Chapter

# Effects of Diabetes Mellitus on the Conduction System of the Heart: Mini-Review

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## Abstract

Diabetes mellitus can induce substantial damage to the conduction system of the heart, especially the sinoatrial node. This is due to hyperglycemia leading to bradyarrhythmia. DM, via the elevation of HG, generates the production of a number of insulting agents in the myocardium known as reactive oxygen species and reactive carbonyl species, which elicit direct damage to neuro-filament-M and $\beta_2$-adrenergic receptors in the conducting system as well as a number of cardiac contractile, cation transporting and channel proteins. One cation channel protein is the hyperpolarization-activated cyclic nucleotide-gated potassium channel. It encodes the protein responsible for the hyperpolarizing-activated current or the "funny current" that participates in spontaneous diastolic membrane depolarization in sinoatrial node cells. Gene expression of these proteins and their physiological functions are decreased in the diabetic heart, which affects the generation of electrical impulses or action potentials resulting in increases in RR and PR intervals and QRS complex duration of the electrocardiogram. The heart rate and force of contraction of the myocardium are decreased leading to bradyarrhythmia and sudden cardiac death. This review attempts to explain the cellular mechanism(s) involved in diabetes-induced bradyarrhythmia with emphasis on cation-transporting proteins, especially the hyperpolarization-activated cyclic nucleotide-gated channels pacemaker current channels.

**Keywords:** diabetes mellitus, sinoatrial node (SAN), heart, cardiac conduction system, arrhythmias

## 1. Introduction

Diabetes mellitus (DM) is a serious global disease that currently affects more than 480 million people, and its number is growing rapidly. DM results from hyperglycemia (HG) and it is responsible for many long-term complications [1]. Cardiovascular

diseases (CVDs) account for more than half of the observed mortality in the diabetic population [2]. Nodal myocytes spontaneously generate APs in the absence of hormonal and neural stimulation [3]. Decreased heart rate (HR) is a common finding in patients with type 1 diabetes mellitus (T1DM) [4] indicating that many of these patients are likely to have impaired pacemaker function [5]. Cardiovascular defects are the major cause of morbidity and mortality in diabetic patients [6]. The cause of cardiac conduction disorders (CCDs) in DM patients is not fully understood. It remains unclear whether autonomic neuropathy or CVDs play a role [7]. This review addresses the effects of DM on the cardiac conduction system (CCS) which in turn can lead to arrhythmias and subsequently, sudden cardiac death (SCD). But first, it is important to understand the normal physiology of the conduction system before considering the mechanism(s) that might underlie the pathophysiology of DM-induced electrical conduction defects in the heart and its treatment.

## 2. Conduction system of the heart

### 2.1 Sinoatrial node action potential

The human SAN is composed of specialized cardiomyocytes. SAN cells spontaneously generate APs [8]. SAN cells are smaller than the surrounding atrial muscle cells and have fewer mitochondria and myofilaments. Atrial myocytes interdigitate with the SAN cells and assist in the conduction of APs from SAN to atrial myocytes. The SAN is the primary pacemaker center of the heart, and it is necessary to describe the normal function of the SAN before considering the effects of DM [8]. In a normal heart, pacemaker cells in the SAN control the rate of contraction of the heart. APs generated by the SAN cells are conducted and spread rapidly through the atria leading to the contraction of the atrial myocardium and the passage of blood into the ventricles [9]. There is a short delay in the atrioventricular node (AVN) before the APs are conducted and spread rapidly through the ventricles leading to contraction of the ventricles and pumping of blood into the pulmonary and systemic circulations. The atria and ventricles are electrically isolated from each other by what is known as the skeleton of the heart [10]. It consists of connective tissue that insulates the atria from the ventricles and provides a framework to support the heart valves [11]. The AVN is connected to the bundle of His. The bundle of His is an effective cable for conducting APs and distributing them to the ventricles. Conduction through the AVN is rather slow (about 100 ms) to prevent ventricular stimulation before the atria have finished contracting. **Figure 1** illustrates the physiological events involved in cardiac muscle contraction (systole) and relaxation (diastole) starting with the initiation of electrical impulses in the SAN and spreading throughout the myocardium [12].

The APs of the SAN occur in three phases. Phase 4 involves a period of gradual depolarization, which is unique to pacemaker cells, that participates in spontaneous diastolic membrane depolarization in SAN cells. Pacemaker currents are generated by the slow influx of $Na^+$ ions through the HCN channels [13]. The passage of electrical currents through L-type and T-type $Ca^{2+}$ channels and reduced $K^+$ conductance also contribute to SAN phase 4 depolarization. This pacing current changes the membrane potential from −60 mV to a threshold potential of −40 mV. The Phase 4 gradient determines HR and varies from region to region and from pacemaker cell to pacemaker cell. The SAN pacemaker cells depolarize at a rate from 60 to 100 per minute, and the AVN depolarizes at a rate from 40 to 60 per minute [14].

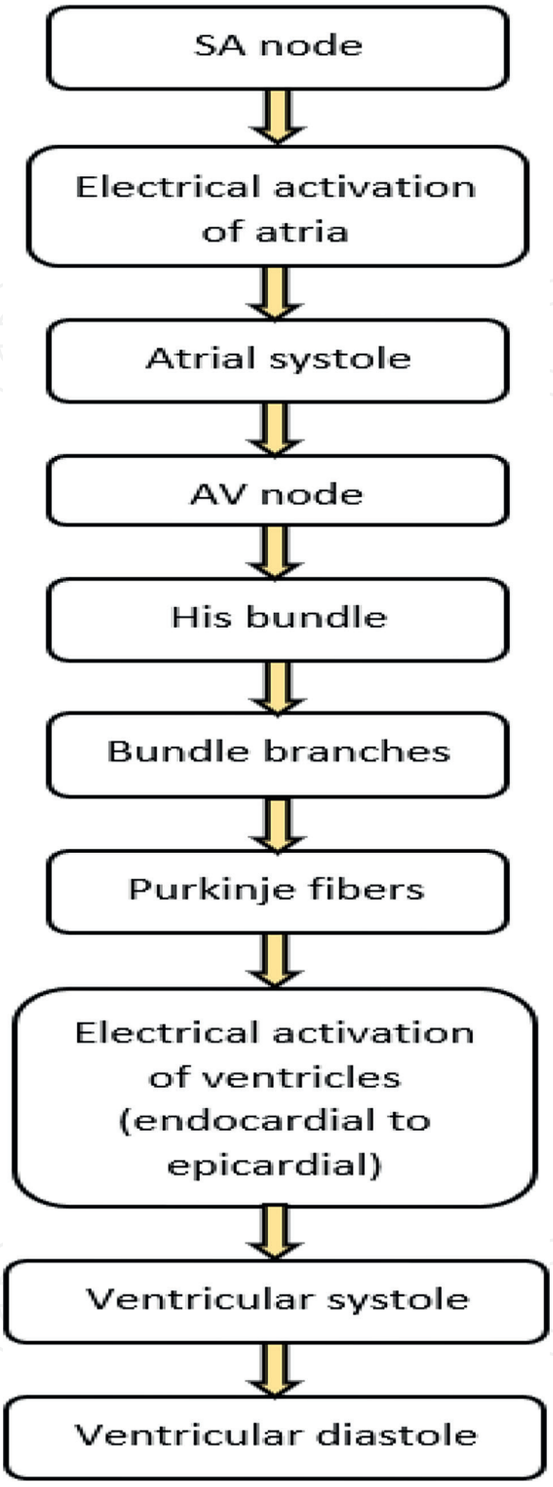


**Figure 1.**
*Flow diagram showing the different physiological events of excitation-contraction-coupling (ECC) in the heart starting from the initiation of an electrical impulse in the SAN, and then transmission of the impulse to the different parts of the conduction system to initiate contraction (ejection of blood) and relaxation (filling) of the myocardium.*

Since the SAN has the highest depolarization rate, it is normally the primary pacemaker center of the heart. Phase 0 is the depolarization phase of the AP. This stage begins when the membrane potential reaches the threshold potential. L-type $Ca^{2+}$ current is the major ionic conductance responsible for phase 0 [15]. This

influx of $Ca^{2+}$ increases the membrane potential from −40 mV to +10 mV. Calcium channels are slow channels (compared to sodium channels), so the depolarizing upstrokes are not as steep as those observed in cardiomyocytes. During repolarization (phase 3), the $Ca^{2+}$ channels close, and the voltage-gated $K^+$ channels open, allowing the outflow of $K^+$. This cation outflow reduces the membrane potential from +10 to −60 mV. Phases 1 and 2 do not exist in pacemaker cells [14]. The slope of phase 4 determines the HR, and it is different for pacemaker cells in different regions of the heart. The rate of AP generation by the SAN is limited by the rate at which $Na^+$ enters through the HCN channel (funny current) [16]. The more HCN channels open, the faster $Na^+$ enters the cell and the steeper the pacemaker potential allowing the cell membrane to reach threshold sooner, thereby shortening the time between APs as illustrated in **Figure 2** [14].

The sympathetic and parasympathetic branches of the autonomic nervous system (ANS) have the opposite effects on HR by opening and closing HCN channels as illustrated in **Figure 3**. Norepinephrine (NEP) released from the sympathetic nerves binds to the β1-adrenergic receptor. The β1-adrenergic receptor binds via the G protein or Gs (stimulation) and stimulates the enzyme adenylate cyclase to increase the production of the second messenger, cyclic adenosine monophosphate (cAMP) [17]. The epinephrine (EPI) that circulates in the blood also binds to β1-adrenergic receptors. HCN channels are sensitive to cAMP, which, in turn, increases HCN "funny current," thereby decreasing the time between APs in the SAN. On the other hand, acetylcholine (ACh), released by the parasympathetic nerves, has the opposite effect because it binds to M2 muscarinic receptors, which are linked to the generation of

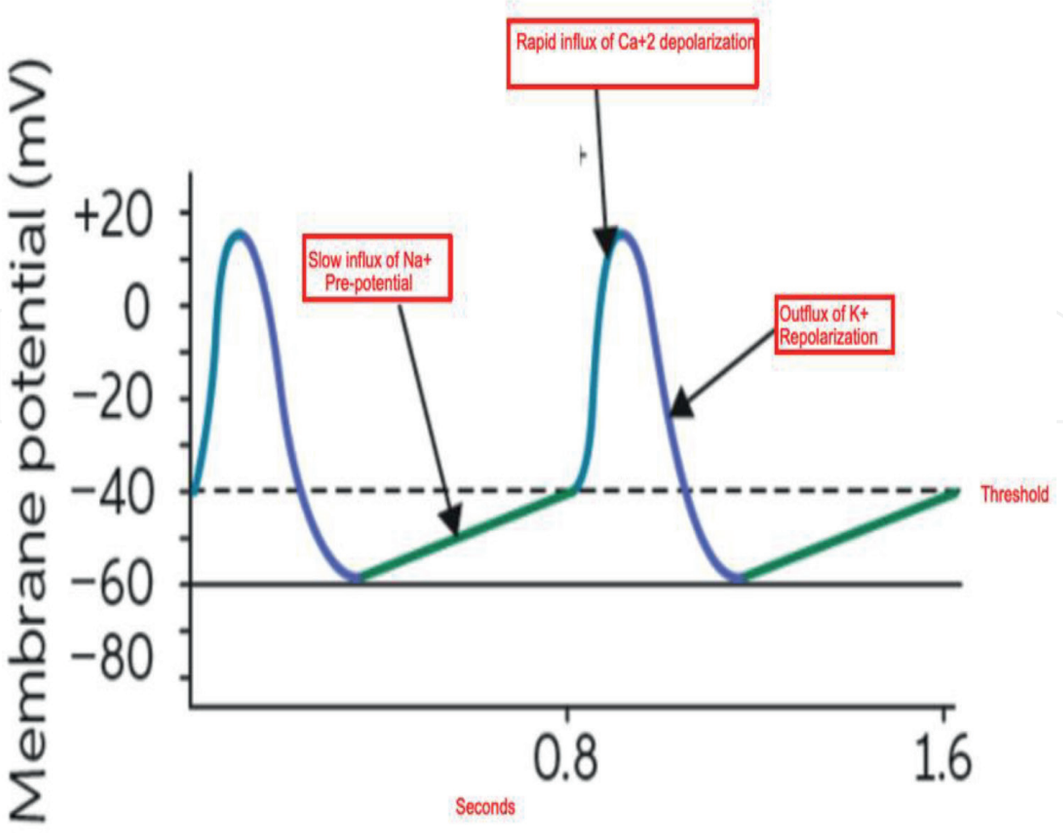


**Figure 2.**
*Different phases of the SAN action potential.*

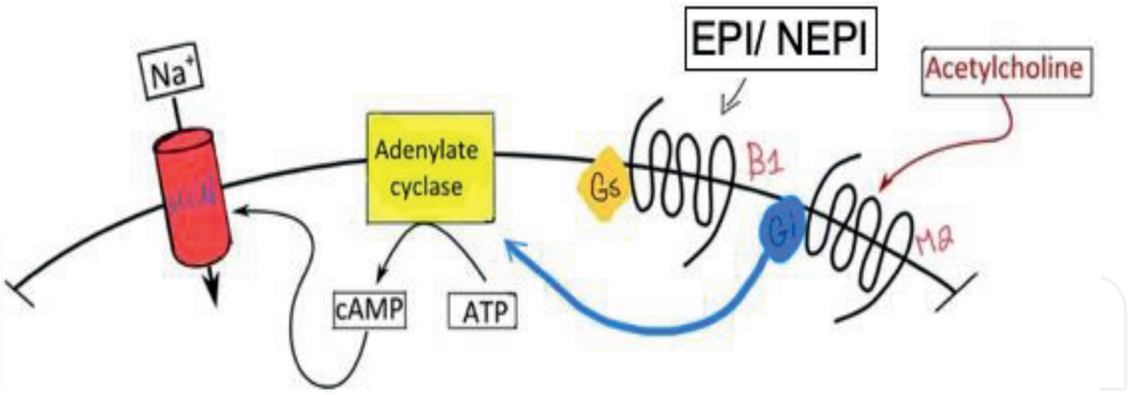


**Figure 3.**
*The opening and closing of HCN channels are regulated by the intracellular second messenger cAMP. Increased cAMP occurs when either norepinephrine or epinephrine binds to Gs-coupled β1 receptors, whereas acetylcholine has the opposite effect when bound to Gi-coupled M2 receptors (ATP = adenosine triphosphate); NEP = norepinephrine; EPI = epinephrine.*

cyclic guanosine monophosphate (cyclic GMP) via the activation of guanylate cyclase and at the same time inhibiting adenylate cyclase; thereby, reducing HCN "funny current." [18].

### 2.2 Automaticity of the sinoatrial node

The spontaneous excitation of pacemaker cells of SAN is responsible for the generation of automaticity in the heart. The presence of diastolic depolarization (DD) is what causes spontaneous activity. This depolarization brings the membrane voltage from the end of the repolarization phase to the threshold of the action potential that will follow. As a reflection of the complex nature of this physiological process, there has been a long-standing and significant amount of debate regarding the ionic mechanisms that are underlying DD [14]. DD in the SAN is caused by the opening of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which pass an inward cation current known as the "funny" current (If) [14]. There are two types of voltage-gated $Ca^{2+}$ channels: T-type and L-type. Subtypes of the T-type include Cav3.1, Cav3.2, and Cav3.3. And the L-type subtypes are Cav1.2 and Cav1.3; Cav1.3 is highly expressed in SAN. As Vm becomes more positive, HCN channels begin to close, and voltage-gated $Ca^{2+}$ channels 3.1 (CaV3.1) and 1.3 (CaV1.3) begin to open, generating the depolarizing transient (T-type) current (ICa,T) and the CaV1.3 component of the long-lasting (L-type) $Ca^{2+}$ current (ICa,L) that result in the continuation of DD [19].

Ryanodine receptors (RyRs) regulate $Ca^{2+}$ release from the sarcoplasmic reticulum (SR) during late diastolic depolarization. This has been shown to be another important factor in regulating APs in pacemaker cells [20]. The sarco/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) recycles some of this $Ca^{2+}$ back into the SR, but the $Na^{+}$-$Ca^{2+}$ exchanger pumps the rest out of the cell via an electrogenic, depolarizing current [20] At a voltage of 40 mV, the CaV1.2 channel opens, producing more ICa, L and stimulating the SAN. By repolarizing Vm, $K^{+}$ currents from both fast and slow delayed rectifiers reactivate If and kick off a new cycle of DD [21].

The autonomic nervous system (ANS) is a major regulator of SAN automaticity and sinoatrial conduction [17]. Autonomic dysfunction is a common cause of SAN dysfunction. Adrenergic or cholinergic dysregulation may contribute to pacemaker and conduction abnormalities within the SAN [18]. Tachycardia-bradycardia

syndrome is the extreme manifestation of a continuum characterized by a significant loss of SAN function integrity [18, 19]. It has been reported that a high concentration (30 mol/L) of ryanodine, which blocks the SR $Ca^{2+}$ release channel, eliminates the spontaneous activity of isolated SA node cells from rabbits, which led them to hypothesize that SR $Ca^{2+}$ release is essential for pace-making. Because of the observation of the chronotropic effect in isolated SA node cells from rabbits is abolished or greatly reduced after the suppression of the $Ca^{2+}$ transient by a submaximal concentration of ryanodine (3 mol/L), another study reported that the positive chronotropic effect of β-adrenergic stimulation is the result of the increase in the $Ca^{2+}$ transient caused by β-adrenergic stimulation [18].

### 2.3 Atrioventricular node action

The atrioventricular node (AVN) is a complex structure that performs various functions in the heart and works primarily as an electrical gatekeeper between the atria and the ventricles. It introduces a delay between atrial and ventricular excitation; thereby, facilitating the emptying of the atria and filling of the ventricles. This delay prevents simultaneous ventricular excitation and ensures one-way blood flow through the heart chambers [22]. The AVN transmits electrical stimulation from the atria to the ventricles via fast or slow pathways. Many electrophysiological differences between these pathways predispose the atrioventricular junction to arrhythmias [23]. These different electrophysiological properties of fast and slow signaling pathways are due to their unique structural and molecular composition (tissue and cellular geometry, ion channels, and gap junctions). Similar to SAN cells, AVN cells spontaneously depolarize. In a normal heart, the rate of spontaneous depolarization of the AVN is slower than that of the SAN; and thus, the rate of AVN cell depolarization is controlled by impulses generated by the SAN [21].

The depolarization phase 0 of the AP in AVN cells is due to voltage-gated $Ca^{2+}$ channels, and most of the current is due to $Ca^{2+}$ influx through L-type $Ca^{2+}$ channels. These voltage-gated ion channels are closed in the resting state and become either active or open when the threshold voltage is reached. When active, these channels allow $Ca^{2+}$ ions to flow into the cell [24]. The influx of $Ca^{2+}$ into the cell causes the release of additional $Ca^{2+}$ from the SR. This is called calcium-induced calcium release (CICR) and occurs through a specific channel in the SR membrane known as the ryanodine receptor (RyR). Over time, L-type $Ca^{2+}$ channels undergo a conformational change to an inactive, closed, or non-conductive state, even if the cell membrane potential remains above the threshold voltage [14]. At this time, the SR ryanodine receptor channel also closes, stopping the influx of $Ca^{2+}$ into the cytoplasm. Thereafter, $Ca^{2+}$ released into the cytoplasm of AV node cells is removed from the cytoplasm by two mechanisms. They include the sodium-calcium exchanger (NCX), which transports $Ca^{2+}$ from inside the cell in exchange for $Na^{+}$ entering the cell. During phase 3 of action potentials, the AVN cell membrane is repolarized by the outflow of $K^{+}$ from the cell due to the activation of voltage-gated $K^{+}$ channels. The relative gradient of $Na^{+}$ and $K^{+}$ and the electrical gradient across the cell membrane are finally restored by the action of the $Na^{+}/K^{+}$ ATPase pump, and the AV nodule cells are ready for depolarization again [25].

Gap junctions are important in impulse conduction in the heart. Over the last decade, research has revealed that gap junctions are encoded by the connexins, a multigene family [22]. There are at least 15 connexin genes in the vertebrate genome. Connexins have been classified into two groups based on their molecular weight

or their class as determined by protein sequence. There are three major connexin isotypes expressed in the heart: connexin (Cx)43 (1 connexin), Cx45 (6 connexin), and Cx40 (5 connexin). Each of these connexins has distinct channel properties and is regulated by distinct gating mechanisms. The distribution of Cx channels varies within the SAN. Electrical coupling is weak in the center of the SAN because Cx40 and Cx43, which form large and medium conductance channels, are only sparingly expressed or absent. However, Cx45, which forms small-conductance channels, is expressed in the SAN's center. Cx40, Cx43, and Cx45 are all present at the SAN's periphery; however, the strong electrical coupling is required to drive the atrial myocardium [22].

## 3. Diabetes mellitus induces changes in the conduction system of the heart

DM is a major risk factor for the development of cardiovascular complications, including cardiac arrhythmias, prolonged QT intervals, and SCD [26]. AVN blockade and bradycardic arrhythmia [27] are significantly higher in DM patients. There is considerable evidence for cardiac remodeling and altered ion channel activity/expression which are involved in HR and rhythm regulation [28]. In particular, Type 1 diabetes mellitus (T1DM) affects a range of cardiac ion channel currents, including L-type calcium currents (ICaL) and fast and slow delayed rectifier potassium currents (IKr and IKs) [29], as well as transient outward potassium current (Ito) [30].

Insulin treatment of rat ventricles and human atrial cardiomyocytes has been reported to increase ICaL density with significant upregulation of mRNA and protein expression of L-type calcium channels [31]. Altered SR-$Ca^{2+}$ content and RyR2 binding, as well as altered RyR2 mRNA protein levels [32], are normalized after insulin treatment in STZ-induced T1DM animals. In addition, decreased SR Ca-ATPase (SERCA2a) activity in rats with STZ-induced T1DM can be reversed by insulin treatment [33]. Insulin therapy has also been shown to restore decreased levels of NCX1 protein and mRNA in the ventricles [34]. Taken together, these findings suggest a direct stimulatory effect of insulin on cell contractility, mediated by $Ca^{2+}$ signaling proteins and membrane ion channels. Therefore, insulin treatment may be an important approach that reverses the QT interval and QRS complex prolongation in T1DM.

Among the diabetes-induced electrical disorders is nodular dysfunction, which is due to alterations in HCN channels. Four alpha subunit isoforms have been described, including HCN1, HCN2, HCN3, and HCN4 (encoded by HCN14). HCN channels are mainly expressed in the myocytes of the cardiac conduction system. Genetic studies have characterized the functional role of HCN4 in cardiac physiology. Mice subjected to heart-specific HCN4 ablation showed bradycardia and atrioventricular block [35]. In addition, patch-clamp analysis of SAN cells showed a 70% reduction in the "funny" current (IF) and a 60% reduction in spontaneous beat rate [35]. These results confirm that HCN4 is important in maintaining the molecular mechanism of pacemaker function. Previously, Howarth et al. identified reduced expression of HCN4 mRNA in rats with STZ-induced T1DM. Some diabetics have shown slow depolarization of the ventricles [36]. This is shown in the ECG as an increase in QRS duration. Reduced expression of HCN4, connexin, and ion channels was also identified in various regions of the cardiac conduction system (CCS) in the STZ model of T1DM [37]. Moreover, in a study on hearts of T1DM rats, it was reported that the dysfunction of the CCS plays an integral role in developing cardiac arrhythmias due to increases in RR interval, PR interval and QRS complex duration of the ECG [38]. These alterations were due to

decreases in rate of SAN and HCN4 (pacemaker current) as well as downregulation of the gene expression for HCN4 channels, neuro-filament-M and β2-adrenergic receptor within the SAN of the myocardium during T1DM. It is possible that changes in the expression of these different cardiac proteins within the SAN are closely associated with the regulation of the electrical signaling of the myocardium. In turn, this can adversely affect cardiac AP generation and propagation, leading to arrhythmia [38].

## 4. Pathological effect of diabetes on sinoatrial node activity

Both basic and clinical research studies have shown that diabetes can impair the autonomic control of heart rate (HR) [39]. According to McDowell et al. [40], diabetic rabbits have a significant impairment in the parasympathetic-mediated baroreceptor control of HR. This impairment has been linked to impaired parasympathetic control of the heart in diabetes. The parasympathetic control of HR is also significantly impaired in diabetic rats, as shown by lower heart rate variability (HRV) [41]. Zhang et al. [42] reported that the negative chronotropic response to carbachol (a parasympathomimetic agonist) was blunted in Akita diabetic mice versus wild-type mice. These findings are consistent with results obtained in human T1DM patients who had significant impairments in parasympathetic control of heart rate [43].

Diabetes may also be associated with an increase in harmful arrhythmias due to impaired SAN activity. SAN function is evaluated *in vivo* using intracardiac programmed electrical stimulation and sinus node recovery time (SNRT) [44]. Experimental studies have used both animal and human models to study changes in SNRT. Depending on the conditions in which these alterations take place, sinus node prolongation and shortening of the SNRT can both be pathological and indicative of sinus node dysfunction [44]. This response may reflect the impaired ability of the SAN to correct for physiological changes in heart rate following the development of diabetes [45]. Experimental and clinical studies showed that a diseased or failing heart is prone to develop ventricular fibrillation (VF), which is the main cause of sudden cardiac death, particularly during a heart attack. Slow conduction and fractionated electrocardiograms were recorded in the infarcted human heart [46, 47]. Atrial tachyarrhythmias caused by rapid pacing were more likely to occur in RCx40-deficient mice [48]. As well as a reduction in Cx40 was found in humans with chronic atrial fibrillation (AF) [49]. As a result, it suggests that connexin down-regulation may also be a factor in the persistence of AF. It should be stressed that aging and CVDs are, in addition to structural and gap junction remodeling, characterized by abnormal $Ca^{2+}$ handling [50]. Myocardial conduction in Cx43-deficient mice was noticeably slowed, which encourages re-entrant arrhythmias and sudden arrhythmic death (SAD) [51]. In rats with diabetes mellitus, down-regulation and/or abnormal distribution of myocardial Cx43-positive gap junctions have been linked with increased susceptibility to ventricular arrhythmia. Diabetes was linked to myocardial fibrosis. Reduced gap junction coupling in fibrosis-affected regions of the myocardium may disrupt wave-front propagation and thereby obstruct synchronized and uniform cardiomyocyte function [50]. Given the importance of gap junction connexin channels in cardiac arrhythmogenesis, it appears that aimed modulation of intercellular communication to prevent spatial electrical heterogeneities in viable myocardium is a promising way to combat life-threatening arrhythmias and SCD in humans. Nonetheless, more detailed analysis and research are required to address this issue in search of novel therapeutic approaches.

## 5. Conclusion

**Figure 4** summarizes the various events leading to a decreased HR or bradyarrhythmia and subsequently, SCD. It is postulated that DM, via an elevation in HG, can initiate the production of ROS and RCS to induce cardiac muscle damage, apoptosis, fibrosis, and subsequently cardiac remodeling. These pathophysiological changes are associated with severe damage to nerves and β1-adrenergic receptors as well as electrical and mechanical dysfunction of the myocardium leading to a decrease in HR, cardiac arrhythmias, and subsequently SCD. Experiments with animal models have consistently shown that diabetes can alter the expression and regulation of cardiac ion channels and contractile proteins, which impair impulse generation, conduction,

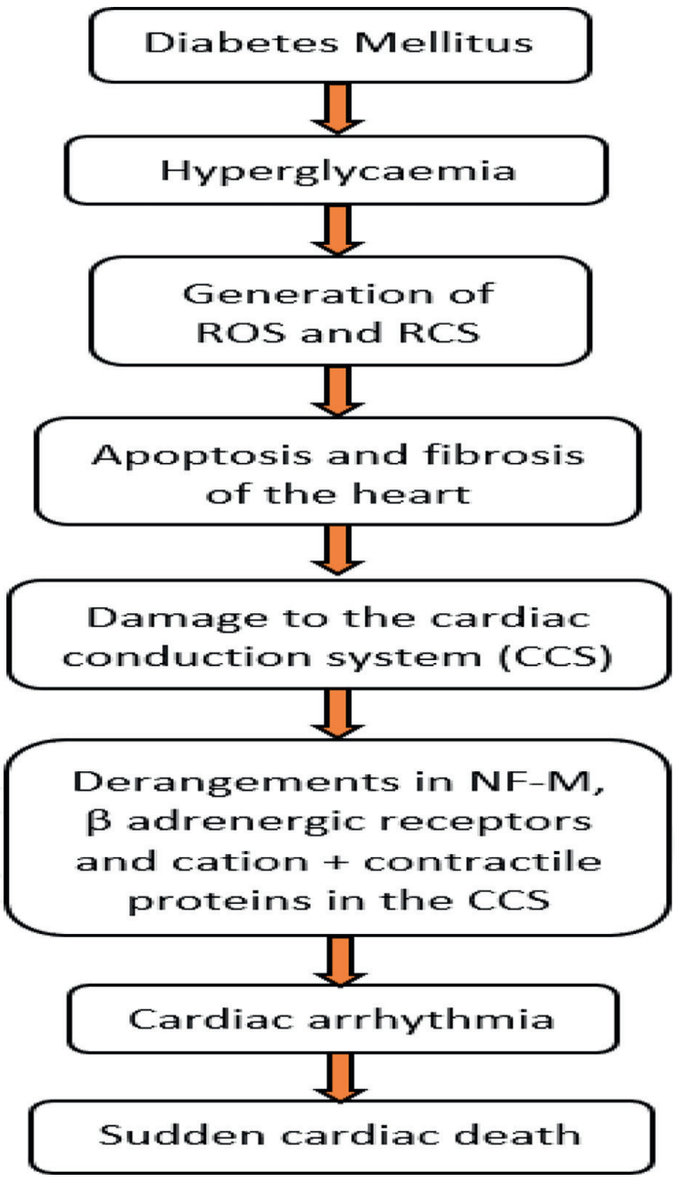


**Figure 4.**
*A flow diagram summarizes the effects of DM on the myocardium starting with hyperglycemia to the generation of ROS and RCS followed by apoptosis, fibrosis, and subsequent damage to the cardiac conduction system and β2-adrenergic nerves and receptors leading to arrhythmias and sudden cardiac death (CCS = cardiac conduction system; ROS = reactive oxygen species; RCS = reactive carbonyl species; NF-M = neuro-filament M). Note that both ROS and RCS exert lethal damage to the different parts of the cardiac conduction system as well as cation and contractile proteins in the myocardium.*

ECC, and subsequently, myocyte contractility. Prolonged QTc intervals persist in many treated diabetic patients, suggesting that glycemic control has to be adequate to normalize electrophysiological and mechanical disorders in the myocardium. Available hypoglycemic agents that can improve cardiovascular prognosis are important for the management of patients with type 2 diabetes (T2DM) who have existing CVDs and high cardiovascular risk. More research is required to understand the exact pathophysiological mechanisms at subcellular, cellular, and molecular levels, which can lead to cardiac conduction disorders in DM patients. In turn, this will help in the development of novel hypoglycemic drugs to treat the condition.

## Conflict of interest

None.

## Authors' participation

Manal Smail, Jaipaul Singh, Sunil Rupee, and Frank Christopher Howarth initiated the idea, and wrote and revised the review. Sunil Rupee, Khemraj Rupee, Abla Mohammed Ahmed Ismail, and Sara Sultan helped with the literature search and drew all the figures.

## Ethical clearance

None since this is a review article.

## Abbreviations

| | |
|---|---|
| DM | diabetes mellitus |
| SAN | sinoatrial node |
| HG | hyperglycemia |
| ROS | reactive oxygen species |
| NFM | neuro-filament-M |
| HCN | hyperpolarization-activated cyclic nucleotide-gated |
| APs | action potentials |
| ECG | electrocardiogram |
| SCD | sudden cardiac death |
| CVDs | cardiovascular diseases |
| HR | decreased heart rate |
| T1DM | type 1 diabetes mellitus |
| CCDs | cardiac conduction disorders |
| AVN | atrioventricular node |
| ECC | excitation-contraction-coupling |
| ANS | autonomic nervous system |
| NEP | norepinephrine |
| ACh | acetylcholine |
| EPI | epinephrine |

| | |
|---|---|
| cyclic GMP | cyclic-guanosine monophosphate |
| DD | diastolic depolarization |
| ICa,T | transient (T-type) current |
| ICa,L | long-lasting (L-type) $Ca^{2+}$ current |
| RyRs | ryanodine receptors |
| SR | sarcoplasmic reticulum |
| SERCA | sarco/endoplasmic reticulum $Ca^{2+}$-ATPase |
| CICR | calcium-induced calcium release |
| NCX | sodium-calcium exchanger |
| Cx | connexin |
| IKr and IKs | slow delayed rectifier potassium currents |
| Ito | transient outward potassium current |
| CCS | cardiac conduction system |
| HRV | heart rate variability |
| SNRT | Sinus node recovery time |
| SAD | sudden arrhythmic death |

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