Lower Sugar, Sweeter Results

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The first reported use of intravenous glucose-insulin-potassium (GIK) solution during myocardial ischemia offered a compelling mechanistic rationale: stabilize the plasma membrane by forcing potassium into cardiomyocytes while simultaneously supporting efficient metabolism to improve cellular viability.[1] Although initially used in acute coronary syndrome, application of GIK treatment to cardiac surgery was a natural extension given the predictable and controlled period of global myocardial ischemia inherent to cardiopulmonary bypass.

The ease of use and attractive scientific premise of GIK infusion to remedy periods of metabolic stress have supported persistent scientific interest in this treatment for decades, despite inconsistent clinical trial results. Although initial proof-of-principle studies suggested favorable effects on early postoperative hemodynamics, later studies with larger sample sizes and more rigorous trial design were unable to demonstrate differences in hard outcomes.[2] Furthermore, prior "high-glucose/low-insulin" GIK solutions were shown to induce hyperglycemia, the deleterious effects of which have recently been demonstrated in multiple randomized controlled trials. Given the metabolic insults of cardiopulmonary bypass and myocardial ischemia that persist to this day as risks for open heart surgery,[3] it is thus encouraging that Zhao and colleagues[4] now present encouraging results with a new, lower 3:1 glucose:insulin GIK formulation that appears to mitigate the hyperglycemic effects of previous, higher glucose to insulin formulations.

The randomized controlled trial reported by Zhao et al in this issue of the *Journal of the American Heart Association* (*JAHA*) studies an impressive 930 subjects enrolled from a single institution with 3-year follow-up data, larger and longer than previous GIK studies.[4] This report adds to the extant literature in 2 principal ways. First, it demonstrates that decreasing the glucose:insulin ratio avoids treatment-induced hyperglycemia without also appreciably increasing potentially deleterious hypoglycemia. Second, they demonstrated improvements in myocardial and systemic metabolism, myocardial function, and major adverse cardiac event rates compared with control patients not receiving GIK treatment.

These conclusions come with some caveats. For one, the increase in ejection fraction seen in these study results may be related to the known vasodilatory actions of GIK on the peripheral vasculature, which would of course lead to improvements in ejection fraction based on afterload-reduction.[4,5] Details on vasopressor or inotrope use are not provided in this article to help adjudicate this issue. The authors suggest that decreased serum lactate represents corroborating evidence of improved systemic perfusion, but decreased lactate levels could simply represent the results of enhanced glucose use, nevertheless a potentially beneficial result of this GIK treatment.[6] Cardiac output data would have likewise helped enlighten the reader on this issue.

Despite these limitations, the GIK group did demonstrate lower rates of postoperative renal complications and supraventricular arrhythmias. These remain as 2 important drivers of postoperative morbidity after cardiac surgery, and are encouraging efficacy end points of the current study.[7,8] Prior investigations in this area have also suggested improvement in atrial fibrillation with the use of GIK solutions, although results have been inconsistent and most studies have been underpowered for this outcome.[2,9–11] Furthermore, as most prior trials have not reported benefits of GIK treatment on postoperative renal function, this outcome may also represent a novel benefit of the current GIK formulation.

Finally, the limitations of the current study include its application to a highly selected patient cohort in a single institution and a highly nondiverse population. More important, the exclusion of patients with diabetes mellitus or chronic renal insufficiency represents a significant limitation on the generalizability of the present results to a broader

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population without broader studies. We look forward hopefully to such further studies and potential demonstrated benefits of this novel effort to apply new knowledge about glucose metabolism in cardiac surgery patients to a tried but yet incompletely proven therapy.

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Disclosures

None.

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