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Even Silent Hypoglycemia Induces Cardiac Arrhythmias

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While many studies have shown that intensive glycemic control can prevent the microvascular complications of diabetes, the benefits of intensive glycemic control in preventing macrovascular complications, including heart attacks, strokes, and overall mortality, have been less clear. Intensive glycemic control almost always increases the frequency and severity of hypoglycemic episodes. What remains unclear is whether hypoglycemia directly contributes to, or is merely associated with, the increased mortality noted in recent large trials (e.g., Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation [NICE-SUGAR], Control of Hyperglycaemia in Paediatric intensive care [CHiP], Action to Control Cardiovascular Risk in Diabetes [ACCORD]) (1–3). In the intensive care setting, noniatrogenic hypoglycemia serves as a harbinger of mortality, but it is unlikely to be a direct cause of mortality (4). By contrast, in the outpatient setting, insulin-induced hypoglycemia can be lethal. Among people with diabetes, the mortality rate due to hypoglycemia has been reported to be as high as 10% (5). Indeed, insulin-induced hypoglycemia has been considered responsible for nocturnal deaths in diabetic patients (6), and has been documented to be associated with the "dead-in-bed" syndrome (7). Therefore in the outpatient setting, the microvascular benefits of intensive glycemic control in people with diabetes have to be weighed against the apparent increased mortality associated with iatrogenic hypoglycemia.

The mechanism(s) by which hypoglycemia may increase mortality remains unknown. In patients with cardiac disease, hypoglycemia has been associated with ischemic chest pain (8). Hypoglycemia also increases markers of thrombosis and inflammation, potentially increasing the risk of acute thrombotic events or accelerating development of atherosclerosis (9). Although hypoglycemia-associated fatal cardiac arrhythmias are understandably difficult to document, arrhythmic deaths were reported as a direct cause of mortality in the NICE-SUGAR trial (4). Furthermore, severe hypoglycemia was noted to increase the risk of arrhythmic death by 77% in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial (9). Whether contributing to the development of coronary artery disease or acutely inducing an ischemic or arrhythmic event, the nature and magnitude of the contribution of hypoglycemia to mortality in diabetes is unknown and almost certainly underestimated.

Iatrogenic hypoglycemia changes cardiac repolarization and induces arrhythmias in people with type 1 and type 2 diabetes (10–15). Recently, animal studies have highlighted examination of cardiac events during very severe hypoglycemia (10–15 mg/dL). Supporting the available clinical data, these animal studies demonstrated that if hypoglycemia is severe enough, cardiac arrhythmias (induced by the counterregulatory sympathoadrenal response) can be lethal (16). Unfortunately, there are few data examining hypoglycemia-induced arrhythmias among patients in the outpatient setting, making these findings difficult to translate to real-world situations.

In this issue, Chow et al. (17) address the question of hypoglycemia-induced arrhythmias in an observational study of patients with type 2 diabetes by simultaneously equipping subjects with outpatient Holter monitors and continuous interstitial glucose monitors (CGM). All patients had insulin-treated type 2 diabetes and a history of either cardiovascular disease or two cardiovascular risk factors. The CGM recordings showed that hypoglycemia (≤63 mg/dL) was common, occurring 6% of the time. The authors also observed that hypoglycemia was associated with possible ischemic changes (T-wave flattening), repolarization defects (increased QT intervals corrected for heart rate), and various cardiac arrhythmias, suggesting that these events could be interconnected. Like another CGM study (18), the vast majority of hypoglycemic episodes were asymptomatic and occurred at night. The authors' most striking data were the eightfold increase in bradycardia and fourfold increase in atrial ectopy during

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nocturnal hypoglycemia when compared with daytime hypoglycemia. Mechanistically, sleep has been shown to blunt the sympathoadrenal response to hypoglycemia (19), likely contributing to the longer duration and greater severity of nocturnal hypoglycemia. The authors propose that during the night and following a blunted sympathetic response to hypoglycemia, there may have been a disproportionate parasympathetic phase leading to bradyarrhythmias and ectopic pacemakers (Fig. 1). Unfortunately, without other biochemical or physiologic markers of sympathetic or parasympathetic activation or potassium levels the authors acknowledge difficultly in establishing causality for these arrhythmias. Clearly, there is a need for further research into the mechanisms mediating cardiac arrhythmias during spontaneous hypoglycemia.

Although current conclusions of Chow et al. are based on older patients with type 2 diabetes and known coronary artery disease (or risk factors), it is not unreasonable to assume that their findings may be widely applicable to people with insulin-treated diabetes. This idea has been suggested by other studies demonstrating arrhythmias and cardiac repolarization anomalies induced by hypoglycemia (10–15). Unfortunately, the small sample size of the current study precluded meaningful subgroup analyses in patients with hypoglycemia-associated autonomic failure, patients with cardiac autonomic neuropathy, or those treated with β-blockers. These subgroups would likely have had a blunted net sympathoadrenal response to hypoglycemia, which could have decreased the incidence of electrocardiogram anomalies (14,15). Blunting of the sympathoadrenal response to hypoglycemia by recurrent hypoglycemia or β-blockade therapy has been shown in animal studies to decrease the incidence of arrhythmias and increase the odds of surviving an episode of severe hypoglycemia (16). Perhaps an interventional study in diabetic patients should be considered in order to determine if cardiac-specific β_1-adrenergic blockade could decrease rates of hypoglycemia-associated arrhythmias, cardiovascular events, and associated mortality.

Despite its interesting findings, the clinical implications of Chow et al. (17) are not entirely clear. Although hypoglycemia was common, mostly asymptomatic, and often associated with arrhythmias, it was reassuring that there were no fatalities or adverse clinical outcomes associated with these "benign" hypoglycemia-induced arrhythmias (although the study size was small). Animal studies, however, show that similar benign cardiac arrhythmias (induced by moderate hypoglycemia) do progress to malignant fatal cardiac arrhythmias during severe hypoglycemia (16). Thus the authors' foreboding data makes the reader feel uncomfortable when pondering what might have happened if the levels of hypoglycemia had been more severe. Even in diabetic patients who may have a relatively blunted sympathoadrenal response,

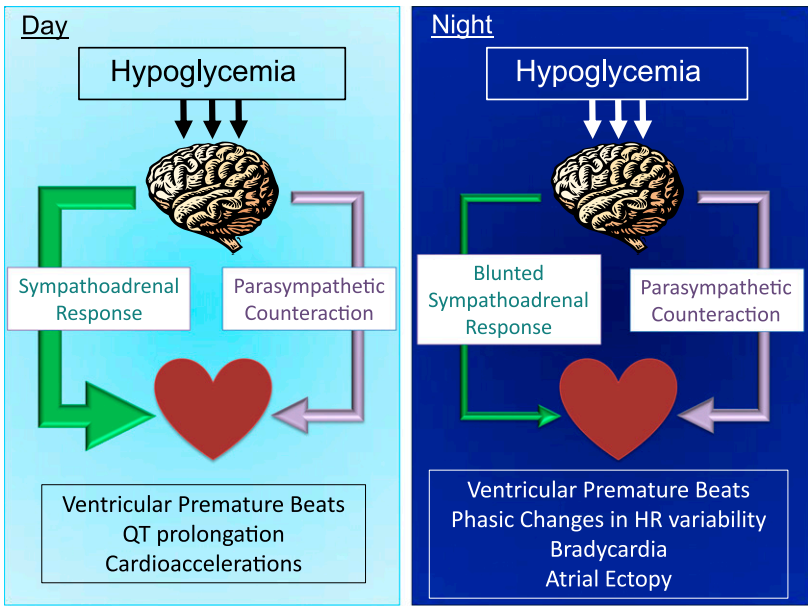

Figure 1—Proposed mechanisms of spontaneous hypoglycemia-induced arrhythmias both during the day (*left*) and night (*right*) in patients with type 2 diabetes either with cardiovascular disease or with two cardiovascular risk factors. Hypoglycemia was associated with increased ventricular premature beats during the day and night, but they were more frequent during nocturnal hypoglycemia. During the day, the dominant sympathoadrenal response to hypoglycemia was associated with QT segment prolongation and cardioaccelerations. During nocturnal hypoglycemia, different phases of heart rate (HR) variability indicated that the initial sympathetic response to hypoglycemia was followed by a parasympathetic (vagal) response. Bradycardia and atrial ectopic arrhythmias were (eightfold and fourfold, respectively) more common during nighttime hypoglycemia, likely due to blunted nocturnal sympathoadrenal response and relatively increased parasympathetic activity. Thus hypoglycemia, though frequently asymptomatic, increases the risk of arrhythmias in patients with type 2 diabetes.

an episode of severe hypoglycemia can still induce a marked rise in catecholamines that could potentially lead to an adverse cardiac outcome.

Studies that assess both fatal and nonfatal arrhythmias attributable to hypoglycemia will help us better understand, and hopefully prevent, this potentially catastrophic side effect of insulin therapy (4,9). Fortunately, hypoglycemia is only rarely fatal. Nonetheless, given the relatively high incidence of hypoglycemia and associated cardiac arrhythmias in patients observed in this study (17), along with the increased mortality seen in the ACCORD study (3), one take-home message for patients and health care providers is that target glycemic goals should be individualized and adjusted to avoid severe hypoglycemia and potentially fatal hypoglycemia-induced arrhythmias.

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