

# Featured research

## Abstracts and commentaries

### **Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery**

Ascione R, Rogers CA, Rajakaruna C, Angelini GD. *Circulation*. 2008;118:113–123.

Over the past decade, the incidence of diabetes mellitus has increased markedly in developed countries. Knowledge of a patient's diabetic status before they undergo surgery has led to advances in perioperative clinical management, including active and continuous blood glucose control, with improved clinical outcome. Nevertheless, derangement of glucose metabolism after surgery is not specific to patients with diabetes mellitus. It has been reported that up to 90% of those without diabetes mellitus had problems with their blood glucose homeostasis as a result of various surgical stresses. In such patients, the disturbances in blood glucose homeostasis have been attributed to insulin resistance, or a failure of pancreatic  $\beta$ -cell function caused by the systemic inflammatory response syndrome after cardiopulmonary bypass and its effects on systemic temperature, or both. More recently, investigators have been focusing on undiagnosed diabetes mellitus, patients without diabetes mellitus, and their likelihood of suffering postoperative derangement of glucose metabolism leading to postoperative complications. The aim of this study was to investigate the effect of different degrees of inadequate blood glucose control on clinical outcomes in a large consecutive series of patients undergoing cardiac surgery.

### **Commentary**

The authors analyzed the findings from 8727 adults operated on between April 1996 and March 2004. The greatest blood glucose concentration recorded over the first 60 h after operation was used to classify patients as having good (<200 mg/dL), moderate (200–250 mg/dL), or poor (>250 mg/dL) blood glucose control. Among the 8727 patients studied, 7547 (85%) had good, 905 (10%) had moderate, and 365 (4%) had poor control of their blood glucose. Patients with inadequate control of blood glucose were more likely to present with advanced New York Heart Association class, congestive heart failure, hypertension, renal dysfunction, and ejection fraction less than 50% ( $P \leq 0.001$ ).

It was found that 52% of patients with poor, 31% with moderate, and 8% with good blood glucose control had diabetes mellitus. Inadequate blood glucose control, but not diabetes mellitus ( $P = 0.79$ ), was associated with in-hospital mortality (good, 1.8%; moderate, 4.2%; poor, 9.6%). The adjusted odds ratio (OR) for poor compared with good blood glucose control was 3.90 (95% confidence interval [CI] 2.47 to 6.15); that for moderate compared with good blood glucose control was 1.68 (95% CI 1.25 to 2.25). Inadequate blood glucose control also was associated with postoperative myocardial infarction (eg, OR for poor compared with good blood glucose control 2.73 [95% CI 1.74 to 4.26]) and with pulmonary and renal complications in patients without known diabetes mellitus (eg, OR for poor compared with good blood glucose control 2.27 [95% CI 1.65 to 3.12] and 2.82 [95% CI 1.54 to 5.14], respectively).

This study showed that more than 50% of patients developing moderate to poor blood glucose control after cardiac surgery were not previously identified as diabetic. The stress of cardiac surgery might uncover a borderline diabetic status causing marked transient or permanent imbalance in body sugar control and leading to hyperglycemia. These findings suggest that inadequate control of blood glucose, regardless of diabetic status, is an independent predictor of in-hospital mortality and postoperative myocardial infarction in patients undergoing cardiac surgery. The projected future number of adults with diabetes mellitus is an underestimate of the number likely to be affected by deranged glucose metabolism and its related complications. These data suggest that strict protocols to maintain blood glucose control should be used for all patients. However, the efficacy of these protocols and the pathophysiologic mechanisms of this condition need further research.

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### **CD36 expression contributes to age-induced cardiomyopathy in mice**

Koonen DP, Febbraio M, Bonnet S, et al. *Circulation*. 2007;116:2139–2147.

Cardiac remodeling and impaired cardiac performance in the elderly significantly increase the risk

of developing heart disease. Although vascular abnormalities associated with aging contribute to the age-related decline in cardiac function, myocardium-specific events may also be involved. We found that intramyocardial accumulation of lipid, in addition to a reduction in both fatty acid and glucose oxidation and a subsequent deterioration in cardiac ATP supply, also occurs in aged mice. Consistent with an energetically compromised heart, hearts from aged mice displayed depressed myocardial performance and cardiac hypertrophy. Associated with this was a dramatic increase in the fatty acid transport protein, CD36, in aged hearts compared with young hearts, which suggests that CD36 is a mediator of these multiple metabolic, functional, and structural alterations in the aged heart. In accordance with this, hearts from aged CD36-deficient mice had lower concentrations of intramyocardial lipids, demonstrated improved production of mitochondria-derived ATP, had significantly enhanced function compared with aged wild-type mice, and had a blunted hypertrophic response. These findings provide evidence that CD36 mediates an age-induced cardiomyopathy in mice and suggest that inhibition of CD36 may be an approach for the treatment of detrimental age-related effects on cardiac performance.

### Commentary

Aging is a well recognized risk factor for the development of heart disease. It is associated with a number of changes within the heart muscle, including alterations in cardiac energy metabolism. In addition, a decrease in cardiac mitochondrial function occurs with age, and this has been suggested to result in a decrease in cardiac energy reserve that may compromise cardiac function. A decrease in mitochondrial function is associated with a decrease in both fatty acid oxidation and carbohydrate oxidation, the two major sources of the ATP necessary to maintain contractile function. It has also been suggested that an impaired ability of the heart to oxidize fatty acids can lead to an accumulation of lipids within the cardiac myocyte, termed "cardiac lipotoxicity". As a result, age-related lipotoxicity could potentially result in the

development of lipotoxic cardiomyopathy in the aging heart.

This study by Koonen et al addressed the relationship between fatty acid metabolism and cardiac function in aging mice. To modify fatty acid metabolism in the heart, the authors utilized mice that lacked cardiac CD36, a major protein involved in the uptake of fatty acids into the heart. The authors showed that, as expected, old wild-type mice have a decrease in both cardiac fatty acid and glucose oxidation, which would be expected if mitochondrial function is compromised. Accompanying this was an increase in intracellular accumulation of lipid and a decrease in cardiac function compared with those in young mice.

Of interest is that deletion of CD36 resulted in a decreased accumulation of lipid, an improvement in glucose oxidation, and an improvement in cardiac function. The absence of CD36 did not modify the low rates of fatty acid oxidation seen in the old mice. These interesting findings support the concepts that lipid accumulation may compromise cardiac function in the aging heart, and that inhibiting myocardial fatty acid uptake can prevent this abnormal accumulation of lipid and improve heart function. The second important observation from this study is that low rates of fatty acid oxidation in the old heart are not contributing either to lipid accumulation or to impaired contractile function. In contrast, the data suggest that decreasing fatty acid uptake in the heart can markedly increase glucose oxidation in the old heart, which is associated with a marked improvement in cardiac function.

These observations have important implications as to whether stimulating or inhibiting fatty acid oxidation has therapeutic potential in treating the elderly patient with heart disease. The data are consistent with inhibition of fatty acid metabolism and stimulation of glucose oxidation as an approach to improve heart function in the elderly. It suggests that agents such as trimetazidine that stimulate glucose oxidation secondary to the inhibition of fatty acid oxidation may be particularly effective in the elderly patient. Further studies are warranted to examine this possibility.

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