The Classically Cardioprotective Agent Diazoxide Elicits Arrhythmias in Type 2 Diabetes Mellitus

Chaoqin Xie, MD, Jun Hu, PhD, Lukas J. Motloch, MD, PhD, Basil S. Karam, BS, Fadi G. Akar, PhD

ABSTRACT

BACKGROUND Type 2 diabetes mellitus (T2DM) is associated with an enhanced propensity for ventricular tachyarrhythmias (VTs) under conditions of metabolic demand. Activation of mitochondrial adenosine triphosphate-sensitive potassium (KATP) channels by low-dose diazoxide (DZX) improves hypoglycemia-related complications, metabolic function, and triglyceride and free fatty acid levels and reverses weight gain in T2DM.

OBJECTIVES In this study, we hypothesized that DZX prevents ischemia-mediated arrhythmias in T2DM via its putative cardioprotective and antidiabetic property.

METHODS Zucker obese diabetic fatty (ZO) rats (n = 43) with T2DM were studied. Controls consisted of Zucker lean (ZL; n = 13) and normal Sprague-Dawley (SprD; n = 30) rats. High-resolution optical action potential mapping was performed before and during challenge with no-flow ischemia for 12 min.

RESULTS Electrophysiological properties were relatively stable in T2DM hearts at baseline. In contrast, ischemia uncovered major differences between groups, because action potential duration (APD) in T2DM failed to undergo progressive adaptation to ischemic challenge. DZX promoted the incidence of arrhythmias, because all DZX-treated T2DM hearts exhibited ischemia-induced VTs that persisted on reperfusion. In contrast, untreated T2DM and controls did not exhibit VT during ischemia. Unlike DZX, pinacidil promoted ischemia-mediated arrhythmias in both control and T2DM hearts. Rapid and spatially heterogeneous shortening of APD preceded the onset of arrhythmias in T2DM. DZX-mediated proarrhythmia in T2DM was not related to changes in the messenger ribonucleic acid expression of Kir6.1, Kir6.2, SUR1A, SUR1B, SUR2A, SUR2B, or ROMK (renal outer medullary potassium channel).

CONCLUSIONS Ischemia uncovers a paradoxical resistance of T2DM hearts to APD adaptation. DZX reverses this property, resulting in rapid and heterogeneous APD shortening. This promotes reentrant VT during ischemia. DZX should be avoided in diabetic patients at risk of ischemic events. (J Am Coll Cardiol 2015;66:1144–56) © 2015 by the American College of Cardiology Foundation.
beta cell rest and inhibition of apoptosis (5). These mechanistic studies in animal models are being rapidly translated to humans. In a proof-of-principle trial, healthy people who received oral DZX (4 mg/kg) exhibited a 30% decrease in glucose production, with no difference in the rate of glucose uptake compared with placebo-treated counterparts (6). Moreover, DZX reversed weight gain in prediabetic obese, hyperinsulinemic people (7,8). The therapeutic utility of DZX was also tested in patients with type 1 diabetes mellitus (T1DM) (9) and in those undergoing coronary bypass surgery (10). Radtke et al. (9) reported that treatment of newly diagnosed T1DM patients with DZX for 6 months improved their glycemic control without affecting their beta cell function. Finally, in a double-blinded randomized study, supplementation of cardioplegia with low-dose DZX protected cardiac mitochondria, metabolism, and function in patients undergoing cardiopulmonary bypass surgery (10).

These highly encouraging clinical findings likely stem from the activation of cardioprotective signaling via mitochondrial adenosine triphosphate-sensitive potassium (mKATP) channels by DZX (11-19). However, at high concentrations (300 μmol/l), DZX was shown to promote arrhythmias in coronary-perfused atria and ventricles from failing and nonfailing human hearts by activating sarcopenal (as opposed to mitochondrial) KATP channels (20).

We hypothesized that owing to its dual nature as an antidiabetic and cardioprotective agent, low-dose (30 μmol/l) DZX may be particularly useful in suppressing ischemia-related arrhythmias in T2DM without altering basal electrophysiology. Contrary to our original hypothesis, we uncovered a potent proarrhythmic effect of DZX exclusively in T2DM hearts during challenge with ischemia. Our findings raise major concerns regarding the safety profile of mKATP channel activation in T2DM patients at risk of ischemic injury.

**METHODS**

**EXPERIMENTAL RAT MODEL OF T2DM.** All procedures involving animal handling were approved by the Animal Care and Use Committee of the Icahn School of Medicine at Mount Sinai and adhered to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health. All animals were purchased from the Charles River Laboratory (Wilmington, Massachusetts). We used 12- to 16-week-old male Zucker obese diabetic fatty (fa/fa) rats (ZO) (n = 43) as a standard model of established insulin resistance and T2DM. This model faithfully recapitulates hallmark features of the clinical disease, including hyperinsulinemia, dyslipidemia, and hyperglycemia (21). Age- and sex-matched Zucker lean (ZL) (n = 13) and normal Sprague-Dawley (SprD) (n = 30) rats were also used. In a subset of experiments involving 6 ZL and 7 SprD rats, we found no significant differences in electrophysiological parameters, including action potential duration at 50%, 75% (APD75), and 90% of repolarization and conduction velocity (CV). Marked hyperglycemia and weight gain in the absence of hypertrophy were confirmed in T2DM compared with control rats (Table 1).

**OPTICAL ACTION POTENTIAL MAPPING OF EX VIVO PERFUSED HEARTS.** Hearts were excised rapidly and Langendorff perfused with Tyrode’s solution containing 121.7 mmol/l NaCl, 25.0 mmol/l NaHCO3, 2.74 mmol/l MgSO4, 4.81 mmol/l KCl, 5.0 mmol/l dextrose, and 2.5 mmol/l CaCl2 (pH 7.40; 95% O2/5% CO2) with Tyrode’s solution. Preparations were immersed in the coronary effluent and maintained at a physiological temperature by a heat exchanger assembly (22). Cardiac rhythm was monitored continuously via silver electrodes connected to an electrocardiogram amplifier. Cardiac rhythm, perfusion pressure, and flow were monitored continuously during each experiment.

**TABLE 1** Average BW, HW, Ratio of BW to HW, and Blood Glucose Levels of T2DM and Control Animals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T2DM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (g)</td>
<td>410 ± 65</td>
<td>283 ± 29</td>
</tr>
<tr>
<td>HW (g)</td>
<td>1.6 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>BW/BW, mg/g</td>
<td>3.9 ± 0.3</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>408 ± 119</td>
<td>128 ± 14</td>
</tr>
<tr>
<td>Age, weeks</td>
<td>13-15</td>
<td>13-14</td>
</tr>
</tbody>
</table>

BW = body weight; HW = heart weight; T2DM = type 2 diabetes mellitus.
Optical action potentials were measured with an 80 × 80-pixel charge-coupled device camera coupled to an imaging macroscope that contained a high numerical aperture lens, a dichroic mirror, excitation and emission filters, a beam splitter, and a light-collimating tube. Excitation light was provided by a low-noise, high-power tungsten-halogen lamp and directed in an epifluorescence configuration onto the heart through a side port of the macroscope in a manner that minimized heterogeneity of incident light across the mapped 8 × 8 mm² region. Emitted light was collected by the front lens of the macroscope, filtered, and directed onto the charge-coupled device detector. High-resolution optical action potentials were measured simultaneously from 6,400 sites during each recording. To improve signal quality, spatial binning was performed, which yielded an array of 400 (20 × 20) high-fidelity optical action potentials that were amenable to accurate automated analyses.

**EXPERIMENTAL PROTOCOL.** Hearts from control (SprD, ZL) and T2DM (ZO) rats underwent steady-state pacing at a wide range of pacing cycle lengths (PCLs) (300 to 100 ms, in 20-ms decrements) during baseline perfusion. Subsequently, hearts underwent ischemia-reperfusion injury while being paced at a PCL of 300 ms. We chose a 12-min global no-flow ischemia challenge because we found in a pilot study that this protocol gave rise to sustained post-ischemic arrhythmias within 1 min of reperfusion in ~50% of hearts. This rate of post-ischemic arrhythmias allows one to examine whether a given drug decreases or increases the incidence of arrhythmias. Untreated hearts were perfused with normal Tyrode's solution throughout the entire protocol, except for the 12-min ischemia phase. DZX-treated hearts were initially perfused with normal Tyrode's solution, followed by Tyrode's containing DZX 30 μmol/l.

**ELECTROPHYSIOLOGICAL MEASUREMENTS. Conduction velocity.** As detailed previously (23,24), conduction delays were assessed by recording action potentials during steady-state pacing. Local activation time at each site was defined as the maximum first derivative during the upstroke of the action potential. Velocity vectors (magnitude and direction) were derived from the activation times of each pixel relative to those of its neighbors. CV was measured by averaging the magnitude of the velocity vectors along the longitudinal and transverse axes. The anisotropic ratio was defined as the ratio of fast (longitudinal) divided by slow (transverse) CV.

**Action potential duration.** Repolarization times at 75% and 90% relative to the action potential amplitude were quantified. Action potential duration (APD) was defined as the temporal difference between the repolarization and activation times at each site.

**REAL-TIME POLYMERASE CHAIN REACTION MEASUREMENTS.** Tissue specimens from SprD (n = 3), ZL (n = 3), and ZO (n = 3) hearts were used to measure messenger ribonucleic acid (mRNA) expression levels of the alpha (Kir6.1, Kir6.2) and beta (SUR1A, SUR1B, SUR2A, SUR2B) subunits that constitute the K_ATP channel, as well as the 2 cardiac isoforms of the renal outer medullary potassium channel (ROMK1 and ROMK2). Total ribonucleic acid was extracted by acid guanidinium thiocyanate-phenol-chloroform using TRIzol reagent (Life Technologies, Carlsbad, California). One microgram of total ribonucleic acid was reverse transcribed into first-strand complementary deoxyribonucleic acid by use of a high-capacity complementary deoxyribonucleic acid reverse transcription kit with ribonuclease inhibitor. Real-time polymerase chain reactions (PCR) were performed with the Applied Biosystems 7500 system and Power SYBR Green PCR Master Mix (Applied Biosystems, Waltham Massachusetts) in triplicate. High-resolution melting curves were generated to confirm the specificity of PCR products. Threshold cycle (C_t) values were determined after rectification by the passive reference dye Rox within the master mix. mRNA expression levels were evaluated by the 2⁻ΔΔCt method. Levels of K_ATP channel subunits were normalized to those of the internal control, beta-actin.

**STATISTICAL ANALYSES.** Summary data are presented as mean ± SD. Welch’s unpaired t test was used to detect differences in blood glucose levels between T2DM and controls. The Student t test was used to compare electrophysiological parameters between T2DM and control hearts. The paired t test was used to compare groups before and after drug treatment. One-way analysis of variance was used to compare differences between more than 2 groups. A Fisher exact test was used to compare differences in susceptibility to arrhythmias. Differences were considered significant at p < 0.05.
No significant differences ($p = 0.65$) in APD$_{75}$ were found between ZL (46.1 ± 7.0 ms) and SprD (47.9 ± 3.0 ms) hearts. APD heterogeneity indexed by the range and standard deviation of APD$_{75}$ values over an 8 × 8 mm$^2$ region of each heart revealed no significant differences between T2DM and controls for either metric (Figure 1C).

Figure 1D shows representative isochrone maps depicting the elliptical spread of the action potential wave front across the epicardium in control and T2DM hearts. There were no significant differences in longitudinal CV ($p = 0.205$), transverse CV ($p = 0.156$), or their ratio ($p = 0.13$) between T2DM and control hearts (Figure 1E). Finally, programmed electrical stimulation with single premature stimuli (S2) was performed in a subset of 4 ZO hearts. S2 coupling intervals were initially varied in 10-ms decrements, followed by 2-ms increments to resolve local refractoriness. No arrhythmias were observed when this protocol was used (not shown).

**ELECTROPHYSIOLOGICAL RESPONSE OF T2DM HEARTS TO ISCHEMIA.** Patients with T2DM are highly susceptible to ischemic injury. We therefore tested whether ischemia-mediated electrophysiological remodeling...
was more severe in hearts from T2DM rats compared with control animals. Figures 2A and 2B show representative action potential traces and APD contour maps measured from control (SprD, ZL) and T2DM (ZO) hearts before and 12 min after no-flow ischemia. As expected, no-flow ischemia resulted in significant APD shortening in hearts from control animals (Figures 2A to 2C). In sharp contrast, hearts from T2DM animals did not undergo progressive APD adaptation in response to an identical ischemic challenge (Figures 2A to 2C). Instead, they exhibited a biphasic response, because early APD shortening was fully reversed during the latter phase (9 to 12 min) of ischemia (Figure 2D).

We next investigated potential differences in ischemia-mediated conduction slowing between groups. Figure 3A shows isopotential contour maps recorded at 1-ms intervals before (baseline) and 12 min after ischemia in control (SprD, ZL), and T2DM (ZO) hearts. Figure 3B shows representative action potential upstrokes (first derivatives) measured from equidistant sites. Figure 3C presents average CV during baseline perfusion and after ischemic challenge. As expected, ischemia resulted in significant CV slowing in all groups. Interestingly, a trend toward a greater percentage reduction of CV by ischemia was noted for T2DM rats than for controls (Figure 3D); however, this trend did not reach statistical significance (p = 0.243).
Finally, after the 12-min ischemia protocol, 4 of 9 control and 3 of 5 T2DM hearts underwent sustained arrhythmias within 1 min of reperfusion (not shown).

**DZX PARADOXICALLY PROMOTES ARRHYTHMIAS IN T2DM.** The main purpose of our study was to determine whether low-dose DZX, which improves metabolic function in experimental models and in humans, would prevent arrhythmias in T2DM. We therefore examined its effects on key electrophysiological properties before and during challenge of T2DM hearts with ischemia.

**Figure 4A** shows the average APD$_{75}$ rate relationships in untreated and DZX-treated T2DM hearts during baseline perfusion. Clearly, DZX 30 μmol/l did not alter baseline APD values at any PCL (**Figure 4A**), which discounts a role for nonischemic activation of sarcolemmal K$_{ATP}$ channels.

We next investigated potential differences in the response of untreated and DZX-treated T2DM hearts to ischemia. Although APD$_{75}$ of untreated T2DM hearts failed to shorten progressively in response to ischemia (**Figure 4B**), DZX treatment caused rapid and sustained APD shortening during the course of ischemia (**Figure 4B**). On average, APD$_{75}$ of DZX-treated T2DM hearts was shorter by 32.6% (p < 0.01) after 6 min of ischemia compared with their untreated counterparts (**Figure 4B**).

The heightened sensitivity of DZX-treated T2DM hearts to ischemia-induced APD shortening was likely significant, because all 7 DZX-treated but none of the 5 untreated T2DM hearts exhibited onset of sustained arrhythmias.
ventricular tachyarrhythmia (VT) during the latter phase (10 to 12 min) of ischemia (Figure 4C). Moreover, none of the 9 untreated or 7 DZX-treated control hearts exhibited VT during ischemia (Figure 4C). As such, DZX provoked VT exclusively in T2DM hearts (Figure 4C).

Figure 4D shows individual measurements of APD75, either before the onset of VT in DZX-treated T2DM hearts or at the end of the 12-min ischemic challenge in untreated T2DM hearts. In all cases, APD75 of untreated T2DM hearts was longer after 12 min of ischemia than that of DZX-treated T2DM hearts, which underwent a 26% to 56% reduction before the onset of VT.

We investigated the potential mechanism underlying the selective proarrhythmic effect of DZX on T2DM hearts. Whereas on average, DZX-treated T2DM hearts exhibited a minor trend toward longer APD75 values during ischemia than DZX-treated controls, differences were not statistically significant (Figure 5A). In contrast, APD heterogeneity, as indexed by the standard deviation and range of APD75 values across the mapping field, was more than 2-fold greater in DZX-treated T2DM than in control hearts at 8 and 10 min of ischemia (Figure 5A). Figure 5B shows representative APD contour maps that illustrate the greater APD heterogeneity at 8 min of ischemia in DZX-treated T2DM than in control hearts. Figure 5C shows representative histograms that illustrate the wider distribution of APD75 values in individual DZX-treated T2DM hearts than in their control counterparts.
We next compared the electrophysiological effects of DZX with those of the classic SUR2A activator pinacidil. Unlike DZX, which did not affect baseline APD75 in either group, pinacidil 100 μmol/l caused significant APD75 shortening in T2DM hearts (p = 0.047) and a strong trend toward shorter levels in controls (p = 0.069) during baseline perfusion (Figure 6A). Pinacidil also promoted the rapid (within 6 to 7 min) onset of VT during ischemia in both control and T2DM hearts (Figure 6B), whereas DZX only exerted a proarrhythmic effect in T2DM (Figure 5). Profound action potential shortening was evident by 5 min of ischemia in pinacidil-treated control and T2DM hearts (Figure 5C).

**EXPRESSION OF K$_{ATP}$ CHANNEL SUBUNITS.** To determine whether the proarrhythmic effect of DZX in T2DM hearts was related to altered expression of K$_{ATP}$ channels, we measured the mRNA expression...
levels of all known K\textsubscript{ATP} channel subunits using real-time PCR. Figure 7A shows the normalized (to beta-actin) mRNA expression of the alpha (Kir6.1 and Kir6.2) and beta (SUR1A, SUR1B, SUR2A, and SUR2B) subunits of the K\textsubscript{ATP} channel in SprD, ZL, and ZO hearts. We found that samples from ZL and ZO animals exhibited a trend toward increased expression of most K\textsubscript{ATP} channel subunits compared with their SprD counterparts (Figure 7A); however, this apparent up-regulation only reached statistical significance in the case of SUR2B between ZO and SprD animals (Figure 7A). Importantly, there were no significant differences in the expression of any of these subunits between ZL and ZO hearts (Figure 7A). As such, none of the observed changes could explain the proarrhythmic effect that was exclusive to ZO animals.

A recent study highlighted the potential importance of ROMK (KCNJ1) in formation of the mK\textsubscript{ATP} channel (27). We therefore measured the mRNA levels of the 2 ROMK isoforms (ROMK1 and ROMK2) that are expressed in the heart. We found no significant differences in the expression levels of either isoform between groups (Figure 7B). Primers used for mRNA measurements are shown in Figure 7C.

**DISCUSSION**

We investigated the electrophysiological consequences of ischemia in T2DM and tested whether low-dose DZX, a potent activator of cardioprotective signaling (11–19), could improve electrical function in that setting. Our major findings were as follows: 1) during normoxic perfusion, T2DM hearts are stable, exhibiting only minor electrophysiological changes; 2) in response to ischemia, T2DM hearts are characterized by repolarization resistance, because their average APD fails to exhibit progressive shortening; 3) DZX treatment exacerbates arrhythmias exclusively in T2DM hearts by promoting rapid and heterogeneous APD shortening during ischemia.

(A) Average APD\textsubscript{75} values for control (n = 4) and T2DM (n = 4) hearts before and after treatment with DZX (30 \textmu mol/l) or pinacidil (100 \textmu mol/l). (B) Summary of VT propensity during ischemia in untreated and pinacidil-treated control and T2DM hearts. Arrhythmogenesis during early ischemia was provoked by pinacidil treatment in both control and T2DM hearts. (C) Representative action potential traces revealing profound action potential shortening at 5 min of ischemia in pinacidil-treated control and T2DM hearts. PIN = pinacidil; other abbreviations as in Figures 1 and 3.
and 4) changes in the mRNA expression of $K_{ATP}$ channel subunits do not cause these phenotypic differences.

**STABILITY OF BASAL ELECTROPHYSIOLOGICAL PROPERTIES IN T2DM.** Our initial objective was to define the electrophysiological substrate of hearts from obese T2DM animals. We focused on conduction slowing and APD prolongation as potentially important features of pathological electrical remodeling. Surprisingly, we found only modest changes in APD and CV in this established model of obesity and T2DM. As such, our present findings discount a major role for these basal electrophysiological properties in the proarrhythmic vulnerability of the diabetic heart. Our present findings are reminiscent of our previous findings in a guinea pig model of streptozotocin-induced T1DM, in which arrhythmias were only encountered on depletion of the scavenging capacity of the heart (28).

**ALTED APD ADAPTATION DURING ISCHEMIA: REPOLARIZATION RESISTANCE IN T2DM?** Because patients with T2DM are highly susceptible to the complications of coronary artery disease, we speculated that acute ischemia might unmask the electrophysiological vulnerability of these hearts. A major finding of the present report was the failure of T2DM hearts to exhibit progressive APD adaptation (shortening) in response to 12 min of no-flow ischemia. The mechanism underlying this repolarization resistance will require additional investigation, although it suggests down-regulation of sarcolemmal $K_{ATP}$ channels, resulting from either reduced expression or function of these channels. Interestingly, Ren et al. (29) found a marked reduction in SUR2A mRNA expression in a model of T1DM. We measured the transcript levels of all known alpha and beta subunits of $K_{ATP}$ channels, including Kir6.1, Kir6.2, SUR1A, SUR1B, SUR2A, SUR2B, ROMK1, and ROMK2. An important advantage of our experimental design was the use of 2 different control groups that were functionally identical but genetically distinct. Specifically, ZL controls share a common genetic background with their ZO counterparts but are functionally identical (in terms of electrophysiology, heart weight, body weight, and blood glucose levels) to age-matched SprD animals. By measuring changes in

![Figure 7](image-url)
the mRNA expression of K<sub>ATP</sub> channel subunits in all 3 groups, we were able to determine whether a given change was functionally important. Surprisingly, we only found a significant change in the expression of SUR2B between ZO and SprD animals. Therefore, our data indicate that the unique functional response of T2DM hearts to ischemia is unrelated to the transcript levels of K<sub>ATP</sub> channel subunits. This suggests involvement of post-transcriptional mechanisms that regulate protein synthesis, trafficking, insertion, stability, or gating of these channels. Of note, AMP-activated protein kinase (AMPK) signaling has been implicated in preconditioning-induced shortening of the action potential through effects on K<sub>ATP</sub> channel activity and recruitment (30). Moreover, drugs that activate AMPK signaling are a mainstay of treatment of T2DM patients (31). Impaired AMPK in T2DM may contribute to repolarization resistance. Clearly, identification of the exact molecular mechanisms underlying impaired APD adaptation of T2DM hearts to ischemia warrants investigation.

**DZX FOR TREATMENT OF DIABETES MELLITUS.** In a recent clinical study, DZX suppressed endogenous glucose production (6). The presumed antidiabetic efficacy of DZX has been linked to preservation of pancreatic beta cells through promotion of beta cell rest and inhibition of apoptosis. Indeed, pilot clinical trials using DZX have demonstrated improvement of metabolic function in pre-diabetic obese, hyperinsulinemic patients and in those with T1DM (7–9).

Numerous experimental studies have established DZX as a potent cardioprotective agent that reduces reperfusion injury by promoting activation of beneficial mitochondrial pathways (11–19). Indeed, a pilot study demonstrated that supplementation of cardioplegia with DZX improved the outcome of patients undergoing coronary bypass surgery (10); however, the infarct-sparing efficacy of DZX in diabetes is less

---

The proarrhythmic effect of mitochondrial adenosine triphosphate-sensitive potassium (mK<sub>ATP</sub>) channel activation by low-dose diazoxide (DZX) in hearts from rats with type 2 diabetes mellitus (T2DM) is illustrated. Electrophysiological properties were stable at baseline but revealed impaired adaptation to increased metabolic demand during acute ischemia in diabetic (red) compared with nondiabetic (blue) rats. The classically cardioprotective agent DZX caused paradoxical exacerbation of arrhythmias in diabetic but not normal animals, owing to a rapid and spatially heterogeneous shortening of action potentials across the heart, which in turn, created a substrate for reentrant ventricular tachyarrhythmia. APD = action potential duration; APD<sub>75</sub> = action potential duration at 75% of repolarization.
clear, because DZX failed to reduce infarct size after 30 min of left anterior descending coronary artery occlusion in T2DM animals (32). This is consistent with the notion that cardioprotective stimuli (such as ischemic preconditioning), which likely depend on mKATP channels, are defective in diabetes (33).

Although the infarct-sparing effects of DZX have been widely studied, there are no reports of its role in the modulation of electrophysiological properties of T2DM hearts. A major finding of the present report was that DZX elicited a potent proarrhythmic effect exclusively in the setting of diabetes, because all DZX-treated T2DM hearts but none of the untreated T2DM or control hearts exhibited sustained ischemia-mediated VT. We used a widely accepted DZX concentration (30 μmol/l) that is relatively specific for the mitochondrial pool of KATP channels (15–19). At this concentration, DZX did not alter basal electrophysiological properties. The lack of effect of low-dose DZX on baseline APD strongly discounts a role for nonselective activation of sarcolemmal KATP channels in the proarrhythmic effect that we uncovered. Unlike DZX, the classic SUR2A-specific KATP channel activator, pinacidil, provoked ischemia-mediated VT in all hearts (T2DM and control), consistent with previous findings in failing and nonfailing human heart preparations (20). Finally, the lack of arrhythmia protection by DZX in T2DM hearts on ischemic challenge is consistent with the lack of protection against myocardial infarction by ischemic preconditioning and DZX (33).

CONCLUSIONS

Our current study raises important safety concerns regarding the use of DZX in diabetic patients (Central Illustration). Specifically, a potent proarrhythmic effect during ischemic challenge should caution against the rapid translation of DZX-based therapies for the treatment of T2DM patients, who are indeed at high risk of coronary artery disease, acute myocardial infarction, and silent myocardial ischemia (4,34–36).

REFERENCES

13. Sato T, Sasaki N, Seharsayen J, O’Rourke B, Mrábl E. Selective pharmacological agents implicate mitochondrial but not sarcolemmal KATP...