Glucose for the Heart
Too Much of a Good Things?

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Heart disease, often presenting as premature and accelerated coronary artery disease, is a frequent complication of diabetes mellitus (1,2). The systemic metabolic dysregulation, manifested as hyperglycemia and hypertriglyceridemia with increased plasma fatty acid levels, affects both the vasculature and the myocardium and, ultimately, metabolic dysregulation results in contractile dysfunction of the heart (3). There is strong evidence for a close association between postprandial hyperglycemia and the development of cardiovascular diseases (4), and practitioners of cardiovascular medicine are well aware of the importance of strict glycemic control to forestall early morbidity and mortality of patients with diabetes from cardiovascular disease. Intensive blood glucose control substantially decreases the risk of microvascular complications in patients with type 2 diabetes (5). Furthermore, an independent line of evidence suggests that impaired coronary flow reserve is an early indicator of adverse outcomes of coronary heart disease (6). Insulin increases coronary flow in the normal heart (7), most likely by nitric oxide–induced vasodilation (8,9). It seems, therefore, reasonable to argue that insulin deficiency assumes a causative role for the development of an impaired coronary flow reserve in the heart of patients with type 1 diabetes mellitus and that this impaired coronary flow reserve may also trigger early metabolic (10) and structural remodeling of the myocardium (11,12). The hypothesis is strengthened by reduced (endothelium-dependent and endothelium-independent) coronary vasodilator function in type 1 and 2 diabetes (13) and in obesity associated with insulin resistance (14).

The study of Srinivasan et al. (15) in this issue of the Journal presents evidence in support of the hypothesis that hyperglycemia negates any salutary effects of hyperinsulinemia on coronary vasodilatory function in patients with type 1 diabetes mellitus and is in line with the notion that exposure to high concentrations of glucose has consistently been demonstrated to impair endothelium–dependent nitric oxide–mediated vasodilatation (16) by inhibiting endothelial nitric oxide synthase (17). The authors used adenosine, a well-known coronary vasodilator, to assess coronary flow reserve and radiolabeled water to measure coronary flow by positron emission tomography. This model is a well-established one in the measurement of myocardial blood flow at rest (MBFr) and during adenosine infusion (MBFa) and to express the myocardial perfusion reserve (MBFa/MBFr). The results suggest that hyperglycemia has deleterious effects on myocardial perfusion reserve and that these effects outweigh any beneficial effects of hyperinsulinemia.

Given the central role of glucose as the main fuel for energy production in the fetal, stressed, hypertrophied, and ischemic heart muscle (18), it seems paradoxical that there should ever be too much of a good thing. Nature probably does not work that way. Yet there is vast array of literature on glucotoxicity (19), including increased flux through the hexosamine biosynthetic pathway, superoxide production, advanced glycation end-products, and modification of protein function by glycosylation. The well-known marker of protein glycation and of glycemic control, hemoglobin Alc, is just the proverbial tip of an iceberg. There is also the famous study from Belgium showing that tight glycemic control improves the survival of patients in intensive care (20). However, is glycemic control really the key? This situation is probably more complex.

Before the results of the present study can be accepted, the critical reader is likely to raise a number of points. First, the data show (not unexpectedly) that adenosine profoundly increases myocardial blood flow without changing the rate pressure product of the heart. Normally, there is tight coupling between myocardial blood flow, myocardial oxygen consumption (MVO2), and cardiac work (21,22). Data on MVO2 would have helped to answer the question of whether the increase in coronary flow was associated with a decrease in efficiency (i.e., a decrease in the amount of useful contractile work for the amount of energy delivered). Data on MVO2 also would have helped to validate the model. Second, there are no controls of age-matched patients without diabetes. Data on coronary perfusion reserve of control subjects with the hyperglycemic hyperinsulinemic clamp protocol would have provided information whether the observed phenomenon is specific for patients with diabetes.

Third, and probably most importantly, the exact infusion rates of insulin in the clamp studies must be known. The results presented in Figure 2 of the paper by Srinivasan et al. (15) show somewhat–lower plasma insulin levels in the hyperglycemic hyperinsulinemic group receiving adenosine than plasma insulin levels in the hyperinsulinemic euglycemic group. This result, taken together with a higher resting myocardial blood flow in the hyperglycemic hyperinsulinemic group (Fig. 3 of the paper by Srinivasan et al. [15]), may have resulted in a low value for the myocardial perfusion reserve. Nonetheless, the multivariable analysis suggested that glucose levels were more important than...
insulin levels with respect to myocardial perfusion reserve. The aforementioned arguments seem complicated; however, it is worthwhile to retrace the steps before we completely abandon an effective treatment for many forms of heart failure and myocardial ischemia. This is the time-honored infusion of glucose, insulin, and potassium, also effective in diabetic patients with acute myocardial infarction (23–25).

That said, Srinivasan et al. (15) have exposed an important and largely overlooked phenomenon in need of further elucidation. To paraphrase Albert Einstein, “Nature tends to hold on to her secrets, but nature is not wicked.” The metabolic dysregulation that underlies the clinical manifestation of type 1 diabetes includes an oversupply of fuel for the heart. The heart fails in the midst of plenty, a phenomenon we described as “glucolipotoxicity” (3,26). In the setting of this study, impaired myocardial perfusion reserve would actually reduce the delivery of substrate to the myocardium. The question is then, could this be a protective phenomenon?

Acknowledgment
The author thanks Roxy Ann Tate for her editorial assistance.

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