CARDIAC ELECTROPHYSIOLOGY IN DIABETES
Elettrofisiologia cardiaca nel diabete

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SUMMARY

Patients with diabetes mellitus are at higher risk of cardiac arrhythmias and sudden death. Although there are several animal and human studies on this topic, the pathophysiology of the increased electrical vulnerability in diabetes is complex and remain undefined. It is conceivable that an interplay of several concomitant factors may facilitate the occurrence of arrhythmias. Atherosclerosis as well as microvascular disease, which are increased in diabetic patients, may facilitate myocardial ischemia that predisposes to cardiac arrhythmias and sudden death. In addition, autonomic neuropathy and/or cardiac repolarization abnormalities such as prolonged QT interval and altered T-waves of the diabetic heart also increases electrical instability. Therefore, all these factors may simultaneously contribute to create an electrical instability leading to cardiac arrhythmias and sudden cardiac death. Recently, we have demonstrated that diabetes is the strongest predictor of AF progression and that diabetic patients frequently have asymptomatic episodes of AF with silent arrhythmia progression. Another recent study has reported that patients with type 2 diabetes and AF are at substantially higher risk of death of any cause compared with those without AF. These seminal studies emphasize that AF in diabetic patients should be regarded as a prognostic marker of adverse outcome and then a prompt aggressive management of all risk factors is required. In conclusion, diabetes mellitus significantly alters the cardiac electrophysiology throughout several complex mechanisms greatly contributing to create an electrical instability of the heart, which may lead to potentially life-threatening arrhythmias and sudden cardiac death.
RIASSUNTO

I pazienti con diabete mellito sono a più alto rischio di aritmie cardiache e di morte cardiaca improvvisa. Nonostante numerosi studi sia nell’animale che nell’uomo, i meccanismi dell’aumentata vulnerabilità elettrica ventricolare nel diabete rimane ancora da definire e si ritiene che una concomitanza di più fattori possa facilitarne l’insorgenza. L’ateroscelosi coronarica nonché la microangiopatia frequentemente presenti nel diabete mellito, favoriscono l’insorgenza di ischemia miocardica che predispone ad aritmie cardiache. Inoltre, la disfunzione del sistema nervoso autonomico sia simpatico che parasimpatico, che spesso si associa al diabete, può influenzare negativamente la stabilità elettrica del cuore predisponendolo ad aritmie anche maligne. Bisogna anche tener conto che in corso di diabete si riscontrano comunemente all’ECG anomalie della ripolarizzazione cardiaca con allungamento dell’intervallo QT/QTc ed alterazione dell’onda T, fenomeni che notoriamente destabilizzano elettricamente il cuore attraverso una profonda dispersione dei periodi refrattari con conseguente predisposizione all’aritmogenesi. Sembra quindi che moltepli fattori, comunemente presenti nel paziente diabetico, contribuiscano con meccanismi differenti e complessi ad alterare l’elettrofisiologia cardiaca a tal punto da rendere il cuore più vulnerabile alle aritmie cardiache e alla morte improvvisa. Un recente studio prospettico della durata di 5 anni ha dimostrato che il diabete è un predittore indipendente di progressione della fibrillazione atriale e che tale progressione può rimanere silente. Un altro studio prospettico ha dimostrato che i pazienti con diabete tipo 2 e fibrillazione atriale sono a più alto rischio di morte rispetto a pazienti diabetici senza fibrillazione atriale. Queste seminali osservazioni dimostrano che la fibrillazione atriale, così frequentemente osservata nei diabetici e nelle persone anziane, non deve essere più considerata come un’aritmia benigna ma come un marker prognostico negativo di morte improvvisa.
Diabetes and cardiac arrhythmias

It is well known that there is a clear correlation between coronary heart disease and type 2 diabetes mellitus. Diabetes increases the risk of coronary artery disease by a factor of 2- to 4-fold. Myocardial ischemia is a major complication in the course of diabetes, causing 75% of diabetes-related deaths. Patients with diabetes also have a higher rate of cardiac arrhythmias, sudden death and poorer outcomes after myocardial infarction. Compared with a non-diabetic person, a patient with type 2 diabetes has a 2- to 4-fold risk of dying from myocardial infarction. In addition, mortality among diabetic patients from a coronary artery incident is rising. In fact more than 65% of people with diabetes die from heart disease or stroke. Despite evidence-based guidelines for healthcare professionals and patients, there is an estimated 20 million people in the United States with diabetes which at present still represents a significant cause of morbidity and mortality. It has been reported among diabetic patients a higher incidence of cardiac arrhythmias and sudden cardiac death. The pathophysiology surrounding this increased electrical vulnerability is multifactorial, complex, and still remains undefined. It is conceivable that an interplay of different concomitant factors contribute to the genesis of arrhythmogenesis by altering cardiac electrophysiology. First, atherosclerosis as well as microvascular disease, which are increased in diabetic patients, may facilitate the development of myocardial ischemia that predisposes to cardiac arrhythmias. In addition, autonomic neuropathy is associated with abnormal reflexes and innervation of the diabetic heart affecting electrical instability. Finally, cardiac repolarization abnormalities manifesting as prolonged QT/QTc intervals and altered T-waves on the ECG are common in patients with diabetes. It seems therefore likely that factors such as coronary artery disease, metabolic and ion channel abnormalities, and autonomic dysfunction may simultaneously contribute to create an electrical instability leading to cardiac arrhythmias and/or sudden cardiac death. Several studies in both animals and humans have addressed the arrhythmogeneity in the diabetic heart. In animal models of diabetes different functional and structural alterations of the heart have been reported. Myocardial fibrosis may result in mechanical and electrical sequelae that affect cardiovascular
prognosis of patients with diabetes. Fibrosis reduces ventricular compliance and promotes arrhythmias by causing local delay in the spread of the action potential (1,2). In an animal model of mild diabetes mellitus, it has been demonstrated an enhanced susceptibility to ventricular arrhythmias, with increased electrophysiological sensitivity to catecholamines and nonhomogeneous collagen accumulation affecting local conduction (3). Diabetic patients have regional cardiac denervation and sympathetic overactivity, which may lead to life-threatening myocardial electrical instability and potentially fatal tachyarrhythmias. However, extrapolating such experimental studies to diabetic patients may be difficult since cardiac electrophysiology may be different in animals and humans. In addition, most studies have been conducted in animals with uncontrolled or poorly controlled diabetes while in human studies the majority of diabetic patients usually receive an optimal treatment. Despite these important limitations, important electrophysiologic data from animal models have been confirmed in human studies. Other animal studies focused on pathogenesis of diabetic cardiomyopathy, which appears to be multifactorial (autonomic dysfunction, metabolic derangement, abnormality in ion homeostasis, alterations in structural proteins, and interstitial fibrosis). Recent studies in humans while confirming many mechanisms derived from animal studies have provided insights into understanding of increased vulnerability of the diabetic heart to cardiac arrhythmias, heart failure and sudden death. At present, an important still debated question is the impact of AF on the already elevated risk of cardiovascular disease, cerebrovascular events, complications and mortality among patients with diabetes mellitus.

**Diabetes mellitus and atrial fibrillation**

It is well known that with the aging of the US and international populations the incidence and prevalence of AF are rising rapidly and AF is a common arrhythmia among diabetic patients. Rising obesity in most developed and developing countries is associated with a consequent rise of diabetes. It is estimated that globally the number of adults affected with diabetes mellitus will progressively increase over time from 135 million in 1995 to 300 million by 2025, and it is projected to increase to 4.4% in 2030 (4). More than 2.2 million Americans currently have AF, and this number is
expected to increase by at least 2.5-fold over the next 50 years. The prevalence of AF varies greatly according to the population's age and other health problems. It ranges between 4% in primary care settings to 15% in hospitalised patients (5,6). There are data to suggest that the prevalence of AF in people with diabetes is about twice that among people without diabetes (7,8) and up to three times higher in patients with coexistent hypertension. (6). Therefore, diabetes and AF are the world's fastest growing diseases with an expanding elderly population, the consequences of this epidemic become increasingly important. In the Manitoba Follow-up Study (9) diabetes was significantly associated with AF development in the univariate analysis, but multivariate analysis was not able to demonstrate diabetes as an independent predictor, suggesting that the increased risk of AF in diabetic men may be due to other factors such as the presence of coronary artery disease, systemic hypertension, or heart failure. On the contrary, the Framingham Heart Study (10), showed that diabetes is associated with AF development even after adjustment for age and other variables, which suggests that diabetes facilitates AF development. Whether and how diabetes facilitates AF development and/or progression to more persistent forms have not well defined in previous studies. Several mechanisms have been hypothesized in diabetic patients to explain AF development which include intra-atrial conduction delay, repolarization abnormalities and/or increased fibrotic deposition in atria. Other studies have reported that abnormality of the autonomic nervous system with cardiac autonomic dysfunction including heterogeneous increase in sympathetic innervation and/or a progressive parasympathetic denervation may also play an important role in facilitating AF development. New onset self-terminating episodes of AF may start as an electrical disease with rapidly discharging foci which "trigger" the arrhythmia, but paroxysmal episodes may become more persistent and progress over the years to permanent AF by involving a diseased atrial substrate. Only few studies have examined the natural history of AF with its progression and its interaction with other risk factors such as diabetes over a long-term follow-up period. The results of studies on natural history of AF have provide evidence that AF represents a heterogeneous disease and that comorbidities frequently modulate its progression over time with potential complications. A recent
retrospective study has reported interesting data on the natural history of the arrhythmia over a 30-year follow-up period (11). After a young patient with lone AF ages or develops heart failure, diabetes, or hypertension, thromboembolic risk increases (11). In relatively young patients, AF may represent primarily an electrophysiological phenomenon while in older patients with comorbidities, the arrhythmia may be considered as the final common pathway of a vascular inflammatory process associated with atrial mechanical and/or electrical remodeling (dilatation, stretch, fibrosis, and electric inhomogeneity), all of which increase the risk of complications. Therefore, an accurate screening for comorbidities such as diabetes or hypertension is essential in this group. Further understanding of the underlying pathophysiology of AF progression with associated comorbidities is required. Finally, preventive strategies to limit both arrhythmia progression and risk of major complications also require identification of independent predictors of such progression. Unfortunately, at present there are no prospective long-term follow-up studies assessing predictors of AF progression over time in a large number of patients. The few available reports have been mainly based on retrospective follow-up data with a limited number of patients (11). Recently, important prospective data focused on the understanding of AF progression and predictors of arrhythmia progression has been provided by our group (12). In this follow-up study, among 106 patients with an initially first detected paroxysmal episode of AF not due to transient causes, about a half of patients, most of whom without comorbidities “lone AF”, did not experience recurrent AF after the first episode remaining in stable sinus rhythm over 5 years (12). Our data while confirming that absence of comorbidities such as diabetes, heart failure, and hypertension is associated with an excellent outcome up to 5 years, clearly demonstrated that in patients with comorbidities AF commonly progresses to more persistent forms despite antiarrhythmic drug therapy or electrical cardioversion. Of note, we observed that in patients with comorbidities early catheter ablation may limit AF progression to persistent/permanent AF. These findings are important and provide strong evidence on the key role of comorbidities such as diabetes mellitus in facilitating AF progression. It is well known that chronic antiarrhythmic drug administration including amiodarone is ineffective
in maintaining a stable sinus rhythm in many patients with safety profiles that are less than ideal considering concomitant comorbidities such as diabetes mellitus. Multivariate analysis demonstrated that diabetes mellitus is the strongest independent risk factor for AF progression although older age and heart failure also predicted arrhythmia progression (12). It is well known that in diabetes silent episodes of paroxysmal AF may be commonly observed, but little is known about their relevance on arrhythmia progression and complications. Our experience also shows that silent undetected episodes of paroxysmal AF if not adequately treated may rapidly progress to more persistent forms and complications as documented by daily transtelephonic ECG recordings (12).

**Diabetes, atrial fibrillation and risk of sudden death**

Since diabetes and AF both independently increase major serious clinical outcomes and the presence of both diseases compounds this risk, the understanding of the complex interplay between diabetes and AF is crucial in developing a therapeutic approach to reduce the risk. General population studies have demonstrated that the presence of AF is associated with increased risks of stroke, heart failure, and cardiovascular death (13,14). Diabetes is a metabolic disease which affects both cardiac structure and function even in the absence of changes in either blood pressure or coronary artery disease, the so called “diabetic cardiomyopathy” (15-19). Increased heart failure rates in patients with diabetes persist despite correction for confounding risk factors such as age, hypertension, obesity, hypercholesterolemia, and coronary artery disease (20). The AF investigators group (21) reported that diabetes was an independent predictor of stroke with a relative risk of 1.7. A relation between the number of additional risk factors in patients with AF, including diabetes, and the presence of echo contrast or reduced flow velocity in left atrial appendage has been reported (22), indicating that other variables such as hypertension and diabetes may influence the complex thromboembolic mechanisms. Current guidelines suggest different risk stratification approaches for stroke prevention among patients with AF, and the presence of diabetes is considered as an important risk factor. Patients are classified as low, moderate, and high risk according to age, previous stroke or TIA, and other risk factors, such as hypertension, diabetes, coronary artery
disease, and heart failure. However, the importance of diabetes as a risk factor for stroke differs among the different stratification schemes. In the 2006 guidelines on AF from the ACC/AHA/ESC task force (23), diabetes is classified as a moderate risk factor together with age >75 years, hypertension, heart failure, and a left ventricular ejection fraction <35%.

It is well known that patients with diabetes after myocardial infarction are at higher risk of death of any cause and cardiovascular death. However, it remains unclear whether diabetes increases sudden cardiac death since there are conflicting results in the literature. In the Framingham study, diabetes was associated with higher risk of sudden cardiac death for all ages (almost four-fold), being significantly higher in women than men diabetic (24). The role of diabetes as a risk factor for sudden cardiac death in women has been assessed in a long-term study (25), which included 121,701 women aged between 30 and 55 years followed for >20 years. Sudden cardiac death occurred as the first clinical manifestation of heart disease in most women (69%), even if almost all of them had at least one cardiac risk factor. Diabetes was a very strong risk factor (three-fold increased risk of sudden death) as compared with hypertension (2.5-fold increased risk), and obesity (1.6-fold increased risk). Other long-term follow-up studies confirmed the role of diabetes as predictor of sudden death (26,27,28). These results based on large long-term follow-up studies provide strong evidence that diabetes is a risk factor for sudden cardiac death. Another study by Jouven et al.,(28) reported that higher levels of glycemia are associated with higher risk of sudden cardiac death, which does not support the ‘dichotomous’ risk approach of comparison between diabetic vs. non-diabetic patients. Of note, after adjustment for age, systolic blood pressure, presence of heart disease, and glucose-lowering treatment, even patients with borderline glicemia levels were at higher risk of sudden cardiac death than those with normoglycemia. Most importantly, microvascular disease (retinopathy or proteinuria), and female gender increased the risk of sudden cardiac death in all groups. These findings are clinically important since suggest that risk begins to increase at glucose levels that are considered fairly normal. It has been previously reported that high glycemic levels are associated with lower heart rate variability (29), which can be found even
in pre-diabetic patients (30). These findings confirm that glucose levels should be considered as a continuous variable affecting heart rate variability parameters (HRV) and autonomic control of the heart. The Rochester diabetic neuropathy study (31) by multivariate analysis, which did not include HRV as a variable, concluded that neither autonomic neuropathy nor QTc are independent predictors of the risk for sudden cardiac death, whereas kidney dysfunction and atherosclerotic heart disease are the most important determinants. These observations taken together suggest that a pre-diabetic stage can be associated with progressive abnormalities predisposing to sudden cardiac death. At present, there are no independent predictors of sudden cardiac death in diabetes to identify patients at higher risk. In a single study, microvascular disease and nephropathy have been identified as indicators of increased risk of sudden cardiac death in diabetic patients. The reduction of mortality from sudden cardiac arrest in the setting of coronary heart disease remains a major challenge, especially among patients with type 2 diabetes. Diabetes is associated with an increased risk of sudden cardiac arrest, which is due to several factors. Increased extent of coronary atherosclerosis due to macrovascular disease has been reported in diabetes, but non-coronary atherosclerotic pathophysiologic processes such as microvascular disease and autonomic neuropathy also increase the risk. Also, glycemia is known to affect the electrolyte balance, potassium and calcium channels, as well as the sympathetic activity, all of which are a key role in the arrhythmogenesis. Recent evidence suggests that higher risk in diabetes is not specific for sudden cardiac arrest since diabetes also is associated with a similar increase in risk for non-SCA CHD death and non-fatal myocardial infarction. These findings are in agreement with prior observations that coronary atherosclerosis is the most important contributor to the higher sudden cardiac arrest risk associated with diabetes. Previous data demonstrate that both clinically-recognized microvascular and autonomic neuropathy also are associated with the risk of sudden cardiac arrest among treated patients with diabetes, after taking into account prior clinically-recognized heart disease and other risk factors for SCA. Although the prediction of sudden cardiac arrest in this "high" risk patient population is likely to remain a challenge, as it is in other "high"
risk clinical populations, current recommendations for the prevention of sudden cardiac death, suggest both lifestyle prescriptions and risk factor decrease, to reduce mortality from sudden cardiac death in diabetes. A recent multicenter international randomized study (ADVANCE-Study) enrolling 11140 diabetic patients while confirming that AF is relatively common in type 2 diabetes, has demonstrated for the first time that among patients with type 2 diabetes, those with AF are at substantially higher risk of death of any cause, cardiovascular death, major cerebrovascular events, and heart failure, compared with those without AF (32). This study emphasizes that AF identifies individuals who are likely to obtain greater absolute benefits from blood pressure-lowering treatment, and then AF in diabetic patients should be regarded as a marker of particularly adverse outcome and prompt aggressive management of all risk factors. Diabetes has long been recognized as a risk factor for AF, but its independent contribution to AF has been recently reported in an observational, age- and sex-matched cohort, longitudinal study of 34,744 patients with and without diabetes (33). In this population, diabetes was an independent determinant of AF prevalence but predicted incidence only among women. These findings have potential public health implications and emphasize the need for further investigation of the mechanistic links between diabetes and AF. Other analyses have shown that the rising prevalence and incidence of AF cannot be explained by aging alone (34,35). Recent findings indicate that AF may be relatively common in diabetic patients and should be regarded as a marker of particularly adverse outcomes, prompting aggressive management of all risk factors (32). The overlap of diabetes and AF also contributes to a well-established increased risk of thromboembolic stroke (36). Although diabetes and AF undoubtedly share common antecedents such as hypertension, atherosclerosis, and obesity (37,38), the confluence of these two conditions clearly warrants additional study. However, the potential independent contribution of diabetes to the prevalence and incidence of AF has not been evaluated. Comparative analyses of the prevalence and incidence of AF in patients with and without diabetes have shown that AF was 44% more prevalent and 38% more likely to develop when diabetes was present (39). In this comparative study controlling for other known risk factors such as hypertension
and heart failure approximately halved the risk of incident AF (39). Recent studies have provided evidence of how comorbidities can have important modulatory effects on the progression and complications of AF (30). Thus far, studies evaluating the specific role of diabetes have been lacking. In the recent development of a risk score for AF, the Framingham Heart Study did not find diabetes to be a significant predictor of AF risk (40). This finding is contrary to a previous Framingham report that found diabetes to be a strong independent risk factor (41). Consistent with the latter study, the recent study by Nichols et al (39) suggests that in their studied population, diabetes made a significant contribution to the prevalence and incidence of AF, independently from hypertension and congestive heart failure. The continuously rising prevalence of diabetes may further increase the prevalence of AF, which represents the most common arrhythmia. It is conceivable that prevention and treatment of diabetes will limit the AF burden. Whether interventions achieving tight glycemic control decrease sudden cardiac death requires further studies.
REFERENCES


