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Arrhythmia Mechanism on Diabetes Mellitus: A Narrative Review

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by an increase in blood sugar levels. The mechanism of arrhythmias in patients with diabetes mellitus is complex and unique. This is an independent factor in the occurrence of arrhythmias through several slightly different mechanisms in non-diabetics. Hyperglycemia, hypoglycemia, remodeling, autonomic neuropathic dysfunction, fibrosis, and oxidative changes, and metabolic stress play an important role in the occurrence of arrhythmias in diabetes. This narrative review was at least to describe the mechanism of arrhythmia in diabetes mellitus.

1. Introduction

Diabetes mellitus is an endocrine disorder caused by reduced insulin production (DM type 1) and increased insulin resistance (DM type 2). Diabetes can cause coronary heart disease, myocardial infarction, heart failure, and sudden death due to arrhythmias.[1] Research has shown the presence of ventricular arrhythmias in patients with type 2 diabetes mellitus due to the prolongation of the QT and QTc intervals due to the prolongation of the ventricular action potential, which predisposes to arrhythmogenesis.[2]

Atrial fibrillation and ventricular arrhythmias are the most common complications of DM.[3,4] According to Framingham, DM is an independent risk factor for atrial fibrillation of about 14.9%.[5] Huxley showed that patients with DM had an increased risk of atrial fibrillation of about 40%.[6] In the general population, the incidence of atrial fibrillation increases with age, so that over the age of 80, the incidence of atrial fibrillation is approximately 20%.[7] The prevalence will increase in patients with hypertension, heart failure, coronary heart disease, kidney failure, and diabetes.[8]

Arrhythmias occur due to abnormalities in impulse formation and conduction (automatization, reentry activity trigger. These two things reinforce each other in the emergence of arrhythmias. Changes in the duration of action potentials due to abnormalities in ion exchange in the cell also cause changes in membrane depolarization that also trigger

arrhythmias.[9] The mechanism of arrhythmias in DM is unique compared to general arrhythmias. The role of autonomic neuropathy, blood sugar levels (hypoglycemia/hyperglycemia) which are rarely found in non-DM patients have a role in the occurrence of arrhythmias in DM.[10] This narrative review was to describe the mechanism of arrhythmia in diabetes mellitus.

Definition of arrhythmia in diabetes

Diabetes mellitus is part of a metabolic disorder in which there is an increase in blood sugar levels. There are two forms, namely, type 1 and type 2 diabetes. Type 1 diabetes has no known etiology and there is loss of pancreatic beta cells resulting in decreased insulin production. It often occurs in adolescence and accounts for about 10% of the diabetic patient population. Type 2 diabetes is the result of insulin resistance, so the body cannot respond to insulin. Generally occurs in adulthood, due to an unhealthy lifestyle, and genetics. In 2015, it was estimated that around 415 million people had diabetes.[5]

Cardiac arrhythmia is a condition in which the heart beats very fast, very slowly, or irregularly, which can be in the form of supraventricular and ventricular arrhythmias.[1, 11, 12] A study conducted by Agarwai and Singh, there is a close relationship between diabetes and the incidence of arrhythmias associated with cardiac autonomic neuropathy (CAN). Sinus tachycardia was mostly found around 32%, followed by total av block 15%, atrial fibrillation 15%, premature ventricular contractions 13%, premature atrial contractions 3%, av block grade 1 1%, supraventricular paroxysmal tachycardia 1% and ventricular tachycardia 1%. Approximately 62% of QTc interval prolongation is also associated with CAN.[1] This is not yet clearly understood, but it can be attributed to the role of coronary heart disease, conduction disorders, autonomic nervous system disorders, and changes in the structure of the atria and ventricles.[5,6]

Normal cardiac action potential

The cardiac action potential arises due to successive closure and opening of ion channel proteins as shown in Figure 1.[13,14] Action potentials can occur in five phases. Phase 0 or rapid depolarization initiated by depolarization of the SA node causes the membrane potential to reach the threshold, resulting in the opening of sodium channels.[15] Extracellular sodium enters the intracellular space and provides positive feedback for the sodium channels to keep them open, resulting in membrane depolarization until the sodium channels close again. Phase 1 or the initial repolarization phase arises due to the activation of fast and slow current pathways K^+ ($I_{to,f}$ and $I_{to,s}$). Phase 2 (plateau) indicates that calcium enters the cell through Ca^{2+} type L ($I_{Ca,\,L}$) and Na^+/Ca^{2+} exchanger (I_{NCX}) and $I_{to,f}$ close thus moving K^+ out of the cell.[3] (final repolarization) occurs when the Ca^{2+} is closed and $I_{to,s}$ is open so that Ca^{2+} leaves the cell and K^+ enters the cell. The transient outflow (I_{to}) not only forms phase 1, but also aids in plate formation, as well as contributes to the final repolarization phase. Phase 4 (resting phase) occurs after the membrane potential returns to rest, stabilizing at –90 mV.[9,13,17]

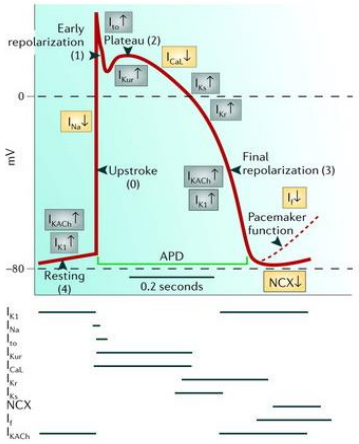

Figure 1. Normal action potential of cardiac cells[14]

The basic mechanism of arrhythmia

The basic mechanism of arrhythmias is the presence of abnormal impulse formation and disturbances in conduction (reentry). Impulse formation abnormalities may result in increased automation and trigger activity.[18] The increase in automation can be seen in Figure 2.

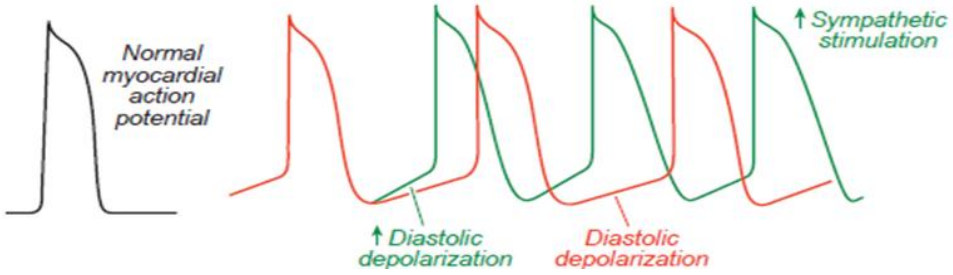

Figure 2. Automation. In normal tissue, no automation is formed. In the injured tissue, abnormal automatization occurs, resulting in diastolic depolarization (red line). Automation is also propagated by sympathetic stimulation increasing diastolic depolarization (green line).[19]

In the injured tissue activity is formed *to trigger* cardiac tissue due to depolarization triggered by one or more previous action potentials.[20] This is called depolarization. *Early After Depolarizations* (EADs) appears in phase 2 as a result the duration of the action potential becomes longer as shown in figure 3. This is due to the activation of $I_{Ca,\,L}$ releases Ca^{2+} from the sarcoplasmic reticulum and becomes positive feedback for membrane depolarization to occur longer after activating I_{NCX}. If the intracellular calcium concentration remains elevated when the membrane potential is negative concerning the equilibrium potential for NCX, I_{NCX} may be activated, causing membrane depolarization. These EADs occur in late phase 3 EADs and cause a shortening of the duration of the action potential.[21] EADs are clinically relevant, as they can occur immediately after termination of other types of tachycardia, such as atrial flutter, AT, VT, and VF. In such cases, the repolarization time is shortened and a transient increase in sarcoplasmic calcium release can be induced upon return to sinus rhythm.[9]

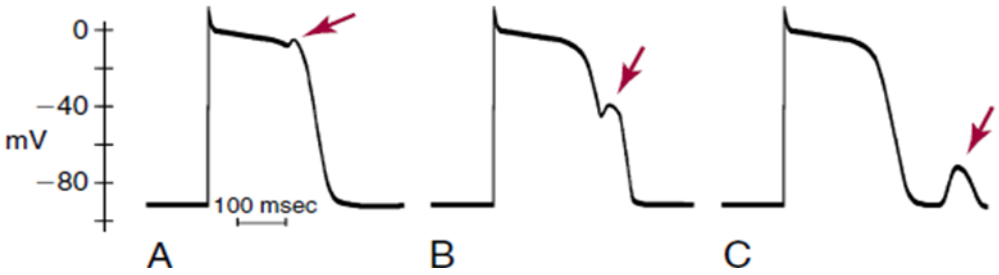

Figure 3. Action potentials in phase 2 EADs (A), phase 3 EADs (B), and DADs (C)[22]

Delayed afterdepolarizations (DADs) can develop after repolarization, corresponding to phase 4 of the action potential. DADs occur due to conditions of excess intracellular calcium, resulting from digitalis, catecholamines, hypokalemia, hypercalcemia, and heart failure. The mechanism of DADs is as follows: high intracellular calcium levels induce spontaneous calcium release from the sarcoplasmic reticulum, activates three calcium-sensitive currents, a nonselective cationic current (I_{NS}), sodium-calcium

exchange current (I_{NCX}), and activated chloride (I_{Cl}).[18] These currents together create an inrush which is responsible for membrane depolarization. If the depolarization produces a sufficiently large DAD, the I_{Na} activated, activating the trigger. DAD-induced trigger activity is the basis of arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia (CPVT).[9]

Late phase 3 EADs are a combination of EAD and DAD but have a special character. Late phase *3* EADs have two principles, namely shortening the duration of the action potential and releasing more Ca^{2+} from the sarcoplasm. This causes the sympathetic and parasympathetic to work together. Simultaneous sympathovagal activation triggers paroxysmal atrial tachycardia and atrial fibrillation in experimental animals (dogs).

The automation of pacemaker cells can increase the action potential. This can result from three mechanisms: a negative shift in the threshold potential, a positive change in the maximum diastolic potential, and an increase in the rate of phase 4 depolarization. When this occurs in the SA node, the heart rate increases. There is also a mechanism for generating action potentials when the dominant pacemaker is taken over by the latent pacemaker, known as parasystole as can be seen in Figure 4.[9] Parasystole occurs when the latent pacemaker is blocked by the dominant pacemaker, thereby releasing action potentials independently. Predominant pacemaker block occurs because it is surrounded by ischemia, infarction, or damaged tissue. The action potentials generated by the latent pacemaker can exit and activate the myocardium at rest.[9,23,24]

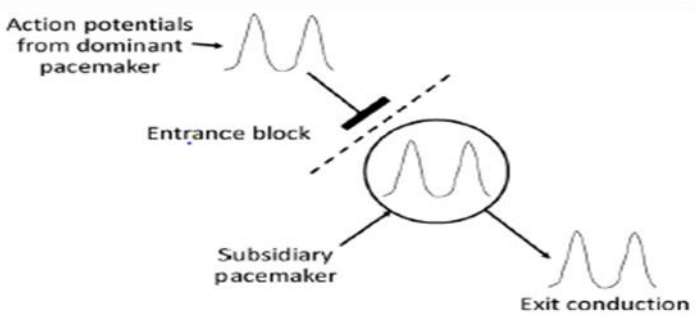

Figure 4. Parasystole[9]

Reentry occurs due to failure of the action potential to stop and instead reactivates the action potential in the refractory area. two conditions for re-entry namely increased formation impulse abnormalities conduction increases impulse generation occurs due to automatization of abnormal cells or trigger activity. Conduction abnormalities arise as a result of abnormal propagation of impulses across. or without a circuit reentry through the circuit occurs because of anatomical, functional, and combined barriers.[25] Reentry without passing through the circuit is divided into two parts, namely reflection and phase 2 reentry.[20]

Reflection occurs due to reentry without going through the circuit.[15] Normally an action potential is generated and travels from the proximal to the distal pathway and back to the original pathway. However, on reflection there is a gap so that conduction slows down, resulting in an extrasystole action potential which is then transmitted to the retrograde pathway. Reflection in a segment can occur in the atrial and ventricular tissues.[26]

Phase 2 reentry is also another mechanism that does not depend on the movement of the circuit. The concept arises because an electric current passes through a section with a long duration of potential to a short duration of the action potential, so re-excitation occurs when a short duration of the action potential is refractory. Arrhythmogenesis in Brugada syndrome is thought to involve re-entry, in which the resulting premature contractions trigger polymorphic spontaneous VT.[9]

Reentry in circuit mode occurs because the action

potential travels around an anatomic and functional barrier and then re-stimulates the original site.[9] Anatomical and functional reentry can occur due to cicatricial tissue in the heart that inhibits action potentials thereby triggering new action potentials before the recovery circuit. Functional reentry occurs because of the heterogeneity of the electrophysiological cell device thus providing an opportunity for the circuit to recover.[22]

Mechanisms of arrhythmias in diabetes mellitus

Chronic hyperglycemia in DM causes long-term damage to the heart such as coronary heart disease, acute myocardial infarction, heart failure, and sudden death due to arrhythmias.[1] Hypoglycemia is associated with intensive blood sugar control and cardiac autonomic neuropathy in DM is associated with heart rate variability (HRV) and changes in ventricular repolarization.[1,27,28]

An increase in the QT interval about heart rate is used for the diagnosis of CAN. Increased QTc and QT dispersion and HbA1C are associated with mortality, especially in older people with diabetes.[1, 28] Conduction and repolarization abnormalities will cause arrhythmias in DM.[10]

Hypoglycemia is a risk factor for sudden death due to arrhythmia.[29] Episodes of hypoglycemia may be associated with myocardial ischemia which can lead to ventricular arrhythmias.[30] Myocardial ischemia due to hypoglycemia can reduce conduction velocity by several mechanisms. Ischemia causes depletion of ATP, metabolic changes to anaerobic glycolysis, accumulation of H^+, and excess $Ca2^+$. Cytosol Ca^{2+} activates Protein Kinase C (PKC). This protein phosphorylates sodium channels, resulting in decreased sodium channel function.[10]

Hypoglycemia enhances adrenergic pathways by proarrhythmic pathways. The release of catecholamines results in abnormal circulating Ca^{2+} and the accumulation of intracellular Ca^{2+}, so that Ca^{2+} exits the sarcoplasmic reticulum, resulting in activation of the calcium-sensitive flow, $ICl_{, Ca}$. Therefore current enters during phase 4 of the action potential causing DAD, thus generating a trigger.[10]

Hyperglycemia produces reactive oxygen species (ROS) causing dysfunction in the human ether-a-go-related-gene (HERG). HERG is a subunit of the K^+, resulting in prolonged repolarization.[10] The increase in ROS also causes more soft tissue damage. Diabetes also increases superoxide production which contributes to reduced endothelial nitric oxide activity through increased NADPH, thereby contributing to atrial remodeling and the development of atrial fibrillation.[5]

Conduction abnormalities

Conduction abnormalities depend on the activation of sodium channels followed by the dispersion of ions through gap junctions, where the electrical circuit pathways are located close to the cardiomyocytes.[10] Each gap junction has two connexons, and each connexons consists of a hexamer connexon (Cx). Changes in each gap junction cause conduction abnormalities and predispose to reentrant. Protein Kinase C can reduce gap junction conduction.[31,32]

Myocardial fibrosis is a pathogenic factor in diabetic cardiomyopathy. Fibrosis is produced by growth factor-mediated activation of fibroblasts, such as factor. This can cause conduction disturbances by two mechanisms: (i) reduced coupling between cardiomyocytes, and (ii) increased membrane capacity. Both of these cause a decrease in the conduction velocity.[10]

Repolarization abnormalities

Action potential repolarization has two phases: (i) rapid repolarization resulting from activation of the transient slow and fast pathways of potassium ($I_{to,f}$ and $I_{to,s}$), (ii) plate lengthening resulting from the balance between the inflow of mediated by L-type calcium The channel (LTCC, $I_{Ca,\ L}$), a sodium-calcium exchange channel and a current mediated by a potassium rectifier (I_K), consists of fast and slow currents (I_{Kr} and I_{Ks}).[10]

In diabetes mellitus, the prolongation of APD results from several mechanisms. Lack of insulin signaling results in electrophysiological remodeling: I_{to} is reduced due to underexpression of the Kv4.2 and KchiP2 genes.

This current is regulated by several different kinases. For example, p90 ribosomal S6 kinase (P90RSK) is a serine/threonine kinase with N- and C-terminal kinase domains. Increased ROS in diabetes can increase the activity of p90RSK and reduce the activity of $I_{to,\,f}$, $I_{K,\,slow,}$ and I_{ss} channels.[33] In gene-crossed mice, overexpression of peroxisome proliferator-activated receptor1 (PPRAR1) showed abnormal accumulation of lipids in cardiomyocytes and reduced $I_{to,f}$, and $I_{K,\,slow}$. An increase in inflow and a decrease in outflow results in prolonged ventricular repolarization. In contrast, gene mutations are key ion channels that cause ventricular repolarization and also lead to diabetes.[10]

In diabetes, there is a shortening of the PPE. Failure of APD adaptation coupled with increased adrenergic pathways, may amplify APD recovery and ultimately result in alternating APD arrhythmogenesis. Hypoglycemia may also be linked to the cause of delayed repolarization.[34] Hypokalemia inhibits Ik1, resulting in prolonged action potential duration and reactivation of LTCC channels, resulting in EAD and trigger activation. Hypokalemia is also common with prolongation of the APD, increasing the repolarization gradient. Furthermore, the increase in PPE recovery develops into alternative PPE so that it damages waves, conduction blocks, and initiates reentrant*t.*[10]

In uncontrolled hyperglycemia activates CAMKII (calmodulin-dependent protein kinase) and then releases Ca^{2+} from the cytoplasmic reticulum. synchronized Ca^{2+} is caused by remodeling of the transverse tubular system in which RyR2 (type 2 ryanodine receptor) becomes dysfunctional when separated from LTCC.[10] Interestingly, CPVT is caused by a RyR2 mutation, and patients suffering from this condition are also susceptible to impaired glucose and insulin secretion. Furthermore, diabetics with RyR2 dysfunction may develop bidirectional VT and may progress to CPVT.[35]

In addition, diabetes mellitus is an independent risk factor for atrial fibrillation, but its physiology is not fully understood. This may involve the remodeling of ion channels in the atria. For example, a small conductance at Ca^{2+} activation of K^{+} (SK) channels contributes to atrial repolarization. SK2 and SK3 isoforms are downregulated leading to PPE prolongation. Usually, SK does not play a role in ventricular repolarization. In heart failure, SK current and ion channel expression can be upregulated and become more sensitive to $Ca2^{+}$, potentially leading to ventricular arrhythmias. The expression of SK channel expression in the ventricles may play a role in diabetes but this remains to be tested experimentally.[10]

Diabetic cardiomyopathy

Changes in the structure of the hearts that occur in diabetes have the potential to become arrhythmias as can be seen in Figure 8.[36] Hypertrophy, fat accumulation and fibrosis can occur in diabetic patients. Fibrous tissue can damage the myocardium resulting in changes in mechanical, electrical, and chemical composition.[37] Research on experimental animals Goto Kakizaki rats, with uncontrolled blood sugar levels there is an accumulation of fibrotic tissue compared to those without diabetes. Electrophysiological remodeling, including a prolonged intra-atrial conduction time, induces atrial fibrillation. A protein or fat, namely advanced glycation end products (AGEs) is a complication of diabetes.[38] Advanced glycation end products bind to AGEs receptors (RAGEs) contributing to the remodeling of cardiac tissue. This fat accumulation can occur in the pericardium and epicardium which ultimately causes left atrial enlargement, changes in heart structure, and slows conduction time.[5]

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy It is a serious complication of DM and is associated with increased mortality.[39] Prevalence occurs in about 17% in type 1 DM and 22% in type 2 diabetes. The incidence of CAN increases with age, duration of diabetes, and irregular blood sugar control. autonomic nerves play an important role in regulating heart rhythm through the sympathetic and parasympathetic nerves. Autonomic dysfunction can put you at risk for atrial fibrillation.[40] The cause of diabetic autonomic neuropathy is not fully understood, it can result from metabolic outcomes, neurovascular insufficiency, and growth that

contribute to nervous system damage.[39]

The beginning of CAN arises as a result of microangiopathic changes due to thickening of the capillary membrane and endothelial hyperplasia, resulting in vasoconstriction which causes a lack of oxygen and neuronal ischemic hypoxia. Furthermore, hyperglycemia via other pathways leads to the accumulation of sorbitol, increased diacylglycerol, and oxidative stress leading to autonomic nerve damage.[39]

A study by Framingham, heart rate variability can be an indicator in CAN which is associated with an increase in blood sugar levels leading to a decrease in HRV.[5,27,39] The presence of abnormalities of the central and peripheral blood vessels resulting from CAN through damage is responsible for the reduced cardiac output. This results in reduced ejection fraction, systolic dysfunction, and diastolic filling dysfunction.[39] This causes an increased tendency for patients to develop arrhythmias as a result of autonomic innervation of the myocardium.[40] Increases It is this altered vascular response and myocardial neuropathy that risk arrhythmias and sudden death.[41]

Diabetic patients have a high risk of coronary artery disease. Almost all diabetic patients are asymptomatic. Damage to the autonomic nerves in the sensory efferent pathway of the myocardium causes the patient to not feel bothersome, so it is too late to get treatment. And usually, patients come in a state of arrhythmia, shortness of breath, and cardiac arrest.[39] Remodeling and changes in autonomic dysfunction and fibrosis favor the progression of arrhythmias. Inflammation can occur as a result of oxidative stress and metabolic changes, which in turn can lead to arrhythmias.[5]

2. Conclusion

The mechanisms of arrhythmias in diabetes are complex. This relationship involves changes in blood sugar levels, both hypoglycemia, and hyperglycemia, CAN, remodeling, fibrosis, oxidative stress, and metabolic changes. Which in turn causes conduction abnormalities, prolonged repolarization duration, activated triggers, reentry processes occur, and cardiomyopathy. Diabetes is also an independent factor in the occurrence of atrial fibrillation, but this mechanism is not fully understood.

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