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Atrial fibrillation and its association with type 2 diabetes

Atrial fibrillation is the common sustained arrhythmia in North American and European patients. In the United States, atrial fibrillation affects approximately 2.2 million adults with a median age of 75; nearly 10% of individuals over the age of 80 manifest this arrhythmia (1). The prevalence of atrial fibrillation is increasing markedly in industrialized nations, secondary to growth in population of elderly individuals in these societies. Atrial fibrillation is approximately 1.5 times more likely to develop in men than in women.

The traditional view of AF mechanisms is that the arrhythmia results from multiple re-entrant wavelets that move randomly throughout the atria. Re-entry is promoted by decreased atrial refractory periods, slowed conduction and an increased mass of cardiac tissue (2).

The clinical presentation of AF is highly variable, ranging from the complete absence of symptoms to heart failure and hemodynamic collapse. Symptoms result from the irregular and often rapid ventricular response, as well as from ensuing autonomic reflex changes and loss of atrial systole. In the Canadian Registry of Atrial Fibrillation, only 21% of patients were asymptomatic on presentation (3). Among the 79% of patients with symptoms, palpitations occurred in 50%, chest pain and fatigue in more than 25% and dizziness, presyncope or syncope in about 25%. The most feared complication of AF is stroke, which is often caused by thromboembolism from clotting in the left atrial appendage: AF increases the risk of stroke about 5 times and is a single factor most commonly associated with stroke in those over 75 years of age. Risk factors for stroke in patients with AF include advanced age, diabetes, hypertension, previous cerebrovascular accident and left ventricular dysfunction (4).

The majority of patients with atrial fibrillation have associated cardiovascular disease that has been shown to correlate with the presence of this arrhythmia. Common cardiovascular conditions that predispose to atrial fibrillation include hypertension, valvular heart disease, arteriosclerotic heart disease and myocardial infarction and congestive heart failure. Non-cardiovascular diseases that predispose to atrial fibrillation include *diabetes mellitus*, hyperthyroidism, acute and chronic alcohol abuse, and a variety of pulmonary diseases such as chronic obstructive lung disease, pneumonia, empyema, and pulmonary embolism. Potential iatrogenic causes of atrial fibrillation include cardiac and non-cardiac surgery and administration of a variety of medications including bronchodilating beta-agonists, various non-prescription cold remedies, antihistamines and local anaesthetics (5).

However, in many patients the cause of atrial fibrillation remains unclear. Lone atrial fibrillation is defined as atrial fibrillation in the absence of structural heart disease or other identifiable cause for the arrhythmia such as hyperthyroidism or alcohol abuse (6).

DIABETES MELLITUS AND CARDIAC FUNCTION

Cardiovascular complications are common causes of morbidity and mortality in diabetic patients. Coronary artheriosclerosis is enhanced in diabetics, whereas myocardial infarction represents 20% of deaths of diabetic subjects. Re-infarction and heart failure are more common in the diabetics. Diabetics cardiomyopathy is characterized by an early diastolic dysfunction and later systolic one, with intracellular retention of calcium and sodium and loss of potassium. *Diabetes mellitus* accelerates the development of left ventricular hypertrophy in hypertensive patients and increases cardiovascular mortality and morbidity. Heart rate variability with respiration and standing are decreased in diabetic patients especially those with evidence of peripheral or autonomic neuropathy. Parasympathetic cardiac nerve dysfunction, expressed as increased resting heart rate and decreased respiratory variation in heart rate, is more frequent than the sympathetic cardiac nerve dysfunction expressed as a decrease in the heart rise during standing (7).

DIABETES MELLITUS AND ATRIAL FIBRILLATION

Diabetes mellitus is one of the most chronic conditions with increasing prevalence of approximately 140 million people worldwide. There are few studies evaluating the association between DM and atrial fibrillation. Patients with atrial fibrillation are more insulin-resistant than subjects with sinus rhythm in the whole study population, as well as in normotensive controls without diabetes. It is, therefore, possible that impaired glucose metabolism can be related to electrophysiological instability in the myocardium. Furthermore, insulin resistance has been shown to be associated with left ventricular hypertrophy (8). The Framingham study found that DM was a significant independent risk factor for atrial fibrillation with an OR of 1,4 (9). However, only a small number of patients, in total of 562, were studied. Barriales et al. studied only 300 patients and found that DM was an independent risk factor for atrial fibrillation (10). In the International Journal of Cardiology Mohaved et al. retrospectively analysed discharge diagnoses and concluded that *diabetes mellitus* was a strong and independent risk factor for occurrence of AF. AF occurred in 14% of their patients with *diabetes mellitus* compared to 10.3% in the control group. On multivariate analysis, diabetes remained independently associated with AF (11). These studies stand in contrast to Wilhelmsen et al. who studied a large number of male patients (7495) over 25 years and found no correlation between DM and atrial fibrillation (12).

PATHOPHYSIOLOGICAL LINKS BETWEEN ATRIAL FIBRILLATION AND *DIABETES MELLITUS*

The causal link between diabetes and atrial fibrillation is likely via various pathways, including hypertension, coronary artery disease and abnormal autonomic tone, but the possibility remains that diabetes may directly (electrophysiologically and mechanically) affect the atrial tissue, leading do AF. The pathogenesis of atrial fibrillation involves two main processes. One is known to be the foci of rapid ectopic activities in initiation of atrial fibrillation. The second process is reentry involving one or more circuits. There are no studies available to suggest any explainable pathogenesis of DM triggering or maintaining atrial fibrillation. *Diabetes mellitus* is associated with many systemic illnesses such infection, electrolytes abnormalities or renal failure, which could cause irritability of atrium, triggering atrial fibrillation. Due to the major risk of stroke in patients with atrial fibrillation, this association will substantially increase the risk of stroke in patients with DM who are already at a high risk of atherosclerotic cerebrovascular disease.

Defects in the cardiac conducting system have also been reported with *diabetes mellitus* and of note, left bundle branch block in diabetic patients has been shown to indicate more advanced

cardiovascular involvement manifesting with more severe left ventricular systolic dysfunction, when compared to both diabetic patients without left bundle branch and nondiabetic patients with left bundle branch block (13). AF is commonly associated with the combined occurrence of type 2 diabetes and hypertension, and insulin resistance may be the common underlying mechanism. Another clinical condition common to both diabetes mellitus and AF is heart failure, and *diabetes mellitus* is also independently related to heart failure.

Atrial fibrillation as complication of hypoglycaemia in diabetic patients has been reported in patients with insulin-dependent *diabetes mellitus* (14).

RISK OF ATRIAL FIBRILLATION IN RELATION TO BODY MASS INDEX

Studies have reported increased AF risk associated with obesity, a common risk factor that is increasing in prevalence. The mechanism by which obesity may increase AF risk is unknown. Several mechanisms have been suggested, including increased left atrial size, chronic inflammation, and development of other cardiovascular risk factors or cardiovascular disease. Dublin et al. showed a strong relationship between BMI and risk of sustained AF than intermittent or transitory AF. Each unit BMI increment was associated with a 3% higher risk of new-onset AF. The relationship between BMI and AF was stronger in subjects with *diabetes mellitus* than in those without and somewhat stronger in subjects with hypertension (15). Obesity may contribute to maintaining AF. Support for this idea comes from studies showing that increased C-reactive protein levels, which are positively associated with obesity, are more strongly associated with persistent than with paroxysmal AF (16).

Diabetes mellitus may play a modest role in mediating the relationship between BMI and AF risk. The mechanism through which *diabetes mellitus* may lead to increased AF risk is not well understood, although several possible mechanisms exist. *Diabetes mellitus* is associated with increased inflammation as measured by CPR and increased CPR level is associated with an increased risk of AF. In addition, diabetes mellitus leads to myocardial fibrosis and diastolic dysfunction, which may lead to increased left atrial volume and thereby to increased AF risk, as left atrial is known to be associated with risk of new-onset AF (17). Wang et al. found that the association between BMI and AF risk became insignificant after adjustment for LA size and concluded that LA enlargement accounted for the entire observed association between BMI and AF risk (18).

DIABETES INFLUENCES THE CARDIAC SYMPTOMS RELATED TO ATRIAL FIBRILLATION

Diabetes mellitus may depress the cardiac symptoms caused by AF, not directly by influencing the impulse conducting system, but rather the neurological mechanisms that sense the changes in heart rhythm. *Diabetes mellitus* neuropathy may decrease the sensitivity of cardiac nerves and thus mask the rapidity or irregularity of heart rhythm during the first-recorded AF. Women with AF are reportedly more sensitive to their own heart rhythm or chest symptoms. Sugishita et al. showed that prevalence of DM neuropathy is significantly higher in asymptomatic patients with atrial fibrillation and diabetes mellitus may mask the cardiac symptoms of the first-recorded episode of AF. They observed a tendency to a more rapid heart rate in sinus rhythm and higher averaged ventricular response at the first-recorded episode of AF. However, the ratio of symptomatic cases at first-recorded AF tended to be lower in DM cases (19). They recommend clinical physicans routinely check the ECG for all DM patients, because of atrial fibrillation should be defibrillated earlier and prevented afterwards. In addition antiplatelet and/ or anticoagulation therapy is also required to prevent cerebral vessel disease or other arterial diseases.

COMPLICATIONS OF ATRIAL FIBRILLATION IN THE PATIENTS WITH DIABETES

Thromboembolic disease and stroke are the most important complications of AF and their occurrence is increased in both paroxysmal and chronic atrial fibrillation (20). Risk factors for stroke include previous stroke or transient ischaemic attack (relative risk 2.5), *diabetes mellitus* (1.7), hypertension (1.6), and increased age (1.4) as well as cardiac failure (including left-atrial and left-ventricular dilatation and left-ventricular dysfunction) and symptomatic ischaemic heart disease. Endothelial damage/dysfunction and platelet abnormalities, which are manifested in AF, DM may underlie the etiology of a prothrombotic state in these conditions, individually and in combination with other factors. The presence of DM augments endothelial damage/dysfunction and increases the platelet activation in patients with AF. *Diabetes mellitus* is associated with high levels of von Willebrand factor (VWF, a marker of endothelial damage and dysfunction). DM independently contributes to the endothelial damage/dysfunction in patients with AF, and this effect is exaggerated futher in individuals with congestive heart failure. *Diabetes mellitus* may reflect the increased prothrombotic and vascular risk seen in high-risk population (21).

REFERENCES

1. Mackstaller L. L., Alpert J. S.: Atrial fibrillation: A review of mechanism, etiology, and therapy. Clin. Cardiol., 20, 640, 1997;
2. Allessie M. A., Konings K., Kirchhof C. F. et al.: Electrophysiologic mechanism of perpetuation of atrial fibrillation. Am. J. Cardiol., 77, 10A, 1996.
3. Kerr C. R., Boone J., Connolly S. J. et al.: The Canadian Registry of Atrial Fibrillation: noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. Am. J. Cardiol., 82, 82N, 1998.
4. Wolf P. A., Abbott R. D., Kannel W. B.: Atrial fibrillation as an independent risk factor for stroke. Framingham Study. Stroke, 22, 983, 1991.
5. Readon M., Camm A. J.: Atrial fibrillation in the elderly. Clin. Cardiol., 19, 765, 1996.
6. Mont L., Sambola A., Brugada J. et al.: Long-lasting sport practice and lone atrial fibrillation. Eur. Heart J., 23, 477, 2002.
7. Mahgoub M. A., Abd-Elfattah A. S.: *Diabetes mellitus* and cardiac function. Mol. Cel. Biochem., 180, 56, 1998.
8. Rutter M., Parise H., Benjamin E. et al.: Impact of glucose intolerance and insulin resistance on cardiac structure and function. Circulation, 107, 448, 2003.
9. Benjamin E. J., Levy D., Vaziri S. M. et al.: Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA, 271, 840, 1994.
10. Barriales Alvarez V., Moris de la Tassa C., Sanchez Posada I. et al.: The etiology and associated risk factors in sample of 300 patients with atrial fibrillation. Rev. Esp. Cardiol., 52, 403, 1999.
11. Movahed M. R., Hashemzadeh M., Jamal M. M.: *Diabetes mellitus* is a strong independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int. J. Cardiol., 105, 315, 2005.
12. Wilhelmsen L., Rosengren A., Lappas G.: Hospitalizations for atrial fibrillation in the general male population: morbidity and risk factors. J. Intern. Med., 250, 382, 2001.
13. Guzman E., Singh N., Khan I. A. et al.: Left bundle branch block in type 2 diabetes: a sign of advanced cardiovascular involvement. Ann. Noninvasive Electrocardiol., 9, 362, 2004.
14. Odeh M., Oliven A., Bassan H.: Transient atrial fibrillation precipitated by hypoglycemia. Ann. Emerg. Med., 19, 565, 19, 1990.

15. Dublin S., French B., Glazer N. L. et al.: Risk of new- onset atrial fibrillation in relation to body mass index. Arch. Intern. Med., 166, 2322, 2006.
16. Chung M. K., Martin D. O., Sprecher D. et al.: C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation, 104, 2886, 2001.
17. Psaty B. M., Manolio T. A., Kuller L. H. et al.: Incidence of and risk factor for atrial fibrillation in older adults. Circulation, 96, 2455, 1997.
18. Wang T. J., Parise H., Levy D. et al.: Obesity and the risk of new-onset atrial fibrillation. JAMA. 292, 2471, 2004.
19. Sugishita K., Shiono E., Sugiyama T. et al.: Diabetes influences the cardiac symptoms related to atrial fibrillation. Circ. J., 67, 835, 2003.
20. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of anti-thrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized trials. Arch. Intern. Med., 154, 1449, 1994.
21. Varughese G. I., Patel J. V., Tomson J. et al.: The prothrombotic risk of *diabetes mellitus* in atrial fibrillation and heart failure. J. Thromb. Haemost., 3, 2811, 2005.

SUMMARY

Atrial fibrillation is the most common sustained cardiac arrhythmia, which is also associated with a risk of mortality and morbidity from stroke. On an epidemiology basis, type 2 *diabetes mellitus* is commonly associated with atrial fibrillation. The precise pathophysiological and clinical relationships between AF (atrial fibrillation) and diabetes mellitus are not completely understood. It is known however, that diabetes mellitus may mask the cardiac symptoms of the first episode of atrial fibrillation, because of diabetic neuropathy. *Diabetes mellitus* may underlie the etiology of a prothrombotic state and increase the risk of stroke in persons with atrial fibrillation.

Migotanie przedsionków i jego związek z cukrzycą typu 2

Migotanie przedsionków jest najczęstszą przewlekłą arytmią serca, która jest związana z ryzykiem śmiertelności i zachorowalności z powodu udaru mózgowego. Na podstawie badań epidemiologicznych wiadomo, że występowanie cukrzycy typu 2 jest powszechnie łączone z migotaniem przedsionków. Precyzyjny patofizjologiczny i kliniczny związek pomiędzy migotaniem przedsionków i cukrzycą nie jest dokładnie zbadany. Natomiast wiadomo, że cukrzyca może maskować sercowe objawy pierwszego napadu migotania przedsionków z powodu neuropatii cukrzycowej. Cukrzyca może także leżeć u podłoża nadkrzepliwości i przez to zwiększać ryzyko udaru mózgowego.