Variation in Glycemia in Patients Hospitalized With Acute Myocardial Infarction. Is It Time for Glucose Monitoring?

Mikhail Kosiborod

Mid America Heart Institute of Saint Luke's Hospital and University of Missouri-Kansas City, Kansas City, Missouri, United States

The initial observation that elevated glucose occurs commonly in patients with acute myocardial infarction (AMI) was made many decades ago.[1] Numerous studies have since definitively established that hyperglycemia is highly prevalent and associated with increased risk of death and in-hospital complications in patients with AMI, particularly in those without established diabetes.[2-4] Moreover, observational data show that persistently elevated glucose in the setting of AMI is even more prognostically important than hyperglycemia on admission, and that resolution of hyperglycemia following admission is associated with improved survival in the setting of AMI, whereas mortality increases in patients with persistent or worsening hyperglycemia.[5,6]

In the inpatient setting, where the duration of care is relatively brief, there is no single laboratory test (such as HbA_{1c}) that can accurately assess the degree of glucose control during hospitalization. Instead, multiple glucose results must be analyzed; these results may be obtained either from plasma samples or from capillary blood ("fingersticks"), and represent a variety of nutritional conditions. Although individual glucose levels provide only brief "snapshots," developing a summary measure of glucose control from multiple inpatient values is important if the nature of the relationship between glucose control and mortality in AMI is to be accurately determined. Therefore, there is a need for a summary measure of inpatient glucose levels that would have a demonstrated impact on patient outcomes, taking into account multiple and random glucose measurements obtained at various times and representing various nutritional conditions,

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Correspondence: Mikhail Kosiborod, MD,
Mid America Heart Institute of Saint Luke's Hospital,
4401 Wornall Rd, Kansas City, MO 64111, United States
E-mail: mkosiborod@cc-pc.com

and would have a demonstrated impact on patient outcomes.

Given the need for such a measure, there has been growing interest in defining the optimal ways to assess glucose-associated risk in patients with AMI, creating the field of comparing various glucose metrics (or "glucometrics"). A number of glucose metrics have been associated with increased risk of mortality and in-hospital complications among patients with AMI, including admission, mean 24 h, mean hospitalization, and fasting glucose.[3,4,7] Furthermore, several additional (and more sophisticated) measures of glucose control have been proposed in other studies: such as time-averaged glucose (area under the glucose curve [TAG])[8] and hyperglycemic index (HGI)[9]—both of which take into consideration not only the glucose values themselves, but also the time period over which these values were recorded. Several of these metrics have been directly compared for their ability to discriminate AMI survivors from non-survivors in prior studies.[3] While higher glucose values were strongly associated with increased risk of in-hospital mortality for all glucose metrics, measures of persistent hyperglycemia performed significantly better than admission glucose alone. Overall, mean hospitalization glucose appeared to be the most practical metric of glucose control during AMI hospitalization, due to the combination of its discriminating power and ease of calculation and clinical implementation. Other studies have also demonstrated that fasting glucose is superior to admission glucose in predicting short and long-term AMI outcomes.[7]

In this issue of the *Revista Española de Cardiología*, Monteiro et al[10] add to this growing field by analyzing the association between a novel glucose metric—magnitude of glycemia variation— and both in-hospital and 18-month major cardiovascular endpoints, including readmission for acute coronary syndromes, worsening heart failure, revascularization, and death. Rather than concentrating on measures that assess severity of hyperglycemia, the authors focus

on the degree of variation in glucose levels during AMI hospitalization. Examining the quartiles of glycemia variation (defined as the difference between admission glucose and lowest fasting glucose recorded during hospitalization), they show that this metric predicted long-term (but not in-hospital) outcomes in patients without known diabetes, but had no prognostic value among those with established diabetes.

Variation in glucose values (not just mere severity of hyperglycemia) has been previously demonstrated to be an important determinant of outcomes in other patient populations. Metrics of glucose variation, such as glucose lability index (GLI), and mean amplitude of glycemic excursions (MAGE) were independently associated with in-hospital mortality among critically ill patients with sepsis in prior studies.[11] Potential mechanistic explanation for this epidemiologic observation comes from physiologic studies in which glycemic variation (measured, in part, by MAGE) exhibited a greater triggering effect on oxidative stress than chronic sustained hyperglycemia in patients with type 2 diabetes.[12] While this mechanism may be even more important in the setting of acute myocardial ischemia, the role of glycemia variation as a measure of prognosis in patients hospitalized with AMI has not been systematically examined until now.

Should the findings of Monteiro et al[10] compel the cardiologists to embrace the measures of glycemia variation in risk stratification of patients with AMI? The answer is that these metrics are not yet ready for clinical prime time. First, the metric used to assess the magnitude of glycemia variation in this study was relatively basic, only representing the absolute difference between the admission and lowest fasting glucose during hospitalization. This metric is unlikely to capture the full magnitude of glycemic excursions, and probably underestimates the true impact of glycemia variation on patient outcomes. Furthermore, the simplicity of this metric may introduce misclassification bias. As an example, a patient with significant hyperglycemia on admission whose glucose steadily normalizes during the course of hospitalization without excessive swings in glucose values is likely to have good prognosis, based on prior investigations.[5,6] However, this patient would be classified as having significant glycemic variation in this study. In contrast, a patient with hyperglycemia on arrival that persists throughout hospitalization may experience little glycemic variation. Yet, patients with persistent hyperglycemia tend to experience the worst outcomes, as demonstrated in several well-conducted prior studies.[3,5,6] It would also be unwise to suggest that patients' hyperglycemia

should remain untreated just to avoid increasing their glycemia variation. These examples highlight the inherent limitations of this metric, and may be one of the reasons for the absence of a relationship between glycemic variation and in-hospital mortality observed in the study.

Second, and more importantly, the results were not corrected for either admission or mean hospitalization glucose levels (both known and well established predictors of prognosis).[3,4] Therefore, it remains unclear whether any measure of glycemia variation has incremental prognostic value above and beyond the metrics of average glucose control.

To be sure, we need to know more about the potential role of glycemia variation as a risk factor in patients with AMI. Future studies need to examine various metrics of glucose variation (including GLI and MAGE), and directly compare those with the measures of average glucose control during hospitalization (such as mean glucose or hyperglycemic index). These studies would help determine whether measures of glycemia variation are superior metrics of glucose-associated risk, or whether their value is complementary and should be used in combination with more standard measures of glucose control. Until this is established, clinicians should concentrate on well established, validated, and easily available glucose metrics, such as admission, fasting, or average glucose.

Of course, the ultimate question is whether any glucose metric is a modifiable risk factor, and whether target-driven glucose control may improve outcomes in AMI. This remains to be established in large, well designed randomized clinical trials. The findings of Monteiro et al[10] remind us that protocols used in these future clinical trials should be designed not just to lower glucose, but also to avoid frequent and severe shifts in glucose values, including extremes of both hyper- and hypoglycemia.

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