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Glycemic Control for Organs

A New Approach to a Controversial Topic

TIGHT glycemic control has been a topic of intense and sometimes heated discussion for the past 7 yr. The prospect of a low-cost, high-impact intervention has spawned a movement to define best practices and apply intensive insulin therapy to a wide variety of patients. Contrarily, skeptics are concerned about overstatement of benefit and inappropriate extrapolation, and have called for restraint. The concept that glycemic control might benefit certain tissues under certain circumstances is lost in the larger debate. The study by Blasi-Ibañez *et al.* in this month's ANESTHESIOLOGY[1] refocuses attention on specific organ function, crosses the boundary between clinical and bench research, and raises new interesting questions.

Cadaveric organ donation provides a unique set of circumstances under which biology and medicine might be studied in both an isolated model and a living patient. Although it is not completely clear which patient populations benefit most from tight glycemic control, one of the major suggested benefits has been a reduced incidence of renal dysfunction.[2,3] It is therefore reasonable to wonder if tight glycemic control in kidney donors might be associated with improved graft function in the recipient. In rodent models of diabetes, a variety of specific mechanisms of injury to the kidneys have been described, including mesangial glycosylation, protein deposition, impaired vasoregulation, overfiltration, loss of membrane integrity, and proteinuria,[4,5] some of which might be improved by glycemic control, insulin therapy, or both. The unique circumstances of cadaveric organ donation permit a thorough analysis of the mechanisms of renal injury to the point that phenomena in animals may now be studied in humans *meta vivo*. Blasi-Ibañez *et al.* collected demographic and clinical data, including 4512 glucose measurements, from 458 brain-dead organ donors. Multivariate analysis demonstrated that average serum glucose in the donor was the strongest predictor of serum creatinine and calculated glomerular filtration rate at organ procurement. Perhaps as importantly, greater variability in glucose level was also strongly associated with worse graft function.

As with any retrospective study, the analysis by Blasi-Ibañez *et al.* is limited to available data, which did not include information about graft function in the kidney recipients. Readers of this study are intensely interested in whether glomerular filtration rate (or even more specific measures of renal physiology) at procurement predicts function in the recipient and whether proteinuria in the donor foreshadows proteinuria in the recipient, two critical questions unanswered in this study. As with all good studies, this paper is likely to stimulate further inquiry into the relationship between renal injury and hyperglycemia.

Disentangling cause and effect is difficult in medicine, and extraordinarily difficult in retrospective studies. For example, in this study thrombocytopenia also correlated with decreased renal function in the donor. Thrombocytopenia, almost certainly a marker of severity of illness, could also cause renal injury. Thrombocytes produce prostaglandins, and this process is altered in diabetes[6]; prostaglandins modulate renal blood flow. The correlation in this study does not clarify the mechanism of the finding. Another important consideration is the definition of glycemic control in this study. Glucose in the patients at intensive care unit admission was 205 ± 81 mg/dL, rising to 241 ± 68 mg/dL before organ procurement, and exceeding 200 mg/dL in 72% of donors. These values exceed levels in control groups in several major clinical trials of glycemic control.[2,3,7] Protein glycosylation may be a relevant source of tissue damage at glucose levels > 180 mg/dL, and osmotic diuresis at levels > 200 mg/dl might strain the ratio of oxygen supply to demand in the renal medulla. It is tempting to speculate that even modest decrements in glucose levels might produce better outcomes. This intervention is the type of low-cost/high-benefit one that the proponents of tight glycemic control have hoped for.

The hypothesis that glycemic control might improve the function of a transplanted kidney is particularly interesting because several controversies from the ongoing conversation about glycemic control are systematically different in the setting of organ donation. One such controversy is: What serum glucose should we seek? The answer is not obvious and remains incompletely informed by clinical studies thus far. Some argue that the goal for glycemic control should be matched to metabolic activity, gradually changing over the course of critical illness.[8] In organ donors, resolution of illness is not a possibility; gradual progression of dysfunction is the norm. A second controversy is: What are the risks of glycemic control? Several critical outcomes (mortality and stroke) are no longer relevant in donors. The opportunity to study various strategies for glycemic control in brain-dead organ donors may substantially inform the discussion about management of glu-

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cose in a variety of other settings, including the operating room, or in other critically ill patients.

As the conversation about glycemic control evolves, several points are clear. Insulin is not a simple antiglycemic drug, the relevant endpoints of metabolic control have not been adequately defined, patients are different, and risks are imperfectly measured. The observational study by Blasi-Ibañez *et al.*[1] offers a new perspective for discussion and a new clinical approach to generate data. Instead of looking at broad application across heterogeneous populations, they have created a model to tease out what matters and how. They have, in effect, reverse-translated clinical research when the results were unclear. It is almost certain that further study, inspired by this work, will shed badly needed light on this controversial topic.

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