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Review

Acute glucose dysmetabolism in the elderly with ST elevation myocardial infarction submitted to mechanical revascularization

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ABSTRACT

Though age is a predictor of adverse events after acute coronary syndrome, including in-hospital and post-hospital mortality rates, elderly patients are under-represented in randomized trials evaluating strategies of early coronary revascularization in acute myocardial infarction.
Several factors can account for the unfavorable outcome of the elderly, comprising increased glucose values. Diabetes is more common in the elderly patients with acute myocardial infarction in respect to younger patients and elevated glucose, though common, are rarely treated and associated with increased mortality, particularly in those without recognized diabetes.
Age itself is thought to affect the acute glucose response to stress. Human aging is associated with impaired β-cell sensitivity to glucose and impaired β-cell compensation to insulin resistance and older people exhibit an impaired glucose response after injury characterized by a more marked increases in endogenous glucose production.
In the early phase of ST elevation myocardial infarction (STEMI), the acute glucose response to stress comprises not only hyperglycemia but also insulin-resistance (assessed by the Homeostatic Model Assessment). Recently it has been documented in 346 STEMI patients submitted to mechanical revascularization that the acute glucose response to myocardial injury differs in respect to age, since older patients showed the highest glucose levels and the poorest glycemic control during ICCU stay in the lack of differences in insulin resistance incidence.
Taking into account that aging impairs the acute glucose response to stress in elderly STEMI patients, further studies are needed to establish whether a different (more aggressive) therapeutic regime is needed in this subgroup of patients at higher risk.

1. Introduction

The elderly are the fastest growing segment of our population and coronary artery disease is a leading cause of mortality and morbidity in this subgroup of patients [1,2]. Though age is a predictor of adverse events after acute coronary syndrome, including in-hospital and post-hospital mortality rates [3–5], elderly patients are under-represented in randomized trials evaluating strategies of early coronary revascularization in acute myocardial infarction [6] and we are often forced to extrapolate the existing evidence and guidelines while treating the elderly [7].

Claessen et al. [8] recently reported an increasing proportion of octogenarians treated with primary PCI from 1997 to 2007, who showed increased short and long-term mortality when compared to younger patients. This finding is in keeping with earlier clinical trials such as GISSI-2 and GUSTO-1 [9,10] as well as with previous studies in the era of mechanical revascularization by others [11–16] and us [17].

Several factors can account for the unfavorable outcome of the elderly: structural and functional changes in the cardiovascular system with aging, atypical symptoms (inducing a delay in seeking medical care) and higher co-morbidities, including increased glucose values. In fact, the elderly have a high prevalence of unrecognized and established diabetes [18] and diabetes is more common in the elderly patients with acute myocardial infarction (AMI) in respect to younger patients [17,19–21]. In the Cooperative Cardiovascular Project (CCP), a nationally representative, community-based sample of elderly patients hospitalized with AMI [22], elevated glucose was common, rarely treated and associated with increased mortality, particularly in those without recognized diabetes.

In the present manuscript we are going to focus on the available evidence on the acute glucose dysmetabolism in elderly patients in the early phase of ST elevation myocardial infarction submitted to mechanical revascularization.

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2. Acute glucose dysmetabolism in the early phase of STEMI

In healthy subjects, despite large timely fluctuations in supply and demand, in a fasting state, plasma glucose levels are normally regulated within a narrow range between 80 and 125 mg/dl. Interestingly, 80% of systemic glucose utilization occurs by non-insulin mediated glucose uptake under basal conditions, mainly by the central nervous system [23]. Glucose transport into cells occurs as facilitated diffusion using one of the five glucose transported (GLUT) channel proteins (GLUT1-mediated insulin independent transport mostly in basal conditions; GLUT4 specifically and reversibly upregulated by insulin). During moderate hyperglycemia, cells usually respond with an internationalization of GLUT transport molecules to protect themselves from glucose overload [24]. In the heart, oxidation of FFAs is the preferred source of energy in the resting aerobic state; FFAs are taken up into the cardiac mitochondria where they undergo beta-oxidation. Carbohydrate metabolism, representing a relative minor source of ATP in normal myocardium, involves a glycolytic component followed by production of acetyl–CoA from pyruvate and entry into the Krebs cycle [25].

The stress imposed by any type of acute illness leads to the development of insulin resistance, glucose intolerance and hyperglycemia [26]. In the acute phase of critical illness, despite high plasma glucose levels and abundantly released insulin, hepatic glucose production is upregulated probably due to elevated levels of cytokines, growth hormone, glucagons and cortisol [27–29]. Hepatic glycogenolysis is further enhanced by catecholamines which also inhibit glycogenesis [29]. Glucose uptake in heart, skeletal muscle, and adipose tissue is compromised because of impaired insulin-stimulated glucose uptake by the glucose transporter 4 (GLUT4) and impaired glycogen synthase [25]. Nevertheless it has been observed that the total body glucose uptake is massively increased but it is accounted for by tissues that do not depend on insulin for glucose uptake such as brain and blood cells [30]. The higher levels of insulin, impaired peripheral glucose uptake and elevated hepatic glucose production reflect the development of *insulin resistance* during critical illness.

In the setting of acute coronary syndrome (ACS), acute hyperglycemia is associated with adverse metabolic effects that may contribute to a poor outcome [31].

Myocardial ischemia results in an increased rate of glycogen breakdown and glucose uptake via translocation of glucose transporter-4 receptors to the sarcolemma [32]. This adaptive mechanism is important because glucose oxidation requires less oxygen than FFA oxidation to maintain adenosine triphosphate (ATP) production so that myocardial energetics is more efficient during the increased dependence on glucose oxidation. With relative insulinopenia (insulin resistance or frank diabetes) exacerbated by the stress of ACS, the ischemic myocardium is forced to utilize FFAs more than glucose for an energy source because myocardial glucose uptake is acutely impaired. Thus, the hypoxic myocardium becomes less energy efficient in the setting of frank diabetes or insulin resistance, as FFA oxidation results in the generation of fewer ATP molecules per molecule of oxygen as compared with glucose oxidation. Catecholamine release with stress further stimulates the release of FFAs, which may contribute to myocardial damage and arrhythmia risk by increasing oxygen demand and oxidative stress [33,34]. During myocardial ischemia, high concentration of FFAs increases myocardial oxygen requirement, depresses myocardial activity and contraction, impairs calcium homeostasis and increases the production of free radicals [35]. During reperfusion, since FFA oxidation quickly recovers and dominates as the source of energy, there is a marked inhibition of glucose inhibition. Consequently, high glycolitic rates (probably due to increased glucose transport) and low glucose oxidation rates can result in a substantial rise of non-oxidative glucose disposal. The uncoupling of glycolysis from glucose oxidation may lead to the production of protons from glucose metabolism during reperfusion, thus exacerbating the ischemic injury.

3. Acute insulin resistance in the early phase of STEMI

Acute insulin resistance is known to be part of the glyco-metabolic response to stress [36], but few studies assessed the role of insulin resistance, evaluated by means of Homeostatic Model Assessment (HOMA index), in the early phase of acute myocardial infarction [37,38].

HOMA index reflects basal insulin sensitivity and responsiveness [39]; it has been firstly proposed for the assessment of insulin resistance [30] in stable patients, but it has been recently used to estimate insulin resistance in critically ill patients with acute renal failure [40]. In a group of 30 critically ill medical patients (continuously sedated and ventilated), Holzinger et al. [41], documented that HOMA index, though indicating insulin resistance, did not correlated with the M-values and concluded that the euglycemic hyperinsulinemic clamp, which reflects stimulated insulin sensitivity, remains the gold standard technique in critically ill patients. However, euglycemic hyperinsulinemic clamp is time consuming, labor intensive and requires an experienced operator to manage the technical difficulties, so it is known to be not appropriate for routine clinical applications [40].

In 168 consecutive patients with acute myocardial infarction but without previously known diabetes, Wallander et al. [37] evaluated glucose abnormalities by means of HOMA index (assessed on day 1 after admission) and OGTT (performed on the day of hospital discharge (day 4 or 5)). The Authors documented that in these patients glucose abnormalities are quite common and can be to a significant extent related to impaired beta cell secretion of insulin. They supposed that hyperglycemia immediately after an infarction cannot be considered mainly a stress epiphenomenon but it may reflect a stable disturbance of glucose regulation preceding the event. In the era of mechanical reperfusion, Nishio et al. [38] identified, by means of HOMA index two different subgroups among 61 nondiabetic MI patients: the non-insulin resistant (IR) group and the insulin resistant group which consisted of transient IR, which correlated with stress hormones, and the continuous IR, which correlated with leptin (associated with endothelial dysfunction) thus contributing to restenosis after coronary stenting at 4 month follow-up.

We recently documented, in 253 nondiabetic STEMI patients submitted to mechanical revascularization, that insulin-resistance, as assessed by HOMA index proved to be an independent predictor for in-hospital mortality. Insulin-resistance was quite common in nondiabetic STEMI patients, since it affected more than half of the population. In our series nondiabetic STEMI patients with insulin-resistance exhibited a larger infarct size (as inferred by higher values of cardiac enzymes) and a more severe metabolic derangement (as indicated by NT-proBNP and lactic acid levels) [42].

4. Aging and acute glucose dysmetabolism

Previous studies, mainly performed in normal subjects [43,44], documented that human aging is associated with impaired β-cell sensitivity to glucose and impaired β-cell compensation to insulin resistance. Several factors can account for this phenomenon, such as lower insulin secretion and serum insulin responses to glucose. Aging could be associated with loss of β-cell mass or simply impaired function of a preserved β-cell mass or a combination of these two factors. Alterations in visceral adiposity and lipid parameters such as free fatty acids and triglycerides associated with age-related changes in body composition and increased adiposity could also be playing a role [43]. It has also been documented that older people exhibit an impaired glucose response after injury characterized by a more marked increases in endogenous glucose production [44]. In trauma patients, age was associated with an increase in serum glucose (also related to degree of injury as reflected in Glasgow Coma Scale on admission and Injury Severity Score subsequently) but not with

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serum insulin [45]. Moreover, the hyperinsulinemia typical of young and middle-aged trauma patients is thought to reflect a predominance of β-adrenergic activity [46] and it could contribute to the observed differences in the insulin responses of young and older trauma patients.

Few studies investigated the relation between hyperglycemia and cardiovascular disease in elderly patients and results are quite intriguing.

Recently Crandall et al. [47] observed that older adults with post-challenge hyperglycemia experience significant fasting and post-prandial metabolic dysregulation, which is accompanied by a pro-atherosclerotic and pro-thrombotic vascular profile. In elderly patients admitted to a sub-intensive care unit [48], newly recognized hyperglycemia was associated with a higher mortality rate than in those with a prior history of diabetes.

In the CCP [22], in a large nationally representative study of 141,680 elderly AMI patients, the relationship between admission glucose and mortality was different in patients with and without recognized diabetes, elevated glucose was associated with a steep linear mortality increase in patients without recognized diabetes, but not in diabetic patients, except at severe levels of hyperglycemia. The authors suggested several explanations for this phenomenon. Some hyperglycemic AMI patients without a history of diabetes could have been true diabetics, neither diagnosed nor adequately managed. Hyperglycemic patients without recognized diabetes could have been treated with insulin less frequently than those with established diabetes. An underlying insulin-resistance could have been present in a substantial proportion of hyperglycemic patients without recognized diabetes. The CCP, though retrospective, strengthens the prognostic value of admission glucose and its utility in risk stratification in elderly STEMI patients. In this study population, STEMI accounted for about one-third (29.2%) and PCI was performed in the 9.9% of patients [22].

While Kosiborod et al. [22] observed that elevated glucose is associated with increased mortality in elderly acute myocardial infarction, the same group of investigators [49] did not find any significant association between admission glucose levels and mortality in a large cohort of elderly patients hospitalized with heart failure suggesting that the relationship between hyperglycemia and adverse outcomes seen in acute myocardial infarction cannot be automatically extended to patients hospitalized with other cardiovascular conditions.

These discrepancies may be related to the differences in age response to metabolic stress in acute and chronic conditions. In particular it has been observed in animal models, that with age, there is a loss of plasticity in physiological adaptive response mechanisms associated with metabolic responses to stress [50].

5. Aging and acute insulin-resistance

Chang et al. [51] in a retrospective analysis, examined the HOMA model in comparison with dynamic testing of insulin sensitivity and β-cell function with the frequently sampled i.v. glucose tolerance test in a large cohort of both older men and women with normal and impaired glucose tolerance. HOMA measures of insulin resistance were able to detect increased insulin resistance in older people with impaired glucose tolerance, though overall agreement between HOMA and the frequently sampled i.v. glucose tolerance test was moderate. The authors concluded that HOMA may detect age-related insulin resistance when comparing large populations of older people, though dynamic testing appears to be necessary to quantitate diminished insulin secretion in older people.

We recently investigated [52] the interaction between age and glucose metabolism response in the acute phase of patients with STEMI without previously known diabetes in 346 STEMI patients consecutively admitted to our Intensive Cardiac Care Unit (ICCU) after primary percutaneous coronary intervention (PCI). We observed that, the very old patients (aged >79 yrs) exhibited the highest values of glycemia and peak glycemia, together with lowest values of insulin, while the incidence of insulin resistance (as inferred by HOMA index) remained unchanged across the age subgroups. Very old STEMI patients also showed a more marker inflammatory activation (as inferred by Erythrocyte Sedimentation Rate – ESR – and fibrinogen values) which may contribute for the increased glucose values, even if it cannot be ruled out that the elevation of ESR in the older patients might be related to a possible higher prevalence of anemia in these patients, which agrees with the observed decrease in the renal function. It is interesting to note that infarct size (as inferred by Tn I values) was not significantly different among age groups. We further confirm that elderly STEMI patients show an increased in-hospital mortality as well as increased values of NT-proBNP. We concluded that the acute glucose response to myocardial injury differs in respect to age, since older patients showed the highest glucose levels and the poorest glycemic control during ICCU stay in the lack of differences in insulin resistance incidence. These findings were confirmed after exclusion of patients with a poor glycemic control in the previous 2–3 months (that is patients with Hb A1c >6.5%).

6. Acute glucose management in elderly STEMI patients

The complexity of the glyco-metabolic response to stress during acute myocardial infarction, as well as the scarcity of data on this topic, can be inferred by still existing controversies on how to manage increased glucose values in patients with acute coronary syndromes, even in the elderly. According to recent guidelines [53], it is reasonable to consider intensive glucose control in patients with significant hyperglycemia (that is plasma glucose >180 mg/dl), but strategies for the management of patients with milder degrees of hyperglycemia are far to be elucidated. We recently [54] observed that in nondiabetic STEMI patients the poorer in-hospital glucose control was associated with higher mortality; peak glycemia >180 mg/dl was associated with the highest mortality, whereas patients with peak glycemia comprised between 140 and 180 mg/dl exhibited intermediate mortality rates. In a previous paper [42] we documented that the elderly STEMI patients exhibited the poorest glycemic control during ICCU stay (as inferred by peak glycemia).

Taking into account that aging impairs the acute glucose response to stress in elderly STEMI patients, further studies are needed to establish whether a different (more aggressive) therapeutic regime is needed in this subgroup of patients at higher risk. Moreover, no recommendation is so far available on whether (and, if so, how) to treat STEMI insulin-resistant patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [55].

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