JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 1, 2021

EDITORIAL COMMENT

Is IL-1 the Bridge Connecting Type 2 Diabetes and Cardiac Arrhythmias?*

Lisa Stoll, PhD, James C. Lo, MD, PhD

A growing diabetes pandemic is unfolding worldwide, with a relentless increase in people affected by both type 1 and type 2 diabetes. It is currently estimated that already 10.5% of the U.S. population is diabetic. Although type 1 diabetes is characterized by an autoimmune destruction of the beta cells, type 2 diabetes involves insulin resistance and a failure of the beta cells to produce sufficient amounts of insulin to maintain glucose homeostasis. Despite their different pathophysiology, both type 1 and type 2 diabetes have been associated with major adverse cardiovascular events. Aside from diabetes causing elevated rates of cardiovascular disease, diabetes also exacerbates the severity of arrhythmias. Diabetes has been linked to increased rates of sudden cardiac death in the general population, which is a consequence of arrhythmias as well as myocardial infarction (MI) (1,2). The cellular and molecular mechanisms linking diabetes to malignant arrhythmias and sudden cardiac death are still under investigation, with no specific antiarrhythmic treatments available for patients with diabetes. Many mechanisms have been postulated. Hyperglycemia for example can trigger oxidative stress, inflammation, and abnormal Ca^{2+} signaling in the cardiac myocytes.

In this issue of *JACC: Basic to Translational Science*, Liu et al. (3) investigate the effect of interleukin (IL)-1β, oxidative stress, and calcium handling on diabetic arrhythmia risk. The idea that IL-1β itself triggers inflammation and reactive oxygen species (ROS) generation in hearts has been shown in type 1 diabetic mice (4). In fact, IL-1β released by macrophages renders type 1 diabetic mice more vulnerable to the development of arrhythmias. In addition, it has been shown to be implicated in the development of heart failure. Besides IL-1β, other inflammatory proteins such as IL-6, nuclear factor-κB, and tumor necrosis factor-α have been shown to be involved in heart failure, arrhythmias, and oxidative stress in type 1 diabetes. However, the primary problem in type 1 diabetes is insulin deficiency, whereas insulin resistance and obesity are prominent features of type 2 diabetes. Thus, it was unknown if IL-1β might also play a critical role in arrhythmogenesis in the complex setting of type 2 diabetes. This question has now been addressed by Liu et al.

Liu et al. used a model of diet-induced obesity to mimic the milieu that the heart faces in the setting of type 2 diabetes. They observed that the diabetic mice displayed a prolonged QT interval as a consequence of a prolonged action potential duration. They described that increased cardiac IL-1β expression triggered a release of ROS from the mitochondria that in turn oxidized the RyR2 channel, which triggered sarcoplasmic reticulum Ca^{2+} leak, allowing for inducible ventricular tachycardia (VT) in half the study animals. In contrast, control nondiabetic mice showed no evidence of VT inducibility. IL-1 or mitochondrial ROS blockade substantially reduced inducible VT to near nondiabetic levels. These impressive findings may provide a new and unexpected therapeutic of blocking a cytokine for treatment of arrhythmias, blurring the distinction between anti-inflammatory and antiarrhythmic agents.

One of the major study outcomes used was VT inducibility. Although a convenient diagnostic tool to

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Weill Center for Metabolic Health, Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York, New York, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.12.003

utilize, it is artificial and may not reliably reflect spontaneous VT. If IL-1 blockade can decrease spontaneous ventricular ectopy or VT in animal models of type 2 diabetes, then this would further support potential clinical use. Liu et al. have shown that IL-1β is involved in the susceptibility of diabetic hearts to arrhythmia, but there are likely other important proarrhythmogenic mechanisms at play in the diabetic heart. In their paper, they did not observe any alteration in the potassium current, which is in contrast to previous studies in which diet-induced obesity results in QT prolongation as a consequence of a reduction of the potassium current mediated through protein kinase D (5). Whether this divergence is due to the heterogenous response to obesity or differences in the degree of obesity, composition of diets, or other factors remains to be determined. Besides changes in ion currents, it has previously been described that hearts of diabetic *db/db* mice display altered sympathetic nerve innervation, which can result in an increased susceptibility to arrhythmia (6). Might there be cross-talk between IL-1β and the sympathetic nervous system?

This study further opens the door to working out the connection between diabetes, inflammation, and dysrhythmia. One outstanding question will be if antagonizing IL-1β might be additive or synergistic with beta-blockers, which are commonly used in clinical practice. This question could not be addressed in the study because the IL-1 receptor antagonist nearly completely suppressed inducible VT. Ultimately, it remains to be seen if IL-1β could be targeted directly to decrease the arrhythmia risk associated in patients with diabetes. Several clinical studies were performed to assess the utility of IL-1 blockers anakinra and canakinumab in heart failure and post-MI. Although there were positive effects on cardiovascular outcomes in patients treated with IL-1 antagonists, severe side effects were observed. Drugs used to treat diabetes itself, such as SGLT2 (sodium-glucose cotransporter 2) inhibitors, decrease oxidative stress and fibrosis as well as action potential duration in type 2 diabetic mouse hearts, but they also result in episodes of hypoglycemia. This highlights the importance of developing a drug that lowers the risk of arrhythmia in patients with diabetes without increasing their risk of developing severe infection and hypoglycemia. Therefore, further studies are required to identify other key regulators that mediate the increased arrhythmia risk in diabetes.

AUTHOR DISCLOSURES

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. James C. Lo, Weill Center for Metabolic Health, Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Weill Cornell Medicine, 413 East 69th Street, New York, New York 10021, USA. E-mail: jlo@med.cornell.edu.

REFERENCES

1. Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. Heart Rhythm 2010;7:1396–403.

2. Lynge TH, Svane J, Pedersen-Bjergaard U, et al. Sudden cardiac death among persons with diabetes aged 1-49 years: a 10-year nationwide study of 14 294 deaths in Denmark. Eur Heart J 2020;41:2699–706.

3. Liu H, Zhao Y, Xie A, et al. Interleukin-1β, oxidative stress, and abnormal calcium handling mediate diabetic arrhythmic risk. J Am Coll Cardiol Basic Trans Science 2021;6:42–52.

4. Monnerat G, Alarcon ML, Vasconcellos LR, et al. Macrophage-dependent IL-1beta production induces cardiac arrhythmias in diabetic mice. Nat Commun 2016;7:13344.

5. Huang H, Amin V, Gurin M, et al. Diet-induced obesity causes long QT and reduces transcription of voltage-gated potassium channels. J Mol Cell Cardiol 2013;59:151–8.

6. Jungen C, Scherschel K, Flenner F, et al. Increased arrhythmia susceptibility in type 2 diabetic mice related to dysregulation of ventricular sympathetic innervation. Am J Physiol Heart Circ Physiol 2019;317:H1328–41.

KEY WORDS calcium handling, inflammation, mitochondria, oxidation, sudden cardiac death