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Blood Glucose Variability

A New Paradigm in Critical Care?

BLOOD glucose has only recently emerged as an important variable in critical care. In the past, this biologic marker has been largely ignored or considered as adaptive to the stress conditions observed in critically ill patients. In this issue of ANESTHESIOLOGY, Egi *et al.*[1] report observations from a large database that included 7,049 critically ill patients in whom blood glucose was frequently monitored. They observed that variability of blood glucose concentration was an independent predictor of intensive care unit (ICU) and hospital mortality.

It is now obvious that blood glucose plays a key role in both the short- and long-term consequences of neurologic injury.[2,3] In the heart, high blood glucose level abolishes ischemic preconditioning,[4] amplifies reperfusion injuries,[5] and provokes coronary endothelial dysfunction[6,7] and thus further increases the incidence of myocardial ischemic events. Numerous clinical studies have identified diabetes mellitus as an independent risk factor for perioperative morbidity and mortality,[8] and there is compelling evidence that perioperative glycemic control improves early clinical outcome of diabetic patients.[9] In a randomized study in critically ill patients, Van der Berghe *et al.*[10] reported that intensive insulin therapy is associated with a lower mortality. In patients undergoing coronary artery bypass surgery, we have recently demonstrated that a poor intraoperative glucose control despite intensive insulin therapy is associated with a worsened hospital outcome in diabetic patients.[11] As emphasized recently by Malhotra,[12] the days of ignoring blood glucose levels or tolerating marked hyperglycemia in the ICU are over.

In the report by Egi *et al.*,[1] blood glucose was closely monitored; on average, glucose was measured every 4 h. The mean measures were 24 per patient, and the variability of blood glucose predicted ICU and hospital mortality. In multivariate analyses, the odds ratio associated with blood glucose variability (1.28 per 1 mM of SD) and that associated with mean blood glucose (1.21 per 1 mM) were comparable in predicting ICU mortality. The results were comparable when considering hospital mortality. These results should be considered with caution because this was a retrospective study and we cannot rule out the possibility of hidden bias. Although these results are impressive and the methodology used is appropriate, including a very large number of critically ill patients, it should be noted that these associations were observed; however, this does, in itself, not prove causality. Therefore, the study from Egi *et al.*[1] should be considered as the first important step toward a new paradigm concerning the prognostic value of blood glucose concentrations: Not only the level of blood glucose but also its variability might be of paramount importance. This study constitutes a unique opportunity to orient future research, both experimental and clinical, to test this new hypothesis.

If blood glucose variability is as important as blood glucose level, some recent findings should be reconsidered. For example, using intensive insulin therapy in the ICU, the first study by Van der Berghe *et al.*[10] showed a reduction in mortality, whereas a second large trial did not.[13] Many factors might explain this discrepancy.[12] However, it should be pointed out that neither of these clinical trials assessed blood glucose variability, which might have played a crucial role. Two large ongoing randomized trials on intensive insulin therapy in the ICU might also consider blood glucose variability as an important factor.*†

Blood glucose variability has been simply assessed by the SD (or the coefficient of variation) in the study by Egi *et al.*[1] However, this variable is in fact a very complex factor that could encompass several pathophysiologic processes: variation of blood glucose around abnormal high values, variation of blood glucose between abnormal high (hyperglycemia) and low (hypoglycemia) values. Future research should be also directed to assess the more appropriate definition of blood glucose variability and to delineate the possible pathophysiologic mechanisms involved. The initial results of blood glucose variability as insulin treatment is initiated should probably be discarded. Also, this may depend on the therapeutic effort to maintain blood glucose using intensive insulin therapy. The mode of administration of insulin may affect blood glucose variability; continuous intravenous administration is better than continuous and bolus subcutaneous administration, which is better than intravenous bolus administration. Insulin itself may also induce biologic effects aside from gly-

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* National Institutes of Health: Glucontrol study: Comparing the effects of two glucose control regimens by insulin in intensive care unit patients. Available at: http://clinicaltrials.gov/show/NCT00107601. Accessed February 20, 2006.

† Current Controlled Trials: A multi-centre, open label, randomized controlled trial of two target ranges for glycaemic control in intensive care unit (ICU) patients. Available at: http://controlled-trials.com/isrctn/trial/ISRCTN04968275/0/04969275.hlml. Accessed February 20, 2006.

cemic variation; these include a decrease in level of free fatty acids, scavenging of free radicals, and even nonmetabolic biologic actions.[14–17] Here, it should be emphasized that the results observed by Egi *et al.*[12] may not apply to critically ill patients receiving intensive insulin therapy.

In the study by Egi *et al.*[1] and in a subgroup analysis, the results were not markedly modified based on whether the patients were diabetic. Also, the sample size for diabetic patients was too small to test their blood glucose level and blood glucose variability. This is important because there is evidence that the deleterious effects associated with high blood glucose in critically ill patients are not the same in diabetic and nondiabetic patients.[18] Moreover, diabetes should not be considered as a single disease because there are marked differences in diabetes types I and II. Blood glucose variability is usually less pronounced in type II diabetic patients in whom endogenous insulin secretion exists. We therefore suggest that the hypothesis for a critical role of blood glucose variability should be tested separately in nondiabetic patients and diabetic critically ill patients. Even diabetic patients should be divided by type and will require a very large multicenter study.

In conclusion, blood glucose variability and not only blood glucose level should probably be taken into account in future research on perioperative glucose monitoring and outcome. This is not really surprising because blood glucose variability has long been considered as important for the long-term care of diabetic patients.

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