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Clinical Reviews

PROPOSAL OF A NEW APPROACH TO STUDY AND CATEGORIZE STRESS HYPERGLYCEMIA IN ACUTE MYOCARDIAL INFARCTION

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☐ **Abstract—Background: Stress hyperglycemia (SH) is a valid prognosticator of in-hospital complications and mortality in the intensive care unit, and is universally available, simple, and cost-effective. Even small refinements of SH can improve the risk stratification of patients with one of the most important diseases today—acute myocardial infarction (AMI). Objective: The aim of the review was to analyze whether SH nomenclature and methodology have been consistent in the medical literature in order to identify possible methodological faults and to suggest possible solutions. Discussion: SH nomenclature and glycemic targets have been relatively uniform in recent years, but there has been a pronounced variability in the methodology. Recent meta-analysis showed that AMI patients with new hyperglycemia had a 3.6-fold increased risk of mortality during hospitalization in comparison to those who were normoglycemic. Four SH methodological mistakes were identified. First, using one cutoff value for SH instead of two different values (one for patients with diabetes mellitus [DM] and one for patients without DM). Second, analyzing, for example, either tertiles or quintiles without dividing AMI patients into subgroups according to their DM status. Third, studying only two subgroups (with SH and without SH), without determining the presence of DM, when DM is not analyzed. Fourth, failure to measure glycated hemoglobin. Conclusions: The same admission blood glucose (BG) is a marker of different mortality risks in diabetic compared to nondiabetic AMI patients. For example, when admission BG is 108–126 mg/dL (6–7 mmol/L), then the risk of in-hospital mortality is higher in DM patients; however, with an admission BG of 162–180 mg/dL (9–10 mmol/L), the risk is lower in diabetic patients. We can improve the clinical utility of the admission BG in AMI if we analyze four groups of patients (those with and without previously diagnosed DM, and above and below the admission glycemia cutoff values for in-hospital mortality). Those cutoffs should be calculated separately for diabetic and nondiabetic AMI patients.** © 2016 Elsevier Inc. All rights reserved.

☐ **Keywords—acute myocardial infarction; stress hyperglycemia; mortality; heart failure**

INTRODUCTION

Stress hyperglycemia (SH) in acute myocardial infarction (AMI) has been defined by a scientific statement of the Diabetes Committee of the American Heart Association as admission plasma glucose >140 mg/dL (7.77 mmol/L) (1). The importance of the topic springs from two facts. First, AMI is one of the most common lethal diseases, and second, glycemia is one of the crucial parameters in general and in AMI in particular. SH has been recognized as a good prognostic marker of mortality and morbidity in critical illnesses, including AMI (1).

SH correlates very well with the most important prognosticators in AMI: age, hemodynamic stress (e.g., Killip class), extent of myocardial necrosis, dysrhythmias, and other complications. The motivation for this paper comes from the observation that the methodology used for analysis of such an important parameter as glycemia in AMI

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has been suboptimal. Even small refinements of SH as a prognostic marker may improve risk stratification of patients with one of the most serious diseases today, AMI.

DISCUSSION

Consensus on methodology would help to avoid wasting time, effort, and resources of the investigators, as well as the patience of readers.

Differences in Nomenclature and Methodology for High Admission BG and Recommendations for Target BG in AMI

The nomenclature for high admission BG in AMI is not so variable: acute hyperglycemia, stress hyperglycemia, and admission hyperglycemia (2–4). However, there is still pronounced variability in the methodology used to analyze hyperglycemia in acute coronary syndrome (ACS). Some of the most recent publications have used a variety of methodologies for comparison of admission BGs, including various admission BG ranges, admission BG quintiles, higher and lower values than median glucose, same admission BG cutoff for patients with and without diabetes mellitus (DM), or different admission BG cutoffs for DM and non-DM patients (1–3,5–10).

Cutoffs for admission hyperglycemia were also found to be different, ranging from 108 to 198 mg/dL (6–11 mmol/L) in earlier publications and, similarly, in the most recent ones an admission serum glucose level of ≥200 mg/dL (≥11.1 mmol/L) or ≥140 mg/dL (≥7.8 mmol/L) (2,11–13). Thus, the instruction by the Diabetes Committee of the American Heart Association to define SH in AMI as admission plasma glucose >140 mg/dL (7.77 mmol/L) has not been followed consistently (1). Recommendations for target glycemia in AMI differ somewhat in the guidelines: <180 mg/dL (<10 mmol/L), 140–180 mg/dL (7.7–10.0 mmol/L), and ≤198 mg/dL (≤11.0 mmol/L) (14–16).

Importance of Stress Hyperglycemia in AMI

SH is an ominous prognostic marker and possibly a mediator of in-hospital mortality in AMI patients (10,17). A meta-analysis demonstrated that nondiabetic AMI patients with an admission glycemia ≥8.0 mmol/L had an almost fourfold higher mortality risk compared to patients with an admission BG concentrations <6.1 mmol/L (11).

To our knowledge, the prognostic significance of SH has been documented in all published papers on the topic. Compared with DM, hyperglycemia was a better discriminator for 30-day mortality after an AMI (18). Recent meta-analysis demonstrated that AMI patients with new hyperglycemia showed a 3.6-fold ($p < 0.0001$) increased risk of mortality during hospitalization, as compared to those who were normoglycemic (19). Addition of admission BG improved the prognostic value of widely used risk scores (e.g., GRACE and TIMI) in a cohort of nondiabetic patients (but not in diabetic patients) with ST-elevation myocardial infarction (STEMI) complicated by cardiogenic shock (5).

Many pathophysiological mechanisms can contribute to the possible detrimental action of high BG in AMI, for example, increased concentration of free fatty acids, microvascular obstruction with white blood cells, endothelial dysfunction, “no-reflow phenomenon,” decrease of collateral blood flow to the ischemic area, and prothrombotic state (3,20–25). Furthermore, SH is significantly more prevalent in AMI patients with known prognostic factors, such as advanced age, heart failure, large myocardial necrosis, atrial fibrillation, ventricular rhythm disorders, and conduction abnormalities (26). Importantly, numerous studies (although not all) used multivariate analysis and found that high admission BG was an independent predictor of mortality in AMI (10,27–31). For example, The Cooperative Cardiovascular Project demonstrated a significant increase in 30-day and 1-year mortality (up to 77% and 46%, respectively) in patients with hyperglycemia among 141,680 AMI patients analyzed. The higher mortality risk persisted after controlling for comorbidities (such as previous myocardial infarction [MI] and heart failure) and disease severity (Killip class, peak creatine kinase and creatinine concentrations, and left ventricular ejection fraction). Despite the earlier mentioned causality of hyperglycemia-induced AMI prognosis, deterioration has been debatable (32). With the improved methodology, risk stratification using SH is expected to be even better, as demonstrated in Koracevic et al. (33).

Therefore, the importance of SH is twofold: as a risk marker (proven in dozens of studies and registries) and as a therapeutic target (the universal approach has been to treat high glycemia in AMI patients, although recommendations differed as to how tight the glycemia control should be; current guidelines suggest less tight glycemic control) (14–16). The term *AMI* in this paper refers to both STEMI and non-STEMI (NSTEMI). For example, in a study of 4,111 AMI patients, the strength of association between admission glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI (30). One unexplored and underestimated topic, but one that is important for emergency physicians, is management of hyperglycemia in patients with AMI at the point of first medical contact. It is of particular concern in STEMI patients who are treated with prehospital fibrinolysis if prolonged time is needed to obtain primary