

Insulin, Glycemic Control, and C-Reactive Protein During Myocardial Infarction

In recent years, much attention has been paid to the evidence that hyperglycemia during myocardial infarction enhances the risk of mortality (1). A frequent event in medicine is the “new” discovery of an old finding, and the story of hyperglycemia and acute myocardial infarction is one of these cases. An unusually high prevalence of glycosuria in nondiabetic patients who have acute myocardial infarction was noted as early as 1931 (2). In 1975, it was reported that “[fasting blood glucose] level shortly after an acute myocardial infarction is a better guide to prognosis” (3). An association between hyperglycemia during a myocardial infarction and subsequent mortality was then reported in 1987 (4) and confirmed in 1989 (5), 1991 (6), and 1993 (7).

However, in 2000, the large meta-analysis of Capes et al. (1) raised the question to the scientific community, even though the evidence that lowering glucose decreases mortality in diabetic patients who have myocardial infarction was available (8). Recently, data are accumulating, reinforcing the evidence that the presence of hyperglycemia during a myocardial infarction is a strong risk factor for a worse prognosis (9,10). Consequently, understanding the mechanisms through which hyperglycemia worsens the prognosis of a myocardial infarction, as well as the effectiveness of its control during acute myocardial infarction, seems to be of great relevance.

A growing body of evidence suggests that myocardial infarction is associated with local and systemic inflammation (11). Indeed, inflammatory cells infiltrate nearly all plaques, and culprit lesions of infarcted hearts appear to be particularly enriched in activated T-cells (12). Although circulating immune markers are also chronically elevated in patients with chronic stable angina, a transient burst of T-cell activation can be detected only in patients with unstable angina and myocardial infarction (12), suggesting that immune factors might precipitate plaque

complications such as thrombus formation and vasoconstriction at the site of the culprit lesion. A recent article (13) demonstrated an association between inflammatory immune markers and functional cardiac outcome in patients with a first uncomplicated myocardial infarction. Stress hyperglycemia was found to be associated with amplified inflammatory immune reaction and worse functional cardiac outcome (13). Interestingly enough, acute hyperglycemia increased inflammation markers (14). Following this line of thought, it might be speculated that the detrimental effect of stress hyperglycemia in acute myocardial infarction might also stem from its ability to increase inflammation.

The Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (8), published in 1997, reignited interest in the use of insulin following acute myocardial infarction. DIGAMI actually refers to a series of four articles (15–18) published since 1994. The first article (15) reported on the feasibility of the use of an insulin-glucose infusion following myocardial infarction in patients with plasma glucose of ≥ 11 mmol/l. Two later articles (16,17) reported the 1-year mortality and morbidity results. The final article (18), published in May 1999, reported the long-term mortality data. DIGAMI showed that an insulin-glucose infusion followed by at least 3 months of multiple-dose insulin reduced long-term mortality in patients with diabetes who had had a myocardial infarction (8,18). However, not all were convinced by the results, particularly regarding which were the mechanisms of action and whether all the benefits accrued were solely from the insulin-glucose infusion used acutely. The question concerning the use of insulin-glucose infusion during myocardial infarction is still open; a recent trial (19) did not show the beneficial effect on total mortality in patients treated after primary angioplasty for acute myocardial infarction.

However, it is necessary to distin-

guish between a favorable metabolic effect of glucose-insulin infusion and the control of acute hyperglycemia. In terms of metabolic efficacy, it has been suggested that insulin by itself should have direct beneficial effect, particularly in reducing the level of free fatty acids that are known to be associated with a deterioration of clinical outcomes and may have toxic effects of their own on the myocardium. Moreover, insulin may exert a direct anti-inflammatory and profibrinolytic action (20). However, it is also remarkable that glucose exerts several powerful direct damaging effects, as described above, which are all able to worsen the prognosis of myocardial infarction. Therefore, there are the following open questions: Is treating hyperglycemia or insulin infusion the true therapeutic strategy during a myocardial infarction and/or is hyperglycemia to be treated with intensive insulin therapy even in nondiabetic patients?

In this issue of *Diabetes Care* Wong et al. (21) report that in patients with or without known diabetes and hyperglycemia during myocardial infarction, maintaining normoglycemia with glucose-insulin infusion in the first 24 h during the myocardial infarction was accompanied by a significantly lesser increase of C-reactive protein. Interestingly, they found a positive correlation between the mean glucose levels during the first 24 h and serum C-reactive protein levels after 2 days of admission. Unfortunately, this correlation was found only when the control and the treated group were pooled, even if no correlation was found with the insulin dose. Therefore, even though this report is of great interest, the question regarding the major usefulness of insulin infusion versus tight glycemic control still remains open.

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