

# Stress Hyperglycaemia and Acute Myocardial Infarction

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Myocardial infarction is currently the most frequent cause of death all over the world. The course and outcome of myocardial infarction is affected by the presence of risk factors like diabetes mellitus, hypertension, age, smoking and family history. Hyperglycaemia often occurs in the acute phase of myocardial infarction. There has been a controversy about the meaning of this hyperglycaemia whether it is a temporary manifestation or precipitation of latent diabetes. The transient hyperglycaemia is considered to be related to stress. Patients with stress hyperglycaemia form a special category in which the course of myocardial infarction is essentially different from normoglycaemics and they need a longer course of follow-up for further management and detection of latent diabetes. In-patients with acute myocardial infarction, a correlation have been described between hyperglycaemia on admission and development of cardiogenic shock, independent of the state of premorbid glucose tolerance. Thus, hyperglycaemia alone might possibly contribute to poor outcome in patients, with and without diabetes. Recent studies show that stress hyperglycaemia is an important prognostic indicator and is mainly a reflection of severity of the underlying condition and not a cause of it. In 1994, Opie's stated that "Provision of glucose is good and a raised free fatty acid (FFA) level is bad." In-patients with acute myocardial infarction – i.e. a changing trend from "Glucotoxicity" to "FFA toxicity" on the myocardium – has prompted a reappraisal on stress hyperglycaemia [1, 2].

For many years, carbohydrate intolerance during acute myocardial infarction (AMI) has been investigated by a number of authors. As early as 1922, Levine [3] linked coronary artery disease and diabetes and pointed out that 'Coronary artery disease produces by itself a glycosuria that need not be indicative of diabetes'. In 1933, Scherf [4] reported transient glycosuria and hyperglycaemia in patients with acute myocardial infarction. In 1936, Raab and Rabinowitz [5] postulated that abnormal glucose tolerance was a constant consequence of myocardial infarction but not dependent on latent diabetes. They suggested that it could be due to disturbances in the vegetative centres in the brain.

In 1952, Ellenberg, Osserman and Pollack [6] gave a new interpretation to hyperglycaemia in non-diabetic patients with acute myocardial infarction. Hyperglycaemia is a clinical manifestation of shock and it was thought that hyperglycaemia was associated with a greater incidence of conduction

defects and arrhythmias. In 1962, Goldberger [7] established that some of the patients showing abnormal glucose tolerance during acute myocardial infarction became diabetic after sometime. In 1967, Datey and Nanda [8] found that 14% of their patients of abnormal glucose tolerance during infarction later developed diabetes.

In 1969, both Taylor et al and Allison and Hinton [9] provided an explanation for carbohydrate abnormalities of cardiogenic shocks – failure of insulin secretion. Taylor et al showed that the secretion of insulin in response to intravenous tolbutamide (IVTT) was depressed in circulatory shock following myocardial infarction [10]. Opie, in 1971, showed that metabolic complications of acute myocardial infarction were similar to that found in any other situation of acute stress [11].

Number of recent studies have shown that elevated blood glucose following acute myocardial infarction is likely to be due to pre-existing abnormal glucose tolerance rather than a temporary stress-induced phenomenon [12-14]. Glycosylated haemoglobin estimation helps to distinguish between pre-existing diabetes and stress hyperglycaemia. Also some prospective studies, where patients with increased stress response (humoral and carbohydrate response), have been followed upto 3 years, have shown that people who developed diabetes mellitus in the future have had a high level of immuno reactive insulin (IRI), reduced IRI/BS (blood sugar) ratio and higher urinary excretion of catecholamines during the period of acute infarction. This probably indicates the predictive value of stress responses to the future development of diabetes mellitus [15].

The other predictive value of stress response is probably the early phase in-hospital outcome following AMI. Mak et al have shown that non-diabetic patients with high fasting blood sugar levels following first AMI had a complicated in-hospital outcome. He concluded that FBS level is a determinant for the outcome for patients with AMI during the in-hospital early period.

The glucose metabolism of the damaged myocardium following AMI has also been studied using sugar analogues, FDG and Positron Emission Tomography. Two different patterns of glucose utilisation in the infarcted area were described. In one group, decreased myocardial perfusion and decreased

glucose utilisation and in the second group, a disproportionately increased glucose uptake and reduced perfusion was seen. The second group was found to still have a viable myocardium. This study probably indicates the importance of maintaining the blood sugar at a higher level to salvage the viable myocardium following infarction.

### **Pathogenesis of acute cardiac stress hyperglycaemia, increased FFA and elevated catecholamine**

Acute myocardial infarction is an example of acute physical and emotional stress. The factors promoting glucose intolerance are the same as those which elevate plasma FFA, thereby showing close links between glucose and FFA metabolism in acute myocardial infarction [16].

#### *Hyperglycaemia*

The rise in blood sugar level is due to rise in stress hormones (catecholamines, cortisol, glucagon and growth hormone). As a result of sympathetic stimulation, increased secretion of catecholamines results in increased hepatic glucose output (neoglucogenesis, glycogenolysis) leading to stress hyperglycaemia. Catecholamines blunts insulin secretion from cells of pancreas and hence there is decreased peripheral utilisation of plasma glucose by muscle and adipose tissue.

#### *Increased FFA*

In addition to carbohydrate intolerance, the increased catecholamine activity leads to other metabolic changes like elevation of triglycerides, lipolysis and elevation of circulating plasma free fatty acids in acute myocardial infarction. The FFA level is increased within 30 minutes of AMI. Gupta et al, in 1969, observed highest degree of elevation of FFA in patients with AMI who had serious complications such as acute left ventricular failure, congestive cardiac failure, hypotension or cardiogenic shock than those without such complications.

Veter et al, in 1974, observed persistent elevation of FFA for seven days in patients with AMI [16, 17].

#### *Catecholamines*

In AMI, increased catecholamine secretion occurs as a result of sympathetic stimulation, which might be either local or general. The three cardiac related events that might trigger increased sympathetic stimulation are

- 1) Fear and pain of acute myocardial infarction.

- 2) Hypoxia and hypotension that may occur in AMI through stimulation of vascular neurons.
- 3) Local damage to cardiac vascular neurons at the ischaemic or infarcting myocardium.

In 1961, Russel et al showed that the damaged myocardium itself releases catecholamines. Braunwald, Haris and Clidsay in 1964, suggested that locally released catecholamines also might have a peripheral effect which could set up a vicious cycle with release of catecholamines, stimulation of lipolysis, further infarction and so on.

#### *Glucagon*

The role of glucagon in the early hours of AMI has not been adequately studied. Hyperglycaemia, by itself does not produce hyperglucagonaemia in diabetics unless there is deficiency of insulin.

### **Local Changes at the ischaemic area of myocardium [18-20]**

#### *Mechanism of FFA toxicity*

To function normally, the myocardium depends on aerobic metabolism. The preferred fuels for myocardial oxidative mechanism are FFA during fasting and glucose after meals and lactate and FFA during exercise. When part of the myocardium becomes anaerobic as in ischaemia, the balance of substrate is disturbed and unoxidised products of FFA accumulate locally. In addition, mobilisation of FFA from adipose tissue occurs due to adrenergic stimulation. FFA are directly arrhythmogenic even in the absence of ischaemia, if the molar ratio of FFA to albumin is sufficiently high,  $\beta$ -oxidation of lipids in the mitochondria is inhibited and there is accumulation of intracellular acyl carnitine and acyl CoA. Acyl carnitine inhibits the Ca pump of sarcoplasmic reticulum as well as  $\text{Na}^+ - \text{Ca}^{2+}$  pump and  $\text{Na}^+ - \text{K}^+$  pump. It can activate  $\text{Ca}^{2+}$  channels and this promotes cytosolic  $\text{Ca}^{2+}$  overload which has now been linked to arrhythmias. FFA also causes an increase in cyclic-AMP which in turn promotes  $\text{Ca}^{2+}$ -dependent reperfusion arrhythmia.

#### *Cellular lipid abnormalities*

FFA has a detergent action on cell membrane with the accumulation of detergent CoA derivatives. There are in addition, the arrhythmogenic effects of hypophospholipids derived from breakdown of membrane lipids during ischaemia and of acyl carnitine. Accumulation of acyl carnitine can directly activate  $\text{Ca}^{2+}$  channels producing arrhythmia via  $\text{Ca}^{2+}$  overload. Further accumulation of tissue FFA

late in ischaemia can open an abnormal channel that shortens action, potential duration and wasteful turnover of endogenous triacylglycerol which might also contribute to FFA damage.

## TREATMENT

### Treatment of Metabolic cause of Myocardial Injury

The metabolic means to lessen ischaemic damage, should include raising blood glucose concentration, inhibition of lipolysis and decreasing FFA levels and inhibition of increase in adrenergic activity. Administration of Glucose Insulin Potassium (GIK) drip helps in improving the balance between glycolysis and fatty acid metabolism in the ischaemic area thereby reducing FFA release and increase blood glucose levels. GIK infusion has also shown to be valuable in reducing the reperfusion injury following thrombolytic therapy and the risk of cardiogenic shock following bypass surgery. Beta-blockers have been useful in reducing adrenergic activity following myocardial infarction.

### Treatment of Stress Hyperglycaemia during myocardial infarction

Glycosylated haemoglobin helps in differentiating pre existing diabetes from stress hyperglycaemia following acute myocardial infarction [21, 22]. A normal glycosylated haemoglobin and raised blood glucose is suggestive of stress hyperglycaemia. But hyperglycaemia due to any cause should be treated with regular insulin and frequent monitoring of blood glucose levels. Care should be taken to avoid hypoglycaemia and it is best to maintain the blood glucose concentration between 200-250 mg% during the acute phase. Here also, GIK infusion will be helpful in maintaining blood glucose levels and avoiding hypokalemia.

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