant la fibrillation atriale au diabète, ainsi que les études cliniques qui incluent les patients ayant un diabète et une fibrillation atriale ; les options thérapeutiques et l'apport de la pharmacologie moderne sont également discutés.

Introduction

Type 2 diabetes mellitus is one of the most common chronic conditions and its prevalence is increasing. In 2014, the number of patients with diabetes was estimated at 387 millions people worldwide, of whom around half were undiagnosed [1]. The projection for 2035 is that the number of patients with diabetes will have risen to 592 millions [1]. It is well known that cardiovascular and cerebrovascular diseases are substantially more frequent among patients with diabetes [2]. However, the mechanisms of this influence are still not completely understood. It is not known whether permanent hyperglycaemia or wide fluctuations in glucose levels—from hypoglycaemia to hyperglycaemia, which is commonly seen in diabetes subjects, especially the treated ones—is most responsible for cardiovascular damage.

Atrial fibrillation (AF), the most frequent sustained cardiac arrhythmia, is associated with an increased risk of stroke, thromboembolism, heart failure and recurrent hospital admissions [3]. The prevalence of AF is constantly increasing, and it affects about 2.2 million individuals in America and 4.5 millions in Europe [4,5].

Studies have shown that diabetes is frequently associated with AF [6]. However, it is difficult to determine whether diabetes directly affects the atrial tissue or whether different pathways are involved, including hypertension, coronary artery disease and abnormal activity of the autonomic nervous system. The aim of this review is to summarize current knowledge of the relationships between diabetes and AF, from mechanisms to clinically relevant studies.

Mechanisms of the relationship between diabetes and AF

Diabetes is associated with numerous metabolic defects including insulin resistance, impaired glucose tolerance, proinflammatory mediators, abnormalities of haemostasis, fibrinolysis, angiogenesis and extracellular matrix turnover [7—9] (Fig. 1). All of these metabolic changes lead to endothelial dysfunction, abnormal activation of the renin-angiotensin-aldosterone system (RAAS) and acceleration of atherogenesis, which could be responsible for AF occurrence [2,7—9]. Diabetes could also cause structural, electrical, electromechanical and autonomic remodelling [10].

Atrial structural remodelling

Most evidence obtained from animal studies has demonstrated that structural remodelling of the left atrium, primarily atrial dilatation and interstitial fibrosis is the major trigger of AF in patients with diabetes [11,12]. Structural remodelling leads to ionic remodelling and increases atrial tissue vulnerability, which induces inter-atrial conduction delay and, subsequently, initiation and maintenance of AF [11,12].

Atrial fibrosis could be caused by inflammation (oxidative stress), increased production of advanced glycation end products, increased expression of transforming growth factor-β and expression changes of gap junction proteins [10].

Atrial electrical remodelling

The principal characters of atrial electrical remodelling involve atrial effective refractory period shortening and its dispersion, as well as impairment of its frequency adaptation and consequent inter-atrial conduction delay [10]. Changes in left atrial diameter, atrial activation time and voltage in patients with diabetes have been associated with atrial structural remodelling, not only electrical, especially in patients with AF. Chao et al., for example, studied patients with abnormal glucose metabolism (diabetes and impaired glucose tolerance) who underwent radiofrequency ablation of paroxysmal AF for the first time, and revealed that right and left atria voltages in these patients were significantly decreased due to atrial electrical remodelling and atrial fibrosis [13].

Atrial electromechanical remodelling

Findings from our group show that left and right atrial reservoir and conduit function, assessed by emptying fractions and strain, are decreased among subjects with prediabetes and patients with diabetes compared with controls [14]. On the other hand, left and right atrial pump function increased