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Hyperglycemia and Adverse Outcomes in Acute Coronary Syndromes: Is Serum Glucose the Provocateur or Innocent Bystander?

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Hyperglycemia at the time of hospital admission predicts increased mortality in patients with acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction (STEMI) (1–6), revascularization procedures such as thrombolysis or percutaneous coronary intervention (PCI) (7–10), and other critical illnesses (11–13). The relationship between blood glucose and mortality appears linear with escalating risk associated with increasing blood glucose levels and is independent of a diagnosis of diabetes (14). However, there is ongoing debate as to whether hyperglycemia directly contributes to the adverse outcomes or whether it is simply a marker of higher risk.

There are three main hypotheses as to why hyperglycemia portends higher mortality in acutely ill patients (overview shown in Fig. 1). First, elevated blood glucose can be a physiologic response to hormones, such as epinephrine or cortisol, that are released under high systemic stress and, hence, may indicate greater overall illness severity (15). For example, those subjects with larger areas of myocardial ischemia and more impaired left ventricular function may have stronger sympathetic activation, leading to higher glucose levels. Second, hyperglycemia may be an indicator of systemic and organ-specific metabolic dysregulation, especially impaired insulin signaling. In this regard, insulin resistance causes not only hyperglycemia but also may lead to a reduction in energy production in the heart and other organs, producing a lower tolerance to hypoperfusion. In a similar vein, reduced insulin signaling may increase vulnerability to ischemic injury because downstream molecules in the insulin-signaling cascade have well-established cytoprotective effects and these are lost when insulin-signaling pathways are disrupted (16,17). Third, acute hyperglycemia is implicated in the activation of other pathologic processes that could contribute to cellular and tissue injury, such as increasing free radial formation and oxidative stress, inducing of a prothrombotic state, and worsening endothelial function (18–21).

Most clinical studies addressing the impact of hyperglycemia in critically ill cardiac patients are correlative in nature and cannot distinguish between the above mechanisms. Older studies in ACS patients used metabolic interventions intended to increase cellular energy production from glycolysis by infusing solutions containing glucose, insulin, and potassium (also known as GIK) (22–24). These studies met with very limited success. Based on the apparent lack of efficacy, the strategy of enhancing energy production through glycolysis has largely been abandoned in the modern era. Subsequently, a number of studies attempted to improve patient outcomes by directly lowering blood glucose levels with goal-directed insulin treatment (25–27). Overall, these studies did not produce relevant improvements in survival or other major clinical end points, although they may be criticized for generally failing to produce normalization of blood glucose. Enthusiasm for this approach has also waned. More recently, there has been increasing interest in GLP-1, a member of a novel class of intestinally secreted hormones known as incretins. These hormones are thought to lower blood glucose by stimulating insulin secretion by pancreatic β-cells, slowing intestinal absorption of nutrients and increasing satiety (28). Incretins are believed to have other beneficial effects, such as enhancement of endothelial function and mobilization of progenitor cells, that could potentially attenuate ischemic damage

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COMMENTARY

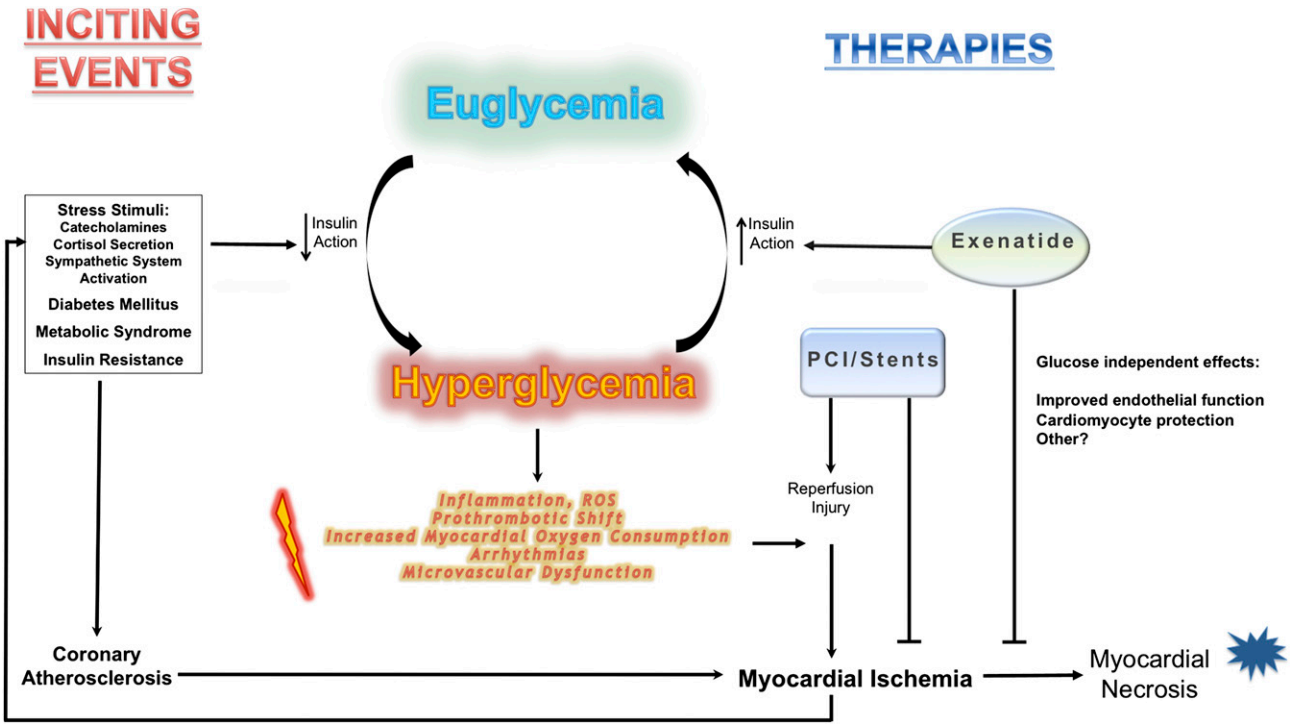

Figure 1—Summary of hypothetical relationship(s) between hyperglycemia and adverse outcomes in patients with ACS and posited mechanisms of the beneficial effects of exenatide.

(29,30). Longer-lasting analogs of these naturally occurring hormones, including a compound called exenatide, are currently being evaluated as a treatment for type 2 diabetes and other conditions, with some trials focusing on cardiovascular end points (31).

A major question still facing cardiovascular clinicians is whether pharmacologic manipulation of blood glucose levels or cellular metabolic signaling pathways has benefits in patients with ischemic events, particularly when done in conjunction with modern coronary reperfusion techniques. Reperfusion of a totally occluded coronary artery is mandatory for saving myocardium in the ischemic territory. PCIs are very effective for this purpose. However, acute reoxygenation of ischemic tissue following PCI may cause a large spike in free radical formation, inducing a reperfusion injury that irreversibly damages myocardium that otherwise might have been salvaged. An appealing tactic for further limiting cardiac injury would be to combine timely reperfusion with another intervention that could reduce the portion of injury related to reoxygenation. This was the design used in a trial reported by Lønborg et al. (32) in this issue of *Diabetes*. Two significant obstacles impact the ability to test new approaches for reducing ischemia reperfusion injury in the heart. First, it is difficult to accurately distinguish the components of injury that result from ischemia versus those that are related to reperfusion. Second, discriminating between greater tissue damage that simply parallels larger ischemic territories and that which is due to less efficient myocardial salvage may be vexing. Measuring serum biomarkers of cardiomyocyte necrosis, such as creatine kinase MB or cardiac-specific troponin isoform, cannot resolve these different components. Recent advances in cardiac magnetic resonance imaging (cMRI) allow quantitative noninvasive assessment of ischemic territories (area at risk) and final infarct size (33). Newer MRI sequences can delineate edematous tissue (area at risk) using T2-weighted imaging acutely and scar tissue (final infarct size) using late gadolinium enhancement. Combining these imaging sequences and the well-known high-resolution MRI images that allow reproducible measures of left ventricular size and function brings new opportunities to define myocardial salvage (e.g., the difference between the area at risk and the final infarct size divided by the area at risk) and to better assess outcomes of cardioprotective treatment strategies in patients with ACS.

Based on prior cMRI studies with an aggregated number of 611 ACS patients, three main findings have emerged (34–36). First, admission hyperglycemia is associated with larger infarct size in both diabetic and nondiabetic cohorts, and the relationship is stronger in nondiabetic patients when compared with patients with diabetes. Second, hyperglycemia is associated with a greater degree of microvascular obstruction in both diabetic and nondiabetic cohorts, though the association is more evident in diabetic compared with nondiabetic patients. Third, hyperglycemia is associated with depressed left

ventricular ejection fraction regardless of diabetes status. Importantly, the definitions of "stress hyperglycemia" vary somewhat from article to article, and the presence of this acute laboratory finding does not necessarily equate with a diagnosis of diabetes.

Lønborg et al. now report a post hoc analysis from a previously reported randomized clinical trial using exenatide or placebo given intravenously 15 min before and continued for 6 h after PCI in patients with STEMI (32,37). They assessed the relationship between admission hyperglycemia (defined as blood glucose 149 mg/dL in patients without known diabetes and 231 mg/dL in patients with diabetes) and area at risk, infarct size, and myocardial salvage index using a combination of T2-weighted imaging done 1 to 7 days post infarction and late gadolinium enhancement performed approximately 3 months after infarction. Of the 387 randomized patients, only 210 with measurements of infarct size and 185 with data for area at risk were included in this analysis. The main goals of the study were to determine *1*) the association between hyperglycemia on admission and area at risk and myocardial salvage index and *2*) the interaction between glycemic status on admission and the cardioprotective effect of exenatide. This study, like its predecessors, showed that hyperglycemia was associated with larger area at risk and infarct size. However, the novel finding was that hyperglycemia failed to independently predict infarct size or salvage index after adjustment for area at risk in the multivariable analysis. These findings support the hypothesis that hyperglycemia is more likely a proxy for larger ischemic territory, rather than a direct mediator of ischemic or reperfusion injury. The authors previously reported that exenatide was an effective cardioprotection agent, as indicated by an increase in myocardial salvage index and a reduction in infarct size in those receiving exenatide and by having shorter door to balloon times (37,38). The beneficial effect of exenatide was independent of whether or not patients had hyperglycemia, an observation forming the basis for the authors' argument that hyperglycemia may be a distractor for other more relevant therapeutic targets.

The findings from the study by Lønborg et al. (32) offer some of the best mechanistic insights obtained so far into the significance of hyperglycemia during ACS in humans. If these results are repeatable and correct, perhaps we can now answer the conundrum posed at the beginning of this commentary. It is likely that hyperglycemia in the ACS setting is mainly a marker of a larger ischemic burden, and hence the innocent bystander rather than the provocateur. This may explain why the majority of trials using insulin as a means of achieving better glycemic control during ACS have failed to show significant clinical benefits. Future studies may be better served by exploring other therapeutic interventions that play a more direct role in cardioprotection during and after coronary reperfusion. Incretin-based therapies appear to hold significant promise.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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